Acute Kidney Injury and Regenerative Medicine

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Preface

The disease concept of acute kidney injury (AKI) has been established in the last 10 years. In the past, the pathology associated with sudden renal impairment was characterized as acute renal failure (ARF). However, in the twenty-first century, the joint efforts of specialists in fields including nephrology, intensive care medicine, cardiovascular medicine, and pediatric nephrology have led to the development of a novel concept of AKI. Changes in the composition of the global population and in the incidence of disease, especially the rapid rise in chronic kidney disease (CKD) and diabetes mellitus, have increased the number of people at high risk for acute kidney injury. There is now widespread awareness of the surge in the frequency of AKI and of the fact that it markedly worsens patients' long-term prognoses. Thus, AKI was proposed as a novel disease concept to emphasize early diagnosis and early intervention for the improvement of prognoses.

Several types of diagnostic criteria of AKI have been introduced in the pursuit of a consistent international standard. Kidney Disease Improving Global Outcomes (KDIGO) guidelines (2012) are widely accepted as the criteria for the diagnosis of AKI. The Japanese Society of Nephrology, the Japanese Society of Intensive Care Medicine, the Japanese Society for Dialysis Therapy, the Japan Society for Blood Purification in Critical Care, and the Japanese Society for Pediatric Nephrology came together to develop "The AKI Clinical Practice Guideline 2016." In this guideline, we opted to use the term "AKI," which includes the existing concept of ARF. As the diagnosis of AKI is based on changes in the serum creatinine and the urine output only, it encompasses diverse pathologies. In clinical practice, AKI requires early diagnosis as well as constant differentiation of the causes (pre-renal, renal, and post-renal) and elimination of the reversible factors. Numerous clinical trials on early biomarkers for the diagnosis of AKI and treatments including renal replacement therapy (RRT) have also been published in the past few years. The chapters in this textbook on clinical fields were written by the authors of the recent AKI guideline (2016) and by internationally distinguished researchers.

Basic research on AKI has also made great progress in recent years. There have been many research results showing that the kidney and multi-organ linkages, especially the nervous system and immune system, are involved in the pathology of

AKI. There are great hopes that these basic research results will be clinically applied. Epidemiological studies have revealed that AKI shifts to CKD at a high rate, and that when AKI occurs, cardiovascular accidents increase and life expectancy decreases. Regenerative medicine research including that in iPS cells, which is given much attention today, has also made great progress in the field of kidney research.

In this textbook, the latest topics have been written by cutting-edge researchers on AKI and kidney regeneration. The epidemiology, early diagnosis, risk factors, and prevention and management of AKI are described in clinical chapters. In the basic research field, multiple organ linkages in AKI, AKI-to-CKD transition, and regenerative studies are from top international researchers. We hope this textbook will be useful not only to nephrologists but also to many physicians in other specialties and to basic researchers.

Finally, we wish to thank all the authors for their contributions to this volume.

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Part I
Diagnosis and Risk Factors of AKI

Chapter 1
Acute Kidney Injury: Definition and Epidemiology

Taro Horino

Abstract Acute kidney injury (AKI) complicates the course and worsens the outcome in a significant number of hospitalized patients. Recent advances in clinical and basic research will aid in providing a more accurate definition of this syndrome and elucidate its pathogenesis, which would allow more accurate epidemiologic studies to be conducted in an effort to gain a better understanding of the impact of this syndrome. AKI rarely has a sole and distinct pathophysiology. Recent evidence, from both basic science and clinical research, is beginning to change our view of AKI as a single-organ failure syndrome to a syndrome in which the kidneys play an active role in the progression of multi-organ dysfunction. The accurate and prompt recognition of AKI and a better understanding of the pathophysiologic mechanisms underlying the various clinical phenotypes are of great importance to the search for effective therapeutic interventions. In this review, we provide the most recent updates in the definition, epidemiology, and pathophysiology of AKI.

Keywords Acute kidney injury · Epidemiology · Pediatric · Sepsis · Surgical outcomes · Serum creatinine

1.1 Introduction

Recently, "acute kidney injury" (AKI) replaced the term "acute renal failure" (ARF) [1]. Traditionally, the pathology associated with sudden renal impairment has been characterized as ARF, with emphasis given to the most severe acute reduction in kidney function, as manifested by severe azotemia and frequently by oliguria or anuria. However, recent evidence suggests that even a relatively mild injury or impairment of kidney function, as manifested by small changes in serum creatinine (sCr) and/or urine output (UO), is a predictor of serious clinical consequences [2, 3].

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ARF was first described in 1802 as "ischuria renalis" [4] and then described in 1909 as a consequence of toxic agents, pregnancy, burns, trauma, or surgery involving the kidneys, known as "acute Bright's disease." During the First World War, the syndrome was reported as "war nephritis" [5] and was then forgotten until the Second World War, at which time Bywaters and Beall published their classical paper on "crush syndrome" [6]. "Acute tubular necrosis" (ATN) was used to describe this clinical entity because of the histological evidence for patchy necrosis of the renal tubules at autopsy. Homer W. Smith introduced the term "ARF" in a chapter on ARF related to traumatic injuries in his 1951 textbook *The Kidney - Structure and Function in Health and Disease*. The terms "ATN" and "ARF" were then used interchangeably in clinical practice for many years. Furthermore, until recently, a precise biochemical definition for ARF was lacking. As a consequence, there was no consensus on the diagnostic criteria, resulting in multiple definitions. In fact, a 2002 survey revealed at least 35 definitions in the scientific literature [7].

The current diagnostic approach in AKI is based on an acute decrease in the glomerular filtration rate (GFR), as reflected by an acute rise in sCr and/or a decline in UO over a given time interval [1, 8, 9]. Although several biomarkers have been recently proposed for diagnosing AKI, these remain in various stages of development and validation [10, 11]. Moreover, it remains unclear whether a single or multiple biomarker approach is necessary to diagnose the complicated and multifactorial aspects of AKI [12, 13]. Furthermore, in addition to the analytical difficulties associated with each specific biomarker, there are concerns regarding the appropriate reference points and, more specifically, the use of sCr as the standard for the clinical evaluation of these biomarkers. sCr is known to be insensitive to acute changes in renal function, and levels can vary widely according to age, sex, muscle mass, diet, medications, and hydration status. Moreover, sCr is not a direct marker of tubular damage but is rather a marker of the GFR. Additionally, substantial increases in sCr can be observed in renal hypoperfusion, even when the kidneys are structurally intact, resulting in prerenal azotemia. For these reasons, sCr is considered as an "imperfect gold standard" in the diagnosis of AKI [14]. Another issue with sCr is that its true baseline value is unknown for most clinical situations, which makes the evaluation of patients very difficult [15]. Moreover, given the phenotypic variability in AKI (i.e., there are different clinical phenotypes with distinct underlying pathophysiology), it is unclear whether different approaches are necessary for the diagnosis, treatment, and monitoring of the clinical course. Herein, we discuss the epidemiology and definitions of AKI.

1.2 Definitions of AKI

1.2.1 RIFLE Criteria

Although the term "AKI" was initially used in 1918 by William MacNider in regard to a case of acute mercury poisoning, it did not become the preferred term until 2004, after the redefining of ARF in the widely accepted consensus criteria known as RIFLE (an acronym of Risk-Injury-Failure-Loss-End Stage kidney disease) [8].

Table 1.1 RIFLE criteria

	GFR criteria	Urine output criteria
Risk	Increase in sCr ≥ 1.5 × baseline or decrease in GFR ≥ 25%	UO < 0.5 mL/kg/h × 6 h
Injury	Increase in sCr ≥ 2.0 × baseline or decrease in GFR ≥ 50%	UO < 0.5 mL/kg/h × 12 h
Failure	Increase in sCr ≥ 3.0 × baseline or an absolute sCr ≥ 4.0 mg/dL with an acute rise of at least 0.5 mg/dL or decrease in GFR ≥ 75%	UO < 0.3 mL/kg/h × 24 h or anuria × 12 h
Loss	Complete loss of kidney function >4 weeks	
ESKD	End-stage renal disease (dialysis dependent >3 months)	

GFR glomerular filtration rate, *sCr* serum creatinine, *ESKD* end-stage kidney disease, *UO* urine output

The RIFLE criteria (Table 1.1) [8] resulted from the 2002 efforts of the Acute Dialysis Quality Initiative (ADQI) group to develop a system for the diagnosis and classification of acute impairments in kidney function via a broad consensus of experts. This system comprises three severity grades (Risk, Injury, and Failure) and two outcome classes (Loss and End-Stage Renal Disease [ESRD]). In the RIFLE system, the principal tools for detecting AKI comprise consecutive measurements of sCr, serum urea (sUr), and UO and urinalysis. The severity criteria of AKI are defined in terms of changes in sCr or UO, using the worst of each criterion. Urine indices, such as the fractional excretion of sodium (FeNa) and urea (FeUr), are also used to differentiate transient from persistent AKI. The outcome criteria are defined by the duration of kidney function impairment [8].

The RIFLE criteria are important in that that they moved the field beyond the concept of ARF. The replacement term of "acute kidney injury/impairment" was proposed in an effort to encompass the entire spectrum of the syndrome, from minor changes in markers of renal function to the requirement of renal replacement therapy (RRT). Therefore, the concept of AKI, as defined by the RIFLE criteria, created a new paradigm. AKI encompasses ATN and ARF, as well as other, less severe conditions. Moreover, it includes patients without actual kidney damage, but with functional impairment relative to physiologic demands. Including such patients in the classification of AKI is conceptually attractive because these are precisely the patients that may benefit from early intervention. The RIFLE criteria have also been successfully modified for use in pediatric settings [16]. Nevertheless, the RIFLE definition is not free of ambiguity. For example, Pickering et al. showed that there is a mismatch between an increase in sCr and decrease in the GFR (estimated using Modification of Diet in Renal Disease Study or Cockroft-Gault formulae) in the descriptions of the Risk and Failure severity grades [17].

1.2.2 AKIN Criteria

In 2007, the Acute Kidney Injury Network (AKIN) group proposed a modified version of the RIFLE criteria, in an effort to improve the sensitivity of the AKI diagnostic criteria (Table 1.2) [9]. The changes can be summarized as follows: an absolute increase in sCr of at least 0.3 mg/dL (26.5 μmol/L) was added to the stage 1 classification; the

Table 1.2 AKIN criteria

Definition	1. Increase in SCr of ≥0.3 mg/dL (48 h)	
	2. sCr changes ≥1.5 × baseline (48 h)	
	3. UO < 0.5 mL/kg/h × 6 h	
	sCr criteria	UO criteria
Stage 1	Increase in sCr of ≥0.3 mg/dL or increase to 1.5–2.0 × baseline	UO < 0.5 mL/kg/h × 6 h
Stage 2	Increase in sCr to 2.0–3.0 × baseline	UO < 0.5 mL/kg/h × 12 h
Stage 3	Increase in sCr > 3.0 × baseline or sCr ≥ 4.0 mg/dL with an acute rise of at least 0.5 mg/dL or initiation of RRT	UO < 0.3 mL/kg/h × 24 h or anuria × 12 h

sCr serum creatinine, *UO* urine output, *RRT* renal replacement therapy

Table 1.3 KDIGO criteria

Definition	1. Increase in SCr of ≥0.3 mg/dL (48 h)	
	2. sCr changes ≥1.5 × baseline (7 days)	
	3. UO < 0.5 mL/kg/h × 6 h	
	sCr criteria	UO criteria
Stage 1	Increase in sCr of ≥0.3 mg/dL or increase to 1.5–1.9 × baseline	UO < 0.5 mL/kg/h × 6 h
Stage 2	Increase in sCr to 2.0–2.9 × baseline UO <0.5 mL/kg/h × 12 h	
Stage 3	Increase in sCr > 3.0 × baseline or sCr ≥ 4.0 mg/dL or initiation of RRT	UO < 0.3 mL/kg/h × 24 h or anuria × 12 h

sCr serum creatinine, *UO* urine output, *RRT* renal replacement therapy

GFR criterion was removed; patients starting RRT were classified as stage 3, irrespective of sCr values; and the outcome classes were removed. Only one criterion (sCr or UO) must be fulfilled to qualify for a particular stage. Furthermore, time becomes more important in diagnosing AKI using the AKIN system: changes between two sCr values within a 48-h period are required, while the ADQI group proposed a period of 1 week in the original RIFLE criteria. Additionally, AKI severity in the AKIN system is staged over the course of 7 days by the fold change in sCr from baseline.

1.2.3 KDIGO Criteria

The most recent classification system of AKI, proposed by the Acute Kidney Injury Working Group of KDIGO (Kidney Disease: Improving Global Outcomes), is based on the previous two classifications, with the aim of unifying the definitions of AKI (Table 1.3) [1]. In the KDIGO system, AKI is diagnosed by an absolute increase in sCr of at least 0.3 mg/dL within 48 h, a 50% increase in sCr from baseline within 7 days, or a urine volume of less than 0.5 mL/kg/h for at least 6 h.

A patient's progress can be staged over the entire timeframe encompassed by an episode of AKI. An increase in sCr of up to threefold that at baseline, a sCr of more

than 4.0 mg/dL, and the initiation of RRT are all classified as stage 3. The KDIGO system removes the criterion of a 0.5 mg/dL increase in sCr for sCr levels >4 mg/dL to diagnose stage 3. Furthermore, the KDIGO criteria explicitly state that a rolling baseline can be used over 48-h and 7-day periods for the diagnosis of AKI; in contrast, it was unclear how this was to be handled in the RIFLE and AKIN systems. Changes were also made to the definition of stage 3 severity to enable the incorporation of the pediatric population into both the definition and staging of AKI.

1.3 Etiology of AKI

AKI is defined as an abrupt (within hours) decrease in kidney function, which encompasses both injury (structural damage) and impairment (loss of function). AKI rarely has a sole and distinct pathophysiology. Most patients with AKI have a mixed etiology, with sepsis, ischemia, and nephrotoxicity often co-existing and complicating the recognition and treatment of AKI. Furthermore, AKI is quite common among patients without a critical illness, and it is essential that healthcare professionals, particularly those without a specialization in renal disorders, are able to detect it easily.

There are numerous potential causes of AKI, mainly related to a focal mismatch between oxygen and nutrient delivery to the nephrons (because of microcirculation impairment) and increased energy demands (due to cellular stress) [18]. For many years, the diagnosis and management of AKI was based on its classification to three main categories: pre-renal, intrinsic, and post-renal [19, 20]. Of these, only "intrinsic" AKI represents true kidney disease; pre-renal and post-renal AKI are the consequence of extra-renal diseases that lead to a decreased GFR. If these pre- and/or post-renal conditions persist, they will eventually result in renal cellular damage and, hence, intrinsic renal disease. The timely reversion of pre-renal or post-renal causes usually results in the prompt recovery of function, but a late correction can lead to kidney damage.

Pre-renal AKI reflects renal hypoperfusion, leading to a decreased GFR (without damage to the renal parenchyma), that occurs as an adaptive response to various extra-renal insults [21]. Maintaining a normal GFR is known to depend on adequate renal perfusion. The kidneys receive up to 25% of the cardiac output; thus, any reduction in the systemic circulating blood volume or an isolated failure in the intrarenal circulation can have a profound impact on renal perfusion.

Post-renal AKI occurs after an acute obstruction of the urinary flow, which increases the intra-tubular pressure and, thus, decreases the GFR [22]. In addition, an acute urinary tract obstruction can lead to renal blood flow impairment and the induction of inflammatory processes, which also contribute to a diminished GFR [23]. Post-renal AKI can develop from obstructions located at any level within the urinary collection system (from the renal tubule to the urethra). An obstruction involving both kidneys produces significant renal failure [24], but a patient with pre-existing renal insufficiency may develop AKI with the obstruction of only one kidney. The

urinary obstruction may present as anuria or intermittent urine flow (such as polyuria alternating with oliguria) but may also present as nocturia or nonoliguric AKI.

Intrinsic renal etiologies of AKI can be challenging to evaluate because of the wide variety of kidney injuries that can occur. Generally, four structures of the kidney can be affected: the tubules, glomeruli, interstitium, and intra-renal blood vessels. ATN refers to AKI resulting from damage to the tubules and is the most common type of intrinsic kidney injury. AKI resulting from glomerular damage occurs in severe cases of acute glomerulonephritis. AKI can result from vascular damage because injury to intra-renal vessels decreases renal perfusion and diminishes the GFR. Finally, acute interstitial nephritis can occur as a result of an allergic reaction to a variety of medications or an infection.

1.4 Epidemiology

The widespread adoption of standardized criteria to define the presence and severity of AKI has facilitated comparisons in the epidemiology and outcomes of AKI across hospital settings [25]. However, this standardization should not imply that AKI comprises a single entity. Rather, AKI is a syndrome that encompasses a multitude of clinical scenarios, underlying etiologies, comorbidities, drug exposures, and severities of renal dysfunction. AKI also involves several different pathophysiological processes. The long-standing lack of a standard definition of the syndrome has greatly affected the reported incidence and clinical significance of AKI; thus, its true impact is not well understood.

The reported incidence of AKI varies, depending on the definition used, patient population, and geographical area studied [26]. A recent review described the similarities and differences in the incidence, cause, pathophysiology, and public health implications of AKI in developed and developing regions of the world [27], with large differences observed in the incidence and causes of AKI. In the urban areas of developing countries, AKI is mainly hospital acquired (due to renal ischemia, sepsis, and nephrotoxic drug use), while in rural areas, AKI is more commonly a consequence of community-acquired diseases (e.g., diarrhea, dehydration, infectious diseases, and animal venoms). The under-reporting of AKI, especially in developing countries, is a major problem, obscuring the true impact of AKI in many parts of the world [28]. Below, we summarize the data regarding the epidemiology of AKI in various settings.

1.4.1 Hospitalized Patients

Hospitalized patients often have risk factors for AKI (e.g., older age; male sex; and comorbidities, such as diabetes, heart failure, and hypoalbuminemia) [29–31]. AKI is estimated to occur in up to 15% of hospitalized patients and is more common in critically ill patients, among whom its prevalence is estimated to be as high as 60% [27, 32–36]. In contrast, community-acquired AKI is usually uncommon; a recent

study estimated its incidence as 4.3% among all hospital admissions [37]. However, this is likely an underestimation of the true impact of community-acquired AKI due to the non-referral of patients to hospitals.

Several factors are important to consider when evaluating studies describing the epidemiology of AKI in hospitalized patients: most such studies use sCr criteria alone to define AKI and generally do not report the etiology of AKI or the characteristics of the hospitals studied [38]. Additionally, between-study differences in AKI epidemiology might result from variation in the way that relevant terms, such as baseline sCr, are defined [39], as well as in the use of RIFLE, AKIN, or KDIGO criteria [40]. Differing applications of the AKI diagnostic criteria could influence study sensitivity (e.g., in one study, inclusion was based on a mix of biochemical and coded diagnoses, whereas in another, inclusion was based on a biochemical screening with nephrologist adjudication of the diagnosis). Differences in case mix could also influence the findings (e.g., one study only included patients in main regional hospitals, whereas another included patients in both academic centers and smaller rural hospitals).

In studies that used the current criteria to define AKI, the proportion of hospitalized adult patients who develop AKI ranges from 3.0 to 18.3% [38]. Even when considering the low end of this range, it is abundantly clear that AKI affects a very large number of hospitalized patients worldwide. Furthermore, in most healthcare systems, the majority of these patients receive care outside specialized clinics.

Only a minority (<5%) of patients with AKI require RRT [41]. However, AKI is associated with poor outcomes. Even among non-ICU hospitalized patients with AKI, the mortality rate is typically 10–20% [3, 41, 42]. Further research on the epidemiology of AKI in discrete clinical cohorts would be valuable, as mortality from AKI has been shown to differ according to settings, including the exacerbation of bronchiectasis due to infection (33%) [43], heart failure (11–13%) [44], urological conditions (7.8%) [45], liver disease (36%) [46], and pneumonia (36.2%) [47].

Furthermore, a strong and graded relationship between AKI severity and increased mortality is clearly evident [3]. The inclusion of numerically small increases in the sCr level in the current diagnostic criteria results from the strong association of such changes with adverse outcomes, which persists even after adjustment for important confounders, such as age and comorbidities [2, 42]. Both the presence and severity of AKI are associated with a longer hospital stay, increased rates of unplanned critical care admissions and RRT (although <10% of patients in this setting receive RRT), and an increased risk of subsequent chronic kidney disease (CKD). In 9–23% of hospitalized patients, AKI progresses, resulting in an increased chance of adverse outcomes [48].

1.4.2 Pediatric Patients

Although several studies have focused on special populations, such as the elderly and children, large epidemiologic studies of children are lacking, and the incidence of pediatric AKI is inadequately described. In a recent large-scale epidemiologic study, the incidence of AKI in hospitalized children in the United States was 3.9 per

1000 admissions [49]. The majority of pediatric AKI cases are secondary to volume-responsive mechanisms (e.g., diarrhea and postoperative renal hypoperfusion) and sepsis [50]. Other conditions, such as uremic-hemolytic syndrome and glomerulonephritis, have increased frequency in specific parts of the world, with varied outcomes, usually due to the late referral of children to hospitals.

Among children admitted to the ICU, the in-hospital mortality rate was higher in those with AKI than in those without AKI (32.9% versus 9.4%) [49]. Stages 2 and 3 AKI in critically ill children are, therefore, unquestionably associated with increased in-hospital morbidity and mortality, as well as an increased risk of CKD.

1.4.3 Elderly Patients

Multiple studies have shown that AKI in the elderly (usually defined as age greater than 65 years) is increasingly common and that there is a relationship between AKI and older age [51]. This has been attributed in part to anatomic and physiologic changes in the aging kidney and, in part, to various comorbidities (e.g., hypertension, cardiovascular disease, and CKD) that may require procedures and/or medications that stress the kidneys and alter renal hemodynamics or are nephrotoxic [52].

Additionally, several studies have shown that AKI is associated with short- and long-term adverse outcomes in the elderly population. Using the RIFLE system, a previous study found that the mortality rate was 18.9% in the "Risk" class, 36.1% in the "Injury" class, and 46.5% in the "Failure" class. In contrast, the mortality rate was 6.9% in non-AKI patients [53]. Among patients with AKI, the relative risk for death (with respect to that in non-AKI patients) was 2.40 for the "Risk" class, 4.15 for the "Injury" class, and 6.15 for the "Failure class" [53]. Observational studies of ICU populations have reported that 4–5% of all critically ill patients develop severe AKI requiring RRT, with the mortality rate often exceeding 60% [33, 54, 55]. Although mortality and the development of CKD are clearly reported as increased with AKI in these studies, their incidence is quite variable. The factors associated with the long-term prognosis (especially CKD progression) are poorly understood. The pre-AKI baseline renal function must be known, and post-AKI recovery must be clearly defined in order to determine such outcomes. However, in many studies, the former is often missing or estimated, and the latter lacks a standard definition [56].

1.4.4 Critically Ill Patients

In the majority of critically ill patients, AKI is a complication of severe illness. In only a small minority of patients, AKI is caused by a specific kidney disease, such as vasculitis, glomerulonephritis, or interstitial nephritis. AKI, as defined by the sensitive RIFLE, AKIN, or KDIGO criteria [1, 8, 9], occurs in one-third to two-thirds of patients in the ICU [57, 58]. The variation in the incidence of AKI in

critically ill patients (as well as their counterparts in general wards) can be explained by differences in the baseline characteristics of the cohort studied and the length of the observation period and in the way that the definitions of AKI were applied, such as the use of sCr criteria only [57]. RRT was used in 23.5% of critically ill patients with AKI in the large, multicenter Acute Kidney Injury-Epidemiologic Prospective Investigation (AKI-EPI) study [58].

Both the incidence of AKI and the use of RRT in ICU patients appear to be increasing over time. Analyses of administrative databases using the International Statistical Classification of Diseases and Related Health Problems codes have shown a marked increase in the incidence of AKI over time [59–61]. In the United Kingdom, the use of RRT in patients with AKI increased from 15.9 per million patients in 1998–1999 to 208.7 per million patients in 2012–2013 [62]. Similarly, RRT use increased fourfold between 1996 and 2010 in Canada [63]. The increases in the incidence of AKI and RRT use may be explained by changes in the spectrum of patients treated in ICUs. Today's ICU patients are older and have more comorbidities (such as diabetes, hypertension, and CKD) than did the ICU patients of the past [64]. Changes in attitudes regarding the initiation of RRT and improved medical record-keeping in administrative databases may have also contributed to this observation.

Multiple large studies using multivariate analyses to evaluate the contribution of AKI to patient outcomes in different settings have found that, after correction for potential confounders, AKI is independently associated with increased morbidity and mortality. Specifically, in the AKI-EPI study, moderate and severe AKI (stages 2 and 3) was associated with increased in-hospital mortality (AKI stage 2 adjusted odds ratio [OR], 2.9; AKI stage 3 adjusted OR, 6.9) [58]. AKI has the least adverse effect on outcomes in the most severely ill patients [65]. Patients with AKI who receive RRT are among the most severely ill individuals in the ICU. Despite advances in treatment, the mortality rate in this group has remained more or less constant over time (at approximately 50%) [66]. This observation can be explained by the increasing severity of the underlying diseases and comorbidities over time. Although patients with severe AKI and anuria will inevitably die without RRT, the exact effects of several aspects of RRT—specifically, the choice of modality and timing of treatment—on outcomes remain unclear [67]. Several large studies suggest that continuous RRT is associated with improved renal recovery; however, these findings are based on observational data and might be subject to bias [68]. Other studies suggest that the early initiation of RRT is associated with improved outcomes [69].

1.4.5 Sepsis

Sepsis was redefined in 2016 as "a life-threatening organ dysfunction caused by a dysregulated host response to infection" [70]. Although sepsis is a major public health issue and a leading cause of morbidity and mortality worldwide, few studies

to date have utilized this new definition. Thus, sepsis and AKI both remain hampered by imperfect consensus definitions [1, 70]. The concurrent manifestation of sepsis and AKI is termed “septic AKI” [1, 70]. Sepsis is consistently identified as the most common contributor to AKI in critically ill patients; ~50% of all patients with AKI in ICU settings have sepsis [32, 58]. Patients with sepsis are also exposed to numerous additional potential renal insults, including hypotension, contrast media use, major surgery, and nephrotoxins, which can confound the prognosis as well as our understanding of the AKI etiology.

The risk of AKI rises incrementally with worsening sepsis severity [71]. In a single-center cohort study of 315 critically ill patients, the incidence of AKI increased, from 4.2% in patients with sepsis, to 22.7% in patients with severe sepsis, and to 52.8% in patients with septic shock [71]. Patients with septic shock and those with AKI were both likely to experience delays before receiving effective antimicrobial therapy, with each successive l-hour delay associated with a 14% increase in the likelihood of developing AKI [72]. Furthermore, AKI increases the short-term and long-term risk of incident sepsis [73, 74]. In a secondary analysis of data from 618 critically ill patients with AKI, 40% of patients developed sepsis, occurring at a median of 5 days after AKI onset [74]. The adjusted relative risk of developing severe sepsis requiring readmission to the hospital was approximately twofold higher in patients with severe AKI than in those without AKI [73]. In a secondary analysis of data from the BEST Kidney study [75], the in-hospital mortality rate was significantly higher in patients with septic AKI than in patients with non-septic AKI (70.2% versus 51.8%). Similar increments in the risk of death in patients with septic AKI, as compared to that in patients with non-septic AKI, have been found in other studies [76]. Additionally, mortality is increased in patients with septic AKI compared to that in patients with sepsis who do not have AKI [77]. Moreover, 20% of patients with septic AKI have at least two further episodes of recurrent AKI following their initial recovery, while still in the ICU [78]. Septic AKI is also associated with prolonged ICU and hospital stay durations compared to those in non-septic AKI [75]. Among patients with AKI who survived to hospital discharge, septic AKI was associated with trends toward improved kidney function recovery and a reduced rate of RRT dependence compared to those in non-septic AKI [75]. Survivors of septic shock who recovered from AKI before hospital discharge had l-year survival comparable to that of patients without AKI, whereas non-recovery from AKI at discharge was associated with a threefold increase in the risk of death at l year [79].

1.4.6 Cardiac Surgery

AKI is a common complication of cardiac surgery and has been identified as one of the strongest risk factors of death in patients undergoing such procedures [80]. In two 2016 meta-analyses, the pooled incidence of AKI in patients undergoing cardiac surgery was 22.3% (95% confidence interval, 19.8–25.1) [81, 82].

Although most studies used the standard definitions for AKI based on the RIFLE, AKIN, or KDIGO criteria, modified definitions, without the use of UO criteria, are frequently employed [81, 82]. Studies consistently report that greater AKI severity stage is associated with increased morbidity and mortality [81, 82]. However, the incidence of AKI differs when sCr criteria, rather than UO criteria, are used. For example, in one study, the AKI incidence was 9.7% when sCr criteria were applied and 40.2% when UO criteria were applied [83], nicely illustrating the low sensitivity of sCr-based criteria and the low specificity of UO-based criteria.

Even patients with "mild" AKI after cardiac surgery have higher in-hospital mortality and a longer hospital stay than do their counterparts without AKI [84]. Long-term mortality remains increased in patients with postoperative AKI, with survival rates as high as 44% and 63% for patients with and without AKI, respectively, at 10 years of follow-up [85–87]. This difference in survival is evident even in patients with postoperative AKI who have completely recovered from AKI by the time of hospital discharge [85].

The duration of cardiac surgery-associated AKI is another important prognostic indicator. Persistent AKI is associated with increased in-hospital mortality (15.3% for AKI lasting ≥7 days versus 4.1% for AKI lasting l–2 days) and reduced 5-year survival (hazard ratio, 3.40 for AKI lasting ≥7 days or longer versus 1.66 for AKI lasting l–2 days) [88]. Conversely, early recovery from AKI is associated with improved long-term survival [89].

Patients with AKI also have higher rates of postoperative complications, including cerebrovascular and cardiovascular events and infections, and a longer duration of mechanical ventilation than do their AKI-free counterparts [90]. Furthermore, the 5-year risk of a composite cardiovascular endpoint (stroke, myocardial infarction, or heart failure) was reported as 24.9% in patients with postoperative AKI, compared to 12.1% in patients without AKI after cardiac surgery [90]. Additionally, the risk of developing CKD is increased after episodes of postoperative AKI [91].

1.4.7 Contrast Administration

AKI is associated with the intravascular administration of iodinated contrast media, either intravenously for contrast-enhanced computed tomography (CT) or by intra-arterial injection for coronary or non-coronary angiography. The incidence of contrast-associated AKI in epidemiological studies and clinical trials is highly variable, depending on the specific diagnostic criteria used and the characteristics of the population studied. Most individuals have a low risk of developing AKI after contrast exposure; however, patients with pre-existing kidney disease, heart failure, advanced liver disease, volume depletion, or concomitant exposure to other nephrotoxins are at a substantially increased risk.

In a previous retrospective study, the overall incidence of hospital-acquired AKI was 7.2%, and the third most common etiology of AKI was contrast administration, which accounted for 11.3% of AKI episodes [92]. In the same study, AKI occurred

after 2.8% of coronary catheterization procedures and after 1.7% of contrast-enhanced CT scans [92]. In an observational analysis of patients undergoing percutaneous coronary intervention (PCI), the overall incidence of contrast-associated AKI was 2.0% [93].

Contrast-associated AKI is associated with both renal and non-renal adverse outcomes, including the development and progression of CKD, the development of dialysis-dependent ESRD, cardiovascular complications, and death [93, 94]. Patients who develop contrast-associated AKI after PCI have an increased risk of stent re-occlusion, myocardial infarction, and hospitalization for heart failure [93, 94]. However, the extent to which these risks are attributable to the development of AKI per se, versus being associated with the same risk factors that predispose one to the development of AKI [94], remains unknown.

1.4.8 AKI in Developing Countries

Despite the high burden of AKI in developing countries [27, 38, 82, 95], reliable information on the incidence of AKI in such countries is lacking due to limitations in the quantity and availability of local and regional data, the use of outdated AKI classification systems, and barriers to the publication of such data in well-regarded scientific journals. A 2015 meta-analysis reported that the use of KDIGO or KDIGO-equivalent definitions of AKI is increasing in developing countries, rendering their data comparable to those from other regions of the world [95]. In contrast to the findings of early reports, the pooled incidence of AKI in developing countries is increasingly approaching that in developed countries. AKI affects 21% of hospital admissions in developing countries, a figure that is broadly in agreement with the worldwide incidence of AKI. However, the overall proportion of patients with AKI requiring RRT in developing countries is lower than that in developed countries. Additionally, data from the International Society of Nephrology 0 by 25 Global Snapshot, a multinational cross-sectional study [95], showed that mortality at 7 days was higher in developing countries than in the developed countries combined [95].

The etiology of AKI in developing countries often differs from that in developed countries and differs between urban and rural environments. In developed countries, rural community-acquired AKI is associated with severe gastroenteritis, acute glomerulonephritis, envenomation, intoxication from traditional remedies, and complications from endemic infections (including malaria, HIV/AIDS, leptospirosis, and dengue). Conversely, the etiologies of AKI in large urban centers resemble those in developed countries [38, 95, 96].

1.5 Long-Term Outcomes

The notion that AKI survivors have an increased risk of developing CKD or ESRD is now widely accepted but is not well appreciated beyond nephrology specialists [97]. Given the adverse prognosis of many patients after an AKI episode and the

public health ramifications of progression to late-stage CKD, efforts to identify clinical risk factors of progression in patients with and without pre-existing CKD who have survived an episode of AKI are urgently needed.

The observed increased cardiovascular risk after AKI relates to the occurrence of major adverse cardiovascular events, including stroke [98, 99]. Increased risks for an assortment of other diseases have been linked to AKI, including gastrointestinal bleeding, organ fibrosis, and liver injury [100, 101]. The development of AKI heralds a strong likelihood of increased morbidity, with adverse outcomes not limited to kidney-centric effects. Given the current absence of therapeutics for AKI, efforts to prevent and rapidly diagnose AKI, and thereby to attenuate its severity and duration, are key clinical priorities.

1.6 Conclusions

AKI is an important clinical syndrome associated with poor clinical outcomes in hospitalized patients. Considerable advances have been made in refining the definition of this syndrome and in the elucidation of the pathophysiologic mechanisms underlying its different clinical phenotypes. The challenges in the diagnosing of AKI and the lack of a "gold standard" for its identification mean that AKI incidence estimates are likely to be flawed. In some series, the AKI incidence might be overestimated due to the labelling of unrecognized CKD as AKI. However, in most studies, AKI rates are probably underestimated due to the inclusion of patients with subclinical disease or the failure to recognize patients with detectable but subtle, clinical features. It is obvious that the many clinical phenotypes of AKI cannot fit into a single pathophysiologic pathway. AKI facilitates organ cross-talk and distant organ injury. However, recent innovations will aid in the design of epidemiologic studies and randomized trials of preventive and therapeutic interventions.

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References

1. Kidney disease improving global outcomes (KDIGO) clinical practice guideline for acute kidney injury. Section 1: Introduction and Methodology. Chapter 1.1: Introduction. Kidney Int Suppl. 2012;2:13–8.
2. Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. J Am Soc Nephrol. 2005;16:3365–70.
3. Uchino S, Bellomo R, Goldsmith D, Bates S, Ronco C. An assessment of the RIFLE criteria for acute renal failure in hospitalized patients. Crit Care Med. 2006;34:1913–7.
4. Eknoyan G, Agodoa L. On improving outcomes and quality of dialysis care, and more. Am J Kidney Dis. 2002;39:889–91.
5. Davies FC, Weldon RP. A contribution to the study of "war nephritis". Lancet. 1917;190:118–20.

6. Bywaters EG, Beall D. Crush injuries with impairment of renal function. Br Med J. 1941;1:427–32.
7. Kellum JA, Levin N, Bouman C, Lameire N. Developing a consensus classification system for acute renal failure. Curr Opin Crit Care. 2002;8:509–14.
8. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the second international consensus conference of the acute dialysis quality initiative (ADQI) group. Crit Care. 2004;8:R204–12.
9. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al. Acute Kidney Injury Network Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11:R31.
10. Vanmassenhove J, Vanholder R, Nagler E, Van Biesen W. Urinary and serum biomarkers for the diagnosis of acute kidney injury: an in-depth review of the literature. Nephrol Dial Transplant. 2013;28:254–73.
11. Siew ED, Ware LB, Ikizler TA. Biological markers of acute kidney injury. J Am Soc Nephrol. 2011;22:810–20.
12. Katagiri D, Doi K, Matsubara T, Negishi K, Hamasaki Y, Nakamura K, et al. New biomarker panel of plasma neutrophil gelatinase-associated lipocalin and endotoxin activity assay for detecting sepsis in acute kidney injury. J Crit Care. 2013;28:564–70.
13. Katagiri D, Doi K, Honda K, Negishi K, Fujita T, Hisagi M, et al. Combination of two urinary biomarkers predicts acute kidney injury after adult cardiac surgery. Ann Thorac Surg. 2012;93:577–83.
14. Waikar SS, Betensky RA, Emerson SC, Bonventre JV. Imperfect gold standards for kidney injury biomarker evaluation. J Am Soc Nephrol. 2012;23:13–21.
15. Pickering JW, Endre ZH. Back-calculating baseline creatinine with MDRD misclassifies acute kidney injury in the intensive care unit. Clin J Am Soc Nephrol. 2010;5:1165–73.
16. Akcan-Arikan A, Zappitelli M, Loftis LL, Washburn KK, Jefferson LS, Goldstein SL. Modified RIFLE criteria in critically ill children with acute kidney injury. Kidney Int. 2007;71:1028–35.
17. Pickering JW, Endre ZH. GFR shot by RIFLE: errors in staging acute kidney injury. Lancet. 2009;373:1318–9.
18. Tögel F, Westenfelder C. Recent advances in the understanding of acute kidney injury. F1000Prime Rep. 2014;6:83.
19. Lameire N, Van Biesen W, Vanholder R. Acute renal failure. Lancet. 2005;365:417–30.
20. Rahman M, Shad F, Smith MC. Acute kidney injury: a guide to diagnosis and management. Am Fam Physician. 2012;86:631–9.
21. Blantz RC. Pathophysiology of pre-renal azotemia. Kidney Int. 1998;53:512–23.
22. Basile DP, Anderson MD, Sutton TA. Pathophysiology of acute kidney injury. Compr Physiol. 2012;2:1303–53.
23. Hegarty NJ, Young LS, Kirwan CN, O'Neill AJ, Bouchier-Hayes DM, Sweeney P, et al. Nitric oxide in unilateral ureteral obstruction: effect on regional renal blood flow. Kidney Int. 2001;59:1059–65.
24. Dager W, Hallilovic J. Acute kidney injury. In: DiPiro JT, Talbert RL, Yee GC, et al., editors. Pharmacotherapy: a pathophysiologic approach. 8th ed. New York: McGraw-Hill; 2011. p. 746.
25. Hsu CY, McCulloch CE, Fan D, Ordoñez JD, Chertow GM, Go AS. Community-based incidence of acute renal failure. Kidney Int. 2007;72(2):208–12.
26. Li PK, Burdmann EA, Mehta RL. World kidney day 2013: acute kidney injury-global health alert. Am J Kidney Dis. 2013;61:359–63.
27. Lameire NH, Bagga A, Cruz D, De Maeseneer J, Endre Z, Kellum JA, et al. Acute kidney injury: an increasing global concern. Lancet. 2013;382:170–9.

28. Prakash J, Singh TB, Ghosh B, Malhotra V, Rathore SS, Vohra R, et al. Changing epidemiology of community-acquired acute kidney injury in developing countries: analysis of 2405 cases in 26 years from eastern India. Clin Kidney J. 2013;6:150–5.
29. Siew ED, Deger SM. Recent advances in acute kidney injury epidemiology. Curr Opin Nephrol Hypertens. 2012;21(3):309–17.
30. Roberts G, Phillips D, McCarthy R, Bolusani H, Mizen P, Hassan M, et al. Acute kidney injury risk assessment at the hospital front door: what is the best measure of risk? Clin Kidney J. 2015;8(6):673–80.
31. Wiedermann CJ, Wiedermann W, Joannidis M. Causal relationship between hypoalbuminemia and acute kidney injury. World J Nephrol. 2017;6(4):176–87.
32. Case J, Khan S, Khalid R, Khan A. Epidemiology of acute kidney injury in the intensive care unit. Crit Care Res Pract. 2013;2013:479730.
33. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, et al. Beginning and ending supportive therapy for the kidney (BEST kidney) investigators. Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA. 2005;294:813–8.
34. Liaño F, Pascual J. Epidemiology of acute renal failure: a prospective, multicenter, community-based study. Kidney Int. 1996;50:811–8.
35. Lameire N, Van Biesen W, Vanholder R. The changing epidemiology of acute renal failure. Nat Clin Pract Nephrol. 2006;2:364–77.
36. Lameire N, Van Biesen W, Vanholder R. The rise of prevalence and the fall of mortality of patients with acute renal failure: what the analysis of two databases does and does not tell us. J Am Soc Nephrol. 2006;17:923–5.
37. Wonnacott A, Meran S, Amphlett B, Talabani B, Phillips A. Epidemiology and outcomes in community-acquired versus hospital-acquired AKI. Clin J Am Soc Nephrol. 2014;9:1007–14.
38. Susantitaphong P, Cruz DN, Cerda J, Abulfaraj M, Alqahtani F, Koulouridis I, et al. Acute Kidney Injury Advisory group of the American Society of Nephrology. World incidence of AKI: a meta-analysis. Clin J Am Soc Nephrol. 2013;8(9):1482–93.
39. Lafrance JP, Miller DR. Defining acute kidney injury in database studies: the effects of varying the baseline kidney function assessment period and considering CKD status. Am J Kidney Dis. 2010;56(4):651–60.
40. Zeng X, McMahon GM, Brunelli SM, Bates DW, Waikar SS. Incidence, outcomes, and comparisons across definitions of AKI in hospitalized individuals. Clin J Am Soc Nephrol. 2014;9(1):12–20.
41. Selby NM, Crowley L, Fluck RJ, McIntyre CW, Monaghan J, Lawson N, et al. Use of electronic results reporting to diagnose and monitor AKI in hospitalized patients. Clin J Am Soc Nephrol. 2012;7(4):533–40.
42. Uchino S, Bellomo R, Bagshaw SM, Goldsmith D. Transient azotaemia is associated with a high risk of death in hospitalized patients. Nephrol Dial Transplant. 2010;25(6):1833–9.
43. Iwagami M, Mansfield K, Quint J, Nitsch D, Tomlinson L. Diagnosis of acute kidney injury and its association with in-hospital mortality in patients with infective exacerbations of bronchiectasis: cohort study from a UK nationwide database. BMC Pulm Med. 2016;16:14.
44. Thakar CV, Parikh PJ, Liu Y. Acute kidney injury (AKI) and risk of readmissions in patients with heart failure. Am J Cardiol. 2012;109(10):1482–6.
45. Caddeo G, Williams ST, McIntyre CW, Selby NM. Acute kidney injury in urology patients: incidence, causes and outcomes. Nephrourol Mon. 2013;5(5):955–61.
46. Belcher JM, Garcia-Tsao G, Sanyal AJ, Bhogal H, Lim JK, Ansari N, et al. Association of AKI with mortality and complications in hospitalized patients with cirrhosis. Hepatology. 2013;57(2):753–62.
47. Murugan R, Weissfeld L, Yende S, Singbartl K, Angus DC, Kellum JA. Genetic and inflammatory markers of sepsis (GenIMS) investigators. Association of statin use with risk and outcome of acute kidney injury in community-acquired pneumonia. Clin J Am Soc Nephrol. 2012;7(6):895–905.

48. Holmes J, Rainer T, Geen J, Roberts G, May K, Wilson N, et al. Welsh AKI Steering Group. Acute kidney injury in the era of the AKI E-alert. Clin J Am Soc Nephrol. 2016;11(12):2123–31.
49. Sutherland SM, Ji J, Sheikhi FH, Widen E, Tian L, Alexander SR, et al. AKI in hospitalized children: epidemiology and clinical associations in a national cohort. Clin J Am Soc Nephrol. 2013;8(10):1661–9.
50. Cerdá J, Lameire N, Eggers P, Pannu N, Uchino S, Wang H, et al. Epidemiology of acute kidney injury. Clin J Am Soc Nephrol. 2008;3:881–6.
51. Coca SG. Acute kidney injury in elderly persons. Am J Kidney Dis. 2010;56:122–31.
52. Chronopoulos A, Cruz DN, Ronco C. Hospital-acquired acute kidney injury in the elderly. Nat Rev Nephrol. 2010;6:141–9.
53. Ricci Z, Cruz D, Ronco C. The RIFLE criteria and mortality in acute kidney injury: a systematic review. Kidney Int. 2008;73:538–46.
54. Bagshaw SM, Laupland KB, Doig CJ, Mortis G, Fick GH, Mucenski M, et al. Prognosis for long-term survival and renal recovery in critically ill patients with severe acute renal failure: a population-based study. Crit Care. 2005;9:R700–9.
55. Metnitz PG, Krenn CG, Steltzer H, Lang T, Ploder J, Lenz K, et al. Effect of acute renal failure requiring renal replacement therapy on outcome in critically ill patients. Crit Care Med. 2002;30:2051–8.
56. Swaminathan M, Stafford-Smith M. Changing terminology in renal research: the impact of consensus. Am J Kidney Dis. 2012;59:584–5.
57. Srisawat N, Sileanu FE, Murugan R, Bellomod R, Calzavacca P, Cartin-Ceba R, et al. Variation in risk and mortality of acute kidney injury in critically ill patients: a multicenter study. Am J Nephrol. 2015;41(1):81–8.
58. Hoste EA, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med. 2015;41(8):1411–23.
59. Kolhe NV, Muirhead AW, Wilkes SR, Fluck RJ, Taal MW. The epidemiology of hospitalised acute kidney injury not requiring dialysis in England from 1998 to 2013: retrospective analysis of hospital episode statistics. Int J Clin Pract. 2016;70(4):330–9.
60. Waikar SS, Curhan GC, Wald R, McCarthy EP, Chertow GM. Declining mortality in patients with acute renal failure, 1988 to 2002. J Am Soc Nephrol. 2006;17(4):1143–50.
61. Xue JL, Daniels F, Star RA, Kimmel PL, Eggers PW, Molitoris BA, et al. Incidence and mortality of acute renal failure in Medicare beneficiaries, 1992 to 2001. J Am Soc Nephrol. 2006;17(4):1135–42.
62. Kolhe NV, Muirhead AW, Wilkes SR, Fluck RJ, Taal MW. National trends in acute kidney injury requiring dialysis in England between 1998 and 2013. Kidney Int. 2015;88(5):1161–9.
63. Wald R, McArthur E, Adhikari NK, Bagshaw SM, Burns KE, Garg AX, et al. Changing incidence and outcomes following dialysis-requiring acute kidney injury among critically ill adults: a population-based cohort study. Am J Kidney Dis. 2015;65(6):870–7.
64. Ostermann ME, Taube D, Morgan CJ, Evans TW. Acute renal failure following cardiopulmonary bypass: a changing picture. Intensive Care Med. 2000;26(5):565–71.
65. Sileanu FE, Murugan R, Lucko N, Clermont G, Kane-Gill SL, Handler SM, et al. AKI in low-risk versus high-risk patients in intensive care. Clin J Am Soc Nephrol. 2015;10(2):187–96.
66. Ympa YP, Sakr Y, Reinhart K, Vincent JL. Has mortality from acute renal failure decreased? A systematic review of the literature. Am J Med. 2005;118(8):827–32.
67. Bagshaw SM, Darmon M, Ostermann M, Finkelstein FO, Wald R, Tolwani AJ, et al. Current state of the art for renal replacement therapy in critically ill patients with acute kidney injury. Intensive Care Med. 2017;43(6):841–54.
68. Schneider AG, Bellomo R, Bagshaw SM, Glassford NJ, Lo S, Jun M, et al. Choice of renal replacement therapy modality and dialysis dependence after acute kidney injury: a systematic review and meta-analysis. Intensive Care Med. 2013;39(6):987–97.
69. Gaudry S, Hajage D, Schortgen F, Martin-Lefevre L, Pons B, Boulet E, et al. Initiation strategies for renal-replacement therapy in the intensive care unit. N Engl J Med. 2016;375(2):122–33.

70. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (SEPSIS-3). JAMA. 2016;315(8):801–10.
71. Lopes JA, Jorge S, Resina C, Santos C, Pereira A, Neves J, et al. Acute kidney injury in patients with sepsis: a contemporary analysis. Int J Infect Dis. 2009;13(2):176–81.
72. Bagshaw SM, Lapinsky S, Dial S, Arabi Y, Dodek P, Wood G, et al. Acute kidney injury in septic shock: clinical outcomes and impact of duration of hypotension prior to initiation of antimicrobial therapy. Intensive Care Med. 2009;35(5):871–81.
73. Lai TS, Wang CY, Pan SC, Huang TM, Lin MC, Lai CF, et al. Risk of developing severe sepsis after acute kidney injury: a population-based cohort study. Crit Care. 2013;17(5):R231.
74. Mehta RL, Bouchard J, Soroko SB, Ikizler TA, Paganini EP, Chertow GM, et al. Sepsis as a cause and consequence of acute kidney injury: program to improve care in acute renal disease. Intensive Care Med. 2011;37(2):241–8.
75. Bagshaw SM, Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M, et al. Septic acute kidney injury in critically ill patients: clinical characteristics and outcomes. Clin J Am Soc Nephrol. 2007;2:431–9.
76. Hoste EA, Lameire NH, Vanholder RC, Benoit DD, Decruyenaere JM, Colardyn FA. Acute renal failure in patients with sepsis in a surgical ICU: predictive factors, incidence, comorbidity, and outcome. J Am Soc Nephrol. 2003;14:1022–30.
77. Oppert M, Engel C, Brunkhorst FM, Bogatsch H, Reinhart K, Frei U, et al. Acute renal failure in patients with severe sepsis and septic shock—a significant independent risk factor for mortality: results from the German prevalence study. Nephrol Dial Transplant. 2008;23:904–9.
78. Rodrigo E, Suberviola B, Santibáñez M, Belmar L, Castellanos Á, Heras M, et al. Association between recurrence of acute kidney injury and mortality in intensive care unit patients with severe sepsis. J Intensive Care. 2017;5:28.
79. Kellum JA, Chawla LS, Keener C, Singbartl K, Palevsky PM, Pike FL, et al. The effects of alternative resuscitation strategies on acute kidney injury in patients with septic shock. Am J Respir Crit Care Med. 2016;193:281–7.
80. Chertow GM, Lazarus JM, Christiansen CL, Cook EF, Hammermeister KE, Grover F, et al. Preoperative renal risk stratification. Circulation. 1997;95:878–84.
81. Hu J, Chen R, Liu S, Yu X, Zou J, Ding X. Global incidence and outcomes of adult patients with acute kidney injury after cardiac surgery: a systematic review and meta-analysis. J Cardiothorac Vasc Anesth. 2016;30:82–9.
82. Vandenberghe W, Gevaert S, Kellum JA, Bagshaw SM, Peperstraete H, Herck I, et al. Acute kidney injury in cardiorenal syndrome type 1 patients: a systematic review and meta-analysis. Cardiorenal Med. 2016;6:116–28.
83. Lagny MG, Jouret F, Koch JN, Blaffart F, Donneau AF, Albert A, et al. Incidence and outcomes of acute kidney injury after cardiac surgery using either criteria of the RIFLE classification. BMC Nephrol. 2015;16:76.
84. Dasta JF, Kane-Gill SL, Durtschi AJ, Pathak DS, Kellum JA. Costs and outcomes of acute kidney injury (AKI) following cardiac surgery. Nephrol Dial Transplant. 2008;23:1970–4.
85. Hobson CE, Yavas S, Segal MS, Schold JD, Tribble CG, Layon AJ, et al. Acute kidney injury is associated with increased long-term mortality after cardiothoracic surgery. Circulation. 2009;119:2444–53.
86. Lafrance JP, Miller DR. Acute kidney injury associates with increased long-term mortality. J Am Soc Nephrol. 2010;21:345–52.
87. Najjar M, Salna M, George I. Acute kidney injury after aortic valve replacement: incidence, risk factors and outcomes. Expert Rev Cardiovasc Ther. 2015;13:301–16.
88. Brown JR, Kramer RS, Coca SG, Parikh CR. Duration of acute kidney injury impacts long-term survival after cardiac surgery. Ann Thorac Surg. 2010;90:1142–8.
89. Swaminathan M, Hudson CC, Phillips-Bute BG, Patel UD, Mathew JP, Newman MF, et al. Impact of early renal recovery on survival after cardiac surgery-associated acute kidney injury. Ann Thorac Surg. 2010;89:1098–104.

90. Hansen MK, Gammelager H, Jacobsen CJ, Hjortdal VE, Layton JB, Rasmussen BS, et al. Acute kidney injury and long-term risk of cardiovascular events after cardiac surgery: a population-based cohort study. J Cardiothorac Vasc Anesth. 2015;29:617–25.
91. Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. Kidney Int. 2012;81:442–8.
92. Nash K, Hafeez A, Hou S. Hospital-acquired renal insufficiency. Am J Kidney Dis. 2002;39:930–6.
93. Bartholomew BA, Harjai KJ, Dukkipati S, Boura JA, Yerkey MW, Glazier S, et al. Impact of nephropathy after percutaneous coronary intervention and a method for risk stratification. Am J Cardiol. 2004;93:1515–9.
94. James MT, Samuel SM, Manning MA, Tonelli M, Ghali WA, Faris P, et al. Contrast-induced acute kidney injury and risk of adverse clinical outcomes after coronary angiography: a systematic review and meta-analysis. Circ Cardiovasc Interv. 2013;6:37–43.
95. Mehta RL, Mehta RL, Burdmann EA, Cerdá J, Feehally J, Finkelstein F, García-García G, et al. Recognition and management of acute kidney injury in the International Society of Nephrology 0by25 global snapshot: a multinational cross-sectional study. Lancet. 2016;387:2017–25.
96. Mehta RL, Cerdá J, Burdmann EA, Tonelli M, García-García G, Jha V, et al. International Society of Nephrology's 0by25 initiative for acute kidney injury (zero preventable deaths by 2025): a human rights case for nephrology. Lancet. 2015;385:2616–43.
97. Chawla LS, Eggers PW, Star RA, Kimmel PL. Acute kidney injury and chronic kidney disease as interconnected syndromes. N Engl J Med. 2014;371:58–66.
98. Arias-Cabrales C, Rodríguez E, Bermejo S, Sierra A, Burballa C, Barrios C, Soler MJ, Pascual J. Short- and long-term outcomes after non-severe acute kidney injury. Clin Exp Nephrol. 2018;22(1):61–7.
99. Chawla LS, Amdur RL, Shaw AD, Faselis C, Palant CE, Kimmel PL. Association between AKI and long-term renal and cardiovascular outcomes in United States veterans. Clin J Am Soc Nephrol. 2014;9(3):448–56.
100. Dépret F, Prud'homme M, Legrand M. A role of remote organs effect in acute kidney injury outcome. Nephron. 2017;137(4):273–6.
101. Wu PC, Wu CJ, Lin CJ, Wu VC, National Taiwan University Study Group on Acute Renal Failure Group. Long-term risk of upper gastrointestinal hemorrhage after advanced AKI. Clin J Am Soc Nephrol. 2015;10(3):353–62.

Chapter 2
Causes of AKI (Prerenal, Intrarenal, Postrenal)

Hiroki Ikai and Yoshiro Fujita

Abstract There are various causes of acute kidney injury (AKI). Previously published textbooks by other authors classify these causes into three categories, partly for the purpose of differentiation (Sesso, Am J Kidney Dis 44:410–419, 2004). This chapter provides a general explanation of the causes of AKI. For AKI diagnostic criteria, refer to Chap. 1.

Keywords Causes of AKI · Prerenal AKI · Intrarenal AKI · Postrenal AKI

AKI is frequently classified into the following three categories based on the origin:

1. Prerenal AKI
2. Intrarenal AKI
3. Postrenal AKI

However, in actual clinical practice, some cases of AKI cannot be distinctly classified into these categories. Treatment must be performed with the consideration that the causes/backgrounds of AKI overlap.

2.1 Prerenal AKI

Prerenal AKI is the most frequent cause of AKI.

Prerenal AKI constitutes approximately 40% of all causes of AKI [1].

Prerenal AKI occurs as a result of a decrease in effective circulating plasma volume in the kidneys. It is not normally accompanied by structural disorders of the kidneys.

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Prerenal AKI is caused by diseases in which effective circulating plasma volume frequently decreases [2–4]. Causes of prerenal AKI include the following:

1. Bleeding (traumatic or gastrointestinal bleeding or bleeding due to surgery)
2. Shock (cardiogenic, septic, hemorrhagic, etc.)
3. Loss from the gastrointestinal tract (vomiting, diarrhea, drainage from an NG tube placed for an extended period of time)
4. Loss from the kidneys (osmotic diuresis accompanied by polyuria, diabetes insipidus, or hyperglycemia)
5. Loss from the skin (burn injury, excessive sweating)
6. Loss to a third space (pancreatitis, crash syndrome, hypoproteinemia)

The above causative diseases decrease blood flow to the kidneys, causing prerenal AKI.

Normally, kidney function is reversible with early treatment. However, persistent prerenal AKI, i.e., persistent low reflux to the kidneys, leads to ischemia of the tissues. This is believed to progress to acute tubular necrosis (ATN).

2.1.1 Cardiorenal Syndrome

Cardiorenal syndrome (CRS), cardiogenic AKI, is described below. CRS is defined as a "pathological state in which dysfunction of the heart or one of the kidneys causes dysfunction in the other kidney." It is classified into five categories [5]:

– Acute CRS (CRS Type 1): Renal dysfunction due to acute dysfunction of the heart
– Chronic CRS (CRS Type 2): Renal dysfunction due to chronic dysfunction of the heart
– Acute Renocardiac Syndrome (CRS Type 3): Acute decreased cardiac function due to AKI
– Chronic Renocardiac Syndrome (CRS Type 4): Decreased cardiac function due to CKD
– Secondary CRS (CRS Type 5): Decreased cardiac/renal function accompanied by systemic disease (sepsis, connective tissue disease, etc.)

CRS Type 1, caused by the heart, is described below.

The mechanism is believed to be a decrease in effective circulating plasma volume accompanied by a decrease in cardiac output or venous stasis.

When effective circulating plasma volume in the kidneys decreases as a result of decreased cardiac output, the sympathetic nervous system and the renin-angiotensin system activity increases, causing renal blood flow to decrease.

Venous stasis in heart failure causes a decrease in differential pressure of the renal veins and arteries accompanied by an increase in central venous pressure, causing the glomerular filtration rate to decrease. Also, in venous stasis, the glomerular filtration rate is reported to decrease in response to increased venous pressure in the veins surrounding the convoluted tubules as well as in the renal

parenchyma. Treatment involves the use of loop diuretics to eliminate the blood congestion, and nowadays, vasopressin V2 receptor antagonists are also used. However, these do not increase RAS activity, suggesting that renal function might be maintained [6].

2.2 Intrarenal AKI

Normal renal kidney failure is diagnosed by exclusion.

When a clinician encounters AKI, he or she must use abdominal ultrasound and CT scans to evaluate the presence of hydronephrosis. Those results are used to rule out postrenal kidney failure. Then a detailed interview or confirmation of medical history is performed, and if the renal failure is not believed to be prerenal, it is diagnosed as intrarenal AKI.

When performing tests, various indicators are used to differentiate prerenal from renal. Commonly used indicators include urine Na and FeNa test. Refer to the following chapter "Diagnosis of AKI" for details.

There are many causes of intrarenal AKI. When the location of the disorder in the renal parenchyma is considered, it is easy to understand the causes of AKI in terms of a system. Each of the causes of AKI should be considered and organized according to the site of disorder in the renal parenchyma, i.e., the blood vessels (relatively large blood vessels, small blood vessels, and glomeruli), the convoluted tubules, and the interstitium.

1. Large renal vessels
2. Renal microvasculature and glomeruli
3. AIN (ischemic AIN, nephrotoxic AIN)
4. TIN (tubulointerstitial nephritis).

The causative diseases/backgrounds that cause disorder at each site are described below.

2.2.1 Large Vessels

Kidney injury rarely occurs due to a problem in the large vessels. When it does, it occurs as a result of bilateral stenosis of the renal arteries or unilateral stenosis of the renal artery in one of the functional kidneys. It also occurs as a result of trauma, thrombotic occlusion, thrombosis, or aortic dissection.

2.2.1.1 Renal Artery Stenosis

As renal artery stenosis presents with chronic progression, it is not usually expressed as acute glomerular filtration rate (GFR) reduction.

2.2.1.2 Atheroembolism

Renal function worsening due to atheroembolism is considered in patients who exhibit AKI after angiography or aortic surgery. Pathologically, it causes a cholesterol embolus, described as cholesterol embolization syndrome (CES). For a multitude of reasons, an atherosclerosis plaque formed in the aorta ruptures, and cholesterol crystals flow out into the peripheral small- to mid-sized arteries, causing peripheral organ disorder due to mechanical occlusion and inflammatory response.

It is considered to be caused by cardiac catheterization, heart surgery, or aortic stent therapy, but there are also cases in which it occurs naturally [7]. As this results in not only cases of AKI but also renal function disorder with chronic progression, there is a type that is considered to occur as the result of acute worsening of chronic kidney failure, which can be overlooked if it is not considered during differentiation. The organs that are damaged by CES are the skin, kidneys, and digestive tract. In the kidneys, occlusion due to cholesterolemia occurs in the blood vessels from the arcuate artery to the interlobular artery level, which is sensed by toll-like receptors that transmit signals resulting in local inflammation. As a result, AKI develops from inflammatory cell infiltration into the peripheral interstitium.

2.2.1.3 Renal Artery Thrombosis

Renal artery thrombosis occurs after trauma or as a postoperative complication of transplantation. Although rare, it occurs in transplantation at a rate of approximately 1% or less. It can occur during surgery and for several weeks after the operation [8, 9].

Renal artery thrombosis also occurs as a result of other increased coagulation states, such as antiphospholipid antibody syndrome [10, 11].

Clinical signs are severe new-onset hypertension and exacerbation of existing hypertension. Flank pain and hematuria may also occur.

2.2.1.4 Renal Vein Thrombosis

It is often the case that renal vein thrombosis is asymptomatic.

Abdominal pain and hematuria are uncommon.

It can occur during states of increased coagulation and in kidney disease (particularly membranous nephropathy) [12].

Other causes are considered to include connective tissue disease, diabetic nephropathy, trauma, and embolism due to tumor. Renal vein thrombosis is diagnosed by Doppler ultrasound, CT, and MRI. Though rare, there are cases of acute renal vein thrombosis after the ingestion of cannabinoids or alcohol, with pathological thrombus formation in the veins of the ren arcuatus and peripheral inflammatory cell infiltration [13, 14].

2.2.2 *Renal Microvasculature and Glomeruli*

All diseases that affect the renal microvasculature can cause renal (intrinsic) AKI. Vascular lesions due to inflammation (glomerular nephritis, vasculitis) and non-inflammatory vascular lesions (malignant hypertension), thrombotic microangiopathy (TMA) (including thrombotic thrombocytopenic purpura [TTP], hemolytic-uremic syndrome [HUS], aHUS, DIC, APS, and malignant hypertension), hyperviscosity syndrome, cholesterol embolization, etc. cause intrinsic AKI.

2.2.2.1 **TMA** (Table 2.1)

A general description of TMA is provided below.

TMA is primarily characterized by microangiopathic hemolytic anemia, thrombocytopenia, and microvascular thrombi.

TTP includes: TTP due to decreased ADAMTS13 (a disintegrin-like and metalloproteinase with thrombospondin Type 1 motif 12), HUS caused by vascular endothelial damage due to pathogenic *E. coli*, narrowly defined atypical HUS that occurs

Table 2.1 Cause of TMA

Primary TMA
aHUS with complement gene mutation (hereditary acquired)
TTP with ADAMTS13 mutation (hereditary acquired)
DGKE TMA
Cobalamin C deficiency-mediated TMA
Infection-related TMA
STEC HUS
Pneumococcal HUS
HIV-associated TMA
Secondary TMA
Pregnancy-associated TMA: HELLP syndrome, eclampsia
Drug-induced TMA
Calcineurin inhibitors (tacrolimus, cyclosporine)
Anti-VEGF drug, chemotherapy (gemcitabine, mitomycin C), quinine, cocaine, ticlopidine
Transplant-associated TMA
De novo TMA (after solid organ transplant (lung, coronary, spleen, liver)), TMA after bone marrow transplant
TMA with severe hypertension
Malignancy-associated TMA
TMA with glomerular diseases
ANCA-associated vasculitis, IgA nephropathy, C3 nephropathy, membranoproliferative glomerulonephritis, membranous nephropathy, FSGS
TMA with autoimmune conditions
Catastrophic antiphospholipid syndrome, SLE (systemic lupus erythematosus), scleroderma renal crisis

from damage to the vascular endothelium caused by abnormal activation of the complement system (complement regulatory protein genetic abnormalities, autoantibodies, etc.), and secondary TMA in response to drugs, transplantation, connective tissue disease, etc. TMA is caused by multiple diseases (see Table 2.1). Classic HUS arises after enteritis due to Shiga toxin-producing *E. coli*, and it causes bloody diarrhea [15].

Many of the disease causes are still unknown, but there are also reports that TMA is a result of multiple pathologies.

For example, there are reports that complement activation occurs in SLE and antiphospholipid antibody syndrome, and there are reports that complement loss occurs in MPGN and C3 glomerulopathy.

AKI due to TMA is frequently accompanied by hematuria and proteinuria. Although not described in detail here, there are specific therapies for certain pathologies, such as immunosuppressive therapy for SLE and vasculitis, which cause secondary TMA, and plasma exchange for TTP. Therefore, renal function might be able to be recovered by administering specific therapies, depending on the cause. When TMA is suspected, renal function improvement may be attempted by differentiating diseases based on their backgrounds.

2.2.3 Tubulointerstitial Nephritis

Tubulointerstitial nephritis has multiple causes. A typical example is an allergic response to antibiotics or NSAIDs. However, AKI can occur from interstitial nephritis in response to other causes, including leukemia, lymphoma, sarcoidosis, bacterial infection, and viral infection.

A systemic allergic response does not occur very often in acute interstitial nephritis due to NSAIDs [16]. Meanwhile, a systemic allergic response (fever, rash, eosinophilia, etc.) sometimes occurs in acute interstitial nephritis as a result of antibiotics. However, the frequency is between 5 and 10%, so it is not frequent.

Ischemic renal damage and nephrotic syndrome are also known to occur with NSAIDs, which are frequently used without much consideration, so caution is required when using NSAID medication.

Nowadays, tubulointerstitial nephritis is known to be caused by PPI. PPI-related tubulointerstitial nephritis does not frequently occur as a result of allergic hypersensitivity syndrome, such as that which occurs with the use of antibiotics; renal disorders can progress asymptomatically [17, 18].

In urinalysis, sterile pyuria can occur which might suggest interstitial nephritis. Urine protein is not common.

Interstitial nephritis is diagnosed by renal biopsy [19]. If a renal biopsy shows inflammatory cell infiltration into the interstitium accompanied by tubulitis, it is pathologically diagnosed as “tubulointerstitial nephritis.”

Differentiation can be considered pathologically according to the significant types of infiltrative cells. For interstitial nephritis with plasma cell infiltration, TIN

due to Sjogren's syndrome or IgG4-related disease is differentiated. When 50% or more of the infiltrative cells are plasma cells, plasma cells are deemed dominant. For Sjogren's syndrome, the presence of extranodal margin zone B-cell lymphoma must be evaluated. For IgG4-related interstitial nephritis, the presence of other organ disorders (pseudotumor, pulmonary lesions, cholangitis, pancreatitis, salivary gland, prostate, etc.) must be evaluated. If the interstitial nephritis has an infiltrative cell pathology characterized by eosinophils, interstitial nephritis involving an allergic reaction must be investigated, i.e., TINU syndrome, allergic granulomatous angiitis, and IgG4-related renal disease. TINU syndrome is a disease that causes interstitial nephritis accompanied by uveitis in young people [20].

2.2.4 Acute Tubular Injury (ATI)

Acute tubular injury is a concept that was once called acute tubular necrosis (ATN). Normally, ATN is a term that indicates ischemic renal AKI. In reports that studied the actual renal histopathology of the condition, necrosis of the renal tubules was rarely found. Therefore, it is presently called acute tubular injury (ATI) [21].

ATI is the most common cause of intrarenal AKI. Although prerenal kidney failure is the most common cause of AKI onset in the community, ATI is known to be the most common cause of AKI inside medical facilities. Therefore, it is very important for clinicians to know the cause of ATI.

ATI has two mechanisms, ischemic and toxic. Ischemic ATI occurs when prerenal AKI is severe or prolonged. Prerenal and renal ATI are conceptually distinguished from one another, but actually, decreased renal perfusion causes ischemic acute tubular injury. Therefore, they can be difficult to differentiate and sometimes cannot be strictly distinguished from one another. A summary of the causes of ATI is shown below. Causes are classified as extrinsic and intrinsic.

2.2.4.1 Extrinsic Causes

Extrinsic causes include antibiotics, chemotherapy, calcineurin inhibitors, organic solvents, toxins, contrast agents, NSAIDs, IVIG, and oral phosphate bowel preparations. Refer to the table for drugs that cause ATI (Table 2.2).

Table 2.2 Main agents that may cause ATI

Antibiotics	Aminoglycosides, amphotericin B, antiviral (acyclovir, foscarnet, tenofovir), pentamidine, vancomycin
Chemotherapy	Cisplatin, 5-fluorouracil, methotrexate, cytarabine, etc.
Calcineurin inhibitors	Tacrolimus, cyclosporine
Others	Toluene, ethylene glycol, NSAIDs, iodinated radiocontrast

NSAIDs

The general kidney injury caused by NSAIDs is ischemic kidney injury due to suppression of prostaglandin production resulting from the inhibition of cyclooxygenase.

NSAIDs are also known to cause nephrotic syndrome (minimal change) and acute interstitial nephritis.

Contrast-Induced Nephropathy (CIN)

In the Japanese "Guidelines for Using Iodine Contrast Agents in Patients with Renal Impairment," "CIN is defined as when the serum creatinine value increases by at least 0.5 mg/dL or at least 25% of the previous value within 72 h after administration of iodine contrast agent" [22].

Contrast-induced nephropathy is the third most common cause of AKI onset in medical facilities. Decreased urinary output and increased serum creatinine values are observed after administering an iodine contrast agent. Mostly, contrast-induced nephropathy is reversible, so when it is suspected, other causes must be ruled out.

The pathology of CIN is believed to be due to the contrast agent directly causing tubule toxicity and decreasing medullary blood flow. Risk factors of contrast-induced nephropathy include pre-existing kidney disorders, diabetes mellitus with renal impairment, congestive heart failure, old age, and concomitant use of nephrotoxic drugs. In patients who are at risk for contrast-induced nephropathy, administration of an IV drip of physiological saline solution prior to performing the contrast CT is recommended for purposes of prevention. If onset occurs, conservative/supportive maintenance is performed, combined with dialysis if necessary [23].

2.2.4.2 Intrinsic Causes

The typical examples of compounds with intrinsic renal toxicity are myoglobin and hemoglobin. Other compounds known to cause intrinsic ATI are uric acid and the light chain of immunoglobulin. A general summary is provided below.

Myoglobin

Myoglobin is produced in response to muscle disorders such as rhabdomyolysis. Myoglobin is also released for reasons other than muscle disorders (electrolyte abnormalities, infections, drugs, autoimmune disorders, etc.). Refer to the table below for the causes of rhabdomyolysis (Table 2.3). Drugs also frequently induce myoglobin production. Examples of such drugs include statins, fibrates, and antipsychotics.

In rhabdomyolysis, it is believed that a large quantity of myoglobin and heme from inside muscle cells flow into the circulating plasma, producing excessive

Table 2.3 Causes of rhabdomyolysis

Muscle injury	Trauma, electric shock, burn
Increased exertion	Seizures, excessive exercise, heart stroke
Muscle hypoxia	Artery occlusion, limb compression during prolonged immobilization
Toxin	Alcohol, toluene, mushroom poisoning, heroin, stimulant drug, snake toxin, etc.
Medication	Statins, fibrates, azathioprine, lithium, theophylline, diuretic
Metabolic and electrolyte disorders	Hypophosphatemia, hypokalemia, hypocalcemia, nonketotic hyperosmotic conditions, diabetic ketoacidosis
Infections	Viral (influenza A and B virus, HIV, enterovirus, EBV)
	Bacterial (*Legionella* species, *Streptococcus pyogenes*, *Staphylococcus aureus*, *Clostridium*, Clostridium tetani, *Salmonella*), etc.
Body temperature changes	Heart stroke, malignant hyperthermia, hypothermia
Genetic defects	Familial McArdle disease, carnitine palmitoyltransferase deficiency, malignant hyperthermia
Others	Hypothyroidism, dermatomyositis/polymyositis, vasculitis

ferrous iron and reactive oxygen species (ROS) and ultimately causing necrosis of the renal tubules. Okubo et al. are researching the mechanisms of renal impairment. Heme-activated platelets released from necrotic muscle cells during rhabdomyolysis enhanced the production of macrophage extracellular traps (METs). These mechanisms are believed to be part of the cause of renal impairment [24].

Hemoglobin

Free hemoglobin is produced as a result of intravascular hemolysis. A small quantity of free hemoglobin binds to haptoglobin and is eliminated by monocytes and macrophages.

If there is a large quantity of hemoglobin due to intravascular hemolysis, the hemoglobin forms dimers and tetramers. The hemoglobin dimers are filtered by the glomeruli and reabsorbed in the proximal convoluted tubules causing nephropathy to develop due to heme.

Autoimmune hemolytic anemia, paroxysmal nocturnal hemoglobinuria, glucose-6-phosphate dehydrogenase deficiency, RBC fragmentation syndrome, incompatible blood transfusion, etc. are believed to be the causes of kidney injury due to hemoglobin.

Monoclonal Gammopathy of Renal Significance (MGRS)

Immunoglobulin is produced by multiple myeloma (MM), filtered by the glomeruli, and catabolized in the proximal convoluted tubules. If the light chain cannot be reabsorbed by the proximal convoluted tubules, it reaches the distal convoluted tubules and binds with Tamm-Horsfall protein, causing cast nephropathy. Also, the light chain itself is believed to be a mechanism of tubule injury. These can cause ATI.

With respect to MGRS as a whole, sometimes treating MGRS can improve renal failure, so keep in mind that treatment should be pro-actively pursued after a thorough consultation with a hematology specialist. Examples of the pathology of MGRS exhibiting lesions in the tubulointerstitium are described below, including cast nephropathy, which was mentioned earlier [25].

1. Fanconi syndrome (considered to be caused by κI of the κ chain)
2. Proximal tubulopathy (Progression of kidney injury ranges from gradual to relatively rapid. Also, crystals can form as a result of the κ chain or the λ chain.)
3. Cast nephropathy (The CDR3 [complementarity-determining region 3] portion of the hypervariable region of the light chain is the determining region for cast formation.)
4. Tubulointerstitial nephritis (rare, but the pathological picture cannot be distinguished from that of drug-induced nephritis.)
5. Light-chain deposition disease, etc. (LCDD, HCDD, LHCDD, etc.)

Tumor Lysis Syndrome (TLS)

AKI associated with tumor lysis syndrome normally occurs in response to chemotherapy for lymphoma or leukemia. TLS occurs as the result of intracellular contents being released. Patients with TLS usually show hyperkalemia, hyperphosphatemia, or hyperuricemia. In the case of rapidly progressing and expanding tumors, TLS may develop naturally, before chemotherapy administration, and cause AKI.

Nucleic acids are released from inside the cell and are metabolized by hypoxanthine, followed by xanthine. Xanthine is converted to uric acid by xanthine oxidase. Classically, in AKI associated with tumor lysis syndrome, crystals are believed to enter the tubules and cause AKI [26].

In addition to causing tubule occlusion, hyperuricemia can affect the hemodynamics of the kidneys and cause kidney injury [27]. The hydrostatic pressure of the tubule capillaries is reported to increase by a factor of 2, and vascular resistance is reported to increase by a factor of 3, although these reports were based on animal models [28].

AKI associated with TLS is not as common as it is used to be. This is because drugs such as rasburicase and allopurinol are now used in high-risk patients before chemotherapy in order to prevent TLS onset.

2.3 Postrenal AKI

Postrenal AKI occurs as a result of urinary tract occlusion (from the renal pelvis to the ureteral opening). In other words, postrenal AKI occurs as a result of occlusion of the ureters or occlusion from outside the ureters. Postrenal AKI constitutes less than 5–10% of all cases of AKI.

Urinary calculi, kidney/urinary tract tumors, and occlusive urinary tract disorder constituted 0.1%, 0.5%, and 0.2%, respectively, of the underlying diseases in patients newly started on dialysis in Japan in 2016. This totaled 0.8% of all patients started on dialysis [29].

The causes of most cases of postrenal AKI are reversible, so rapid diagnosis and intervention is required. Therefore, when we actually encounter cases of acute azotemia in clinical practice, abdominal ultrasound tests and abdominal CT scans must be used to evaluate the presence of urinary tract occlusion (the presence of hydronephrosis or hydroureter) [30]. If evaluation can be performed at the bedside, diagnosis can be made very easily. If evaluation is performed properly, diagnosis is never difficult. Specific symptoms do not exist, and while hypouresis and back pain are considered to be clinical symptoms of postrenal AKI, they do not have high sensitivity or specificity.

One point to be aware of during diagnosis is that the presence of hydronephrosis and hydroureter may not be obvious if the occlusion is in its initial stages or if the ureters cannot expand. If postrenal azotemia is not clear, sometimes postrenal AKI can be diagnosed by increasing visibility near the occlusion. This is accomplished by performing fluid replacement to increase urine production and the GFR to the ureters, allowing the ureters to expand near the occlusion.

Treatment consists of removing the occlusion. If the occlusion has not been present for an extended period of time, removing the occlusion normally improves renal function (therefore, early diagnosis is required, as has been mentioned a few times already). The extent of the recovery depends on the duration and severity of the occlusion.

References

1. Sesso R, Roque A, Vicioso B, et al. Prognosis of ARF in hospitalized elderly patients. Am J Kidney Dis. 2004;44:410–9.
2. Shum H-P, Yan W-W, Chan TM. J Crit Care. 2016;31(1):82–9.
3. Clark A, Neyra JA, Madni T, Imran J, Phelan H, Arnoldo B, Wolf SE. Burns. 2017;43(5):898–908.
4. Moore PK, Hsu RK, Liu KD. Am J Kidney Dis. 2018;72(1):136–48.
5. Ronco C, Haapio M, House AA, et al. Cardiorenal syndrome. J Am Coll Cardiol. 2008;52:1527–39.
6. House AA, Ronco C, et al. National kidney foundation primer on kidney diseases. 7th ed. Vol. 29. pp. 283–9.e1.
7. Flory CM, et al. Arterial occlusions produced by emboli from eroded aortic atheromatous plaques. Am J Pathol. 1945;21:549–65.
8. Inaba A, Karim M, et al. Clin Exp Nephrol. 2014;18(4):676–7.
9. Barlow AD, Nicholson ML, et al. Comp Clin Nephrol. 103:1174–1185.e1.
10. Bienaimé F, Legendre C, Terzi F, Canaud G, et al. Kidney Int. 2017;91(1):34–44.
11. Sciascia S, Cuadrado MJ, Khamashta M, Roccatello D, et al. Nat Rev Nephrol. 2014;10:279–89.
12. Fine EJ, et al. Interventions in renal scintigraphy. Semin Nucl Med. 1999;29:128–45.
13. Redfern A, Mahmoud H, McCulloch T, Shardlow A, Hall M, Byrne C, Selby NM, et al. Clin J Am Soc Nephrol. 2015;10(2):180–6.
14. Eldehni MT, Roberts ISD, Naik R, Vaux E, et al. NDT Plus. 2010;3(5):459–60.

15. Fox LC, et al. Nephrology. 2018;23:507–17.
16. Stürmer T, Elseviers MM, De Broe ME. Curr Opin Nephrol Hypertens. 2001;10:161–3.
17. Blank ML, Parkin L, Paul C, Herbison P. Kidney Int. 2014;86(4):837–44.
18. Nochaiwong S, Ruengorn C, Awiphan R, Koyratkoson K, Chaisai C, Noppakun K, Chongruksut W, Thavorn K. Nephrol Dial Transplant. 2018;33(2):331–42.
19. Perazella MA. Adv Chronic Kidney Dis. 2017;24(2):57–63.
20. Pakzad-Vaezi K, Pepple KL. Curr Opin Ophthalmol. 2017;28(6):629–35.
21. Jennette JC, et al. Heptinstall's pathology of the kidney. 7th ed. Alphen aan den Rijn: Wolters Kluwer; 2014. p. 1496.
22. Guidelines for Iodine Contrast Agent Use in Patients with Renal Failure. Japanese society of Nephrology, Japan Radiological Society, The Japanese Circulation Society, Tokyo-Igakusya; 2012.
23. Mark A, et al. National kidney foundation primer on kidney diseases, vol. 35. 7th ed. Amsterdam: Elsevier; 2017. p. 334–44.
24. Okubo K, Kurosawa M, Kamiya M, Urano Y, Suzuki A, Yamamoto K, Hase K, Homma K, Sasaki J, Miyauchi H, Hoshino T, Hayashi M, Mayadas TN, Hirahashi J. Nat Med. 2018;24(2):232–8.
25. Fermand JP, Bridoux F, Kyle RA, Kastritis E, Weiss BM, Cook MA, Drayson MT, Dispenzieri A, Leung N, International Kidney and Monoclonal Gammopathy Research Group. Blood. 2013;122(22):3583–90.
26. Wilson FP, Berns JS, et al. CJASN. 2012;7(10):1730–9.
27. Wilson FP, Berns JS, et al. Adv Chronic Kidney Dis. 2014;21(1):18–26.
28. Conger JD, Falk SA, et al. J Clin Invest. 1977;59(5):786–93.
29. An overview of regular dialysis treatment in Japan as of Dec. 31, 2016. Jpn Soc Dial Ther.
30. Meola M, Nalesso F, Petrucci I, Samoni S, Ronco C. Contrib Nephrol. 2016;188:11–20.

Chapter 3
Pathophysiology of AKI

Hideo Yasuda

Abstract The causes of acute kidney injury (AKI) are diverse, and the developmental pathological conditions associated with the disease are heterogeneous and complex. The clinical majority of pathological conditions associated with hemodynamics is normotensive ischemic acute kidney injury (AKI) caused by decreased autoregulation of glomerular pressure. It is usually referred to the occurrence of AKI in a patient that already has chronic kidney disease (CKD), what is called acute-on-chronic AKI. In sepsis, changes in renal hemodynamics, particularly in the appearance of shunts in the kidney, are thought to occur during a hyperdynamic state with resultant reduction of renal function. Renal tubule cells are main targets of the pathology of renal parenchymal AKI. Inflammatory cell infiltration into the kidney also exacerbates renal tubule injury. Mechanisms by which the glomerular filtration rate (GFR) decreases due to renal tubule injury include intrarenal vasoconstriction, backleak of primary urine, and renal tubular obstruction. Renal congestion has recently been focused on as a contributing factor in the decrease of renal function. Moreover, innate immunity is associated with the development of AKI in sepsis, and the mitochondrial DNA-TLR9 pathway plays an important role.

Keywords Acute-on-chronic AKI · Vasoconstriction · Renal tubule damage Backleak · Renal tubular obstruction · Neutrophil · Macrophage · Mitochondrial DNA · Sepsis

3.1 Introduction

The pathophysiology of acute kidney injury (AKI) is multifactorial and complex. It has historically been classified as prerenal AKI caused by renal hypoperfusion and renal parenchymal AKI characterized by acute tubular necrosis (ATN) due to

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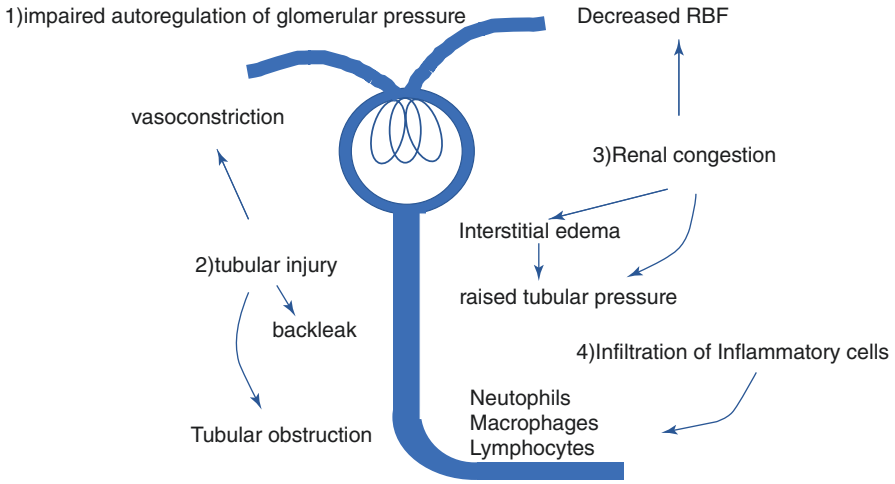

Fig. 3.1 Various mechanisms of the decrease in GFR: (1) Impaired autoregulation of glomerular pressure contributes to a decrease in GFR by a fall in glomerular pressure within the normal range of blood pressure. (2) Tubular injury contributes in a decrease in GFR by vasoconstriction, backleak of tubule fluid into interstitium, and tubular obstruction. (3) Renal congestion contributes to a decrease in GFR by reduction of renal blood flow and increased tubular luminal pressure with interstitial edema. (4) Infiltration of inflammatory cells including neutrophils, macrophages, and lymphocytes contributes to a decrease in GFR in renal ischemia-reperfusion injury

ischemia and nephrotoxicity. Recently, this classification has been questioned as there are some reasons; (1) some cases show their renal function continues to deteriorate after resuscitation despite findings indicating prerenal AKI. These cases suggest that AKI should be regarded as a series of pathological conditions that transition from prerenal to renal parenchymal. (2) ATN, which has been considered to be synonymous with renal parenchymal AKI, is actually not a common histological finding. (3) Some cases show their renal function decreases as a result of renal congestion. The pathology of deterioration of renal function in intrinsic AKI is associated with renal tubule cell damage and vasoconstriction due to hypoxia, toxicity, inflammation, and congestion although further studies are required in order to fully understand AKI.

In this section, the pathological conditions are divided into (1) hemodynamics, (2) renal tubular damage, (3) renal congestion, and (4) inflammation and will be outlined (Fig. 3.1). And the latest findings on innate immunity in septic AKI are explained.

3.2 Hemodynamics

Glomerular pressure in the cortex is autoregulated and maintained at a constant level by changes in the tone of the afferent arterioles and efferent arterioles, even when there is a fluctuation in systemic blood pressure. Afferent arterioles are

primarily dilated by prostaglandin, while efferent arterioles are primarily contracted by angiotensin II. The autoregulation function of the glomerular pressure decreases when on nonsteroidal anti-inflammatory drugs (NSAIDs), which inhibit prostaglandin, and angiotensin II receptor blockers (ARB) and angiotensin-converting enzyme (ACE) inhibitors, which suppress the action of angiotensin II. When patients take NSAIDs or ARB/ACE inhibitors, the glomerular filtration rate (GFR) easily drops as a result of decreased blood pressure, which would usually not cause low glomerular pressure. Additionally, autoregulation of glomerular pressure is also impaired in chronic kidney disease (CKD), and glomerular pressure drops when blood pressure decreases, even within the normal range of blood pressure. Hence, the GFR decreases with a fall in the glomerular pressure within an apparently normal range of blood pressure, without the patient suffering shock (Fig. 3.2). Elderly patients with CKD and patients on ARB/ACE inhibitors are prone to develop acute-on-chronic AKI due to causes such as dehydration during summer. This pathological condition is known as "normotensive ischemic AKI" since the patient develops AKI without suffering shock [1].

In case of ATN, renal blood flow is reduced by 30–50%, and additionally renal perfusion decreases due to renal vasoconstriction [2]. Renal ischemia-reperfusion injury (IRI) and cisplatin-induced AKI affect renal hemodynamics via the action of vasoactive substances and increased nitric oxide (NO) production. The concentration of endothelin, a potent vasoconstrictor, increases in the kidney in AKI, and endothelin receptor antagonists and endothelin antibodies attenuate renal IRI [3, 4]. Renal production of PGI2 and PGE2, which have a vasodilating effect, and vasoconstrictive TXA2 increases during AKI, and the balance of these proteins affects hemodynamics [5, 6]. NO is also an important factor in the regulation of renal hemodynamics. NO synthases (NOSs) include iNOS, which is induced in association with inflammation, in addition to eNOS and nNOS, which are constantly expressed. Large amounts of NO produced by iNOS exacerbate renal damage via peroxynitrite, while NO produced by eNOS provides renal protection via its vasodilation effect. Renal eNOS increased after moderate ischemic preconditioning, and renal ischemic reperfusion damage is subsequently attenuated. This effect disappears when eNOS is knocked out [7].

Sepsis is a pathological condition in which systemic blood pressure and microcirculation in the kidney do not correspond. In septic shock, the patient progresses to a hypodynamic state from a hyperdynamic state causing death. Renal blood flow (RBF) in sepsis varies by study, and a study on sepsis and RBF that analyzed 159 animal experiments reported that RBF decreased in about 2/3 experiments, while it did not change or increased in 1/3 experiments, with cardiac output being the only significant factor defining RBF. In cecal ligation and puncture (CLP), which is an animal model for sepsis, the severity of survival differs depending on the study. While a common timeline across different studies cannot be identified, the serum creatinine level often begins to rise after 6–12 h and peaks after 18–24 h in models where AKI is induced, while with regard to the survival curve, animals begin to die after 18–24 h, and the survival rate is around 50% after 48 h [8, 9]. In the CLP model described above, a hyperdynamic state is maintained for up to 2 h, and after

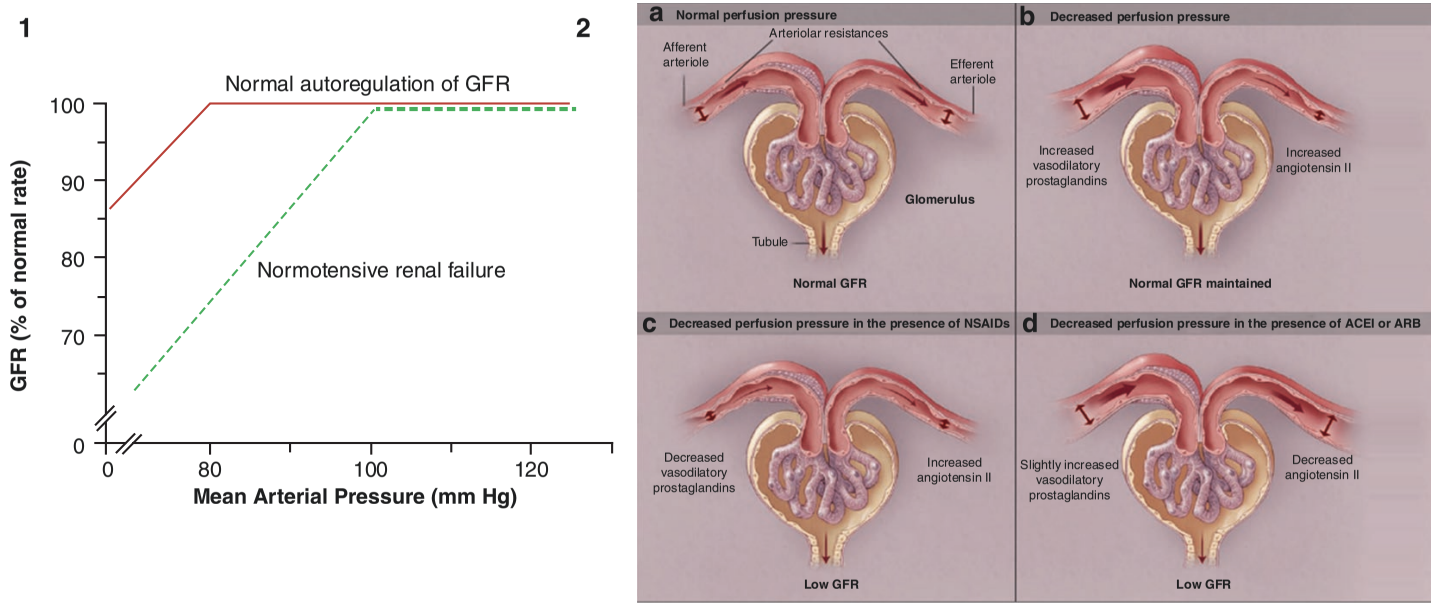

Fig. 3.2 Impaired autoregulation of glomerular pressure in patients with CKD and/or taking NSAIDs or ARB/ACE inhibitors (cited from [1]). (1) GFR falls when the mean arterial pressure decreases within the normal range in case of CKD or taking NSAIDs or ARB/ACE inhibitors, resulting in normotensive renal failure. (2) Panel A shows normal conditions and a normal glomerular filtration rate (GFR). Panel B shows reduced perfusion pressure within the autoregulatory range. Normal glomerular capillary pressure is maintained by afferent vasodilatation and efferent vasoconstriction. Panel C shows reduced perfusion pressure with a NSAID. Loss of vasodilatory prostaglandins increases afferent resistance; this causes the glomerular capillary pressure to drop below normal values and the GFR to decrease. Panel D shows reduced perfusion pressure with an ACEI or an ARB. Loss of angiotensin II action reduces efferent resistance; this causes the glomerular capillary pressure to drop below normal values and the GFR to decrease

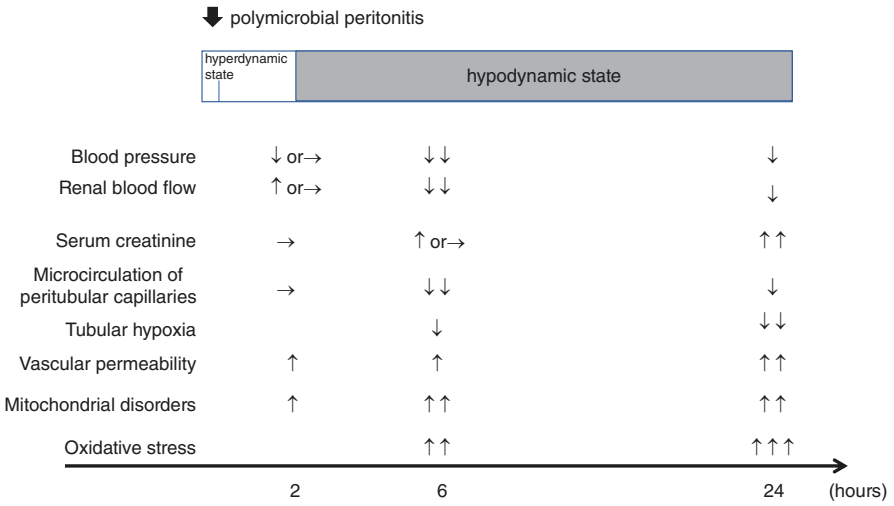

Fig. 3.3 Course of the septic AKI model by polymicrobial infections. The renal intrinsic disorders start under hyperdynamic state of septic shock

that, the blood pressure continues to fall for up to 6–8 h in tandem with a drop in heart rate [10, 11]. RBF is maintained for 2 h but decreases after 6 h, while the blood flow of the cortical juxtaglomerular capillaries as observed under intravital microscopy also follows a similar course as RBF [11].

In septic AKI, the GFR will have already declined by the time the patient is in a hyperdynamic state. Although the state of RBF in septic AKI is currently unclear, it was reported in the 1970s that RBF increased to 171% when GFR had decreased to 85% in a septic patient [12]. A cause for this phenomenon, in which the GFR decreases and RBF is maintained while the peripheral vessels are dilated, has been proposed in recent years as being due to the formation of shunts between the afferent arterioles and efferent arterioles as a result of decreased glomerular pressure and vasodilation in the efferent arterioles [13]. In fact, the GFR recovered when angiotensin II, which contracts efferent arterioles, was administered in a continuous bacterial administration model [14]. Although this hypothesis has not been fully verified, it proposes a very interesting mechanism. In addition, renal vascular permeability increases 2 h after CLP and continues to do so for 24 h [11]. This renal vascular permeability may be related to kidney edema and inflammation [9] (Fig. 3.3).

3.3 Renal Tubule Damage

RBF is heterogeneous; the pressure is 50–100 mmHg in the cortex and as low as 10–20 mmHg in the deeper layer of the inner stripe of the medulla. Despite the low partial pressure of oxygen in the medulla, the proximal tubules, especially the S3 segment and the medullary thick ascending limb (mTAL), are susceptible to

ischemic injury because there is high metabolic activity including reabsorption of solutes. In addition, proximal tubules tend to be exposed to nephrotoxic substances at high concentrations. ATN has been considered to play a primary role in renal tissue damage in AKI induced by ischemia and nephrotoxic substances. However, necrosis of the proximal tubules is uncommon, and various factors including apoptosis and oxidative stress are involved in proximal tubule cell injury.

How does renal tubule damage lead to a rapid decrease in the GFR? Mechanisms proposed to answer this question include the renal tubule damage inducing renal vasoconstriction and thereby reducing RBF, backleak of primary urine into the stroma from the renal tubular lumen, and a decrease in the glomerular filtration coefficient as a result of increased pressure from the renal tubule lumen to the glomeruli due to renal tubular obstruction.

3.3.1 Cell Death

ATN has been believed to play a central role in renal tissue damage in AKI induced by ischemia and nephrotoxic substances. In the renal ischemia-reperfusion model, depletion of ATP, which provides intracellular energy in renal tubule cells, disappearance of brush borders, and loss of polarity associated with the disruption of the actin cytoskeleton are observed in the early stages. Subsequently, renal tubule cell death due to renal tubule cell necrosis and apoptosis is observed, and renal tubular epithelial cells desquamate into the renal tubule lumen. In the renal ischemia-reperfusion model, this histological finding of acute renal tubule necrosis is widely observed in the S3 segment, but in human AKI, ATN is minimal and uncommon. Nevertheless, therapeutic intervention that targets cell death including apoptosis and necroptosis (regulated necrosis) has the effect of attenuating AKI.

3.3.2 Autophagy

Autophagy is a major intracellular degradation system together with the ubiquitin-proteasome system, and it maintains intracellular homeostasis. When cells are under stress, autophagy is upregulated in order to actively eliminate damaging substances. Autophagy also plays an important role in maintaining homeostasis in the proximal tubules. Renal IRI is exacerbated in mice lacking autophagy only in the proximal tubules [15], and proximal tubule autophagy acts protectively against AKI.

3.3.3 Backleak

When renal tubule cells undergo cell death or enter a sublethal state, they detach from the renal tubular basement membrane and desquamate into the renal tubular lumen. Even if the cells do not desquamate, if polarity disappears and the junction

between the renal tubular cells becomes weak, primary urine filtered by the glomeruli flows back into the stroma from the renal tubular lumen, and renal function decreases as a result. In a unilateral renal IRI model, much of the inulin injected into the proximal tubule area of the injured kidney was recovered from the contralateral ureter, while only a small portion of the inulin injected into the distal tubules of the injured kidney was recovered from the contralateral ureter. This suggests backleak of tubule fluid into the stroma in necrotic areas [16]. However, this alone cannot explain decreased GFR caused by ATN.

3.3.4 Renal Tubular Obstruction

The urine of patients with suspected ATN due to renal parenchymal AKI is turbid with multiple granular casts, and muddy brown casts are observed in urine sediments. It is assumed that tubule fluid stagnates in the renal tubules when casts obstruct the renal tubules, and glomerular filtration is reduced due to increased renal tubular pressure. In fact, a study that used the micropuncture technique confirmed that renal tubular pressure increased due to renal IRI [17].

It is believed that if desquamated renal tubular cells are promptly phagocytized, the number of casts will decrease, and the rise in renal tubular pressure will be suppressed. Recently, new discoveries were made with regard to phagocytosis of desquamated cells. Apoptosis inhibitor of macrophage (AIM) is expressed when proximal tubule cells undergo apoptosis after renal IRI and desquamate into the renal tubular lumen. On the other hand, KIM-1 is expressed in proximal tubule cells that have not desquamated. AIM acts as a ligand for KIM-1, and the remaining renal tubule cells are able to be phagocytized as a result of the AIM-KIM-1 interaction, which prevents renal tubular obstruction. Furthermore, this interaction suppresses NF-κB in the remaining renal tubule cells and helps to suppress inflammation in the kidney [18].

3.3.5 Renal Tubular Injury in Sepsis

Acute renal tubular necrosis is not observed in sepsis. During the late stages of sepsis, vacuolar degeneration of the renal tubules is observed as tissue damage under light microscopy [9, 19], and it has been suggested that reactive oxygen/nitrite species (ROS/RNS) are stored in the vacuoles [11]. Furthermore, accumulation of ROS/RNS is observed in the neighboring tubules, where microcirculation of the juxtaglobular capillaries is decreased, and it has been suggested that renal microcirculation impairment leads to the production of peroxynitrite in the renal tubular epithelial cells [11] (Fig. 3.3). Reduction in renal tubular oxidative stress with the use of antioxidants improved microcirculation of the cortical juxtaglomerular capillaries [20]. Mitochondrial dysfunction in renal tubular epithelial cells can be regarded as early-stage renal tubular injury. In fact, reduced and swollen

mitochondria can be observed in proximal renal tubules under electron microscopy 2 h after CLP. Furthermore, renal tubules are exposed to ischemia as a result of decreased systemic blood pressure and RBF, and uptake of pimonidazole, which is a marker of tissue ischemia, is detected 4–6 h after CLP [11] (Fig. 3.3). Apoptosis of renal tubules is not observed in evaluation using TUNEL staining and detection of cleaved caspase 3[21], but renal biopsies performed immediately after death caused by septic shock showed apoptotic bodies in 2.9% of renal tubular epithelial cells [22].

3.4 Renal Congestion

High central venous pressure (CVP) and low diastolic blood pressure are considered to be risks for AKI in sepsis in the intensive care unit (ICU) [23]. A rise of 5 mmHg in CVP increases the risk of developing or continuously suffering from AKI 2.7-fold. The risk of developing or continuously suffering from AKI is 80% when CVP is 15 mmHg or higher. Additionally, cardiac renal syndrome (CRS) type 1 is classified as AKI caused by acute heart failure, but renal congestion is involved in its pathology. While the pathology surrounding the development of AKI includes reduced RBF and concomitant vasoconstriction due to activation of the sympathetic nervous system, increased renal venous pressure and renal congestion associated with right-sided heart failure is drawing attention as playing a central role in its pathology. In fact, in a study reporting that 58 (40%) out of 145 acute heart failure patients, who received pulmonary artery catheters, developed AKI; CVP rather than decreased cardiac index was a primary hemodynamic factor that led to renal dysfunction [24]. As we have seen so far, increased renal venous pressure and renal congestion are involved in the pathology of AKI.

Increased renal venous pressure decreases renal perfusion pressure and reduces RBF. The kidney is covered in a membrane, and there is no way of releasing pressure inside the kidney. Renal congestion is accompanied by interstitial edema, and renal function deteriorates due to increased tubular luminal pressure as a result of interstitial edema and a decrease in the net pressure gradient across the glomeruli. In an animal experiment, the GFR decreased when renal venous pressure was increased to 18.75 mmHg, and GFR was restored after renal venous pressure was decreased [25].

3.5 Inflammatory Cells

Robust inflammation is involved in the development and progression of renal IRI. This includes the expression of downstream molecules in the hypoxia-inducible factor (HIF) pathway induced by ischemia (erythropoietin, vascular endothelial growth factor, endothelin 1, NOS, etc.), release of damage-associated

molecular patterns (DAMPs) due to cell dysfunction in the renal parenchyma, and enhanced expression of adhesion factors that recruit inflammatory cells into the kidney. The resulting increased renal inflammation is involved in histological damage and dysfunction of the kidney, along with enhanced permeability in the renal vessels, activation of the toll-like receptor (TLR) pathway, cytokines, and chemokines.

3.5.1 Neutrophils

After renal IRI, inflammatory cytokines such as TNFα, IL-6, and IL-1β and chemokines such as MCP-1 and RANTES are produced in the kidney, by renal tubular cells in particular, and promote neutrophil infiltration into the kidney [26]. Furthermore, IL-17 produced by neutrophils that have infiltrated within a few hours of IRI further regulates neutrophil migration via IFNγ [27]. Infiltrating neutrophils release proteases and promote renal damage. Deficiency of ICAM-1, which is an adhesion factor expressed on vascular endothelial cells that promotes local neutrophil infiltration, suppresses neutrophil infiltration and leads to resistance to renal damage in renal IRI [28].

Among the activated neutrophils, some undergo morphological changes and become what are called neutrophil extracellular traps (NETs), which extracellularly release nuclear chromatin and remain concentrated locally to capture bacteria [29]. In the process of NET formation, histone-DNA binding is attenuated as PAD4 in the neutrophils converts histone arginine into citrulline. As a result, chromatin becomes filamentous. NETs are found in the outer medulla after renal IRI and continue to increase for at least 6–24 h [30]. Renal IRI is attenuated in PAD4-deficient mice that cannot form NETs [31], and the involvement of PAD4 in the pathology of AKI has been confirmed.

3.5.2 Macrophages

Monocytes infiltrate the vasa recta 2 h after renal IRI primarily as a result of the release of MCP-1 from renal tubules, and differentiated macrophages become widely observed in the outer medulla after 24 h [32]. In this early phase, the macrophages are primarily classified as MI (classically activated pro-inflammatory macrophages) and are involved in renal damage by releasing pro-inflammatory cytokines, including IL-1, IL-6, IL-12, and TNFα, and are also associated with apoptosis and debris removal. CCR2, an MCP-1 receptor, is expressed in macrophages, and histological renal damage was attenuated in CCR2-deficient mice [33]. IL-18 is an important mediator for infiltration of macrophages into the kidney in renal IRI, and it is one of the candidates for next-generation urinary biomarkers of AKI.

Furthermore, macrophages in the kidneys increase over the following 7 days, and the percentage of M2 (alternatively activated) macrophages increases. M2 macrophages facilitate wound healing and are involved in renal recovery.

3.5.3 Lymphocytes

T cells accumulate in the kidney early in renal IRI, and CD4+ T cells appear to be involved in renal damage. Renal IRI was attenuated in the presence of CD4 deficiency [34]. CD4+ T cells functionally differentiate into Th1, which produces IFNγ, and Th2, which produces IL-4, while IFNγ-producing Th1 cells were involved in renal IRI [35]. Although it is reported that B-cell deficiency also attenuates renal IRI [36], it is not attenuated in mice deficient in both T and B cells [37]. Thus, the roles of T cells and B cells are controversial as the results regarding them are incongruent.

Regulatory T cells (Tregs) are a subset of CD4+ T cells expressing IL-2 receptors (CD25) and forkhead box P3 (Foxp3). They are found in approximately 2% of mononuclear cells in normal kidney tissue [38]. Removal of Tregs by administering CD25 antibodies potentiated renal IRI [39].

3.6 Innate Immunity in Septic AKI

In sepsis, inflammatory cytokines are induced by molecules called pathogen-associated molecular patterns (PAMPs) that detect bacterial invasion, and the patient develops systemic inflammatory response syndrome (SIRS). The PAMPs activate uncontrollable inflammatory mediators and cause multiple organ failure including AKI. Innate immunity is activated, and inflammatory cells in the spleen undergo apoptosis simultaneously with the excessive induction of inflammatory cytokines. Apoptosis of immune cells is associated with immunosuppression, and prevention of this immunosuppression is important in the life expectancy of sepsis patients [40]. It is possible to attenuate AKI by regulating innate immunity in this way. TLRs are also known as PAMPs, and among the identified TLR1 through TLR11, mice deficient in TLR4 and TLR9 show reduced mortality and attenuated AKI in a lipopolysaccharide (LPS) administration model and CLP model, respectively [41–43]. Furthermore, it is reported that administration of TLR9 siRNA attenuates AKI caused by CLP [44].

Endogenous molecules are also involved in TLR-induced sepsis. Known endogenous ligands of TLR4 include heat-shock proteins and HMGB-1, also known as DAMPs. TLR9 ligands are DNA sequences derived from bacteria with a CpG motif, while endogenous mitochondrial DNA acts as a ligand for TLR9 and is a major mediator that causes SIRS by trauma [45]. Blood mitochondrial DNA is detected in severe sepsis patients and is related to mortality in the ICU [46, 47]. Blood mitochondrial DNA in the CLP model was systemically circulated in large amounts in early CLP after 2 h and was maintained for at least 6 h. When mitochondrial debris containing mitochondrial DNA was injected into mice, blood IL-12 increased after 2 h, and mitochondrial dysfunction was induced in the renal tubules. These systemic

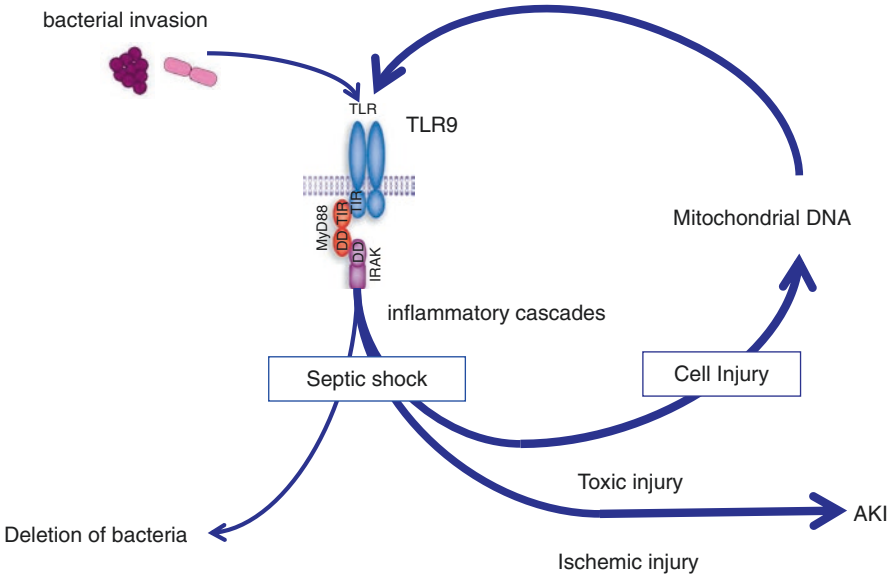

Fig. 3.4 Endogenous mitochondrial DNA amplifies septic AKI via TLR9. Innate immunity, which starts from exogenous bacterial invasion, releases endogenous mitochondrial DNA as a damage-associated molecular pattern. Mitochondrial DNA binds TLR9 and amplifies septic AKI

immune responses and renal damage were attenuated in TLR9-deficient mice. Mitochondrial DNA, which circulates systemically as a result of septic shock, is involved in the development of AKI in this way [48] (Fig. 3.4).

References

1. Abuelo JG. Normotensive ischemic acute renal failure. N Engl J Med. 2007;357:797–805. https://doi.org/10.1056/NEJMra064398.
2. Jefferson AJ, Thurman JM, Schrier RW. Pathophysiology and etiology of acute kidney injury. In: Johnson RJ, Feehally J, Floege J, Tonelli M, editors. Comprehensive clinical nephrology. 6th ed. Amsterdam: Elsevier; 2018. p. 797–812.
3. Chan L, Chittinandana A, Shapiro JI, et al. Effect of an endothelin-receptor antagonist on ischemic acute renal failure. Am J Phys. 1994;266:F135–8. https://doi.org/10.1152/ajprenal.1994.266.1.F135.
4. Jerkić M, Miloradović Z, Jovović D, et al. Relative roles of endothelin-1 and angiotensin II in experimental post-ischaemic acute renal failure. Nephrol Dial Transplant. 2004;19:83–94.
5. Badr KF, Kelley VE, Rennke HG, Brenner BM. Roles for thromboxane A2 and leukotrienes in endotoxin-induced acute renal failure. Kidney Int. 1986;30:474–80.
6. Chaudhari A, Kirschenbaum MA. Alterations in rabbit renal microvascular prostanoid synthesis in acute renal failure. Am J Phys. 1988;254:F684–8. https://doi.org/10.1152/ajprenal.1988.254.5.F684.
7. Yamashita J, Ogata M, Itoh M, et al. Role of nitric oxide in the renal protective effects of ischemic preconditioning. J Cardiovasc Pharmacol. 2003;42:419–27.
8. Miyaji T, Hu X, Yuen PST, et al. Ethyl pyruvate decreases sepsis-induced acute renal failure and multiple organ damage in aged mice. Kidney Int. 2003;64:1620–31. https://doi.org/10.1046/j.1523-1755.2003.00268.x.

9. Yasuda H, Yuen PST, Hu X, et al. Simvastatin improves sepsis-induced mortality and acute kidney injury via renal vascular effects. Kidney Int. 2006;69:1535–42. https://doi.org/10.1038/sj.ki.5000300.
10. Doi K, Hu X, Yuen PST, et al. AP214, an analogue of alpha-melanocyte-stimulating hormone, ameliorates sepsis-induced acute kidney injury and mortality. Kidney Int. 2008;73:1266–74. https://doi.org/10.1038/ki.2008.97.
11. Wang Z, Holthoff JH, Seely KA, et al. Development of oxidative stress in the peritubular capillary microenvironment mediates sepsis-induced renal microcirculatory failure and acute kidney injury. Am J Pathol. 2012;180:505–16. https://doi.org/10.1016/j.ajpath.2011.10.011.
12. Rector F, Goyal S, Rosenberg IK, Lucas CE. Sepsis: a mechanism for vasodilatation in the kidney. Ann Surg. 1973;178:222–6. https://doi.org/10.1097/00000658-197308000-00021.
13. Calzavacca P, May CN, Bellomo R. Glomerular haemodynamics, the renal sympathetic nervous system and sepsis-induced acute kidney injury. Nephrol Dial Transplant. 2014;29:2178–84. https://doi.org/10.1093/ndt/gfu052.
14. Wan L, Langenberg C, Bellomo R, May CN. Angiotensin II in experimental hyperdynamic sepsis. Crit Care. 2009;13:R190–10. https://doi.org/10.1186/cc8185.
15. Kimura T, Takabatake Y, Takahashi A, et al. Autophagy protects the proximal tubule from degeneration and acute ischemic injury. J Am Soc Nephrol. 2011;22:902–13. https://doi.org/10.1681/ASN.2010070705.
16. Donohoe JF, Venkatachalam MA, Bernard DB, Levinsky NG. Tubular leakage and obstruction after renal ischemia: structural-functional correlations. Kidney Int. 1978;13:208–22. https://doi.org/10.1038/ki.1978.31.
17. Arendshorst WJ, Finn WF, Gottschalk CW. Micropuncture study of acute renal failure following temporary renal ischemia in the rat. Kidney Int Suppl. 1976;6:S100–5.
18. Arai S, Kitada K, Yamazaki T, et al. Apoptosis inhibitor of macrophage protein enhances intraluminal debris clearance and ameliorates acute kidney injury in mice. Nat Med. 2016;22:183–93. https://doi.org/10.1038/nm.4012.
19. Doi K, Leelahavanichkul A, Yuen PST, Star RA. Animal models of sepsis and sepsis-induced kidney injury. J Clin Invest. 2009;119:2868–78. https://doi.org/10.1172/JCI39421.
20. Holthoff JH, Wang Z, Seely KA, et al. Resveratrol improves renal microcirculation, protects the tubular epithelium, and prolongs survival in a mouse model of sepsis-induced acute kidney injury. Kidney Int. 2012;81:370–8. https://doi.org/10.1038/ki.2011.347.
21. Dear JW, Yasuda H, Hu X, et al. Sepsis-induced organ failure is mediated by different pathways in the kidney and liver: acute renal failure is dependent on MyD88 but not renal cell apoptosis. Kidney Int. 2006;69:832–6. https://doi.org/10.1038/sj.ki.5000165.
22. Lerolle N, Nochy D, Guérot E, et al. Histopathology of septic shock induced acute kidney injury: apoptosis and leukocytic infiltration. Intensive Care Med. 2010;36:471–8. https://doi.org/10.1007/s00134-009-1723-x.
23. Legrand M, Dupuis C, Simon C, et al. Association between systemic hemodynamics and septic acute kidney injury in critically ill patients: a retrospective observational study. Crit Care. 2013;17:R278. https://doi.org/10.1186/cc13133.
24. Mullens W, Abrahams Z, Francis GS, et al. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. J Am Coll Cardiol. 2009;53:589–96. https://doi.org/10.1016/j.jacc.2008.05.068.
25. Firth JD, Raine AE, Ledingham JG. Raised venous pressure: a direct cause of renal sodium retention in oedema? Lancet. 1988;1:1033–5. https://doi.org/10.1016/s0140-6736(88)91851-x.
26. Donnahoo KK, Meng X, Ayala A, et al. Early kidney TNF-α expression mediates neutrophil infiltration and injury after renal ischemia-reperfusion. Am J Phys Regul Integr Comp Phys. 1999;277:R922–9. https://doi.org/10.1152/ajpregu.1999.277.3.R922.
27. Li L, Huang L, Vergis AL, et al. IL-17 produced by neutrophils regulates IFN-gamma-mediated neutrophil migration in mouse kidney ischemia-reperfusion injury. J Clin Invest. 2010;120:331–42. https://doi.org/10.1172/JCI38702.
28. Kelly KJ, Williams WW, Colvin RB, et al. Intercellular adhesion molecule-1-deficient mice are protected against ischemic renal injury. J Clin Invest. 1996;97:1056–63. https://doi.org/10.1172/JCI118498.

29. Brinkmann V, Reichard U, Goosmann C, et al. Neutrophil extracellular traps kill bacteria. Science. 2004;303:1532–5. https://doi.org/10.1126/science.1092385.
30. Nakazawa D, Kumar SV, Marschner J, et al. Histones and neutrophil extracellular traps enhance tubular necrosis and remote organ injury in ischemic AKI. J Am Soc Nephrol. 2017;28:1753–68. https://doi.org/10.1681/ASN.2016080925.
31. Raup-Konsavage WM, Wang Y, Wang WW, et al. Neutrophil peptidyl arginine deiminase-4 has a pivotal role in ischemia/reperfusion-induced acute kidney injury. Kidney Int. 2018;93:365–74. https://doi.org/10.1016/j.kint.2017.08.014.
32. De Greef KE, Ysebaert DK, Dauwe S, et al. Anti-B7-1 blocks mononuclear cell adherence in vasa recta after ischemia. Kidney Int. 2001;60:1415–27. https://doi.org/10.1046/j.1523-1755.2001.00944.x.
33. Furuichi K, Wada T, Iwata Y, et. al. CCR2 signaling contributes to ischemia-reperfusion injury in kidney. J Am Soc Nephrol. 2003;14:2503–15. https://doi.org/10.1097/01.ASN.0000089563.63641.A8.
34. Burne MJ, Daniels F, Ghandour EA, et al. Identification of the CD4+ T cell as a major pathogenic factor in ischemic acute renal failure. J Clin Invest. 2001;108:1283–90. https://doi.org/10.1172/JCI200112080.
35. Yokota N, Burne-Taney M, Racusen L, Rabb H. Contrasting roles for STAT4 and STAT6 signal transduction pathways in murine renal ischemia-reperfusion injury. Am J Physiol Renal Physiol. 2003;285:F319–25. https://doi.org/10.1152/ajprenal.00432.2002.
36. Burne-Taney MJ, Ascon DB, Daniels F, et al. B cell deficiency confers protection from renal ischemia reperfusion injury. J Immunol. 2003;171:3210–5. https://doi.org/10.4049/jimmunol.171.6.3210.
37. Park P, Haas M, Cunningham PN, et al. Injury in renal ischemia-reperfusion is independent from immunoglobulins and T lymphocytes. Am J Physiol Renal Physiol. 2002;282:F352–7. https://doi.org/10.1152/ajprenal.00160.2001.
38. Kinsey GR, Okusa MD. Expanding role of T cells in acute kidney injury. Curr Opin Nephrol Hypertens. 2014;23:9–16. https://doi.org/10.1097/01.mnh.0000436695.29173.de.
39. Kinsey GR, Sharma R, Huang L, et al. Regulatory T cells suppress innate immunity in kidney ischemia-reperfusion injury. J Am Soc Nephrol. 2009;20:1744–53. https://doi.org/10.1681/ASN.2008111160.
40. Hotchkiss RS, Chang KC, Grayson MH, et al. Adoptive transfer of apoptotic splenocytes worsens survival, whereas adoptive transfer of necrotic splenocytes improves survival in sepsis. Proc Natl Acad Sci U S A. 2003;100:6724–9. https://doi.org/10.1073/pnas.1031788100.
41. Cunningham PN, Wang Y, Guo R, et al. Role of toll-like receptor 4 in endotoxin-induced acute renal failure. J Immunol. 2004;172:2629–35. https://doi.org/10.4049/jimmunol.172.4.2629.
42. Plitas G, Burt BM, Nguyen HM, et al. Toll-like receptor 9 inhibition reduces mortality in polymicrobial sepsis. J Exp Med. 2008;205:1277–83. https://doi.org/10.1084/jem.20080162.
43. Yasuda H, Leelahavanichkul A, Tsunoda S, et al. Chloroquine and inhibition of toll-like receptor 9 protect from sepsis-induced acute kidney injury. Am J Physiol Renal Physiol. 2008;294:F1050–8. https://doi.org/10.1152/ajprenal.00461.2007.
44. Liu L, Li Y, Hu Z, et al. Small interfering RNA targeting toll-like receptor 9 protects mice against polymicrobial septic acute kidney injury. Nephron Exp Nephrol. 2012;122:51–61. https://doi.org/10.1159/000346953.
45. Zhang Q, Raoof M, Chen Y, et al. Circulating mitochondrial DAMPs cause inflammatory responses to injury. Nature. 2010;464:104–7. https://doi.org/10.1038/nature08780.
46. Garrabou G, Morén C, López S, et al. The effects of sepsis on mitochondria. J Infect Dis. 2012;205:392–400. https://doi.org/10.1093/infdis/jir764.
47. Nakahira K, Kyung S-Y, Rogers AJ, et al. Circulating mitochondrial DNA in patients in the ICU as a marker of mortality: derivation and validation. PLoS Med. 2013;10:e1001577. https://doi.org/10.1371/journal.pmed.1001577. discussion e1001577.
48. Tsuji N, Tsuji T, Ohashi N, et al. Role of mitochondrial DNA in septic AKI via toll-like receptor 9. J Am Soc Nephrol. 2016;27:2009–20. https://doi.org/10.1681/ASN.2015040376.

Chapter 4
Diagnosis of AKI: Clinical Assessment, Novel Biomarkers, History, and Perspectives

Kiyoshi Mori and Noriko Mori

Abstract Around year 2005, vague definition of acute renal failure was replaced by diagnosis of AKI, which aimed to establish an internationally unified criteria detecting kidney damage earlier. During the following decade, novel urinary biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL or lipocalin 2), liver-type fatty acid-binding protein (L-FABP or FABP1), kidney injury molecule-1 (KIM-1), and NephroCheck (product of urinary TIMP-2 and IGFBP7) emerged and were intensively investigated, which made it possible to detect kidney damage even earlier than development of AKI. These markers led to concepts of forest fire theory, functional/damage biomarkers, and subclinical AKI. By considering the time course and mechanism, we propose here that those urinary biomarkers may be divided into two categories: tubular dysfunction biomarkers (markers at least partially and potentially reflecting super-acute phase proximal tubule reabsorption impairment, which are urinary NGAL, L-FABP, and NephroCheck) and tubular regeneration biomarkers (early AKI markers but relatively delayed, reflecting proximal tubule regeneration, which contain urinary KIM-1). Future perspectives of novel AKI biomarkers include evaluation of biomarker-based early intervention and biomarker-guided AKI therapy using biomarkers to judge effectiveness of on-going treatments.

Keywords Urinary biomarkers · Emerging biomarkers · Forest fire theory
Functional/damage biomarkers · Subclinical AKI · NGAL · L-FABP · KIM-1
NephroCheck

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4.1 Historical Changes in the Concept of AKI

Correlation of blood creatinine levels with glomerular filtration rate (GFR) or creatinine clearance was first proposed in 1926 and was verified by succeeding works [1–4]. Since then till now, serum creatinine has been long the gold standard to define renal function or GFR in other words. Acute elevation in serum creatinine or blood urea nitrogen levels has been called acute renal failure. It was a vague concept, making it impossible to compare the findings of different clinical studies both horizontally and historically. As described above in this book, national consortiums began to propose internationally united criteria to define acute renal failure, especially in the early phase, and gave a term of acute kidney injury (AKI). Based upon changes in serum creatinine levels and urine outputs, RIFLE criteria by the Acute Dialysis Quality Initiative (ADQI) were published in 2004 [5] and AKI Network criteria in 2007 [6], and they were combined as 2012 AKI criteria by the Kidney Disease: Improving Global Outcomes (KDIGO) [7]. In KDIGO AKI criteria, the mildest stage of AKI (stage 1) was defined as either of the followings: (1) elevation of serum creatinine levels by $\geq$0.3 mg/dL within 48 h, (2) elevation of serum creatinine levels by $\geq$1.5-fold within 7 days, or (3) decrease of urine output to $\leq$0.5 mL/kg/h for more than 6 h [7]. We believe that, for healthy progress of nephrology, international definition of AKI should not be changed for at least 10 years. During years 1998–2013, novel urinary biomarkers representatively listed in Table 4.1 emerged, which are increased both in rodent and human AKI.

4.2 Which Were Earlier, Human Studies or Rodent Studies of Urinary AKI Biomarkers?

Sequences of urinary biomarker reports, in the settings of rodent and human AKI and human CKD, are clearly distinct among biomarkers (Table 4.1). In 2002, NGAL appeared in the nephrology literature for the first time, as one of kidney

Table 4.1 Representative urinary biomarkers for AKI and their first reports in rodent AKI, human AKI, and human CKD

Urinary biomarker	NGAL	L-FABP	KIM-1	NephroCheck
First in rodent AKI	Mishra et al. (2003) [11]	[a]Kamijo et al. (2004b) [19]	Ichimura et al. (2004) [16]	Peng et al. (2016) [22]
First in human AKI	Mori et al. (2005) [12] Mishra et al. (2005) [13]	Portilla et al. (2008) [20]	Han et al. (2002) [15]	Kashani et al. (2013) [21]
First in human CKD	Mori et al. (2005) [12]	Kamijo et al. (2004a) [18]	Timmeren et al. (2007) [17]	Not reported

[a]Indicates that the report dealt with unique transgenic mice harboring human L-FABP genetic locus, whose findings cannot be tested in standard laboratory animals

differentiation/epithelialization inducers [8, 9]. In 2003, upregulation of renal NGAL mRNA expression was reported at 3–24 h after murine renal ischemia-reperfusion injury [10]. Increase of NGAL protein in the urine was reported in murine renal ischemia-reperfusion injury and cisplatin-induced nephrotoxicity in 2003 [11]. Elevation of urinary NGAL levels in human AKI [12, 13] and human CKD [12] was reported in 2005.

In 1998, induction of renal KIM-1 mRNA expression was reported at 48 h after rat renal ischemia-reperfusion injury [14]. Increased excretion of urinary KIM-1 was reported in human AKI in 2002 [15], rat AKI in 2004 [16], and human CKD in 2007 [17].

On the other hand, elevation of urinary L-FABP was first reported in human CKD in 2004 [18], followed by AKI in genetically modified mice in 2004 [19] and human AKI in 2008 [20].

Increase of NephroCheck [product of urinary concentrations of tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP7)] was reported in human AKI in 2013 [21] and in rat AKI in 2016 [22]. NephroCheck in human CKD has not been reported. The sources of urinary TIMP-2 and IGFBP7 in AKI are poorly understood [23]. While IGFBP7 and TIMP-2 are speculated to be synthesized by injured renal tubules [21], there is no supporting evidence.

NGAL and KIM-1 have been the top two most popular biomarkers reported in the annual scientific meetings of the American Society of Nephrology (Fig. 4.1). The ratio of total abstract numbers may not necessarily reflect the numbers of large-scale clinical studies but might indicate reproducibility of the findings across various AKI etiologies in different countries.

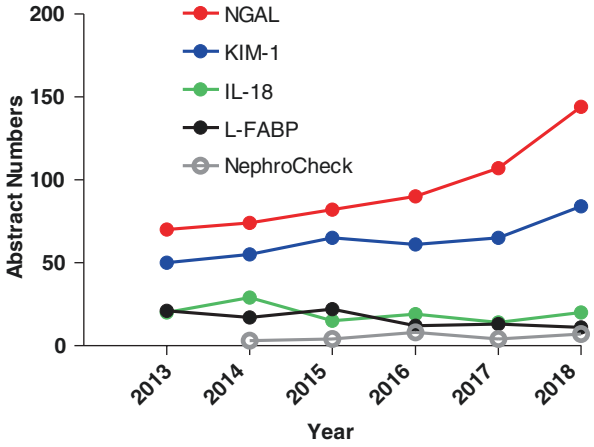

Fig. 4.1 Abstract numbers of five urinary AKI biomarkers in Kidney Week. Online abstracts of the American Society of Nephrology Kidney Week in the recent 6 years were searched using each biomarker name. To enhance screening, other key words such as lipocalin 2 and LCN2 for NGAL and TIMP-2 and IGFBP7 for NephroCheck were also used. The abstract numbers included studies in basic science not related to urinary biomarker levels but dealt with, for instance, biological function of the proteins or phenotypic analysis of knockout and transgenic mice. Of note, publication-only abstracts which were not selected for presentation in the meeting were also included

4.3 Prediction of AKI by Novel Biomarkers

Soon after discovery of those AKI biomarkers, it was recognized that those biomarkers commonly allow early prediction of AKI development (i.e., significant elevation of serum creatinine levels several days later) on the day of kidney insult (Fig. 4.2) [13, 20, 24, 25]. With the introduction of these biomarkers other than GFR indicators (serum creatinine, serum cystatin C, or creatinine clearance) or urine output, the field of AKI entered a new era.

Forest fire theory in 2007 (Fig. 4.3) proposed that blood, urine, and kidney NGAL concentrations are the real-time indicators of active kidney damage (resembling red fire in forest fire), distinctly from markers of functional nephron numbers such as serum creatinine or GFR (ratio between viable and burnt trees) [26].

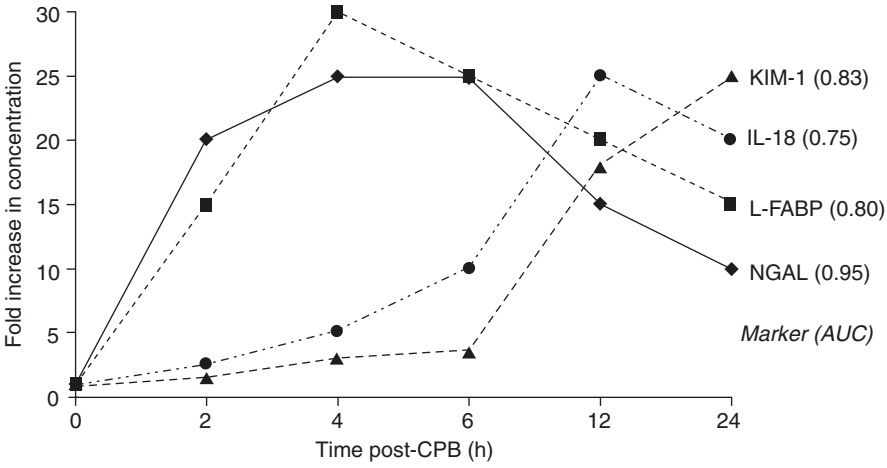

Fig. 4.2 Changes of urinary biomarkers in AKI cases after cardiopulmonary bypass surgery. *CPB* cardiopulmonary bypass, *AUC* area under the curve for the prediction of AKI. Reproduced from Devarajan (2010) [51]

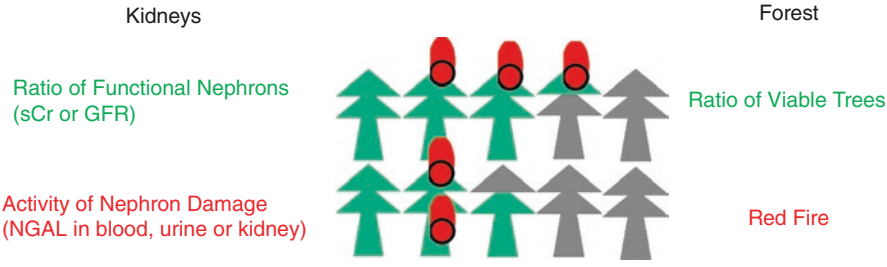

Fig. 4.3 Forest fire theory for worsening renal function. Reproduced from Mori and Nakao (2007) [26]. *sCr* serum creatinine, *GFR* glomerular filtration rate

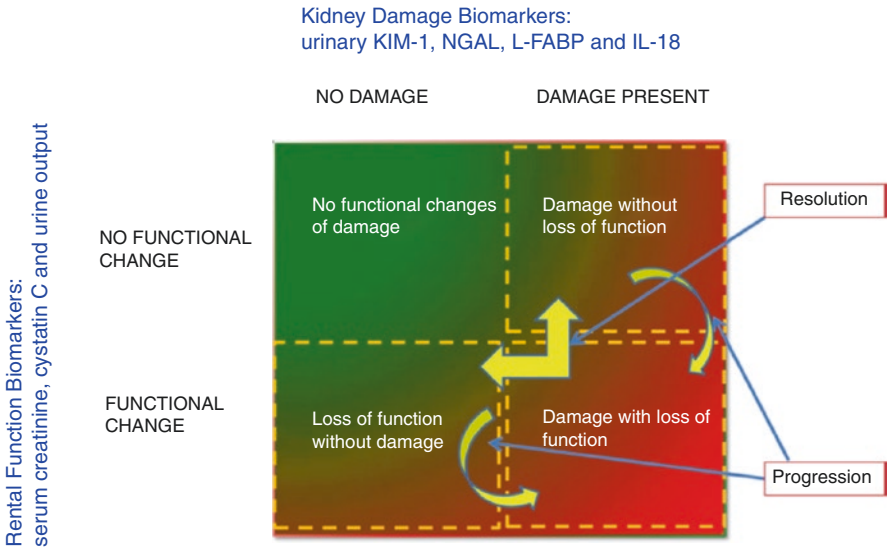

Fig. 4.4 Biomarker-based framework for AKI evaluation. Reproduced from Murray et al. (2014) [28]

In 2013–2014, ADQI 10th Workgroup reported a two-dimensional, biomarker-based framework for AKI evaluation (Fig. 4.4) [27, 28]. In that framework, serum creatinine, serum cystatin C, and urine output are renal function biomarkers, whereas urinary KIM-1, NGAL, L-FABP, and IL-18 are examples of kidney damage biomarkers. The lower left quadrant represents loss of function without damage which is often reversible. This scenario has been called dehydration, prerenal AKI, or transient AKI. The upper right quadrant indicates damage without loss of function, which was alternatively named subclinical AKI [29]. In subclinical AKI, loss of function may not develop at all or be seen at some time interval after detection of damage biomarkers. These patients are at higher risk for renal replacement therapy (RRT) requirement and mortality compared to patients without an increase in damage biomarker levels [29].

4.4 Clinical Use of Novel AKI Biomarkers

Some of the urinary biomarkers are locally available for clinical use [30, 31]: NGAL in Japan (since February 2017) and in Europe, L-FABP in Japan (since August 2011), and NephroCheck in the USA (since September 2014). Additionally, KIM-1 is approved by the Food and Drug Administration (FDA) and European Medicines Evaluation Agency (EMEA) for preclinical drug development and clinical trials [32].

4.5 Novel Classification of AKI Biomarkers: Tubular Dysfunction Biomarkers and Tubular Regeneration Biomarkers

Cardiac surgery with cardiopulmonary bypass (CPB) is a unique situation with high AKI risk, in which the initiation of the renal insult (i.e., renal ischemia) can be clearly defined. It is well established that urinary levels of NGAL and L-FABP in patients who are going to develop AKI start to increase within a few hours after the start of CPB, and they begin to decrease within 6–12 h (Fig. 4.2) [13, 20, 33, 34]. Many literatures insist that de novo synthesis of NGAL occurs in response to AKI, based upon the findings in renal ischemia-reperfusion injury (RIR) of animal studies [12, 35]. However, those experimental settings are quite severe, and it seems unlikely that urinary NGAL levels start to decrease within 12 h in those animals. In rodent RIR, loss of polarity and dislocation of Na-K-ATPase in tubules is the first event, followed by cell death and dedifferentiation/regeneration of tubular cells [36]. Activity of Na-K-ATPase provides an essential force for endocytic reabsorption of proteins in the proximal tubule lumen [37]. Megalin expressed along the apical surface of proximal tubules is responsible of capturing and endocytosis of luminal proteins including NGAL and L-FABP [38, 39]. Transient and reversible dysfunction of proximal tubules as to endocytic capacity is a more reasonable explanation for rapid changes in urinary biomarkers after cardiac surgery, other than de novo mRNA transcription, protein synthesis, secretion from tubular cells, and replacement of dead tubular cells. Since molecular weights of TIMP-2 and IGFBP7 are similar to those of NGAL and L-FABP [23] and elevation of NephroCheck is as early as NGAL in human AKI [21], TIMP-2 and IGFBP7 may undergo similar renal metabolism as NGAL. On the other hand, elevation of urinary KIM-1 levels starts 12 h after CPB initiation [24], likely reflecting the dedifferentiation/regeneration phase [14]. Therefore, we propose here that urinary albumin, NGAL, L-FABP, and NephroCheck, at least partly and potentially, have features of tubular dysfunction biomarkers, while urinary KIM-1 is a tubular regeneration biomarker. Consistently, when a systematic review was carried out for AKI biomarkers in 2008, urine KIM-1 performed best for the differential diagnosis of established AKI, whereas urine NGAL and IL-18 performed best for early diagnosis of AKI [40].

4.6 Future Perspective

A recently published meta-analysis showed a clear and statistically significant mortality benefit to early nephrology consultation [41]. Indeed, in a cardiac surgery study, early detection of post-surgery kidney injury by increase in NephroCheck allowed early intervention by nephrologists and reduced incidence of AKI [42].

There are continued efforts to evaluate whether monitoring of AKI biomarkers, such as urinary NGAL, is useful to judge trend in the kidney injury severity and treatment efficacy in the setting of AKI or subacute CKD [43, 44]. In a dog model of gentamicin-induced AKI, increase and decrease of urinary NGAL levels were earlier than the change of serum creatinine by approximately 4 days [45] (Fig. 4.5a). In our case undergoing intermittent hemodialysis after severe post-infectious glomerulonephritis, serum creatinine levels were not good indicator of renal function due to removal by hemodialysis. Decrease in urinary NGAL levels was steeper than that of urinary L-FABP levels, which occurred 2 weeks earlier than dialysis withdrawal in this case (Fig. 4.5b).

Importantly, theoretical exercises have shown that even a perfect biomarker will perform poorly when compared to an imperfect gold standard [46–48]. In dehydrated conditions, serum creatinine levels increase and may fulfil criteria of AKI, but urinary NGAL is not sensitive to dehydration [49, 50]. In some forms of acute tubular necrosis, serum creatinine or GFR may not be altered significantly in the early phase, despite increase in urinary AKI biomarkers. Therefore, a race to develop and compare biomarkers which have the strongest power (the largest area under the curve in receiver operating characteristic curve analysis) for the prediction of creatinine and urine output-based AKI may not be very fruitful as expected.

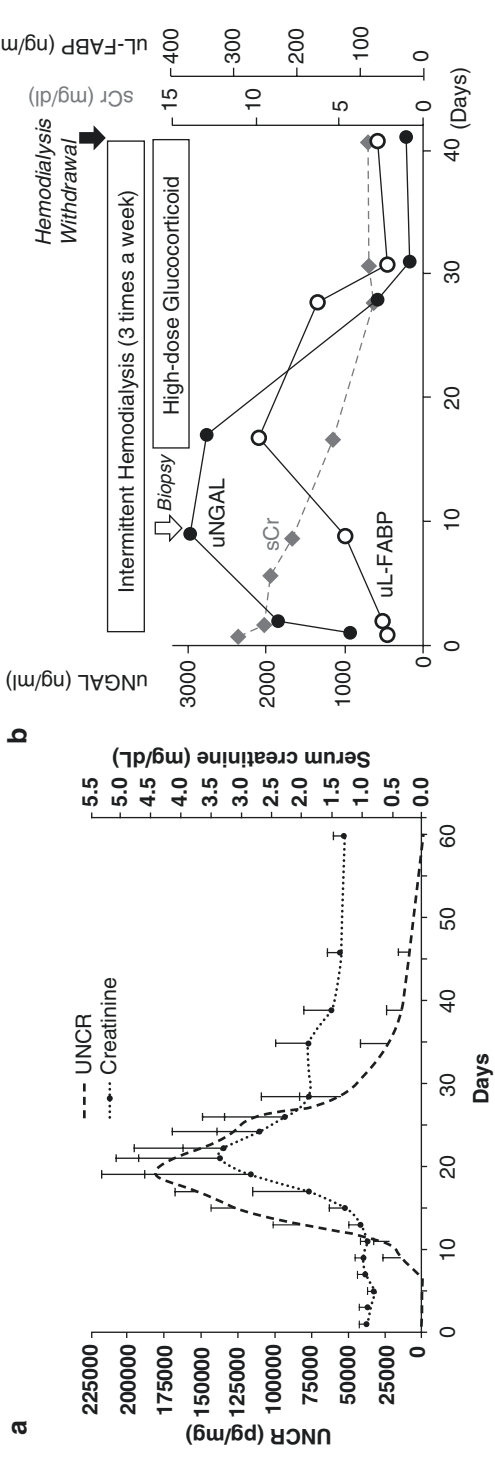

Fig. 4.5 Time course of urinary biomarkers during recovery phase of AKI. (**a**) Changes in serum creatinine and urinary NGAL/creatinine ratio (UNCR) in a dog model of gentamicin-induced AKI. Reproduced from Plam et al. (2016) [45]. (**b**) Changes in serum creatinine (sCr) and urinary NGAL (uNGAL) and L-FABP (uL-FABP) levels in a case with post-*Staphylococcus aureus* infection, acute glomerulonephritis treated with hemodialysis, and high-dose glucocorticoid. A case observed in Shizuoka General Hospital. White and black arrows indicate the timing of renal biopsy and hemodialysis withdrawal, respectively

References

1. Rehberg PB. Studies on kidney function: the excretion of urea and chlorine analysed according to a modified filtration-reabsorption theory. Biochem J. 1926;20:461–82.
2. Doolan PD, Alpen EL, Theil GB. A clinical appraisal of the plasma concentration and endogenous clearance of creatinine. Am J Med. 1962;32:65–79.
3. Steinitz K, Turkand H. The determination of the glomerular filtration by the endogenous creatinine clearance. J Clin Invest. 1940;19:285–98.
4. Narayanan S, Appleton HD. Creatinine: a review. Clin Chem. 1980;26:1119–26.
5. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P, Acute Dialysis Quality Initiative W. Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the second international consensus conference of the acute dialysis quality initiative (ADQI) group. Crit Care. 2004;8:R204–12.
6. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A, Acute Kidney Injury N. Acute kidney injury network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11:R31.
7. Kellum JA, Lameire N, Aspelin P, Barsoum RS, Burdmann EA, Goldstein SL, Herzog CA, Joannidis M, Kribben A, Levey AS, MacLeod AM, Mehta RL, Murray PT, Naicker S, Opal SM, Schaefer F, Schetz M, Uchino S. Kidney disease: improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012;2:1–138.
8. Yang J, Goetz D, Li JY, Wang W, Mori K, Setlik D, Du T, Erdjument-Bromage H, Tempst P, Strong R, Barasch J. An iron delivery pathway mediated by a lipocalin. Mol Cell. 2002;10:1045–56.
9. Mori K, Yang J, Barasch J. Ureteric bud controls multiple steps in the conversion of mesenchyme to epithelia. Semin Cell Dev Biol. 2003;14:209–16.
10. Supavekin S, Zhang W, Kucherlapati R, Kaskel FJ, Moore LC, Devarajan P. Differential gene expression following early renal ischemia/reperfusion. Kidney Int. 2003;63:1714–24.
11. Mishra J, Ma Q, Prada A, Mitsnefes M, Zahedi K, Yang J, Barasch J, Devarajan P. Identification of neutrophil gelatinase-associated lipocalin as a novel early urinary biomarker for ischemic renal injury. J Am Soc Nephrol. 2003;14:2534–43.
12. Mori K, Lee HT, Rapoport D, Drexler IR, Foster K, Yang J, Schmidt-Ott KM, Chen X, Li JY, Weiss S, Mishra J, Cheema FH, Markowitz G, Suganami T, Sawai K, Mukoyama M, Kunis C, D'Agati V, Devarajan P, Barasch J. Endocytic delivery of lipocalin-siderophore-iron complex rescues the kidney from ischemia-reperfusion injury. J Clin Investig. 2005;115:610–21.
13. Mishra J, Dent C, Tarabishi R, Mitsnefes MM, Ma Q, Kelly C, Ruff SM, Zahedi K, Shao M, Bean J, Mori K, Barasch J, Devarajan P. Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. Lancet. 2005;365:1231–8.
14. Ichimura T, Bonventre JV, Bailly V, Wei H, Hession CA, Cate RL, Sanicola M. Kidney injury molecule-1 (KIM-1), a putative epithelial cell adhesion molecule containing a novel immunoglobulin domain, is up-regulated in renal cells after injury. J Biol Chem. 1998;273:4135–42.
15. Han WK, Bailly V, Abichandani R, Thadhani R, Bonventre JV. Kidney injury Molecule-1 (KIM-1): a novel biomarker for human renal proximal tubule injury. Kidney Int. 2002;62:237–44.
16. Ichimura T, Hung CC, Yang SA, Stevens JL, Bonventre JV. Kidney injury molecule-1: a tissue and urinary biomarker for nephrotoxicant-induced renal injury. Am J Physiol Renal Physiol. 2004;286:F552–63.
17. van Timmeren MM, van den Heuvel MC, Bailly V, Bakker SJ, van Goor H, Stegeman CA. Tubular kidney injury molecule-1 (KIM-1) in human renal disease. J Pathol. 2007;212:209–17.
18. Kamijo A, Kimura K, Sugaya T, Yamanouchi M, Hikawa A, Hirano N, Hirata Y, Goto A, Omata M. Urinary fatty acid-binding protein as a new clinical marker of the progression of chronic renal disease. J Lab Clin Med. 2004a;143:23–30.

19. Kamijo A, Sugaya T, Hikawa A, Okada M, Okumura F, Yamanouchi M, Honda A, Okabe M, Fujino T, Hirata Y, Omata M, Kaneko R, Fujii H, Fukamizu A, Kimura K. Urinary excretion of fatty acid-binding protein reflects stress overload on the proximal tubules. Am J Pathol. 2004b;165:1243–55.
20. Portilla D, Dent C, Sugaya T, Nagothu KK, Kundi I, Moore P, Noiri E, Devarajan P. Liver fatty acid-binding protein as a biomarker of acute kidney injury after cardiac surgery. Kidney Int. 2008;73:465–72.
21. Kashani K, Al-Khafaji A, Ardiles T, Artigas A, Bagshaw SM, Bell M, Bihorac A, Birkhahn R, Cely CM, Chawla LS, Davison DL, Feldkamp T, Forni LG, Gong MN, Gunnerson KJ, Haase M, Hackett J, Honore PM, Hoste EA, Joannes-Boyau O, Joannidis M, Kim P, Koyner JL, Laskowitz DT, Lissauer ME, Marx G, McCullough PA, Mullaney S, Ostermann M, Rimmele T, Shapiro NI, Shaw AD, Shi J, Sprague AM, Vincent JL, Vinsonneau C, Wagner L, Walker MG, Wilkerson RG, Zacharowski K, Kellum JA. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. Crit Care. 2013;17:R25.
22. Peng ZY, Zhou F, Kellum JA. Cross-species validation of cell cycle arrest markers for acute kidney injury in the rat during sepsis. Intensive Care Med Exp. 2016;4:12.
23. Schrezenmeier EV, Barasch J, Budde K, Westhoff T, Schmidt-Ott KM. Biomarkers in acute kidney injury—pathophysiological basis and clinical performance. Acta Physiol (Oxf). 2017;219:554–72.
24. Han WK, Waikar SS, Johnson A, Betensky RA, Dent CL, Devarajan P, Bonventre JV. Urinary biomarkers in the early diagnosis of acute kidney injury. Kidney Int. 2008;73:863–9.
25. Doi K, Nishida O, Shigematsu T, Sadahiro T, Itami N, Iseki K, Yuzawa Y, Okada H, Koya D, Kiyomoto H, Shibagaki Y, Matsuda K, Kato A, Hayashi T, Ogawa T, Tsukamoto T, Noiri E, Negi S, Kamei K, Kitayama H, Kashihara N, Moriyama T, Terada Y. Japanese clinical practice guideline for acute kidney injury 2016 committee. Clin Exp Nephrol. 2018;22:985–1045.
26. Mori K, Nakao K. Neutrophil gelatinase-associated lipocalin as the real-time indicator of active kidney damage. Kidney Int. 2007;71:967–70.
27. McCullough PA, Shaw AD, Haase M, Bouchard J, Waikar SS, Siew ED, Murray PT, Mehta RL, Ronco C. Diagnosis of acute kidney injury using functional and injury biomarkers: workgroup statements from the tenth acute dialysis quality initiative consensus conference. Contrib Nephrol. 2013;182:13–29.
28. Murray PT, Mehta RL, Shaw A, Ronco C, Endre Z, Kellum JA, Chawla LS, Cruz D, Ince C, Okusa MD. Workgroup a. potential use of biomarkers in acute kidney injury: report and summary of recommendations from the 10th acute dialysis quality initiative consensus conference. Kidney Int. 2014;85:513–21.
29. Haase M, Devarajan P, Haase-Fielitz A, Bellomo R, Cruz DN, Wagener G, Krawczeski CD, Koyner JL, Murray P, Zappitelli M, Goldstein SL, Makris K, Ronco C, Martensson J, Martling CR, Venge P, Siew E, Ware LB, Ikizler TA, Mertens PR. The outcome of neutrophil gelatinase-associated lipocalin-positive subclinical acute kidney injury: a multicenter pooled analysis of prospective studies. J Am Coll Cardiol. 2011;57:1752–61.
30. Pickering JW, Endre ZH. Bench to bedside: the next steps for biomarkers in acute kidney injury. Am J Physiol Renal Physiol. 2016;311:F717–21.
31. Kashani K, Cheungpasitporn W, Ronco C. Biomarkers of acute kidney injury: the pathway from discovery to clinical adoption. Clin Chem Lab Med. 2017;55:1074–89.
32. Dieterle F, Sistare F, Goodsaid F, Papaluca M, Ozer JS, Webb CP, Baer W, Senagore A, Schipper MJ, Vonderscher J, Sultana S, Gerhold DL, Phillips JA, Maurer G, Carl K, Laurie D, Harpur E, Sonee M, Ennulat D, Holder D, Andrews-Cleavenger D, Gu Y-Z, Thompson KL, Goering PL, Vidal J-M, Abadie E, Maciulaitis R, Jacobson-Kram D, Defelice AF, Hausner EA, Blank M, Thompson A, Harlow P, Throckmorton D, Xiao S, Xu N, Taylor W, Vamvakas S, Flamion B, Lima BS, Kasper P, Pasanen M, Prasad K, Troth S, Bounous D, Robinson-Gravatt D, Betton G, Davis MA, Akunda J, McDuffie JE, Suter L, Obert L, Guffroy M, Pinches M, Jayadev S, Blomme EA, Beushausen SA, Barlow VG, Collins N, Waring J, Honor

D, Snook S, Lee J, Rossi P, Walker E, Mattes W. Renal biomarker qualification submission: a dialog between the FDA-EMEA and Predictive Safety Testing Consortium. Nat Biotechnol. 2010;28:455.
33. Wagener G, Jan M, Kim M, Mori K, Barasch JM, Sladen RN, Lee HT. Association between increases in urinary neutrophil gelatinase-associated lipocalin and acute renal dysfunction after adult cardiac surgery. Anesthesiology. 2006;105:485–91.
34. Wagener G, Gubitosa G, Wang S, Borregaard N, Kim M, Lee HT. Urinary neutrophil gelatinase-associated lipocalin and acute kidney injury after cardiac surgery. Am J Kidney Dis. 2008;52:425–33.
35. Paragas N, Qiu A, Zhang Q, Samstein B, Deng SX, Schmidt-Ott KM, Viltard M, Yu W, Forster CS, Gong G, Liu Y, Kulkarni R, Mori K, Kalandadze A, Ratner AJ, Devarajan P, Landry DW, D'Agati V, Lin CS, Barasch J. The Ngal reporter mouse detects the response of the kidney to injury in real time. Nat Med. 2011;17:216–22.
36. Vaidya VS, Ferguson MA, Bonventre JV. Biomarkers of acute kidney injury. Annu Rev Pharmacol Toxicol. 2008;48:463–93.
37. Féraille E, Doucet A. Sodium-potassium-adenosinetriphosphatase-dependent sodium transport in the kidney: hormonal control. Physiol Rev. 2001;81:345–418.
38. Mori KP, Yokoi H, Kasahara M, Imamaki H, Ishii A, Kuwabara T, Koga K, Kato Y, Toda N, Ohno S, Kuwahara K, Endo T, Nakao K, Yanagita M, Mukoyama M, Mori K. Increase of total nephron albumin filtration and reabsorption in diabetic nephropathy. J Am Soc Nephrol. 2017;28:278–89.
39. Oyama Y, Takeda T, Hama H, Tanuma A, Iino N, Sato K, Kaseda R, Ma M, Yamamoto T, Fujii H, Kazama JJ, Odani S, Terada Y, Mizuta K, Gejyo F, Saito A. Evidence for megalin-mediated proximal tubular uptake of L-FABP, a carrier of potentially nephrotoxic molecules. Lab Investig. 2005;85:522.
40. Coca SG, Yalavarthy R, Concato J, Parikh CR. Biomarkers for the diagnosis and risk stratification of acute kidney injury: a systematic review. Kidney Int. 2008;73:1008–16.
41. Soares DM, Pessanha JF, Sharma A, Brocca A, Ronco C. Delayed nephrology consultation and high mortality on acute kidney injury: a meta-analysis. Blood Purif. 2017;43:57–67.
42. Meersch M, Schmidt C, Hoffmeier A, Van Aken H, Wempe C, Gerss J, Zarbock A. Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: the PrevAKI randomized controlled trial. Intensive Care Med. 2017;43:1551–61.
43. Kuwabara T, Mori K, Mukoyama M, Kasahara M, Yokoi H, Saito Y, Yoshioka T, Ogawa Y, Imamaki H, Kusakabe T, Ebihara K, Omata M, Satoh N, Sugawara A, Barasch J, Nakao K. Urinary neutrophil gelatinase-associated lipocalin levels reflect damage to glomeruli, proximal tubules, and distal nephrons. Kidney Int. 2009;75:285–94.
44. Varnell CD, Goldstein SL, Devarajan P, Basu RK. Impact of near real-time urine neutrophil gelatinase–associated lipocalin assessment on clinical practice. Kidney Int Rep. 2017;2:1243–9.
45. Palm CA, Segev G, Cowgill LD, LeRoy BE, Kowalkowski KL, Kanakubo K, Westropp JL. Urinary neutrophil gelatinase-associated lipocalin as a marker for identification of acute kidney injury and recovery in dogs with gentamicin-induced nephrotoxicity. J Vet Intern Med. 2016;30:200–5.
46. Haase-Fielitz A, Bellomo R, Devarajan P, Bennett M, Story D, Matalanis G, Frei U, Dragun D, Haase M. The predictive performance of plasma neutrophil gelatinase-associated lipocalin (NGAL) increases with grade of acute kidney injury. Nephrol Dial Transplant. 2009;24:3349–54.
47. Waikar SS, Betensky RA, Bonventre JV. Creatinine as the gold standard for kidney injury biomarker studies? Nephrol Dial Transplant. 2009;24:3263–5.
48. Griffin BR, Gist KM, Faubel S. Current status of novel biomarkers for the diagnosis of acute kidney injury: a historical perspective. J Intensive Care Med. 2019. 885066618824531. doi: https://doi.org/10.1177/0885066618824531.

49. Nickolas TL, O'Rourke MJ, Yang J, Sise ME, Canetta PA, Barasch N, Buchen C, Khan F, Mori K, Giglio J, Devarajan P, Barasch J. Sensitivity and specificity of a single emergency department measurement of urinary neutrophil gelatinase-associated lipocalin for diagnosing acute kidney injury. Ann Intern Med. 2008;148:810–9.
50. Doi K, Katagiri D, Negishi K, Hasegawa S, Hamasaki Y, Fujita T, Matsubara T, Ishii T, Yahagi N, Sugaya T, Noiri E. Mild elevation of urinary biomarkers in prerenal acute kidney injury. Kidney Int. 2012;82:1114–20.
51. Devarajan P. Review: neutrophil gelatinase-associated lipocalin: a troponin-like biomarker for human acute kidney injury. Nephrology (Carlton). 2010;15:419–28.

Chapter 5
Risk Factors for AKI Development in Surgery (Non-cardiac Surgery)

Shu Wakino

5.1 Introduction

Although postoperative acute kidney injury (AKI) accounts for 18–47% of nosocomial onset AKI [1], its influence on postoperative prognosis has largely been neglected except in the field of cardiac surgery. Recently, however, interest in the onset of AKI and the types of chronic kidney disease (CKD) that follow has increased. Various risk factors have been identified, and preventative treatment strategies have been proposed. This chapter describes AKI onset and its effects after non-cardiac surgery.

5.2 Incidence Rate

Incidence rates change drastically with the development of new surgical techniques and changes in perioperative management practices. Additionally, as has been described above, the concept of AKI was proposed in 2004, and since then, diagnostic guidelines like RIFLE, AKIN, and KDIGO have changed with it. New numbers bring new meaning. As can be seen in Table 5.1, if we limit ourselves to the scope of only a few years and focus primarily on non-cardiac surgery, incidence rates vary between 1.0 and 31.0% [2]. If we limit ourselves to abdominal, the incidence rate is between 10 and 20%.

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Table 5.1 Incidence of postoperative AKI (non-cardiac surgery)

Year	Case	Design	Operation	Classification	Incidence (%)
2014	1200	Prospective, single-center	Major, non-cardiac, non-vascular	RIFLE	6.7
2016	390	Retrospective, single-center	Major, non-cardiac, non-vascular	KDIGO	18.5
2016	3902	Retrospective, single-center	Major, abdomen	KDIGO	6.8
2016	258	Prospective, single-center	Major, abdomen	AKIN	12.0
2017	898	Retrospective, single-center	Esophagus	AKIN	11.9
2016	845 1334	Retrospective, multicenter	AAA, endovascular AAA, open	Initiation of HD	6.9 13.5
2016	14,475	Retrospective, multicenter	AAA, endovascular	KDIGO and initiation of HD	3.3
2016	95 42	Prospective, single-center	AAA, endovascular AAA, open	AKIN	9.4 31.0
2017	898	Retrospective, single-center	Knee and hip joint	RIFLE	6.8
2017	5609	Retrospective, single-center	Knee and hip joint	RIFLE	1.0

AAA abdominal aortic aneurysm; *RIFLE* Risk, Injury, Failure, Loss, End-Stage; *kidney disease classification KDIGO* Kidney Disease: Improving Global Outcomes classification; *AKIN* Acute Kidney Injury Network classification; *HD* hemodialysis

5.3 Onset Risk Factors

5.3.1 Onset Risk Factors for AKI in Non-cardiac Surgery

Clarifying the risk factors that give rise to postoperative AKI following non-cardiac surgeries and placing high-risk cases under strict management are both incredibly important goals in the prevention of AKI. To date, most research into these risk factors has been in the form of retrospective, observational studies [3]. Nevertheless, many risk factors have been identified (Table 5.2). Some of these studies propose using risk indices to evaluate and classify cases. For example, Kheterpal et al. evaluated 75,952 surgical cases (including cardiac surgery) and found age ≥56, male sex, emergency surgery, abdominal surgery, diabetes, active heart failure, ascites, high blood pressure, and preoperative renal failure to be the main risk factors and have used indices of these risk factors to stratify patient risk [4]. Additionally, Slankamenac et al. have developed a score for predicting the likelihood of AKI onset after liver surgery. They propose stratifying and evaluating risk using factors such as preoperative ALT, cardiovascular disease, CKD, diabetes, red blood cell transfusion, choledochojejunostomy, and risk of intraoperative oliguria [5]. If, however, emergency surgery is not removed as a risk factor in a certain cohort, for example, this leads to

Table 5.2 Risk factor of postoperative AKI in non-cardiac surgery

Abdominal operation	*Vascular surgery (open surgery)*	*Thoracic surgery*
Age	Ischemia time	Hypertension
Male	Bilateral renal artery ischemia	Peripheral artery disease
Emergent operation	Hypotension during operation	ARB
Intra-abdominal	Age	HES solution
Diabetes	Symptomatic AAA	Age
Heart failure	Suprarenal AAA	Smoking
Hypertension	Serum creatinine >1.5 mg/dL	Alcohol dependence
Ascites	Hypertension	ACE inhibitor
Dyslipidemia	Respiratory disease	Coronary artery disease
CKD	*Vascular surgery (endovascular surgery)*	Diabetes
Liver dysfunction	Renal artery ischemia	Dyslipidemia
BMI	Renal artery embolism	Low hematocrit
High-risk case	Dissecting aneurysm	Maximum oxygen demand
Use of vasoconstrictor	Microembolism	FEV1
Use of diuretics	Inflammation	Lung resection volume
Use of anti-hypertensives		Use of vasoconstrictor
ACE inhibitor		
ARB		
General anesthesia		
RBC transfusion		

CKD chronic kidney disease, *BMI* body mass index, *ACE inhibitor* angiotensin II-converting enzyme inhibitor, *ARB* angiotensin II receptor antagonist, *RBC transfusion* red blood cell transfusion, *AAA* abdominal aortic aneurysm, *HES solution* hydroxyethyl starch solution, *FEV1* forced expiratory volume 1.0

variance among reports. This is due to differences in the definition of AKI, differences in operation style at the institution, and the modification of the result by treatment for being retrospective.

5.3.2 Liver Transplant

Generally speaking, the onset of AKI in liver disease puts one at risk for progression of liver dysfunction and death [6]. In liver transplantation, a common liver surgery, AKI is a critical factor that correlates with patient death, and the identification of a risk factor that could predict its onset is important. The incidence rate of AKI in liver transplants has, in recent years, been examined using the AKIN classification system. While this is a retrospective initiative, reports from 2013 to 2015 put the incidence rate between 10 and 30% [7, 8]. In recent reports, Leithead et al. report AKI incidence among 1152 patients that underwent liver transplantation [7]. In this study, AKI was defined as progression beyond KDIGO stage II within 1 week of the operation or a twofold (or higher) increase in serum creatinine. They found an incidence

rate of 33.8% and identified preoperative MELD score, preoperative hyponatremia, a preoperative BMI of 30 kg/m^2, intraoperative red blood cell transfusion, and long warm ischemia time as risk factors for AKI onset. The MELD score is a metric unique to liver transplant surgeries and is used to determine condition severity in patients older than 12 that are enrolled in the American Organ Transplant Network. It is calculated using bilirubin, prothrombin time, creatinine, and presence or absence of dialysis treatment. Specifically, MELD score = (0.957 × ln (serum Cr/dialysis treatment, Cr = 4.0 for calculation) + 0.378 × ln (serum bilirubin) + 1.120 × ln (INR) + 0.643) × 10 [9]. Additionally, in transplant surgeries, the time between stopping blood flow to a particular organ, transplanting it, and restarting blood flow is referred to as ischemia time. When ischemia occurs at body temperature, it is highly likely that cells will die. This time is referred to as "warm ischemia time." For the heart and liver, the ideal warm ischemia time is 0 min. For kidneys and lungs, it is 30 min. In any case, cooling the organ as quickly as possible and stopping cell metabolism is essential. There are 12 reports that discuss post-liver transplant AKI in this way. Of these, six mention intraoperative blood transfusion, and three mention preoperative MELD score, intraoperative low blood pressure, and use of vasopressors as independent risk factors [10].

5.3.3 Lung Surgery

AKI onset in the context of lung surgery has also garnered interest. George et al. report a multicenter study involving 12,108 individuals [11]. After evaluating these individuals in the presence or absence of postoperative renal replacement therapy, the incidence rate of AKI was 5.4%. The following were identified as risk factors for the condition: age, male sex, African-American, preoperative kidney function, preoperative bilirubin, presence or absence of preoperative comorbid lung disease, bilateral lung surgery, intra- or postoperative use of extracorporeal membrane oxygenation (ECMO), and ischemia time. Licker et al. examined AKI onset within 1 week in cases whose RIFLE classification was R and higher. They report an incidence rate of 6.8% and identify FEV1/FVC ratio, ASA score, and time under anesthetic as risk factors. ASA score is a score developed by the American Society of Anesthesiologists that evaluates whole-body status [12].

5.3.4 Bariatric Surgery

In recent years, bariatric surgery has become widely practiced to treat obesity, especially in the West. Because obesity itself causes a decline in renal function, postoperative AKI has garnered much attention. The Mayo Clinic reports that between 2004 and 2011, 1227 bariatric surgeries were performed. If AKI is defined as serum

creatinine exceeding 0.3 mg/dL within 72 h of the surgery, its incidence rate for these operations was 5.8%, and risk factors were preoperative BMI and presence or absence of diabetes [13, 14].

5.4 Measures for Preventing AKI Onset

The first step in preventing AKI is, most importantly, to evaluate patients for the aforementioned preoperative risk factors. However, there are also factors that must be kept in mind during intra- and postoperative management [2] (Table 5.2).

5.4.1 Intraoperative Hemodynamics and Transfusion Management

Ensuring that blood flow is sufficient and that tissues are receiving enough nutrients is a very important part of postoperative management. Tissue hypoperfusion and lack of oxygen supply are some of the largest causes not only of AKI but of many postoperative complications. With regard to colon surgery, 27.7% of patients become dehydrated as part of the preparations for the procedure, and dehydration is a risk factor for postoperative AKI [15]. Dehydration is also the primary risk factor for AKI following plastic surgery [16]. On the other hand, excessive transfusion, particularly during abdominal surgeries, increases intraorgan pressure leading to edema of the kidney capsule, which then causes an increase in intrarenal pressure and causes intra-abdominal hypertension, which causes AKI. While blood flow after circulation to tissues and tissue oxygen consumption are more important than cardiac output in terms of causing intra- and postoperative organ damage, actual tissue blood flow is difficult to estimate due to intra- and postoperative hemorrhage and fluid shift into the interstitial space. Goal-directed therapy (GDT), which has been proposed in recent years, attempts to use indices of circulation to set goals for patient management and thereby improve patient prognosis. In goal-directed fluid management, transfusion volume is not determined by urine volume and blood pressure. Instead, transfusion volume is determined in real time by monitoring stroke volume variation (SVV) and stroke volume variable (SVI) from transesophageal catheters, fingertip pulse waves, etc. The OPTIMISE trial, conducted on patients that had undergone major abdominal surgery, demonstrated that GDT is effective at preventing the occurrence of AKI. Fingertip pulse waves were used to monitor cardiac output, transfusions containing colloids were used as the primary transfusion fluids, and postoperative management was extended to 6 h after surgery. Doing these things reduced the number of postoperative complications, including renal failure [17] (Fig. 5.1). This sort of detailed postoperative

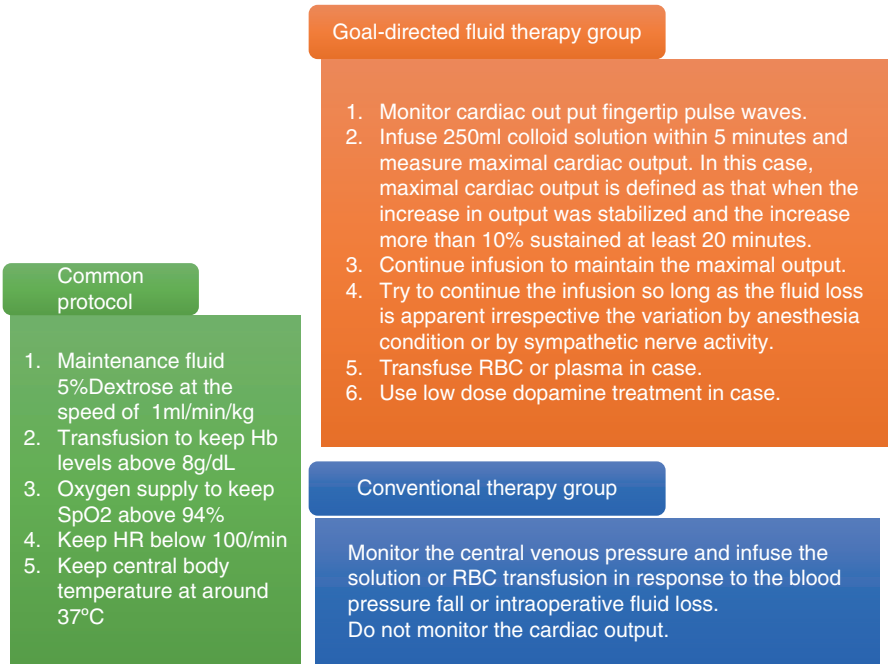

Fig. 5.1 Goal-directed fluid therapy protocol of OPTIMISE study. The protocol for OPTIMISE study. The efficacy of the goal-directed fluid therapy was tested by this study. The details of goal-directed fluid therapy, conventional therapy, and common protocol were listed in orange, blue, and green boxes, respectively

management and invasivity-reducing and recovery-accelerating protocol is known as ERP (enhanced recovery protocol). ERP has been pursued in recent years as a way of preventing AKI and other complications [18] (Fig. 5.2).

5.4.2 Decision to Transfuse

Intra- and postoperative transfusions are correlated with AKI onset. In order to better protect the kidneys, crystalloids are currently recommended over physiological saline [17]. Among the crystalloids, Ringer's acetate solution and Plasma-Lyte are most similar to the composition of human plasma and are therefore called balanced crystalloids. Because they cause fewer side effects such as renal damage or coagulopathy than physiological saline, balanced crystalloids have garnered a great deal of attention in recent years [19]. On the other hand, the postoperative use of one particular sort of crystalloid, hydroxyethyl starch (HES), is limited. HES is an artificially formulated colloid solution prepared from potato and corn starches. It is classified by its molecular weight, and HES heavier than 200 KDa has been reported to significantly increase AKI risk [20].

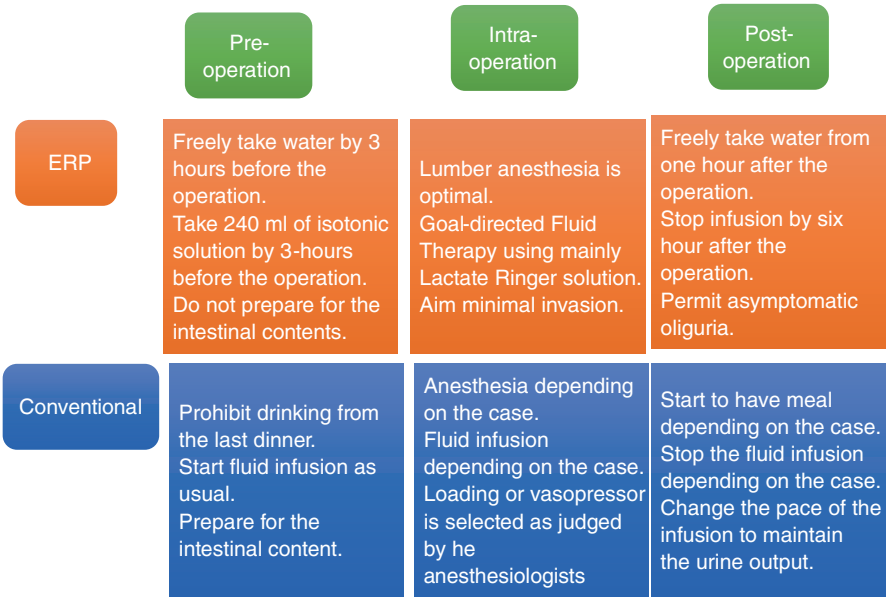

Fig. 5.2 Examples of ERP (enhanced recovery protocol). The details of ERP were described in orange boxes in contrast with those of conventional therapy in purple box

5.4.3 Red Blood Cell Transfusion

Several studies report that red blood cell transfusions are a risk factor for AKI onset in the context of liver surgery. Similar results have been reported in the fields of colon and gastric surgery [2]. The reason for this is believed to be that transfused red blood cells have a short life span and are prone to hemolysis, causing free iron ions to be released into the bloodstream. Free iron ions cause oxidative stress in organs and lead to organ damage. Therefore, unnecessary blood transfusion should be avoided, and it is thought that maintaining a red blood cell concentration of at least 8 g/dL is sufficient.

5.4.4 Others

In addition to that mentioned above, avoiding the use of nephrotoxic drugs and contrast agents, avoiding the use of oral sodium phosphate (OSP) as a pretreatment for the intestinal tract, and using polyethylene glycol (PEG) have all been shown, with evidence, to be important in the prevention of AKI in non-cardiac surgery.

5.5 Clinical Effects of AKI

Postoperative AKI is known to be associated with mortality and the prevalence of other diseases in the short and long term. With regard to death rates within 30 days of the operation, data from the American College of Surgeons-National Surgical Quality Improvement Program (ACS-NSQIP) shows that AKI onset following abdominal surgery increases postoperative death rates by 3.5 times [21]. From a medical economics point of view, it has been shown that the onset of AKI leads to an increase in costs. The same applies to long-term prognosis. As for the incidence of cardiovascular complications, the 10-year survival rates of patients who did not develop AKI after major abdominal surgery in the RIFLE classification and patients who developed stage I, stage II, and stage III AKI were 65%, 50%, 44%, and 39%, respectively [22].

5.6 Conclusion

We reviewed the development of postoperative AKI in non-cardiac surgery. As the definition of AKI changes, so too do its incidence rate and risk factors. Nevertheless, it is clear that intra- and postoperative AKI influence the patient's surgical prognosis. GDT has been widely used in recent years, especially during surgery and postoperative fluid management, and it is possible that it may have a major impact on the development of AKI. In the future, it will be important that renal internists fully grasp the ideas of critical care medicine and surgery.

References

1. Carmichael P, Carmichael AR. Acute renal failure in the surgical setting. ANZ J Surg. 2003;73:144–53.
2. Vaara ST, Bellomo R. Postoperative renal dysfunction after noncardiac surgery. Curr Opin Crit Care. 2017;23(5):440–6.
3. An Y, Shen K, Ye Y. Risk factors for and the prevention of acute kidney injury after abdominal surgery. Surg Today. 2018;48(6):573–83.
4. Kheterpal S, Tremper KK, Heung M, Rosenberg AL, Englesbe M, Shanks AM, et al. Development and validation of an acute kidney injury risk index for patients undergoing general surgery: results from a national data set. Anesthesiology. 2009;110:505–15.
5. Slankamenac K, Beck-Schimmer B, Breitenstein S, Puhan MA, Clavien PA. Novel prediction score including pre- and intraoperative parameters best predicts acute kidney injury after liver surgery. World J Surg. 2013;37:2618–28.
6. Sampaio MS, Martin P, Bunnapradist S. Renal dysfunction in end-stage liver disease and post-liver transplant. Clin Liver Dis. 2014;18(3):543–60.
7. Leithead JA, Armstrong MJ, Corbett C. Hepatic ischemia reperfusion injury is associated with acute kidney injury following donation after brain death liver transplantation. Transpl Int. 2013;26(11):1116–25.

8. Khosravi MB, Milani S, Kakaei F. Serum neutrophil gelatinase-associated lipocalin versus serum creatinine for the prediction of acute kidney injury after liver transplantation. Int J Organ Transplant Med. 2013;4(3):102–9.
9. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, D'Amico G, Dickson ER, Kim WR. A model to predict survival in patients with end-stage liver disease. Hepatology. 2001;33(2):464–70.
10. Wagener G, Minhaz M, Mattis FA, Kim M, Emond JC, Lee HT. Urinary neutrophil gelatinase-associated lipocalin as a marker of acute kidney injury after orthotopic liver transplantation. Nephrol Dial Transplant. 2011;26(5):1717–23.
11. George TJ, Arnaoutakis GJ, Beaty CA, et al. Acute kidney injury increases mortality after lung transplantation. Ann Thorac Surg. 2012;94(1):185–92.
12. Licker M, Cartier V, Robert J, et al. Risk factors of acute kidney injury according to RIFLE criteria after lung cancer surgery. Ann Thorac Surg. 2011;91(3):844–50.
13. Thakar CV, Kharat V, Blanck S, Leonard AC. Acute kidney injury after gastric bypass surgery. Clin J Am Soc Nephrol. 2007;2(3):426–30.
14. Weingarten TN, Gurrieri C, McCaffrey JM, et al. Acute kidney injury following bariatric surgery. Obes Surg. 2013;23(1):64–70.
15. Moghadamyeghaneh Z, Phelan MJ, Carmichael JC, Mills SD, Pigazzi A, Nguyen NT, et al. Preoperative dehydration increases risk of postoperative acute renal failure in colon and rectal surgery. J Gastrointest Surg. 2014;18:2178–85.
16. Kateros K, Doulgerakis C, Galanakos SP, Sakellariou VI, Papadakis SA, Macheras GA. Analysis of kidney dysfunction in orthopaedic patients. BMC Nephrol. 2012;13:101.
17. Pearse RM, Harrison DA, MacDonald N, Gillies MA, Blunt M, Ackland G, Grocott MP, Ahern A, Griggs K, Scott R, Hinds C, Rowan K, OPTIMISE Study Group. Effect of a perioperative, cardiac output-guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: a randomized clinical trial and systematic review. JAMA. 2014;311(21):2181–90.
18. Horres CR, Adam MA, Sun Z, Thacker JK, Moon RE, Miller TE, Grant SA. Enhanced recovery protocols for colorectal surgery and postoperative renal function: a retrospective review. Perioper Med (Lond). 2017;6:13.
19. Shaw AD, Bagshaw SM, Goldstein SL, Scherer LA, Duan M, Schermer CR, et al. Major complications, mortality, and resource utilization after open abdominal surgery: 0.9% saline compared to plasma-lyte. Ann Surg. 2012;255:821–9.
20. Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med. 2012;367:1901–11.
21. Kim M, Brady JE, Li G. Variations in the risk of acute kidney injury across intraabdominal surgery procedures. Anesth Analg. 2014;119:1121–32.
22. Bihorac A, Yavas S, Subbiah S, Hobson CE, Schold JD, Gabrielli A, et al. Long-term risk of mortality and acute kidney injury during hospitalization after major surgery. Ann Surg. 2009;249:851–8.

Chapter 6
Risk Factors for AKI Development in Acute Decompensated Heart Failure

Nobuhiko Joki, Yasushi Ohashi, Yuri Tanaka, Toshihide Hayashi, Ken Sakai, and Hiroki Hase

Abstract Despite the advances in management, acute decompensated heart failure (ADHF) continues to be associated with poor clinical outcomes. Renal dysfunction, especially acute kidney injury (AKI), is one of the strongest predictors of adverse outcomes in ADHF. The association between the heart and the kidney in patients with ADHF is complex, and a complete understanding of this bidirectional interaction has not been elucidated. There are two big issues in this field. First is that many different definitions for renal dysfunction have been used conventionally. This would create different interpretations of renal failure in ADHF. Another problem is that the timing of WRF/AKI onset during hospitalization varies. To reconsider the future direction of AKI, this review focused on the current perspectives on AKI in ADHF patients.

Keywords Cardiorenal syndrome · Worsening renal function · Renal venous congestion · HFrEF · HFpEF

6.1 Introduction

The prevalence of heart failure was 5.7 million people in 2012 in the United States [1] and had been predicted to increase by 1.3 million in 2030 from 1.0 million in 2005 in Japan [2]. Despite the advances in management, heart failure continues to

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be associated with poor clinical outcomes. In particular, acute decompensated heart failure (ADHF) had been reported to have 30-day readmission rates of over 20% and in-hospital mortality rates of 5–6%, both of which have not significantly improved over the past 20 years [3, 4]. Renal dysfunction, especially acute kidney injury (AKI), is one of the strongest predictors of adverse outcomes in ADHF. The association between the heart and the kidney in patients with ADHF is complex, and a complete understanding of this bidirectional interaction has not been elucidated [5].

AKI, which is defined as increase in serum creatinine and/or reduction in urine volume within 72 h [6], had been increasing in incidence worldwide. It is reported that one in five adults and one in three children experience AKI during a hospitalization [7]. The association of heart dysfunction and its management with the progression of renal impairment is well-known and is named as cardiorenal syndrome (CRS) [8]. As mentioned, in the United States, the number of hospitalizations for ADHF was confirmed to increase from 1998 to 2015 [9]. Therefore, understanding the pathophysiology and risk factors for CRS is important for the prevention of AKI.

6.2 Cardiorenal Syndrome

CRS had been defined as the simultaneous dysfunction of the heart and the kidney, regardless of which organ suffered the initial damage and their previous functional status [5]. CRS is divided into five subcategories, according to the direction of the effect and whether the initiating insult is acute or chronic (Fig. 6.1). This five-item classification is based on (1) whether the primary organ of dysfunction is the heart, the kidney, or a third independent process affecting both organs and (2) the acute or chronic nature of the disease. To reconsider the future direction of AKI, this review focused on the current perspectives on CRS type 1 (CRS-1).

6.3 Acute Kidney Injury in Acute Decompensated Heart Failure

6.3.1 Prevalence of Acute Kidney Injury in Acute Decompensated Heart Failure

In the clinical setting, renal failure is often seen in patients with systolic dysfunction. In a retrospective study that included patients with asymptomatic left ventricular systolic dysfunction, with ejection fraction of <35%, 25% of the participants had a creatinine clearance of less than 60 mL/min, despite the fact that patients with serum creatinine over 2.0 mg/dL were excluded from this trial [10]. Interestingly in that study, even moderate renal insufficiency was independently associated with an increased risk for all-cause mortality. These findings implied that adequate management of renal function would be essential to improve the prognosis of heart failure patients. Recent studies on hospitalized acute heart failure (AHF) patients

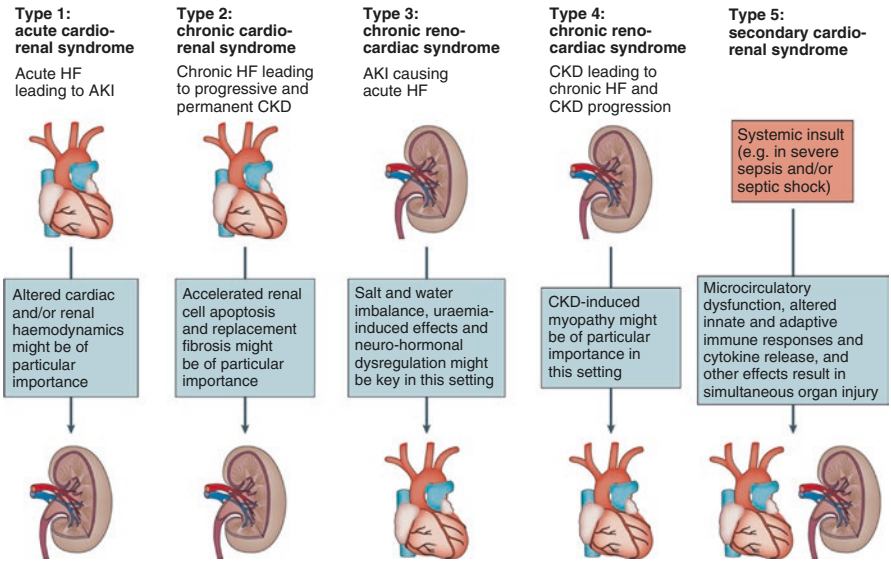

Fig. 6.1 Five types of cardiorenal syndromes. The five subtypes are defined according to the direction of the effect, such as from the heart to the kidney (types 1 and 2), from the kidney to the heart (types 3 and 4), or systemic (type 5), and whether the initiating insult is acute or chronic. The potential key pathophysiology that leads to organ failure differs among these subtypes. In type 5 cardiorenal syndrome, a severe systemic insult, such as severe sepsis or septic shock, can result in acute and simultaneous organ injury. *AKI* acute kidney injury, *CKD* chronic kidney disease, *HF* heart failure

demonstrated the development of renal insufficiency in 20–30% of patients, with associated increase in mortality and in-hospital length of stay [11, 12]. Therefore, understanding the pathophysiology and determining the optimum preventive strategy for AKI are essential to improve the prognosis of heart failure patients.

6.3.2 Definition of Renal Failure in the Past

Traditionally, AKI in AHF patients was defined as worsening renal function (WRF) during hospitalization, with a broad range of serum creatinine changes 0.3–0.5 mg/dL from baseline. To our knowledge, Krumholz et al. were the first to report that WRF during hospitalization of patients with congestive heart failure played an adverse influence on the clinical prognosis [13]. In that retrospective study on 1681 HF patients aged over 65 years, 28% developed WRF, which was conventionally defined as a >0.3 mg/dL increase in serum creatinine during hospitalization, compared with the level on admission. Moreover, the HF patients who developed WRF had poor prognosis, prolonged hospitalization period, and high hospitalization cost. Similar findings were confirmed by a subsequent retrospective study [14]. A recent prospective study reported that 33% of 299 ADHF patients developed WRF and subsequent poor prognosis [15].

6.3.3 Worsening Renal Function and Acute Kidney Injury

Evidence shows that one third of ADHF patients would develop renal failure during hospitalization, despite the advances in HF management. However, in the past, at least 35 different definitions for renal dysfunction have been used conventionally in this field [16, 17]. This created different interpretations of renal failure in ADHF. For instance, baseline and discharge renal insufficiency, but not WRF, were reported to be associated with an increased risks of death and rehospitalization [18]. Therefore, the clinical stance for renal failure in AHF began to shift from conventional WRF to standardized AKI, based on three major guidelines: (1) Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) criteria [19], (2) Acute Kidney Injury Network (AKIN) [20], and (3) Kidney Disease: Improving Global Outcomes (KDIGO) [6] guidelines (Table 6.1) [21]. Improved understanding of the epidemiology and the underlying pathophysiology of heart failure and kidney dysfunction will require the use of uniform terminology. Recently, an intriguing study that compared the clinical impact between two definitions of renal failure, WRF and

Table 6.1 The difference of definition for AKI and WRF

	Criteria	Minimum time to onset for AKI
WRF	Increase in sCr from baseline 0.3 mg/dL (26.5 mmol/L)	The sCr change can occur at any time during admission
RIFLE	Risk: increase in sCr 1.5 times baseline or decrease in eGFR 25% Injury: increase in sCr 2.0 times baseline or decrease in eGFR 50% Failure: increase in sCr 3.0 times baseline or decrease in eGFR 75% or an absolute sCr 4 mg/dL (354 mmol/L) with an acute rise of at least 0.5 mg/dL (44 mmol/L)	The sCr changes over 1–7 days, sustained for more than 24 h
AKIN	Stage 1: increase in sCr of 0.3 mg/dL (26.2 mmol/L) or increase to a value 150–199% (1.5–1.9-fold) Stage 2: increase in sCr to 200–299% (2–2.9-fold) from baseline Stage 3: increase in sCr to 300% (threefold) from baseline or sCr 4 mg/dL (354 mmol/L) with an acute rise 0.5 mg/dL (44 mmol/L) or initiation of RRT	Acute sCr changes occur within a 48-h period during hospitalization
KDIGO	Stage 1: 1.5 times baseline or 0.3 mg/dL increase Stage 2: 2 times baseline Stage 3: 3 times baseline or increase in sCr to 4.0 mg/dL	Definition of AKI requires sCr changes 1.5 times baseline to have occurred within 7 days, or a 0.3 mg/dL increase in sCr must occur within a 48-h time period

AKI acute kidney injury; *AKIN* Acute Kidney Injury Network; *eGFR* estimated glomerular filtration rate; *KDIGO* Kidney Disease: Improving Global Outcomes; *RIFLE* Risk, Injury, Failure, Loss of Kidney Function, and End-Stage Kidney Disease; *RRT* renal replacement therapy; *sCr* serum creatinine; *WRF* worsening renal function

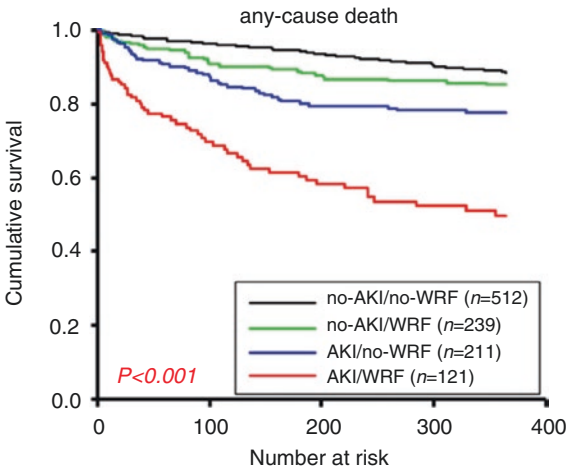

Fig. 6.2 The different prognosis between two different definition WRF and AKI. The all-cause death rate was significantly worse in the WRF/AKI group than in the no-WRF/AKI, WRF/no-AKI, and no-WRF/no-AKI groups and in the no-WRF/AKI group than in the WRF/no-AKI and no-WRF/no-AKI groups. *WRF* worsening renal function, *AKI* acute kidney injury

AKI, in ADHF patients was published [22]. In that study, WRF was defined as a change in serum Cr of 0.3 mg/mL during the first 5 days, and AKI upon admission was defined based on RIFLE criteria; among the 1083 HF patients, the prevalence was 33.2% for WRF and 30.7% for AKI. Only 11.2% of the HF patients met the definition of both WRF and AKI. Interestingly, the presence of AKI on admission was associated with a poor prognosis, despite the lack of a WRF, as shown in Fig. 6.2. Based on this, the prognostic ability of standardized AKI on admission may be superior to that of WRF.

6.4 Potential Mechanism of Acute Kidney Injury in Acute Decompensated Heart Failure

6.4.1 Low Cardiac Output and Low Renal Perfusion

Several compelling findings from experimental animal models implied that hemodynamic mechanisms seem to play a major role in CRS-1 in the setting of ADHF. Immediately after creation of an acute low cardiac output condition in a gout model, renal arterial flow, creatinine clearance, and renal oxygen consumption dramatically decreased to 49%, 48%, and 63%, respectively, of the baseline values, accompanied by a significant increase in renal vascular resistance [23]. A clinical

study reported that ejection fraction, which is a surrogate marker of left ventricular systolic function, was an independent predictor for developing AKI in hospitalized AHF patients [24]. On the other hand, another study found no association between the severity of ejection fraction and the onset of WRF in 1004 HF patients [14]. This discrepancy may be explained by the different hemodynamic profiles of the study participants. In the setting of ADHF, different hemodynamic profiles have been proposed, based on the clinical phenotype of individual patients, and were categorized into four by systemic hemodynamics, including adequacy of perfusion (cold or warm) and extent of congestion (dry or wet) [25]. Interestingly, the differences among these profiles had a great impact on the prognosis of heart failure patients; the AHF patients with wet and cold clinical profile had a worse outcomes, compared with those of other profiles [26]. The different occurrence rates of AKI among the four profiles of AHF patients could play a role in making a difference in prognoses.

6.4.2 Volume Overload and Renal Venous Congestion

An experimental study demonstrated that high central venous pressure (CVP) decreased renal blood flow and glomerular filtration rate (GFR) [27]. Subsequently, increments in renal venous pressure result in increased interstitial intrarenal pressure, which can cause collapse of tubules and direct opposition of filtration, resulting in decreased GFR [28]. Several studies have translated these experimental data into current clinical practice as the significant association of high venous pressures with WRF in heart failure patients [29, 30]. Moreover, these evidences implied that the presence of venous congestion, rather than reduced cardiac output, may be the primary hemodynamic factor that drives CRS-1 in ADHF patents. On the other hand, recent clinical studies reported that CVP was an independent predictor of WRF, especially when cardiac output was low [31]. This different view was probably due to the fact that CVP remains an unreliable surrogate of systemic congestion in the clinical setting. Further strategy is required to precisely detect systemic congestion, and further studies are definitely needed to characterize the role of congestion in CRS-1 pathophysiology. At the present time, a comprehensive evaluation of hydration status must be followed when patients are admitted for ADHF.

6.4.3 Sympathetic and Neurohormonal Activities

The pathogenesis of CRS-1 had been described to involve other mechanisms, including activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS) [32, 33]. Progression of left ventricular systolic dysfunction heightens sympathetic activity, which is a recognized precipitant factor in heart failure decompensation. Diminished renal blood flow and perfusion pressure

due to low cardiac output lead to baroreceptor-mediated renal vasoconstriction, activation of the renal sympathetic nerves, and release of catecholaminergic hormones. Some data implied that renal sympathetic activation somehow affected the renal vascular system. A recent pilot study found significant improvements in GFR in 24% of patients who underwent catheter-based renal sympathetic denervation for resistant hypertension [27]. Although this intervention has not been tested specifically on an ADHF population, sympathetic activity may affect renal function. Further investigation is needed to determine the clinical relevance of this mechanism.

In ADHF, decreases in cardiac output and effective circulating volume of the renal arterial tree result in RAAS activation, as a compensatory mechanism to maintain GFR in acute hypoperfusion states. However, persistent RAAS stimulation plays a key role in kidney damage through cell hypertrophy, fibrosis stimulation, oxidative stress, and activation of inflammatory mechanisms [34]. Angiotensin II is also known to be a potent systemic vasoconstrictor that promotes arteriolar constriction, decrease in renal blood flow, and stimulation of the sympathetic nervous system [21]. The sympathetic nervous system increases the systemic vascular tone and has direct untoward effects on the heart and kidney by promoting apoptosis and fibrosis [21]. Stimulation of the adrenergic receptors on the proximal tubular cells enhances sodium reabsorption, whereas stimulation of the adrenergic receptors on the juxtaglomerular apparatus further stimulates the RAAS. Aldosterone secretion leads to salt and water retention, thereby contributing to edema and congestion [35].

6.4.4 Inflammatory Response

There had been increasing evidence on the role of activation of the inflammatory response on the pathogenesis of different types of heart disease, including heart failure. In fact, elevations of cytokines and other markers of inflammation, such as C-reactive protein, tumor necrosis factor-alpha, and interleukin-6, had been documented in ADHF patients [36]. Inflammatory cytokines have been proposed to play a role in sodium retention, myocardial dysfunction, AKI, vascular dysfunction, and extracellular fluid overload [35]. In addition, inflammation seems to be largely associated with inadequate renal perfusion pressures, peritubular edema, pathologic reduction of glomerular filtration, and tubular damage [21].

6.4.5 Iatrogenic Factors

6.4.5.1 Loop Diuretics

Loop diuretic is the pharmacologic therapy of choice for fluid overload in ADHF patients. However, its use is largely empirical and is commonly associated with WRF [37]. The DOSE trial was a randomized controlled trial that evaluated the

diuretic strategies in 308 ADHF patients who were divided randomly to receive intravenous furosemide as a bolus or continuous infusion by either a low-dose or a high-dose strategy. No significant differences in the primary endpoints of global assessment of symptoms were observed among these strategies. However, we may need to pay attention to their findings on renal function. The changes in serum Cr over 72 h were higher in the continuous or high-dose group than in the bolus or low-dose group, but these did not reach statistical significance. These results suggested that the use of loop diuretics in ADHF patients should be as minimum as necessary. Several observational studies have shown the associations between high-dose loop diuretics and adverse outcomes in heart failure patients [38, 39]. The potential mechanisms for worse outcomes with loop diuretics include RAAS activation and WRF. Administration of loop diuretics to patients with severe chronic heart failure was reported to result in acute decrease in stroke volume index; increase in left ventricular filling pressure and systemic vascular resistance; and neurohormonal activation, such as elevated plasma renin activity, plasma norepinephrine levels, and plasma arginine vasopressin levels [40]. These hemodynamic effects were attributed to RAAS-mediated vasoconstriction. Therefore, loop diuretics represent a double-edged sword, as they may resolve congestion but worsen renal perfusion by arterial underfilling and heightened activation of the sympathetic and RAAS, leading to AKI [41].

Tolvaptan, which is a novel aquaretic, inhibits vasopressin V2 receptors on the renal collecting ducts, and its mechanism of action differs from that of existing diuretics. Addition of tolvaptan to standard therapy, including diuretics, was demonstrated to improve the signs and symptoms of congestion in ADHF, without serious adverse events. In a randomized controlled open-label trial from Japan, 50 patients with heart failure with preserved ejection fraction (HFpEF) were assigned to receive either tolvaptan plus loop diuretics or loop diuretics alone. The incidence of WRF was significantly lower in the tolvaptan group than in the loop diuretics-alone group [42]. These results suggested that tolvaptan can ameliorate congestion with a significantly lower risk for WRF, possibly through the maintenance of renal perfusion and avoidance of intravascular volume depletion [17, 43].

6.4.5.2 Ultrafiltration

Several studies showed the effects of ultrafiltration on the clinical outcomes of AHF patients. The UNLOAD was a prospective, randomized trial [44] that compared the effects between early ultrafiltration alone and intravenous diuretics alone on weight loss, symptoms, and short-term hospitalizations among 200 patients with AHF and volume overload and a mean serum Cr of 1.5 mg/dL. The change in serum Cr at 72 h was about 3 times higher in the ultrafiltration group than in the diuretics group, but this difference was not statistically significant. Recently, another study assessed the efficacy and safety of ultrafiltration in 188 patients with ADHF complicated by persistent congestion and WRF [45]. At 96 h following

enrollment, the effects on weight loss were similar between ultrafiltration and escalating diuretic pharmacologic therapy, but the increase in serum Cr level was significantly higher in the ultrafiltration group than in the group treated pharmacologically. Moreover, the ultrafiltration group had an increased incidence of serious adverse events. Similarly, a recent clinical study found that fluid removal by ultrafiltration, compared with diuretic treatment, was associated with a decrease in serum sodium levels in parallel with an increase in serum Cr level in AHF patients [46]. Based on these, the use of ultrafiltration in ADHF patients should be avoided as much as possible.

6.4.5.3 Renin-Angiotensin-Aldosterone System Inhibitor

The association between the use of RAAS blockade, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers and the onset of AKI can be found in several clinical situations, such as during cardiac surgery [47, 48]. The use of RAAS blockade had a high level of recommendation for the improvement of the prognosis of HF patients with reduced ejection fraction [49]. However, the role of RAAS blockade on the onset of CRS-1 is unclear. Reduction or temporary discontinuation of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers until renal function improves is a common practice when AHF patients develop hypotension and/or WRF during the initial therapy [21, 50]. The PIONEER-HF was a multicenter, randomized, double-blind, active controlled trial that assessed the efficacy and safety between angiotensin-neprilysin inhibition and enalapril therapy in hospitalized ADHF patients [51]. That study concluded that compared with enalapril therapy, angiotensin-neprilysin inhibition therapy led to a greater reduction in the N-terminal pro-brain natriuretic peptide (NT-proBNP) concentration but had similar rates of worsening renal function, hyperkalemia, and symptomatic hypotension.

6.5 Risk Factors

6.5.1 Unmodifiable Factors

The significant association of gender difference with the onset of WRF had been reported; the impact of WRF onset was 1.4 times greater in women than in men [13]. The risk for AKI increases with advancing age. During an 18-month follow-up period from admission, every 10-year increase in age had a 16% higher impact on WRF in ADHF patients [52]. However, this does not indicate the precise risk of aging for AKI. Another article showed that hospitalized AHF patients who experienced WRF, compared with those without WRF, were more likely to be older than 75 years. In a multivariate model, there was a 2.3 times higher risk for WRF in patients older than 75 years than in those less than 75 years [53].

6.5.2 Diabetes

Several studies showed that diabetic patients were susceptible to AKI during hospitalized care for AHF. On multivariate analysis, a history of pharmacologically treated diabetes mellitus was the factor strongly associated with WRF, with a hazard ratio 1.4 [14]. In 382 hospitalized patients with HF, the impact of WRF was 1.7 times greater in diabetic patients than in non-diabetic patients, independent of confounding variables [54].

6.5.3 Chronic Kidney Disease

Generally, one of the strongest factors for the of AKI is preexisting chronic kidney disease (CKD) [6]. In ADHF patients, preexisting renal failure and/or CKD was reported to have a strong association with WRF; the odds ratio for WRF was about 3.7 times higher in the presence of CKD on admission, compared with the absence of CKD [24]. Increased serum Cr level on admission for heart failure was reported to be a good predictor for WRF during a hospitalized period. Heart failure patients with a median value of Cr of over 1.42 mg/dL had 2.1 times higher risk for developing WRF, compared with the risk in patients with Cr of less than 1.42 mg/dL [15]. A study from Japan confirmed this association; a serum Cr >1.1 mg/dL had a great impact (odds ratio 2.96) on AKI in AHF patients [55]. Another study revealed compared with AKI, acute-on-chronic kidney disease was associated with higher risks of in-hospital mortality, diuretic resistance, prolonged hospital stay, and failure of renal recovery [56].

6.5.4 Albumin

Hypoalbuminemia on admission is a risk factor for AKI and mortality in patients with ADHF. Baseline serum albumin of 3 g/dL or less was the only significant predictor of WRF (hazard ratio 2.87); this remained significant even after adjusting for other covariates [57]. A meta-analysis of 17 clinical observational studies provided evidence that hypoalbuminemia was a significant independent predictor of AKI [58]. Moreover, interestingly, decreased serum albumin level during ADHF therapy after admission was found to be associated with AKI [55]. Some potential mechanisms were proposed to explain this. Serum albumin plays a major physiological role on plasma oncotic pressure to maintain renal perfusion and glomerular filtration. A decrease in serum albumin, which induces a fluid shift from the intravascular to the interstitial space, may decrease renal perfusion and contribute to diuretic resistance, leading to AKI [59, 60].

6.5.5 *Heart Failure with Preserved Ejection Fraction or Heart Failure with Reduced Ejection Fraction*

About 50% of HF patients are well-known to have normal or near-normal left ventricular ejection fraction (LVEF); this is known as HFpEF [61]. The prognosis of HFpEF is similar to that of HF with reduced ejection fraction (HFrEF) [62]. However, it remains unclear whether the incidence of WRF during hospitalization is different between HFREF and HFPEF patients. A study using Korean registry data reported that, compared with patients with HFpEF, those with HFrEF had significantly higher rates of WRF (56.9% vs. 50.3%) and persistent WRF (38.7% vs. 34.3%) [63]. Indeed, lower baseline EF is a good predictor of developing WRF in AHF patients [24].

6.6 Summary

AKI in patients with ADHF is a common complication with a complex and still unclear pathophysiology. There are two big issues in this field. First is that many different definitions for renal dysfunction have been used conventionally. This would create different interpretations of renal failure in ADHF. Another problem is that the timing of WRF/AKI onset during hospitalization varies. Therefore, the WRF and/or AKI in several previous articles likely included three mixed pathogenic forms of renal failure, including an apparent hemoconcentration rather than true GFR impairment, true GFR impairment on admission, and transient GFR impairment as a result of aggressive decongestive therapy [17]. Further studies are needed to obtain additional insights into the pathophysiology of AKI in patients with ADHF and to search for ways to improve the diagnostic and prognostic accuracies in a unified way. It is hoped that effective preventive and treatment methods are explored in the near future.

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References

1. Writing Group M, Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Despres JP, et al. Heart disease and stroke statistics-2016 update: a report from the American Heart Association. Circulation. 2016;133(4):e38–360.
2. Okura Y, Ramadan MM, Ohno Y, Mitsuma W, Tanaka K, Ito M, Suzuki K, Tanabe N, Kodama M, Aizawa Y. Impending epidemic: future projection of heart failure in Japan to the year 2055. Circ J. 2008;72(3):489–91.

3. Gheorghiade M, Vaduganathan M, Fonarow GC, Bonow RO. Rehospitalization for heart failure: problems and perspectives. J Am Coll Cardiol. 2013;61(4):391–403.
4. Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the medicare fee-for-service program. N Engl J Med. 2009;360(14):1418–28.
5. Ronco C, McCullough P, Anker SD, Anand I, Aspromonte N, Bagshaw SM, Bellomo R, Berl T, Bobek I, Cruz DN, et al. Cardio-renal syndromes: report from the consensus conference of the acute dialysis quality initiative. Eur Heart J. 2010;31(6):703–11.
6. Kidney Disease Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012;2:1–138.
7. Susantitaphong P, Cruz DN, Cerda J, Abulfaraj M, Alqahtani F, Koulouridis I, Jaber BL, Acute Kidney Injury Advisory Group of the American Society of N. World incidence of AKI: a meta-analysis. Clin J Am Soc Nephrol. 2013;8(9):1482–93.
8. McCullough PA, Kellum J, Mehta RL, Murray PT, Ronco C. ADQI consensus on AKI biomarkers and cardiorenal syndromes. Contrib Nephrol. 2013;182:99–116.
9. Agarwal SK, Wruck L, Quibrera M, Matsushita K, Loehr LR, Chang PP, Rosamond WD, Wright J, Heiss G, Coresh J. Temporal trends in hospitalization for acute decompensated heart failure in the United States, 1998–2011. Am J Epidemiol. 2016;183(5):462–70.
10. Dries DL, Exner DV, Domanski MJ, Greenberg B, Stevenson LW. The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. J Am Coll Cardiol. 2000;35(3):681–9.
11. Liang KV, Williams AW, Greene EL, Redfield MM. Acute decompensated heart failure and the cardiorenal syndrome. Crit Care Med. 2008;36(Suppl 1):S75–88.
12. Hata N, Yokoyama S, Shinada T, Kobayashi N, Shirakabe A, Tomita K, Kitamura M, Kurihara O, Takahashi Y. Acute kidney injury and outcomes in acute decompensated heart failure: evaluation of the RIFLE criteria in an acutely ill heart failure population. Eur J Heart Fail. 2010;12(1):32–7.
13. Krumholz HM, Chen YT, Vaccarino V, Wang Y, Radford MJ, Bradford WD, Horwitz RI. Correlates and impact on outcomes of worsening renal function in patients > or =65 years of age with heart failure. Am J Cardiol. 2000;85(9):1110–3.
14. Forman DE, Butler J, Wang Y, Abraham WT, O'Connor CM, Gottlieb SS, Loh E, Massie BM, Rich MW, Stevenson LW, et al. Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. J Am Coll Cardiol. 2004;43(1):61–7.
15. Cowie MR, Komajda M, Murray-Thomas T, Underwood J, Ticho B, Investigators P. Prevalence and impact of worsening renal function in patients hospitalized with decompensated heart failure: results of the prospective outcomes study in heart failure (POSH). Eur Heart J. 2006;27(10):1216–22.
16. Hoste EA, Cruz DN, Davenport A, Mehta RL, Piccinni P, Tetta C, Viscovo G, Ronco C. The epidemiology of cardiac surgery-associated acute kidney injury. Int J Artif Organs. 2018;31(2):158–65.
17. Bielecka-Dabrowa A, Godoy B, Schefold JC, Koziolek M, Banach M, von Haehling S. Decompensated heart failure and renal failure: what is the current evidence? Curr Heart Fail Rep. 2018;15(4):224–38.
18. Nohria A, Hasselblad V, Stebbins A, Pauly DF, Fonarow GC, Shah M, Yancy CW, Califf RM, Stevenson LW, Hill JA. Cardiorenal interactions: insights from the ESCAPE trial. J Am Coll Cardiol. 2008;51(13):1268–74.
19. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P, Acute Dialysis Quality Initiative W. Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the second international consensus conference of the acute dialysis quality initiative (ADQI) group. Crit Care. 2004;8(4):R204–12.
20. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A, Acute Kidney Injury N. Acute kidney injury network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11(2):R31.
21. Nunez J, Minana G, Santas E, Bertomeu-Gonzalez V. Cardiorenal syndrome in acute heart failure: revisiting paradigms. Rev Esp Cardiol (Engl Ed). 2015;68(5):426–35.

22. Shirakabe A, Hata N, Kobayashi N, Okazaki H, Matsushita M, Shibata Y, Nishigoori S, Uchiyama S, Asai K, Shimizu W. Worsening renal function definition is insufficient for evaluating acute renal failure in acute heart failure. ESC Heart Fail. 2018;5(3):322–31.
23. Hanada S, Takewa Y, Mizuno T, Tsukiya T, Taenaka Y, Tatsumi E. Effect of the technique for assisting renal blood circulation on ischemic kidney in acute cardiorenal syndrome. J Artif Organs. 2012;15(2):140–5.
24. Metra M, Nodari S, Parrinello G, Bordonali T, Bugatti S, Danesi R, Fontanella B, Lombardi C, Milani P, Verzura G, et al. Worsening renal function in patients hospitalised for acute heart failure: clinical implications and prognostic significance. Eur J Heart Fail. 2008;10(2):188–95.
25. Stevenson LW, Perloff JK. The limited reliability of physical signs for estimating hemodynamics in chronic heart failure. JAMA. 1989;261(6):884–8.
26. Nohria A, Tsang SW, Fang JC, Lewis EF, Jarcho JA, Mudge GH, Stevenson LW. Clinical assessment identifies hemodynamic profiles that predict outcomes in patients admitted with heart failure. J Am Coll Cardiol. 2003;41(10):1797–804.
27. Krum H, Schlaich M, Whitbourn R, Sobotka PA, Sadowski J, Bartus K, Kapelak B, Walton A, Sievert H, Thambar S, et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. Lancet. 2009;373(9671):1275–81.
28. Braam B, Cupples WA, Joles JA, Gaillard C. Systemic arterial and venous determinants of renal hemodynamics in congestive heart failure. Heart Fail Rev. 2012;17(2):161–75.
29. Mullens W, Abrahams Z, Skouri HN, Francis GS, Taylor DO, Starling RC, Paganini E, Tang WH. Elevated intra-abdominal pressure in acute decompensated heart failure: a potential contributor to worsening renal function? J Am Coll Cardiol. 2008;51(3):300–6.
30. Mullens W, Abrahams Z, Francis GS, Sokos G, Taylor DO, Starling RC, Young JB, Tang WH. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. J Am Coll Cardiol. 2009;53(7):589–96.
31. Uthoff H, Breidthardt T, Klima T, Aschwanden M, Arenja N, Socrates T, Heinisch C, Noveanu M, Frischknecht B, Baumann U, et al. Central venous pressure and impaired renal function in patients with acute heart failure. Eur J Heart Fail. 2011;13(4):432–9.
32. Bock JS, Gottlieb SS. Cardiorenal syndrome: new perspectives. Circulation. 2010;121(23):2592–600.
33. Haase M, Muller C, Damman K, Murray PT, Kellum JA, Ronco C, McCullough PA. Pathogenesis of cardiorenal syndrome type 1 in acute decompensated heart failure: workgroup statements from the eleventh consensus conference of the acute dialysis quality initiative (ADQI). Contrib Nephrol. 2013;182:99–116.
34. Metra M, Cotter G, Gheorghiade M, Dei Cas L, Voors AA. The role of the kidney in heart failure. Eur Heart J. 2012;33(17):2135–42.
35. Ronco C, Cicoira M, McCullough PA. Cardiorenal syndrome type 1: pathophysiological crosstalk leading to combined heart and kidney dysfunction in the setting of acutely decompensated heart failure. J Am Coll Cardiol. 2012;60(12):1031–42.
36. Milo O, Cotter G, Kaluski E, Brill A, Blatt A, Krakover R, Vered Z, Hershkoviz R. Comparison of inflammatory and neurohormonal activation in cardiogenic pulmonary edema secondary to ischemic versus nonischemic causes. Am J Cardiol. 2003;92(2):222–6.
37. Mentz RJ, Kjeldsen K, Rossi GP, Voors AA, Cleland JG, Anker SD, Gheorghiade M, Fiuzat M, Rossignol P, Zannad F, et al. Decongestion in acute heart failure. Eur J Heart Fail. 2014;16(5):471–82.
38. Domanski M, Norman J, Pitt B, Haigney M, Hanlon S, Peyster E. Diuretic use, progressive heart failure, and death in patients in the studies of left ventricular dysfunction (SOLVD). J Am Coll Cardiol. 2003;42(4):705–8.
39. Hasselblad V, Gattis Stough W, Shah MR, Lokhnygina Y, O'Connor CM, Califf RM, Adams KF Jr. Relation between dose of loop diuretics and outcomes in a heart failure population: results of the ESCAPE trial. Eur J Heart Fail. 2007;9(10):1064–9.
40. Francis GS, Siegel RM, Goldsmith SR, Olivari MT, Levine TB, Cohn JN. Acute vasoconstrictor response to intravenous furosemide in patients with chronic congestive heart failure. Activation of the neurohumoral axis. Ann Intern Med. 1985;103(1):1–6.

41. Chiong JR, Cheung RJ. Loop diuretic therapy in heart failure: the need for solid evidence on a fluid issue. Clin Cardiol. 2010;33(6):345–52.
42. Tamaki S, Sato Y, Yamada T, Morita T, Furukawa Y, Iwasaki Y, Kawasaki M, Kikuchi A, Kondo T, Ozaki T, et al. Tolvaptan reduces the risk of worsening renal function in patients with acute decompensated heart failure and preserved left ventricular ejection fraction-prospective randomized controlled study. Circ J. 2017;81(5):740–7.
43. Ellison DH, Felker GM. Diuretic treatment in heart failure. N Engl J Med. 2017;377(20):1964–75.
44. Costanzo MR, Guglin ME, Saltzberg MT, Jessup ML, Bart BA, Teerlink JR, Jaski BE, Fang JC, Feller ED, Haas GJ, et al. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. J Am Coll Cardiol. 2007;49(6):675–83.
45. Bart BA, Goldsmith SR, Lee KL, Givertz MM, O'Connor CM, Bull DA, Redfield MM, Deswal A, Rouleau JL, LeWinter MM, et al. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. N Engl J Med. 2012;367(24):2296–304.
46. Kitai T, Grodin JL, Kim YH, Tang WH. Impact of ultrafiltration on serum sodium homeostasis and its clinical implication in patients with acute heart failure, congestion, and worsening renal function. Circ Heart Fail. 2017;10(2):e003603.
47. Dreischulte T, Morales DR, Bell S, Guthrie B. Combined use of nonsteroidal anti-inflammatory drugs with diuretics and/or renin-angiotensin system inhibitors in the community increases the risk of acute kidney injury. Kidney Int. 2015;88(2):396–403.
48. Coca SG, Garg AX, Swaminathan M, Garwood S, Hong K, Thiessen-Philbrook H, Passik C, Koyner JL, Parikh CR, Consortium T-A. Preoperative angiotensin-converting enzyme inhibitors and angiotensin receptor blocker use and acute kidney injury in patients undergoing cardiac surgery. Nephrol Dial Transplant. 2013;28(11):2787–99.
49. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the heart failure association (HFA) of the ESC. Eur Heart J. 2016;37(27):2129–200.
50. Clark H, Krum H, Hopper I. Worsening renal function during renin-angiotensin-aldosterone system inhibitor initiation and long-term outcomes in patients with left ventricular systolic dysfunction. Eur J Heart Fail. 2014;16(1):41–8.
51. Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP, McCague K, Rocha R, Braunwald E, Investigators P-H. Angiotensin-neprilysin inhibition in acute decompensated heart failure. N Engl J Med. 2019;380(6):539–48.
52. Damman K, Jaarsma T, Voors AA, Navis G, Hillege HL, van Veldhuisen DJ, Investigators C. Both in- and out-hospital worsening of renal function predict outcome in patients with heart failure: results from the coordinating study evaluating outcome of advising and counseling in heart failure (COACH). Eur J Heart Fail. 2009;11(9):847–54.
53. Verdiani V, Lastrucci V, Nozzoli C. Worsening renal function in patients hospitalized with acute heart failure: risk factors and prognostic significances. Int J Nephrol. 2010;2011:785974.
54. Butler J, Forman DE, Abraham WT, Gottlieb SS, Loh E, Massie BM, O'Connor CM, Rich MW, Stevenson LW, Wang Y, et al. Relationship between heart failure treatment and development of worsening renal function among hospitalized patients. Am Heart J. 2004;147(2):331–8.
55. Takaya Y, Yoshihara F, Yokoyama H, Kanzaki H, Kitakaze M, Goto Y, Anzai T, Yasuda S, Ogawa H, Kawano Y, et al. Impact of decreased serum albumin levels on acute kidney injury in patients with acute decompensated heart failure: a potential association of atrial natriuretic peptide. Heart Vessel. 2017;32(8):932–43.
56. Zhou Q, Zhao C, Xie D, Xu D, Bin J, Chen P, Liang M, Zhang X, Hou F. Acute and acute-on-chronic kidney injury of patients with decompensated heart failure: impact on outcomes. BMC Nephrol. 2012;13:51.

57. Clarke MM, Dorsch MP, Kim S, Aaronson KD, Koelling TM, Bleske BE. Baseline albumin is associated with worsening renal function in patients with acute decompensated heart failure receiving continuous infusion loop diuretics. Pharmacotherapy. 2013;33(6):583–8.
58. Wiedermann CJ, Wiedermann W, Joannidis M. Hypoalbuminemia and acute kidney injury: a meta-analysis of observational clinical studies. Intensive Care Med. 2010;36(10):1657–65.
59. Zamlauski-Tucker M, Cohen JJ. Effect of substrate-free albumin on perfused rat kidney function. Ren Physiol. 1988;10(6):352–60.
60. Hsu CW, Lin SL, Sun SF, Chu KA, Chung HM, Chang HW. Comparison of the diuretic effect of furosemide mixed with human albumin or fresh frozen plasma for patients with hypoalbuminemia in the intensive care unit. J Nephrol. 2006;19(5):621–7.
61. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. J Am Coll Cardiol. 2013;62(16):e147–239.
62. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med. 2006;355(3):251–9.
63. Kang J, Park JJ, Cho YJ, Oh IY, Park HA, Lee SE, Kim MS, Cho HJ, Lee HY, Choi JO, et al. Predictors and prognostic value of worsening renal function during admission in HFpEF versus HFrEF: data from the KorAHF (Korean acute heart failure) registry. J Am Heart Assoc. 2018;7(6):e007910.

Chapter 7
Contrast-Induced Acute Kidney Injury

Yoshihide Fujigaki

Abstract Contrast-induced acute kidney injury (CI-AKI) is a form of kidney damage by recent exposure of iodinated contrast media (CM) without another clear cause for AKI. Now serum creatinine-based definition is generally used; however, there are some problems on the definition and differentiation of CI-AKI. CM is known to induce a variety of alterations in the kidney. The new mechanism of direct tubular injury, specifically the role of inflammatory pathway, has recently been characterized to explain CI-AKI in clinical setting. This might lead to new therapeutic strategy. Both patient-related and procedure-related risk factors for CI-AKI have been identified, and volume depletion and chronic kidney disease (CKD) are known to be high risks for CI-AKI.

It is increasingly recognized that old data from cardiac angiography studies may overestimate the risk of CI-AKI for patients undergoing intravenous contrast-enhanced studies. Recent well-designed studies addressed the incidence of CI-AKI after intravenous administration of CM for computed tomography was quite low. At present the only available preventive action to reduce the risk for CI-AKI is to provide intravenous volume expansion before, during, and after CM administration. Reevaluation of definition, the risk factors, the true impact, and preventative measures for CI-AKI are required in order to better understand CI-AKI.

Keywords Chronic kidney disease · Contrast-induced acute kidney injury Contrast media · Dehydration · Hydration · Inflammation · Intravenous administration

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7.1 Introduction

There is significant evidence for renal injury resulting from contrast media (CM) administration in both animal models and humans. Contrast-induced acute kidney injury (CI-AKI) or contrast-associated nephropathy, also commonly referred to as contrast-induced nephropathy, is caused by recent CM administration for diagnostic or therapeutic imaging.

Most people with normal kidney function who receive CM usually do not experience any renal complications. However, patients with volume depletion or chronic kidney disease (CKD) are recognized to be at increased risk for CI-AKI [1–3]. CI-AKI occurs within 24–72 h following CM administration and could be associated with poor outcomes including AKI requiring dialysis, worsening of CKD, cardiovascular events, and increased medical expenses [2]. Numerous clinical and epidemiological studies have characterized the risk factors and incidence rates for CI-AKI. Pre-existing renal dysfunction (estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2) and diabetes mellitus are the most important risk factors for further deterioration in renal function induced by CM [2, 4]. However, the type of CM administration procedure seems to be an important determinant of CI-AKI. Recent well-designed studies have shown that CI-AKI is much less common than previously believed even in patients with CKD undergoing intravenous (IV) contrast-enhanced computed tomography (CT) [5, 6].

CM is known to induce various alterations in the kidney. Among them, the mechanism of direct tubular injury due to inflammatory pathway has recently been attracted attention for. IV hydration, optimization of hemodynamic status, and minimization of CM volume have been considered for preventive strategies of CI-AKI at present. Any drugs with vasodilative or anti-oxidative effects have not been established to reduce the risk for CI-AKI. The incomplete understanding of CI-AKI has hampered the development of new strategies to prevent or mitigate CI-AKI.

In this review, we aimed to mainly discuss the current understanding and controversy of CI-AKI.

7.2 Manifestations of CI-AKI

In general, CI-AKI is considered to occur when a patient receives CM either intravenously or intra-arterially for diagnostic or therapeutic imaging and subsequently demonstrates a rise in the serum creatinine concentration. In most CI-AKI, accumulation of serum creatinine typically requires 48–72 h. Serum creatinine peaks at 4–5 days and returns to baseline in 7–14 days. A low urine sodium concentration (urine Na < 10 mEq/L) or a low fractional excretion of sodium (<1%) may be found owing to the vasoconstrictive properties of

CM. Acute tubular necrosis occurs as a form of AKI; thus tubular epithelial cells and granular "muddy brown" casts can be seen on urinary microscopy. However, CI-AKI shows broad clinical manifestations, ranging from a mild to moderate increase in serum creatinine to oliguric or non-oliguric AKI requiring temporary or permanent dialysis in small cases.

7.3 Definition of CI-AKI

There is no specific definition of CI-AKI that is generally agreed worldwide. However, it is widely used that CI-AKI is defined by "a condition in which an impairment in renal function (an increase in serum creatinine by more than 25% or 0.5 mg/dL (44 mmol/L)) from baseline occurs within 48–72 h following the intravascular administration of CM in the absence of an alternative etiology" [7]. On the other hand, CI-AKI is evaluated with the Kidney Disease: Improving Global Outcomes (KDIGO) AKI criteria as any of the following: increase in serum creatinine by ≥0.3 mg/dL (≥26.5 μmol/L) within 48 h or increase in serum creatinine to ≥1.5 times baseline that is known or presumed to have occurred within the prior 7 days or urine volume <0.5 mL/kg/h for 6 h [8].

7.4 Differential Diagnosis

An alternative diagnosis of AKI should be suspected when renal injury develops more than 7–10 days following CM administration. In such instances, careful evaluation for alternative causes of AKI, including cholesterol crystal embolization, should be considered especially in patients after cardiac catheterization. However, of note, the American College of Radiology (ACR) Manual on Contrast Media from May 2017 makes a differentiation between CI-AKI and post-contrast acute kidney injury (PC-AKI) [9]. The reason for this differentiation is that we do not recognize at present whether the AKI is actually due to CM administration or if there are concomitant disease processes creating this effect. PC-AKI may occur regardless of whether the CM is the cause of the deterioration of renal function; therefore, CI-AKI is a subgroup of PC-AKI.

In order to evaluate the data across the literature on CI-AKI, it is necessary to establish standardized definition of CI-AKI. Like AKI in general, urinary liver fatty acid binding protein (L-FABP) and serum cystatin C were also reported as an early biomarker for CI-AKI [10, 11]. Recent report indicated serum neutrophil gelatinase-associated lipocalin (NGAL) and serum fibroblast growth factor (FGF)23 might have certain values in early diagnosis of CI-AKI [12]. Onset can be predictable, and the mechanism should be similar among CI-AKI; mechanistic biomarkers that can be applied for CI-AKI diagnosis and prognosis are expected.

7.5 Incidence

CI-AKI is an important complication that accounts for a significant number of patients of hospital-acquired renal failure. Although all of AKI after CM administration are not caused directly by CM, there are several reports on incidence of CI-AKI in various clinical settings. Incidence of CI-AKI is <1% in patients undergoing non-emergent contrast-enhanced CT [13] and is 4% in CKD patients undergoing non-emergent contrast-enhanced CT [14], whereas incidence of CI-AKI is >10% in patients after IV CM administration in an emergency setting [15]. As for intra-arterial CM administration, incidence of CI-AKI is <3% in patients undergoing percutaneous transluminal catheter angioplasty (PTCA) with normal baseline renal function [16]. On the other hand, the incidence of CI-AKI was reported to be around 40% in CKD patients undergoing PTCA, and the reduction of eGFR among these patients was associated with the increase in incidence of CI-AKI [17, 18].

7.6 Prognosis

Some studies have demonstrated that both short-term and long-term mortality rates have been found to be significantly higher in patients with CI-AKI compared with patients without CI-AKI [7]. Furthermore, a prognosis of CI-AKI may be associated with development of CKD and progression to end-stage renal disease in long term [19, 20] like other causes of AKI. However, very recent study reported that the administration of both IV and intra-arterial CM was associated with a risk of AKI and multifactorial AKI was associated with worse outcomes, while CI-AKI was associated with better outcomes [21]. The true impact of CI-AKI seems not to be clear.

7.7 Mechanisms

Many complex pathways possibly involved in the development of CI-AKI have been proposed [4, 22]. Under normal conditions, the renal medulla is poorly oxygenated and works in a less oxygenated condition. After CM administration, renal blood flow decreases due to renal vasoconstriction over a prolonged period, leading to ischemic injury to the renal medulla. Vasoactive substances such as prostaglandins, nitric oxide, endothelin, and adenosine may play a major role in this process. Direct cytotoxicity of CM due to free radical formation and osmotic effects of CM on renal tubular cells also play a role. Among these factors, sterile inflammatory damages attracted attention [23]. Very recently Lau et al., using a mouse CI-AKI model with volume depletion, reported that immune activation occurs in distinct compartments

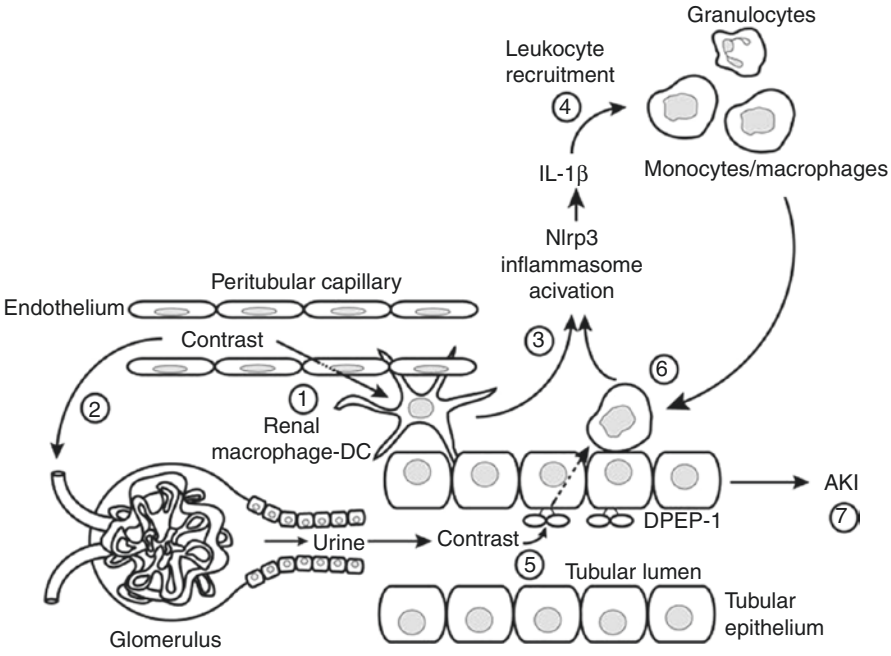

Fig. 7.1 Schematic of CI-AKI. (1) Intravenous or intra-arterial contrast agents enter the renal circulation and peritubular capillaries and are taken up by resident renal phagocytes. (2) Contrast is filtered at the glomerulus and enters the urine and renal tubule. In the hydrated state, contrast is rapidly excreted. (3) Contrast uptake by the resident renal phagocytes activates the Nlrp3 inflammasome to generate IL-1β. (4) IL-1β mediates leukocyte recruitment from the circulation into the kidney. (5) Contrast in the urine is taken up by the tubular cell by the brush border enzyme DPEP-1. The tubular uptake of contrast is enhanced in the volume-depleted state. (6) Recruited leukocytes ingest contrast transported from the urine through a direct interaction with tubular cells that further activates the inflammasome. (7) The activation of resident renal phagocytes, tubular uptake of contrast, and leukocyte recruitment are all necessary, but none alone is sufficient to induce AKI. (From Lau A et al. J Clin Invest. Renal immune surveillance and dipeptidase-1 contribute to contrast-induced acute kidney injury. J Clin Invest. 2018;128:2894–913)

and depends on uptake of CM both by resident and infiltrating phagocytes and by tubular epithelial cells, leading to a massive influx of leukocytes and an excessive inflammatory response that ultimately induces AKI (Fig. 7.1) [24]. They also reported levels of the inflammasome-related urinary biomarkers IL-18 and caspase-1 were increased immediately following CM administration in patients undergoing coronary angiography (CAG), consistent with the acute renal effects observed in mice [24]. The discovery of this pathway might provide opportunities to develop specific and effective therapies for CI-AKI. Moreover, Atkinson SJ commented that the report by Lau et al. has an important implication of the clear mechanistic explanation for the contribution of volume depletion to the activation of a sterile inflammatory state and the likelihood of CI-AKI in patients receiving CM [25].

7.8 Risk Factors

Patients at risk for CI-AKI should be identified before administration of CM. Previously reported factors influencing the incidence of CI-AKI are listed in Table 7.1.

7.8.1 Patient-Related Risk Factors

In addition to states of reduced renal perfusion, pre-existing CKD (eGFR < 60) and diabetes mellitus are the most important patient-related risk factors for further deterioration in renal function induced by CM [26, 27]. Both of them may have additive effect on CI-AKI [28]; however, it is not clear whether the risk of CI-AKI is significantly increased in patients with diabetes mellitus without renal dysfunction. Older age is also a risk for CI-AKI because it is postulated to predispose patients to renal sodium and water wasting due to reduction in renal mass and function.

Comedication with loop diuretics had no difference of a risk for CI-AKI when compared with discontinuation of loop diuretics [29]. In contrast prophylactic use of loop diuretics increased the incidence of CI-AKI despite adjusting dehydration [30]. The meta-analysis showed the risk of comedication with non-steroidal

Table 7.1 Risk factors for CI-AKI

Patient-related risk factors
Older age
Pre-existing renal dysfunction or CKD
Diabetes mellitus and diabetic nephropathy
Hypertension requiring medical therapy
Metabolic syndrome
Hypercalcemia
Hyperuricemia
Multiple myeloma
States of reduced renal perfusion
Dehydration
Congestive heart failure
Liver cirrhosis
Nephrotic syndrome
Hemodynamic instability
Comedication
Diuretics for prophylactic use
Non-steroidal anti-inflammatory drugs
CM- or procedure-related risk factors
High-osmolar CM
High volume of CM
Intra-arterial CM administration
Multiple exposure to CM in short term

anti-inflammatory drugs (NSAIDs) for CI-AKI [27] probably due to reduction of intra-renal blood flow. Thus, discontinuation of NSAIDs 24 h before CM administration should be done [31]. Lately, renin-angiotensin system (RAS) inhibitors have been used often for CKD patients. At present, there is no evidence that RAS inhibitors increase the incidence of CI-AKI. Although metformin is not a nephrotoxic agent, it causes life-threatening lactic acidosis in a patient who develops CI-AKI. Most guidelines recommended transient discontinuation of metformin especially in CKD patients who are planned to have CM administration.

7.8.2 CM- or Procedure-Related Risk Factors

It is well known that high-osmolar CM (HOCM) more frequently causes CI-AKI compared with low-osmolar CM (LOCM) (780–800 mOsm/kg) [32]. Nowadays only iso-osmolar CM (IOCM) and LOCM are used in clinical practice instead of HOCM. In most of studies, there is no difference on the incidence of CI-AKI between IOCM and LOCM. The KDIGO guidelines for AKI stated no recommendation was made about the preference of IOCM or LOCM due to lack of reliable evidence [8].

Lower doses of CM were found to be less nephrotoxic in patients undergoing CAG [33, 34]. Cigarroa advocated maximum allowable CM dose was defined as <5 mL/kg per serum creatinine [33]. A CM dose on the basis of estimated renal function with a planned CM volume restricted to less than preferably twice the calculated creatinine clearance might be valuable in reducing the risk for CI-AKI requiring dialysis in patients undergoing percutaneous coronary intervention (PCI) [35]. However, it is not clear whether low dose of CM is significantly less nephrotoxic in patients undergoing contrast-enhanced CT. It is reported that use of >100 mL of CM was associated with increased risk of CI-AKI among outpatients with mild baseline kidney disease [13]. Though there is not enough evidence, use of lower dose of CM is recommended in patients undergoing contrast-enhanced CT, especially patients with CKD. There are conflicting reports as to whether repeated contrast-enhanced CT scan within 24–72-h interval increases the risk for CI-AKI.

Recently, newer CT modalities have been developed using low tube voltage and low CM dose to reduce radiation exposure and the risk for CI-AKI without sacrificing image quality [36, 37]. However it should be kept in mind that even very low doses of CM may lead to CI-AKI in patients with high-risk factors. The volume of CM should be minimized as much as possible at any time.

7.9 Route of CM Administration

It is increasingly recognized that CI-AKI has been overestimated in clinical practice. LOCM is proved to be less risk for CI-AKI than HOCM [32]. Older studies on CIN frequently include the patients using HOCM, which has since been replaced by

LOCM. In addition, the risk for CI-AKI has been known to be different between routes of CM administration. However, comparing the risks for CI-AKI after IV CM administration and after cardiac catheterization (intra-arterial CM) is difficult because there are so many different conditions, including underlying illness, pre-/comedications, dose of CM, site and number of CM injection, and prophylactic measures. Specifically, CAG differs from IV CM administration as follows: (1) the injection is intra-arterial and supra-renal, (2) CM dose is usually more concentrated, and (3) use of a catheter can induce atheroembolization. Thus, similar patient cohorts for studies on CI-AKI cannot be enrolled adequately. Furthermore, it had been recognized that a high incidence of transient serum creatinine fluctuations exists in hospitalized patients who had not received CM [38] and that the fluctuations are larger in patients with kidney failure than in those with normal kidney function [39]. Although there is no conclusive evidence, some studies have provided circumstantial evidence that the risk for CI-AKI may be higher after intra-arterial than after IV injection [40, 41].

7.9.1 Intra-arterial CM Administration

With a retrospective analysis of the Mayo Clinic PCI Registry, of 7586 patients, 254 (3.3%) experienced AKI. Diabetic patients were at higher risk than non-diabetic patients, whereas all patients with a serum creatinine >2.0 mg/dL are at high risk for AKI. AKI was highly correlated with death [16]. The incidence of CI-AKI after cardiac catheterization was 4.0% in 1157 patients in Japan [42]. Multivariate logistic models revealed that pre-existing renal insufficiency, serum creatinine 1.2 mg/dL or higher, and the use of high-volume (more than 200 mL) CM were independently associated with CI-AKI [42]. A multicenter prospective observational study that enrolled 906 patients with cardiac catheterization showed the incidence of CI-AKI in patients with eGFR <30 mL/min/1.73 m^2 was significantly higher than that in patients with eGFR ≥60 mL/min/1.73 m^2. CI-AKI was found in patient with normal renal function, but incidence of CI-AKI was increased with the reduction of eGFR. Proteinuria and reduced eGFR were independent risk factors for CI-AKI after cardiac catheterization [43]. These data and others indicated intra-arterial, suprarenal CM administration is a risk for CI-AKI especially among patients with CKD.

7.9.2 Intravenous CM Administration

Imaging examinations requiring the use of IV CM administration are sometimes avoided for fear of CI-AKI in clinical practice. Previous studies had problems on the risk determination for CI-AKI affected by lacking controls to cases and many confounders among people undergoing IV contrast-enhanced CT scan. Recent well-designed studies overcame those problems.

McDonald et al. reported the results of a large retrospective analysis with propensity score matching controls to cases to compare risk for CI-AKI after IV contrast-enhanced CT and non-contrast-enhanced CT scanning, and no increased risk for CI-AKI could be found from the contrast-enhanced CT scan, even among high-risk groups [44]. In other studies using propensity score matching, most cases of AKI after contrast-enhanced CT were found not to be attributable to CM. The risk for AKI was independent of CM exposure, even in patients with eGFR of less than 30 mL/min/1.73 m^2 [5], whereas IV LOCM does not appear to be a nephrotoxic risk factor in patients with a pre-CT eGFR of 45 mL/min/1.73 m^2 or greater but a risk factor for CI-AKI in patients with a stable eGFR less than 30 mL/min/1.73 m^2 [45].

To create multiple estimates of the risk for CI-AKI, 5.9 million Nationwide Inpatient Sample in the United States in 2009 was stratified according to the presence or absence of 12 common conditions associated with AKI, and the rate of AKI between strata was evaluated. Then, a logistic regression model was created, controlling for comorbidity and acuity of illness, to estimate the risk of AKI associated with CM administration within each stratum [46]. The authors found that the risk for AKI in patients receiving than not receiving CM was nearly identical, 5.5% vs. 5.6%, respectively [46]. IV CM administration was not associated with an excess risk for dialysis or death, even among patients with CKD [6]. Very recent meta-analysis reported that contrast-enhanced CT scan vs. non-contrast CT did not show significant differences in rates of AKI, need for renal replacement therapy, or mortality [47].

These and other recent well-conducted studies have shown that the risk for CI-AKI, especially after IV CM administration, is much lower than has been commonly thought and might barely exist at all; on the other hand, CI-AKI is unpredictable and largely depending on confounders with sometimes bidirectional roles.

7.10 Prevention and Treatment

In order to prevent CI-AKI, concomitant use of other known nephrotoxic drugs should be withdrawn, or they should not be used if clinically possible. Based on the possible mechanisms of CI-AKI, drugs, which have vasodilative or anti-oxidative effects, they have been considered for preventive strategies of CI-AKI. However, most of them including *N*-acetylcysteine, human atrial natriuretic peptide, theophylline, endothelin-1, fenoldopam, ascorbic acid, and stain were not reported to significantly decrease the risk for CI-AKI.

IV hydration is recognized as the only effective preventive strategy for CI-AKI at present. Saline before, during, and after exposure to CM can increase tubular fluid volume depending on infusion rate and reduce the concentration of CM in the tubular fluid, which might lead to reduced formation of reactive oxygen species. IV saline hydration was reported to decrease both the incidence and severity of CI-AKI in patients undergoing cardiac catheterization from 12 h before the procedure for 24 h (at a rate of 1 mL/kg per hour) when compared with unrestricted oral fluid intake [48]. There is little evidence about oral fluid loading being inferior to IV saline loading especially in patients with mild to moderate renal dysfunction.

Isotonic hydration (0.9% saline) was found to be superior to half-isotonic hydration (0.45% sodium chloride plus 5% glucose) for the prevention of CI-AKI in patients undergoing CAG [49]. However, a recent prospective, randomized controlled study in patients with CKD stage G3 showed that no prophylaxis group was found to be non-inferior to prophylaxis group (0.9% saline) [50].

Sodium bicarbonate infusion can produce the same effects of systemic volume expansion as saline, with the additional benefit of an increase in the bicarbonate anion buffer within the renal tubules. This might lead to alkalization of tubular fluid, which may protect the tubular cells against free radical injury. However, the effectiveness of IV sodium bicarbonate to prevent CI-AKI is controversial. Most of recent meta-analysis indicated a preventive effect of the use of sodium bicarbonate on the risk for CI-AKI when compared with saline was borderline statistical significance [51, 52]. It is noteworthy that the use of sodium bicarbonate had no beneficial effect on requiring renal replacement therapy or mortality. Among the large randomized trials, there was no evidence of benefit for hydration with sodium bicarbonate compared with sodium chloride for the prevention of CI-AKI [53].

At present in clinical practice, hydration is recommended to prevent CI-AKI especially for patients with high risk for CI-AKI. Further examinations are necessary as to which patients with risk factors for CI-AKI get benefit by hydration before and after CM administration because achievement of enough hydration is not easy for outpatients.

There was an exacerbation of renal dysfunction when furosemide was used in addition to IV saline solution. However, there is the RenalGuard System (PLC Medical Systems, Milford, Massachusetts) for very high-risk patients to prevent CI-AKI, which delivers IV fluids matched to urine output with a combination of hydration with normal saline at an initial dose bolus plus a low dose of furosemide and continuous monitoring for a urine output flow of >300 mL/h sustained for 6 h. The meta-analysis reported that furosemide with matched hydration by the RenalGuard System may reduce the incidence of CI-AKI in high-risk patients undergoing PCI or transcatheter aortic valve replacement [54].

Although there is no established therapy using single drug to prevent CI-AKI, combination of drugs and hydration may be effective on CI-AKI prevention. Interestingly, randomized, controlled trials of *N*-acetylcysteine, statins, ascorbic acid, sodium bicarbonate, or saline that used IV or intra-arterial CM and defined CI-AKI indicated that the greatest reduction in risk for CI-AKI has been achieved with low-dose *N*-acetylcysteine plus IV saline or with statins plus *N*-acetylcysteine plus IV saline in patients receiving LOCM [55]. Moreover, a comprehensive analysis of currently utilized CI-AKI prevention interventions by the systematic review and network meta-analysis suggested that some options (particularly allopurinol, prostaglandin E1, and oxygen) deserve further evaluation in larger well-designed retrospective control trials [56].

In the meta-analysis including prophylactic hemodialysis and hemofiltration, these therapies were not found to be protective against CI-AKI [57]. Of note, at least hemodialysis was found to increase the risk for CI-AKI. Thus prophylactic renal replacement therapy should not be done.

7.11 Perspective

CI-AKI is one of the preventable forms of AKI because the timing of renal insult is known in patients with CI-AKI. In order to specify the modifiable risk factors, we still need to revise several factors, which influence on evaluating the CI-AKI incidence, including definition of CI-AKI, underlying risks associated with various conditions, and type of CM administration. Further study is needed to clarify the true impact of CI-AKI, especially after IV CM administration, in light of a growing CKD population and radiological imaging using CM being increased. On the other hand, basic experiments have been revealing the new mechanisms of CI-AKI; thus specific preventive measures and treatments are expected to develop in the future.

References

1. Thomsen HS, Morcos SK. Risk of contrast-medium-induced nephropathy in high-risk patients undergoing MDCT—a pooled analysis of two randomized trials. Eur Radiol. 2009;19:891–7.
2. James MT, Samuel SM, Manning MA, Tonelli M, Ghali WA, Faris P, Knudtson ML, Pannu N, Hemmelgarn BR. Contrast-induced acute kidney injury and risk of adverse clinical outcomes after coronary angiography: a systematic review and meta-analysis. Circ Cardiovasc Interv. 2013;6:37–43.
3. McDonald JS, Leake CB, McDonald RJ, Gulati R, Katzberg RW, Williamson EE, Kallmes DF. Acute kidney injury after intravenous versus intra-arterial contrast material administration in a paired cohort. Investig Radiol. 2016;51:804–9.
4. Azzalini L, Spagnoli V, Ly HQ. Contrast-induced nephropathy: from pathophysiology to preventive strategies. Can J Cardiol. 2016;32:247–55.
5. McDonald JS, McDonald RJ, Carter RE, Katzberg RW, Kallmes DF, Williamson EE. Risk of intravenous contrast material-mediated acute kidney injury: a propensity score-matched study stratified by baseline-estimated glomerular filtration rate. Radiology. 2014;271:65–73.
6. McDonald RJ, McDonald JS, Carter RE, Hartman RP, Katzberg RW, Kallmes DF, Williamson EE. Intravenous contrast material exposure is not an independent risk factor for dialysis or mortality. Radiology. 2014;273:714–25.
7. Morcos SK, Thomsen HS, Webb JA. Contrast-media-induced nephrotoxicity: a consensus report. Contrast media safety committee, European Society of Urogenital Radiology (ESUR). Eur Radiol. 1999;9:1602–13.
8. Kellum JA, Lameire N, Aspelin P, Barsoum RS, Burdmann EA, Goldstein SL, Herzog CA, Joannidis M, Kribben A, Levey AS. Kidney disease: improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012;2:1–138.
9. Ellis JH, Davenport MS, Dillman JR, Hartman RP, Herts BR, Jafri SZ, Kolbe AB, Laroia A, Cohan RH, MacDonald RJ, Needleman L, Newhouse JH, Pahade JK, Sirlin CB, Wang CL, Wasserman N, Weinreb JC. ACR manual on contrast media. American College of Radiology. Version 10.3; 2017. p. 35–46. ISBN 978-1-55903-012-0.
10. Nakamura T, Sugaya T, Node K, Ueda Y, Koide H. Urinary excretion of liver-type fatty acid-binding protein in contrast medium-induced nephropathy. Am J Kidney Dis. 2006;47:439–44.
11. Briguori C, Visconti G, Rivera NV, Focaccio A, Golia B, Giannone R, Castaldo D, De Micco F, Ricciardelli B, Colombo A. Cystatin C and contrast-induced acute kidney injury. Circulation. 2010;121:2117–22.

12. Li H, Yu Z, Gan L, Peng L, Zhou Q. Serum NGAL and FGF23 may have certain value in early diagnosis of CIN. Ren Fail. 2018;40:547–53.
13. Weisbord SD, Mor MK, Resnick AL, Hartwig KC, Palevsky PM, Fine MJ. Incidence and outcomes of contrast-induced AKI following computed tomography. Clin J Am Soc Nephrol. 2008;3:1274–81.
14. Barrett BJ, Katzberg RW, Thomsen HS, Chen N, Sahani D, Soulez G, Heiken JP, Lepanto L, Ni ZH, Ni ZH, Nelson R. Contrast-induced nephropathy in patients with chronic kidney disease undergoing computed tomography: a double-blind comparison of iodixanol and iopamidol. Invest Radiol. 2006;41:815–21. Erratum in: Invest Radiol. 2007;42:94.
15. Mitchell AM, Jones AE, Tumlin JA, Kline JA. Incidence of contrast-induced nephropathy after contrast-enhanced computed tomography in the outpatient setting. Clin J Am Soc Nephrol. 2010;5:4–9.
16. Rihal CS, Textor SC, Grill DE, Berger PB, Ting HH, Best PJ, Singh M, Bell MR, Barsness GW, Mathew V, Garratt KN, Holmes DR Jr. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. Circulation. 2002;105:2259–64.
17. Chong E, Shen L, Poh KK, Tan HC. Risk scoring system for prediction of contrast-induced nephropathy in patients with pre-existing renal impairment undergoing percutaneous coronary intervention. Singap Med J. 2012;53:164–9.
18. Marenzi G, Lauri G, Assanelli E, Campodonico J, De Metrio M, Marana I, Grazi M, Veglia F, Bartorelli AL. Contrast-induced nephropathy in patients undergoing primary angioplasty for acute myocardial infarction. J Am Coll Cardiol. 2004;44:1780–5.
19. Maioli M, Toso A, Leoncini M, Gallopin M, Musilli N, Bellandi F. Persistent renal damage after contrast-induced acute kidney injury: incidence, evolution, risk factors, and prognosis. Circulation. 2012;125:3099–107.
20. Nemoto N, Iwasaki M, Nakanishi M, Araki T, Utsunomiya M, Hori M, Ikeda N, Makino K, Itaya H, Iijima R, Hara H, Takagi T, Joki N, Sugi K, Nakamura M. Impact of continuous deterioration of kidney function 6 to 8 months after percutaneous coronary intervention for acute coronary syndrome. Am J Cardiol. 2014;113:1647–51.
21. Chaudhury P, Armanyous S, Harb SC, Ferreira Provenzano L, Ashour T, Jolly SE, Arrigain S, Konig V, Schold JD, Navaneethan SD, Nally JV Jr, Nakhoul GN. Intra-arterial versus intravenous contrast and renal injury in chronic kidney disease: a propensity-matched analysis. Nephron. 2019;141:31–40.
22. Rudnick MR, Kesselheim A, Goldfarb S. Contrast-induced nephropathy: how it develops, how to prevent it. Cleve Clin J Med. 2006;73:75–80, 83–7.
23. Tan X, Zheng X, Huang Z, Lin J, Xie C, Lin Y. Involvement of S100A8/A9-TLR4-NLRP3 inflammasome pathway in contrast-induced acute kidney injury. Cell Physiol Biochem. 2017;43:209–22.
24. Lau A, Chung H, Komada T, Platnich JM, Sandall CF, Choudhury SR, Chun J, Naumenko V, Surewaard BG, Nelson MC, Ulke-Lemée A, Beck PL, Benediktsson H, Jevnikar AM, Snelgrove SL, Hickey MJ, Senger DL, James MT, Macdonald JA, Kubes P, Jenne CN, Muruve DA. Renal immune surveillance and dipeptidase-1 contribute to contrast-induced acute kidney injury. J Clin Invest. 2018;128:2894–913.
25. Atkinson SJ. Kidney surveillance in the spotlight: contrast-induced acute kidney injury illuminated. J Clin Invest. 2018;128:2754–6.
26. Kooiman J, Pasha SM, Zondag W, Sijpkens YW, van der Molen AJ, Huisman MV, Dekkers OM. Meta-analysis: serum creatinine changes following contrast enhanced CT imaging. Eur J Radiol. 2012;81:2554–61.
27. Moos SI, van Vemde DN, Stoker J, Bipat S. Contrast induced nephropathy in patients undergoing intravenous (IV) contrast enhanced computed tomography (CECT) and the relationship with risk factors: a meta-analysis. Eur J Radiol. 2013;82:e387–99.
28. McCullough PA. Contrast-induced acute kidney injury. J Am Coll Cardiol. 2008;51:1419–28. Erratum in: J Am Coll Cardiol. 2008;51: 2197.
29. Shemirani H, Pourrmoghaddas M. A randomized trial of saline hydration to prevent contrast-induced nephropathy in patients on regular captopril or furosemide therapy undergoing percutaneous coronary intervention. Saudi J Kidney Dis Transpl. 2012;23:280–5.

30. Majumdar SR, Kjellstrand CM, Tymchak WJ, Hervas-Malo M, Taylor DA, Teo KK. Forced euvolemic diuresis with mannitol and furosemide for prevention of contrast-induced nephropathy in patients with CKD undergoing coronary angiography: a randomized controlled trial. Am J Kidney Dis. 2009;54:602–9.
31. Barrett BJ, Parfrey PS. Clinical practice. Preventing nephropathy induced by contrast medium. N Engl J Med. 2006;354:379–86.
32. Lautin EM, Freeman NJ, Schoenfeld AH, Bakal CW, Haramati N, Friedman AC, Lautin JL, Braha S, Kadish EG. Radiocontrast associated renal dysfunction: a comparison of lower-osmolality and conventional high-osmolality contrast media. AJR Am J Roentgenol. 1991;157:59–65.
33. Cigarroa RG, Lange RA, Williams RH, Hillis LD. Dosing of contrast material to prevent contrast nephropathy in patients with renal disease. Am J Med. 1989;86:649–52.
34. Brown JR, Robb JF, Block CA, Schoolwerth AC, Kaplan AV, O'Connor GT, Solomon RJ, Malenka DJ. Does safe dosing of iodinated contrast prevent contrast-induced acute kidney injury? Circ Cardiovasc Interv. 2010;3:346–50.
35. Gurm HS, Dixon SR, Smith DE, Share D, Lalonde T, Greenbaum A, Moscucci M, BMC2 (Blue Cross Blue Shield of Michigan Cardiovascular Consortium) Registry. Renal function-based contrast dosing to define safe limits of radiographic contrast media in patients undergoing percutaneous coronary interventions. J Am Coll Cardiol. 2011;58:907–14.
36. Chen CM, Chu SY, Hsu MY, Liao YL, Tsai HY. Low-tube-voltage (80 kVp) CT aortography using 320-row volume CT with adaptive iterative reconstruction: lower contrast medium and radiation dose. Eur Radiol. 2014;24:460–8.
37. Taguchi N, Oda S, Utsunomiya D, Funama Y, Nakaura T, Imuta M, Yamamura S, Yuki H, Kidoh M, Hirata K, Namimoto T, Hatemura M, Kai N, Yamashita Y. Using 80 kVp on a 320-row scanner for hepatic multiphasic CT reduces the contrast dose by 50% in patients at risk for contrast-induced nephropathy. Eur Radiol. 2017;27:812–20.
38. Bruce RJ, Djamali A, Shinki K, Michel SJ, Fine JP, Pozniak MA. Background fluctuation of kidney function versus contrast-induced nephrotoxicity. Am J Roentgenol. 2009;192:711–8.
39. Ricós C, Iglesias N, García-Lario JV, Simón M, Cava F, Hernández A, Perich C, Minchinela J, Alvarez V, Doménech MV, Jiménez CV, Biosca C, Tena R. Within-subject biological variation in disease: collated data and clinical consequences. Ann Clin Biochem. 2007;44:343–52.
40. Campbell DR, Flemming BK, Mason WF, Jackson SA, Hirsch DJ, MacDonald KJ. A comparative study of the nephrotoxicity of iohexol, iopamidol and ioxaglate in peripheral angiography. Can Assoc Radiol J. 1990;41:133–7.
41. Moore RD, Steinberg EP, Powe NR, Brinker JA, Fishman EK, Graziano S, Gopalan R. Nephrotoxicity of high-osmolality versus low-osmolality contrast media: randomized clinical trial. Radiology. 1992;182:649–55.
42. Abe M, Kimura T, Morimoto T, Furukawa Y, Kita T. Incidence of and risk factors for contrast-induced nephropathy after cardiac catheterization in Japanese patients. Circ J. 2009;73:1518–22.
43. Saito Y, Watanabe M, Aonuma K, Hirayama A, Tamaki N, Tsutsui H, Murohara T, Ogawa H, Akasaka T, Yoshimura M, Sato A, Takayama T, Sakakibara M, Suzuki S, Ishigami K, Onoue K, CINC-J Study Investigators. Proteinuria and reduced estimated glomerular filtration rate are independent risk factors for contrast-induced nephropathy after cardiac catheterization. Circ J. 2015;79:1624–30.
44. McDonald RJ, McDonald JS, Bida JP, Carter RE, Fleming CJ, Misra S, Williamson EE, Kallmes DF. Intravenous contrast material-induced nephropathy: causal or coincident phenomenon? Radiology. 2013;267:106–18.
45. Davenport MS, Khalatbari S, Cohan RH, Dillman JR, Myles JD, Ellis JH. Contrast material-induced nephrotoxicity and intravenous low-osmolality iodinated contrast material: risk stratification by using estimated glomerular filtration rate. Radiology. 2013;268:719–28.
46. Wilhelm-Leen E, Montez-Rath ME, Chertow G. Estimating the risk of Radiocontrast-associated nephropathy. J Am Soc Nephrol. 2017;28:653–9.

47. Aycock RD, Westafer LM, Boxen JL, Majlesi N, Schoenfeld EM, Bannuru RR. Acute kidney injury after computed tomography: a meta-analysis. Ann Emerg Med. 2018;71:44–53.e4.
48. Trivedi HS, Moore H, Nasr S, Aggarwal K, Agrawal A, Goel P, Hewett J. A randomized prospective trial to assess the role of saline hydration on the development of contrast nephrotoxicity. Nephron Clin Pract. 2003;93:C29–34.
49. Mueller C, Buerkle G, Buettner HJ, Petersen J, Perruchoud AP, Eriksson U, Marsch S, Roskamm H. Prevention of contrast media-associated nephropathy: randomized comparison of 2 hydration regimens in 1620 patients undergoing coronary angioplasty. Arch Intern Med. 2002;162:329–36.
50. Nijssen EC, Rennenberg RJ, Nelemans PJ, Essers BA, Janssen MM, Vermeeren MA, Ommen VV, Wildberger JE. Prophylactic hydration to protect renal function from intravascular iodinated contrast material in patients at high risk of contrast-induced nephropathy (AMACING): a prospective, randomised, phase 3, controlled, open-label, non-inferiority trial. Lancet. 2017;389:1312–22.
51. Hoste EA, De Waele JJ, Gevaert SA, Uchino S, Kellum JA. Sodium bicarbonate for prevention of contrast-induced acute kidney injury: a systematic review and meta-analysis. Nephrol Dial Transplant. 2010;25:747–58.
52. Trivedi H, Nadella R, Szabo A. Hydration with sodium bicarbonate for the prevention of contrast-induced nephropathy: a meta-analysis of randomized controlled trials. Clin Nephrol. 2010;74:288–96.
53. Brar SS, Hiremath S, Dangas G, Mehran R, Brar SK, Leon MB. Sodium bicarbonate for the prevention of contrast induced-acute kidney injury: a systematic review and meta-analysis. Clin J Am Soc Nephrol. 2009;4:1584–92.
54. Putzu A, Boscolo Berto M, Belletti A, Pasotti E, Cassina T, Moccetti T, Pedrazzini G. Prevention of contrast-induced acute kidney injury by furosemide with matched hydration in patients undergoing interventional procedures: a systematic review and meta-analysis of randomized trials. JACC Cardiovasc Interv. 2017;10:355–63.
55. Subramaniam RM, Suarez-Cuervo C, Wilson RF, Turban S, Zhang A, Sherrod C, Aboagye J, Eng J, Choi MJ, Hutfless S, Bass EB. Effectiveness of prevention strategies for contrast-induced nephropathy: a systematic review and meta-analysis. Ann Intern Med. 2016;164:406–16.
56. Ahmed K, McVeigh T, Cerneviciute R, Mohamed S, Tubassam M, Karim M, Walsh S. Effectiveness of contrast-associated acute kidney injury prevention methods; a systematic review and network meta-analysis. BMC Nephrol. 2018;19:323.
57. Cruz DN, Goh CY, Marenzi G, Corradi V, Ronco C, Perazella MA. Renal replacement therapies for prevention of radiocontrast-induced nephropathy: a systematic review. Am J Med. 2012;125:66–78.

Chapter 8
Antibiotics- and Immunosuppressants-Related AKI

Kengo Furuichi, Keisuke Sako, and Takashi Wada

Abstract This section explores the epidemiology, risk factors for, and pathogenesis of drug-induced acute kidney injury. This section includes comments on the major drugs responsible for the renal damage, including descriptions of the underlying mechanisms if known. Finally, preventive measures and treatment of drug-induced acute kidney injury are addressed.

Keywords Acute interstitial nephritis · Obstruction of the urinary tract · Allergic mechanism · Antibacterial agents · Immunosuppressive drugs

8.1 Introduction

Drug-induced kidney injury (DKI) is defined in the 2016 clinical practice guidelines in Japan as "a new onset of kidney injury or the worsening of an existing kidney injury due to drug administration" [1]. The frequency of DKI may be increasing due to the diversity of medications currently employed, aging of the population, and an increase in the number of patients with chronic kidney disease. While DKI may be chronic, some cases are drug-induced acute kidney injury (DI-AKI). The pathogenesis of DI-AKI includes renal vasculopathy, tubulointerstitial damage, or glomerular damage with associated thrombotic microangiopathy (TMA).

In this section, we review DKI caused by antibiotics as well as drugs for cancer, organ transplantation, or rheumatic diseases.

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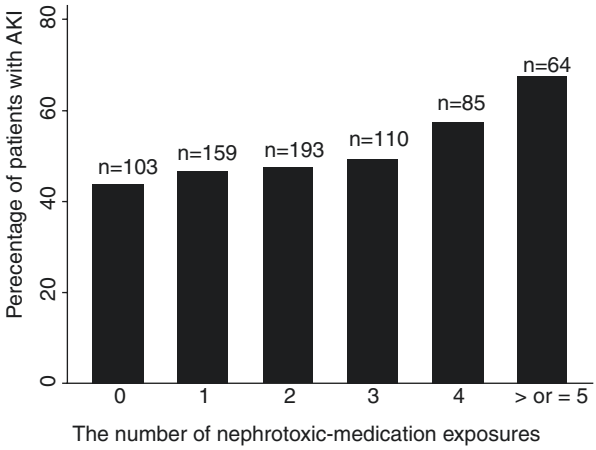

Fig. 8.1 Percentage of patients who developed AKI by nephrotoxic drugs [2]

8.2 Epidemiology of DI-AKI

A retrospective study based on the Medical Expenditure Panel Survey indicates that nephrotoxic medication exposure occurred in 72% of adult patients. Of those, 47.2% were prescribed at least one and 52.8% at least two nephrotoxic medications (Fig. 8.1) [1, 2]. It is reported that each exposure to a nephrotoxic agent increases a patient's odds of developing DI-AKI by 53% [3–5]. The data of the J-RBR from 2007 to 2015 indicates that the frequency of DKI increases with age. Overall, the frequency of DKI was three times higher in the seventh than in the second decade of life (1.86% vs. 0.62%) [6].

Drug-induced acute interstitial nephritis (DI-AIN) is a common cause of DI-AKI, affecting about 20% of patients with unexplained DI-AKI [4, 7]. Only half of all patients with biopsy-proven DI-AIN are diagnosed with DI-AKI. The other half do not meet AKI diagnostic criteria, in spite of the fact that they have slowly progressive kidney dysfunction [8].

Based on clinical and pathologic diagnoses, 328 cases (176 males and 152 females) of renal biopsy-proven DKI were registered in the J-RBR from 2007 to 2015 (1.24% of all cases in the registry). The pathology findings in these cases included glomerular lesions in 105 (32.0%), acute tubulointerstitial lesions in 87 (26.5%), chronic tubulointerstitial lesions in 72 (22.0%), and sclerotic glomerular lesions or nephrosclerosis in 18 (5.5%).

8.3 Risk Factors for DI-AKI

There is no one mechanism by which antibiotics cause DKI. Due to allergic or immunologic mechanisms, or renal tubular obstruction, drugs may induce direct cytotoxicity to the kidney cells.

To avoid DKI, knowledge of the pharmacokinetics and potential nephrotoxicity of drugs is crucial. In patients who already have impaired kidney function, adjustment of dosage and dosing intervals is often required. Details on how to adjust dosing for any drug based on a patient's renal function can be accessed in appropriate databases and guidelines.

8.3.1 Drug Metabolism and Excretion

Drug excretion from the kidney consists of three steps: glomerular filtration, excretion to the luminal side by the renal tubular epithelial cells, and reabsorption from the luminal side by the renal tubular epithelial cells. DI-AKI may occur at each step. In general, a drug's concentration in the renal tubular lumen is 100 times higher than the concentration of the glomerular filtrate. DI-AKI tends to occur in a concentration-dependent manner.

The proximal tubule of the kidney plays a crucial role in the handling of drugs (e.g., diuretics), uremic toxins (e.g., indoxyl sulfate), environmental toxins (e.g., mercury, aristolochic acid), and metabolites (e.g., uric acid). Renal handling of these agents is dependent on many multispecific transporters of the solute carrier superfamily, including the organic anion transporter and organic cation transporter subfamilies and the ATP-binding cassette superfamily [9]. Drugs that compete with other substances in the renal tubular transporter mechanism cause prolonged exposure of the renal tubule cells to the drug and may cause DI-AKI.

8.3.2 Patient Factors Associated with DI-AKI

DI-AKI is increasingly common in elderly individuals. Hypovolemia, sepsis, and iatrogenic complications related to drug toxicity, contrast-induced nephropathy, and perioperative complications often occur in older hospitalized patients [10, 11], all of which are risk factors for DI-AKI. It is important to detect such factors in any particular patient to minimize the risk of DI-AKI.

8.4 Pathophysiology of Drug-Induced AKI

DKI can be classified based on the pathogenetic mechanism as well as on the segment of the kidney that is damaged. The former includes (1) toxic kidney injury (direct toxicity); (2) acute interstitial nephritis (AIN) due to an allergic mechanism (hypersensitivity and direct toxicity); (3) indirect toxicity, such as may occur with electrolyte abnormalities and decreased renal blood flow; and (4) obstruction of the urinary tract. The latter classification system includes (1)

Table 8.1 Drugs causing kidney injury

	Pathophysiology	Drugs
Toxic	Direct nephrotoxicity	Aminoglycoside Vancomycin
	TMA	Calcineurin inhibitors
Allergic	Acute interstitial nephritis	Antibacterial agents
Indirect toxicity	Vasoconstriction	Calcineurin inhibitors
Obstruction of the urinary tract	Vacuolation of the proximal tubule	Calcineurin inhibitors
	Crystal formation	Methotrexate, mizoribine, antiviral drug

glomerular injury, (2) tubular injury, (3) interstitial injury, and (4) vascular injury (Table 8.1).

When using nephrotoxic drugs such as aminoglycosides and glycopeptide antibiotics, therapeutic drug monitoring should be performed.

8.4.1 AIN Due to a Toxic Mechanism

Toxic injury affects the kidney in a dose-dependent manner. In patients who already have kidney dysfunction, the concentration of a renally excreted drug in the blood is increased due to delayed excretion, which simultaneously increases the risk of DKI.

The TMAs are a heterogeneous group of disorders characterized by microangiopathic hemolytic anemia with red cell fragmentation, thrombocytopenia, and signs of organ dysfunction due to disrupted microcirculation [12]. Hypertension and proteinuria are common clinical manifestations of drug-induced TMA. Hemolytic anemia and thrombocytopenia are usually minor clinical manifestation in cases of drug-induced TMA. Calcineurin inhibitors (CNIs) are among the main drugs causing TMA. In CNI-induced TMA, platelet aggregation may be induced by arteriolar contraction and endothelial cell damage. ADAMTS13 activity is usually conserved in CNI-induced TMA [13]. TMA was detected in 14% of biopsy specimens from transplanted kidneys in patients treated with cyclosporin A [14]. Similarly, 1–4.7% of patients treated with tacrolimus after transplant developed TMA [15].

Anti-cancer drugs, such as cisplatin, also have direct toxic effects on tubular epithelial cells [16]. Acute tubular injury is histologically characterized by necrotic cell death and inflammation. Recognition of drug-induced AKI and rapid discontinuation or dose reduction of the candidate agents are critical to maximizing kidney function recovery. It is important to reduce drug-related risk factors, such as low baseline kidney function before initiation of therapy and avoiding use of nephrotoxic drug combinations, and adjusting the drug dosage would be required to avoid AKI by anti-cancer drugs.

8.4.2 AIN Due to an Allergic Mechanism

AIN secondary to an allergic mechanism develops regardless of the drug dose or the length of administration. Various reports indicate that 44–70% of cases of AIN are drug induced [7, 17]. Typical manifestations include rash, fever, and eosinophilia [18]. However, in some cases, no such clinical manifestations occur, kidney dysfunction being the only abnormality detected.

DI-AIN due to this mechanism is a drug hypersensitivity reaction that manifests 7–10 days after exposure to the culprit drug. The process begins with antigen processing and presentation to local dendritic cells. The dendritic cells activate T cells, and the subsequent effector phase of the immune response is mediated by various cytokines [19].

8.4.3 Indirect Toxicity

Indirect toxicity is kidney damage caused by a decrease in renal blood flow and subsequent electrolyte abnormalities. Dose-dependent arteriolar contraction is one of the mechanisms of CNI-induced AKI. This reduces kidney plasma flow and the glomerular filtration rate. In addition to promoting vasoconstriction by activating the renin-angiotensin system and enhanced endothelin production, CNIs may attenuate vasodilatation by reducing prostaglandin E2 production and nitric oxide levels [20].

This vasoconstriction is maximal at 2–4 h after the maximum CNI blood concentration is reached. It improves along with decreases in CNI concentration. AKI with vasoconstriction caused by CNI can be reversed by decreasing or stopping the drug [21].

8.4.4 Obstruction of the Urinary Tract

Obstruction in DI-AKI is induced by vacuolar degeneration of tubular epithelial cells by CNI or tubular obstruction by crystal-forming drugs. The vacuoles are neutral fat droplets or may appear as single membrane-bound structures due to dilatation of the endoplasmic reticulum.

Isometric vacuolation by CNI produces a uniform foamy appearance of the proximal tubule. Although details of the mechanism are unknown, it is speculated that expansion of the endoplasmic reticulum or an increase in lysosomes due to ischemia induced by vasoconstriction or a direct effect of CNI is responsible [22, 23]. Isometric tubular vacuolization detected early after transplantation is reportedly not progressive but is merely associated with higher tacrolimus trough levels [24].

Tubular inclusion bodies are also detected in damaged tubular epithelial cells, which are enlarged autolysosomes filled with distorted mitochondrial fragments [23]. Renal tubular changes characterized by microcalcification have also been detected in cases of CNI-induced injury; however, these changes are not specific to cyclosporine toxicity. They are commonly found in both humans and rats at high doses of cyclosporine.

Antiviral drugs such as acyclovir and indinavir as well as methotrexate may crystallize in the tubular lumen, resulting in obstruction.

8.5 Drugs Causing Kidney Injury

8.5.1 Antibacterial Agents

Antibacterial agents have antibacterial effects that depend on the blood concentration of the drug. Nephrotoxicity of these antibiotics can also be divided into two types: blood concentration-dependent or time-dependent. In addition, metabolites of some antibiotics are also nephrotoxic. β-Lactam antibiotics cause mainly time-dependent nephrotoxicity, whereas new quinolone and aminoglycoside antibiotics mainly cause concentration-dependent toxicity.

Antibiotics and antiviral agents may induce DI-AKI by the following mechanisms:

1. Renal tubular necrosis in a dose-dependent manner, as with vancomycin and aminoglycosides
2. Allergic tubulointerstitial nephritis, as with cephem or quinolone antibiotics or rifampicin
3. Obstruction by tubular crystallization, as with acyclovir and ganciclovir or quinolones

8.5.2 Vancomycin Hydrochloride

Vancomycin-induced renal toxicity is reported in 10–40% of patients treated with the drug [25]. The risk is considered high, with a reported relative risk of 2.45 [26]. The higher the dose, the greater the risk [27]. Combining vancomycin with aminoglycosides increases the risk of DI-AKI [28], as does its combination with piperacillin/tazobactam [29–32].

Thus, vancomycin-induced renal tubular necrosis occurs in a dose-dependent manner. The most likely mechanism of nephrotoxicity is at least in part attributable to increased production of reactive oxygen species and oxidative stress [25]. Risk factors for vancomycin-induced nephrotoxicity are high trough levels (>20 mg/L) or high doses (>4 g/day), concomitant treatment with nephrotoxic agents, prolonged treatment with the drug (more than 7 days), or admission to an intensive care unit (especially with a prolonged stay) [25].

One of the best ways to avoid vancomycin-induced nephrotoxicity is to keep trough levels in the range of 15–20 μg/mL [33, 34]. A systematic review showed that patients who had therapeutic drug monitoring had significantly higher rates of clinical efficacy (OR = 2.62, 95% CI 1.34–5.11, $P = 0.005$) and decreased rates of nephrotoxicity (OR = 0.25, 95% CI 0.13–0.48, $P < 0.0001$) compared with those without monitoring [35].

Although there is no clinical evidence of agents capable of preventing vancomycin-induced nephrotoxicity, animal studies have shown beneficial effects of various antioxidants, such as erdosteine, vitamin E, vitamin C, *N*-acetylcysteine, caffeic acid phenethyl ester, and erythropoietin [36].

8.5.3 Aminoglycosides

Aminoglycosides are freely filtered across the glomerulus. After the drug binds to the anionic phospholipid of the proximal tubule cells, it is transferred rapidly to megalin, a receptor facilitating protein uptake, and is endocytosed. Megalin has a high affinity for positively charged aminoglycosides. Aminoglycosides induce phospholipidosis in the proximal tubule cells and, finally, nephrotoxicity. Vancomycin coadministration, high aminoglycoside trough levels, and heart failure are independent risk factors for AKI in patients receiving aminoglycoside therapy [37].

8.5.4 Trimethoprim/Sulfamethoxazole

Trimethoprim-/sulfamethoxazole-induced renal toxicity has been reported in around 10% of patients being treated with the drug [38]. Trimethoprim-/sulfamethoxazole-induced AKI resolves promptly after discontinuation of therapy.

8.5.5 Amphotericin B

Amphotericin B is a nephrotoxic antifungal drug. However, nephrotoxicity is reduced if the drug is delivered as a locally prepared lipid emulsion or in liposomes [39].

8.5.6 Antiviral Drugs

Since antiviral drugs such as zovirax, valacyclovir, and ganciclovir have low solubility, crystals may precipitate in the distal tubule and collecting duct, resulting in AKI secondary to renal tubular obstruction.

8.5.7 Antituberculosis Drugs

Around 7% of patients being treated for tuberculosis reportedly develop DI-AKI. Renal dysfunction is common in an elderly population treated with these drugs. Fever and rash may occur along with DI-AKI [40].

8.5.8 Kidney Injury Due to Immunosuppressive Drugs

Immunosuppressive drugs are widely used in the treatment of autoimmune diseases, organ transplantation, and glomerulonephritis or nephrotic syndrome. DI-AKI caused by antimetabolites (mizoribine, mycophenolate mofetil, methotrexate [MTX]) are observed during medical treatment of these diseases.

8.5.9 Methotrexate

MTX is a folate antimetabolite. It inhibits the activation of folic acid necessary for nucleic acid synthesis by inhibiting dihydrofolate reductase and thus suppressing cell proliferation. MTX is excreted by the kidney. Precipitation of MTX in the distal tubule and collecting duct lumens may occur, particularly when administered at high doses. This can lead to AKI due to renal tubular obstruction, which is usually reversible.

Prevention of AKI in patients treated with MTX includes hydration and alkalinization of the urine, as the solubility of MTX decreases in acidic urine (pH < 5.5). Therefore, administration of sodium bicarbonate or acetazolamide is recommended when high-dose MTX is prescribed.

8.6 Diagnosis of DI-AKI

DI-AKI is defined as (1) the new onset of kidney dysfunction after administration of a drug and (2) resolution of the kidney dysfunction with discontinuation of the suspected drug. The interval from drug administration to the onset of DI-AKI may suggest particular drugs as the cause. However, in routine clinical practice, it is not easy to correctly identify the culprit drug.

The drug-induced lymphocyte stimulation test is sometimes use to investigate drugs suspected of causing DI-AKI. A negative result does not prove a particular drug is not responsible, as the sensitivity and specificity of the test are low. Eosinophils in the urine are also sometimes used to detect DI-AKI. This test has a

sensitivity of 40%, specificity of 72%, and a positive predictive value of only 38% [41]; therefore, it is not very accurate for the diagnosis of DI-AKI. Uptake of 67Ga by the kidneys has been used to diagnose DI-AKI.

8.6.1 Kidney Biopsy

Definitive diagnosis of DI-AIN or DI-AKI may require a kidney biopsy. The typical findings are normal glomeruli and a patchy but usually heavy interstitial infiltrate of lymphocytes, plasma cells, and eosinophils. Diagnosis of AIN is important because withdrawal of the suspected drugs usually results in rapid improvement in kidney function. Steroid therapy may reduce residual chronic kidney damage [42]. Kidney biopsy should be performed as soon as possible in cases of suspected DI-AIN or DI-AKI (Fig. 8.2) [43].

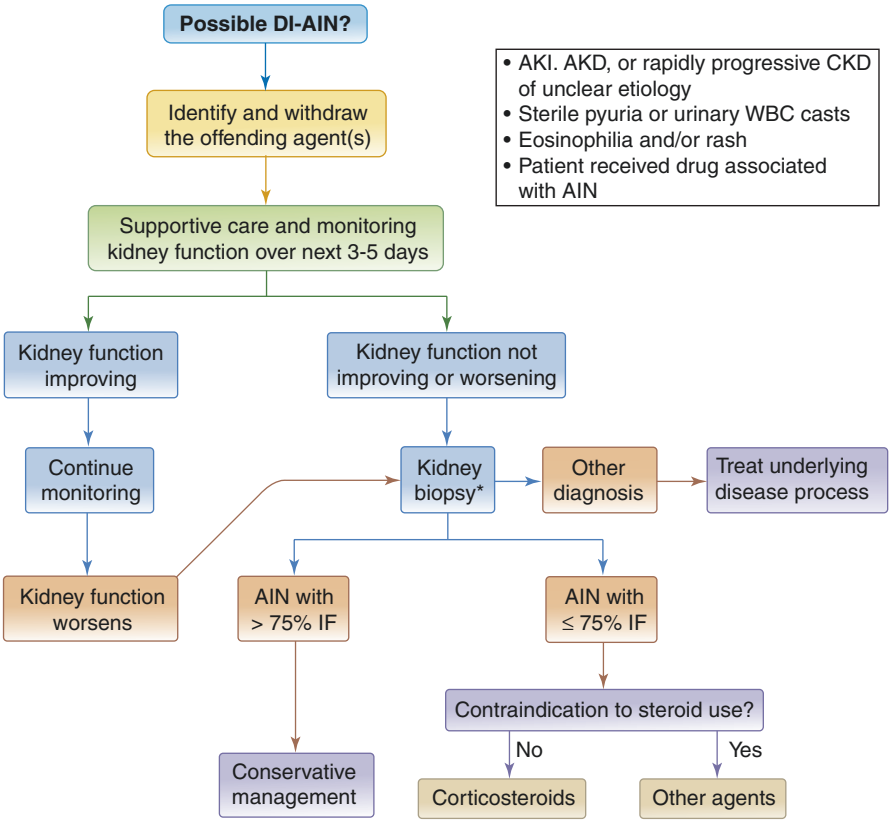

Fig. 8.2 Algorithm for management of drug-induced acute kidney injury [42]

8.7 Prevention and Treatment of DI-AKI

There is no uniform method for preventing DI-AKI. The best ways to prevent DI-AKI are to reduce or avoid the use of nephrotoxic drugs and hydration to prevent high urinary concentrations of drugs. Therapeutic drug monitoring is also useful. Attention should be paid in particular to groups at high risk of DI-AKI, such as elderly people and patients with CKD.

8.7.1 Treatment

First, it is essential to stop or reduce the suspected drugs. In DI-AKI, kidney function declines rapidly; however, it often improves after several days to several weeks once the drugs are discontinued. However, dialysis may be necessary if renal impairment is prolonged and marked hyperkalemia, pulmonary edema, or uremic symptoms are present.

With prolonged renal dysfunction, steroid therapy is required. Prednisone, 1 mg/kg per day, should be continued for approximately 1–1.5 months, as most patients recover their kidney function within this time frame [44, 45].

References

1. Davis-Ajami ML, Fink JC, Wu J. Nephrotoxic medication exposure in U.S. adults with predialysis chronic kidney disease: health services utilization and cost outcomes. J Manag Care Spec Pharm. 2016;22:959–68.
2. Moffett BS, Goldstein SL. Acute kidney injury and increasing nephrotoxic-medication exposure in noncritically-ill children. Clin J Am Soc Nephrol. 2011;6:856–63.
3. Ostermann M, Chawla LS, Forni LG, Kane-Gill SL, Kellum JA, Koyner J, Murray PT, Ronco C, Goldstein SL, Workgroup, A. Drug management in acute kidney disease—report of the acute disease quality initiative XVI meeting. Br J Clin Pharmacol. 2018;84:396–403.
4. Aitken E, Carruthers C, Gall L, Kerr L, Geddes C, Kingsmore D. Acute kidney injury: outcomes and quality of care. QJM. 2013;106:323–32.
5. Martin M, Wilson FP. Utility of electronic medical record alerts to prevent drug nephrotoxicity. Clin J Am Soc Nephrol. 2019;14:115–23.
6. Yokoyama H, Narita I, Sugiyama H, Nagata M, Sato H, Ueda Y, Matsuo S. Drug-induced kidney disease: a study of the Japan renal biopsy registry from 2007 to 2015. Clin Exp Nephrol. 2016;20:720–30.
7. Perazella MA, Markowitz GS. Drug-induced acute interstitial nephritis. Nat Rev Nephrol. 2010;6:461–70.
8. Chu R, Li C, Wang S, Zou W, Liu G, Yang L. Assessment of KDIGO definitions in patients with histopathologic evidence of acute renal disease. Clin J Am Soc Nephrol. 2014;9:1175–82.
9. Nigam SK, Wu W, Bush KT, Hoenig MP, Blantz RC, Bhatnagar V. Handling of drugs, metabolites, and uremic toxins by kidney proximal tubule drug transporters. Clin J Am Soc Nephrol. 2015;10:2039–49.
10. Perazella MA. Renal vulnerability to drug toxicity. Clin J Am Soc Nephrol. 2009;4:1275–83.

11. Chronopoulos A, Cruz DN, Ronco C. Hospital-acquired acute kidney injury in the elderly. Nat Rev Nephrol. 2010;6:141–9.
12. Knobl PN. Treatment of thrombotic microangiopathy with a focus on new treatment options. Hamostaseologie. 2013;33:149–59.
13. Moake JL, Rudy CK, Troll JH, Weinstein MJ, Colannino NM, Azocar J, Seder RH, Hong SL, Deykin D. Unusually large plasma factor VIII: von Willebrand factor multimers in chronic relapsing thrombotic thrombocytopenic purpura. N Engl J Med. 1982;307:1432–5.
14. Usui J, Yamagata K, Imai E, Okuyama H, Kajiyama H, Kanamori H, Kaneko S, Kono E, Sakai Y, Sakai N, Sakamaki Y, Taniguchi Y, Nakai K, Nishiwaki H, Hirata S, Yamaya H, Tsuruoka S, Terada Y, Yokoyama H, Wada T, Narita I. Clinical practice guideline for drug-induced kidney injury in Japan 2016: digest version. Clin Exp Nephrol. 2016;20:827–31.
15. Trimarchi HM, Truong LD, Brennan S, Gonzalez JM, Suki WN. FK506-associated thrombotic microangiopathy: report of two cases and review of the literature. Transplantation. 1999;67:539–44.
16. Izzedine H, Perazella MA. Anticancer drug-induced acute kidney injury. Kidney Int Rep. 2017;2:504–14.
17. Howell M, Sebire NJ, Marks SD, Tullus K. Biopsy-proven paediatric tubulointerstitial nephritis. Pediatr Nephrol. 2016;31:1625–30.
18. Perazella MA. Clinical approach to diagnosing acute and chronic tubulointerstitial disease. Adv Chronic Kidney Dis. 2017;24:57–63.
19. Raghavan R, Shawar S. Mechanisms of drug-induced interstitial nephritis. Adv Chronic Kidney Dis. 2017;24:64–71.
20. Lanese DM, Conger JD. Effects of endothelin receptor antagonist on cyclosporine-induced vasoconstriction in isolated rat renal arterioles. J Clin Invest. 1993;91:2144–9.
21. Ruggenenti P, Perico N, Mosconi L, Gaspari F, Benigni A, Amuchastegui CS, Bruzzi I, Remuzzi G. Calcium channel blockers protect transplant patients from cyclosporine-induced daily renal hypoperfusion. Kidney Int. 1993;43:706–11.
22. Mihatsch MJ, Ryffel B, Hermle M, Brunner FP, Thiel G. Morphology of cyclosporine nephrotoxicity in the rat. Clin Nephrol. 1986;25(Suppl 1):S2–8.
23. Kim JY, Suh KS. Light microscopic and electron microscopic features of cyclosporine nephrotoxicity in rats. J Korean Med Sci. 1995;10:352–9.
24. Naesens M, Kambham N, Concepcion W, Salvatierra O Jr, Sarwal M. The evolution of non-immune histological injury and its clinical relevance in adult-sized kidney grafts in pediatric recipients. Am J Transplant. 2007;7:2504–14.
25. Elyasi S, Khalili H, Dashti-Khavidaki S, Mohammadpour A. Vancomycin-induced nephrotoxicity: mechanism, incidence, risk factors and special populations. A literature review. Eur J Clin Pharmacol. 2012;68:1243–55.
26. Sinha Ray A, Haikal A, Hammoud KA, Yu AS. Vancomycin and the risk of AKI: a systematic review and meta-analysis. Clin J Am Soc Nephrol. 2016;11:2132–40.
27. Lodise TP, Lomaestro B, Graves J, Drusano GL. Larger vancomycin doses (at least four grams per day) are associated with an increased incidence of nephrotoxicity. Antimicrob Agents Chemother. 2008;52:1330–6.
28. Yano Y, Hiraoka A, Oguma T. Enhancement of tobramycin binding to rat renal brush border membrane by vancomycin. J Pharmacol Exp Ther. 1995;274:695–9.
29. Karino S, Kaye KS, Navalkele B, Nishan B, Salim M, Solanki S, Pervaiz A, Tashtoush N, Shaikh H, Koppula S, Martin ET, Mynatt RP, Murray KP, Rybak MJ, Pogue JM. Epidemiology of acute kidney injury among patients receiving concomitant vancomycin and piperacillin-tazobactam: opportunities for antimicrobial stewardship. Antimicrob Agents Chemother. 2016;60:3743–50.
30. Hammond DA, Smith MN, Li C, Hayes SM, Lusardi K, Bookstaver PB. Systematic review and meta-analysis of acute kidney injury associated with concomitant vancomycin and piperacillin/tazobactam. Clin Infect Dis. 2017;64:666–74.
31. Downes KJ, Cowden C, Laskin BL, Huang YS, Gong W, Bryan M, Fisher BT, Goldstein SL, Zaoutis TE. Association of acute kidney injury with concomitant vancomycin and piperacillin/tazobactam treatment among hospitalized children. JAMA Pediatr. 2017;171:e173219.

32. Luther MK, Timbrook TT, Caffrey AR, Dosa D, Lodise TP, LaPlante KL. Vancomycin plus piperacillin-tazobactam and acute kidney injury in adults: a systematic review and meta-analysis. Crit Care Med. 2018;46:12–20.
33. Rybak M, Lomaestro B, Rotschafer JC, Moellering R Jr, Craig W, Billeter M, Dalovisio JR, Levine DP. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm. 2009;66:82–98.
34. Hall RG 2nd, Hazlewood KA, Brouse SD, Giuliano CA, Haase KK, Frei CR, Forcade NA, Bell T, Bedimo RJ, Alvarez CA. Empiric guideline-recommended weight-based vancomycin dosing and nephrotoxicity rates in patients with methicillin-resistant Staphylococcus aureus bacteremia: a retrospective cohort study. BMC Pharmacol Toxicol. 2013;14:12.
35. Ye ZK, Tang HL, Zhai SD. Benefits of therapeutic drug monitoring of vancomycin: a systematic review and meta-analysis. PLoS One. 2013;8:e77169.
36. Elyasi S, Khalili H, Hatamkhani S, Dashti-Khavidaki S. Prevention of vancomycin induced nephrotoxicity: a review of preclinical data. Eur J Clin Pharmacol. 2013;69:747–54.
37. Paquette F, Bernier-Jean A, Brunette V, Ammann H, Lavergne V, Pichette V, Troyanov S, Bouchard J. Acute kidney injury and renal recovery with the use of aminoglycosides: a large retrospective study. Nephron. 2015;131:153–60.
38. Fraser TN, Avellaneda AA, Graviss EA, Musher DM. Acute kidney injury associated with trimethoprim/sulfamethoxazole. J Antimicrob Chemother. 2012;67:1271–7.
39. Mistro S, Maciel Ide M, de Menezes RG, Maia ZP, Schooley RT, Badaro R. Does lipid emulsion reduce amphotericin B nephrotoxicity? A systematic review and meta-analysis. Clin Infect Dis. 2012;54:1774–7.
40. Chang CH, Chen YF, Wu VC, Shu CC, Lee CH, Wang JY, Lee LN, Yu CJ. Acute kidney injury due to anti-tuberculosis drugs: a five-year experience in an aging population. BMC Infect Dis. 2014;14:23.
41. Ruffing KA, Hoppes P, Blend D, Cugino A, Jarjoura D, Whittier FC. Eosinophils in urine revisited. Clin Nephrol. 1994;41:163–6.
42. Cox ZL, McCoy AB, Matheny ME, Bhave G, Peterson NB, Siew ED, Lewis J, Danciu I, Bian A, Shintani A, Ikizler TA, Neal EB, Peterson JF. Adverse drug events during AKI and its recovery. Clin J Am Soc Nephrol. 2013;8:1070–8.
43. Moledina DG, Perazella MA. Drug-induced acute interstitial nephritis. Clin J Am Soc Nephrol. 2017;12:2046–9.
44. Gonzalez E, Gutierrez E, Galeano C, Chevia C, de Sequera P, Bernis C, Parra EG, Delgado R, Sanz M, Ortiz M, Goicoechea M, Quereda C, Olea T, Bouarich H, Hernandez Y, Segovia B, Praga M, Grupo Madrileno De Nefritis, I. Early steroid treatment improves the recovery of renal function in patients with drug-induced acute interstitial nephritis. Kidney Int. 2008;73:940–6.
45. Quinto LR, Sukkar L, Gallagher M. The effectiveness of corticosteroid compared to non-corticosteroid therapy for the treatment of drug-induced acute interstitial nephritis: a systematic review. Intern Med J. 2019;49(5):562–9.

Chapter 9
AKI in Setting of Cancer

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Abstract Though the link between cancer and renal disease has long been known, at present their relationship is emphasized more strongly than ever. Several trends in oncology, including longer survival times, better supportive care, and cancer diagnosis at older ages due to increased life expectancy, are driving an increase in the number of cancer patients developing acute kidney injury. In addition, recent improvements in cancer therapy, including stem cell therapies and newer molecular targeted drugs, have led to the emergence of new etiologies of kidney disease. Renal diseases in cancer patients are different from those in other patients, and they are becoming increasingly complex to manage. It is necessary for both nephrologists and oncologists to stay up to date on the diagnosis and management of cancer-concurrent kidney complications to provide optimal treatment. This chapter addresses the pathophysiology and treatment of various kidney complications in the context of cancer.

Keywords Onco-nephrology · Acute kidney injury · Cancer · Chemotherapy
Molecular targeted drugs · Paraneoplastic glomerulopathy

9.1 Introduction

Acute kidney injury (AKI) is probably the most common form of kidney disease for which a nephrologist would be consulted in a hospitalized cancer patient. Cancer patients can present with AKI as a consequence of the cancer itself or of its treatment, or as an associated severe complication. The largest cohort study of Danish cancer patients revealed that these patients have an increased risk of AKI, defined as

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a >50% increase in creatinine level, with 1- and 5-year risks of 17.5% and 27.0%, respectively [1]. Another study reported that AKI conferred a 6-month mortality as high as 73% in critically ill cancer patients [2]. Recently it was also shown that the probability of survival is reduced as the severity of AKI increases [3]. The increased incidence of AKI in cancer patients is not surprising given the effects of cancer and anti-cancer therapy on several factors that can cause AKI. Although the causes of AKI in cancer patients are often multifactorial, it is clinically useful to categorize the causes of AKI as pre-renal, intrinsic, and post-renal etiologies (Table 9.1). Pre-renal AKI can be due to intravascular volume depletion, as occurs in dehydration, vomiting, or diarrhea. Clinicians should remember that medications such as diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, or non-steroidal anti-inflammatory drugs (NSAID) used for cancer patients could increase the risk of pre-renal AKI. Since renal parenchyma comprises three main histological compartments, namely, glomerular, tubulointerstitial, and vascular compartments, intrinsic AKI includes glomerular, tubulointerstitial, and vascular diseases. Intrinsic causes of AKI can result from cancer itself or from chemotherapeutic treatment, or can be secondary to paraneoplastic conditions. Post-renal AKI results from extra-renal obstruction. In the following, we describe the various etiologies of AKI in detail, with particular attention to those that are specific to cancer patients.

Table 9.1 Etiologies of acute kidney injury in cancer patients

	Etiologies of AKI (common, but non-specific to cancer patients)	Etiologies of AKI usually specific to cancer patients
Pre-renal	• Intravascular volume depletion (dehydration, vomiting, diarrhea) • Contrast-induced nephropathy (via vasoconstriction) • Drug induced (NSAID, calcineurin inhibitor)	• Hypercalcemia • Hepatic sinusoidal obstruction syndrome • Capillary leak syndrome (IL-2)
Intrinsic	• Contrast-induced nephropathy (via damage to tubular cells)	• Thrombotic microangiopathy (cancer-associated, hematopoietic cell transplantation-associated, chemotherapy-associated) • Paraneoplastic glomerulopathies • Intra-renal tubular obstruction (cast nephropathy, uric acid nephropathy in tumor lysis syndrome, lymphomatous infiltration of the kidney, crystal nephropathy) • Acute tubular necrosis (cisplatin) • Acute interstitial nephritis (checkpoint inhibitors) • Interferon-associated nephrotic syndrome
Post-renal		• Extra-renal obstruction due to malignancies and retroperitoneal fibrosis

9.2 Pre-renal Causes of AKI

9.2.1 Hypercalcemia

Hypercalcemia, seen in approximately 20–30% of cancer patients at some time during the course of their disease, can lead to failure of the renal concentration process and result in pre-renal AKI due to volume depletion. There are three known mechanisms of cancer-associated hypercalcemia. The most common cause of hypercalcemia is humoral hypercalcemia of malignancy (HHM), due to the secretion by tumors of parathyroid hormone (PTH)-like substances, specifically parathyroid hormone-related protein (PTHrP); this etiology accounts for approximately 80% of patients with hypercalcemia of malignancy. Squamous-cell carcinomas of the lung, head, and neck as well as certain lymphomas, renal cell carcinoma, and adenocarcinomas of the breast, prostate, and ovary have been reported to cause hypercalcemia via PTHrP release [4]. The second cause of hypercalcemia is local osteolytic hypercalcemia of malignancy (LOH) due to the local osteolysis induced by bone metastasis. This is most commonly noted in patients with metastatic breast and lung carcinomas as well as extensive multiple myeloma (MM) [4]. The third cause, which is less common, is the activation of vitamin D by the tumor itself such that intestinal calcium absorption is increased. This mechanism is almost exclusively noted in patients with lymphomas. In these patients, 1α-hydroxylase, which converts 25-hydroxyvitamin D to activated vitamin D, 1,25-dihydroxyvitamin D, calcitriol, is highly expressed in neoplastic tissues. The mainstay of therapy for cancer-associated hypercalcemia is intravenous hydration with an aim to increase kidney clearance of calcium. The use of loop diuretics should be restricted to patients who develop fluid overload after vigorous hydration. To block the mobilization of calcium from bone, anti-resorptive therapy with intravenous bisphosphonates is generally mandatory. However, it should be noted that intravenous bisphosphonates can cause adverse effects such as flu-like symptoms, osteonecrosis of the jaw, and kidney complications (focal segmental glomerulosclerosis, minimal-change disease, and acute tubular necrosis). Denosumab, an alternative anti-resorptive agent, is a monoclonal antibody directed against RANKL. Denosumab is not cleared by the kidneys and hence does not require dosing adjustments for renal insufficiency. For patients with hypercalcemia resulting from activation of vitamin D by the tumor, corticosteroid therapy is often beneficial.

9.2.2 Hepatic Sinusoidal Obstruction Syndrome

Hepatic sinusoidal obstruction syndrome (SOS) typically occurs in the context of hematopoietic cell transplantation (HCT). SOS is characterized by hepatomegaly, jaundice, and ascites. It is generally seen within 30 days after HCT, and its incidence varies widely among studies, ranging from 0 to 62.3% with a mean of 13.7% [5]. SOS is considered to begin with acute radiochemotherapy-induced damage to

sinusoidal endothelial cells and hepatocytes in zone 3 of the liver acinus (the area surrounding the central veins). SOS occurs less frequently in myeloablative autologous HCT compared to myeloablative allogenic transplantation, probably due to the absence of methotrexate and allogenic immunological elements. Risk factors that predispose patients to the development of hepatic SOS also include preexisting liver disease and high doses of total body irradiation. In non-myeloablative transplantation, SOS is almost non-existent, probably because of the much lower intensity of the radiochemotherapy [6]. A transvenous approach that allows both biopsy and hepatic venous pressure measurements is the most accurate diagnostic test. A hepatic venous pressure gradient >10 mmHg is highly specific for SOS. Most of the patients will do well with supportive care, including management of fluid balance, minimizing exposure to hepatoxic agents, paracentesis for ascites to relieve abdominal discomfort and pain control. In contrast, patients with severe SOS have high mortality rates with supportive care alone. Unfortunately, at present, there are no established therapies for severe SOS, but the effectiveness of defibrotide, a single-stranded oligodeoxyribonucleotide with antithrombotic and profibrolytic properties, was recently evaluated in a large international clinical trial. In that study, 102 patients with SOS and multiorgan failure were treated with defibrotide, and their outcomes were compared with those of 32 historical controls. Findings revealed that use of defibrotide was associated with higher rates of 100-day survival and complete response [7]. The efficacy of heparin or ursodiol in the prophylaxis of SOS remains controversial.

9.2.3 Capillary Leak Syndrome

The cytokine interleukin-2 (IL-2) used for the treatment of malignancy has been shown to cause capillary leak syndrome. Manifestations include fluid retention, pulmonary interstitial edema, dyspnea, fever, and chills [8]. This form of capillary leak syndrome is characterized by the onset of symptoms minutes to hours after its administration. In an animal model, IL-2 was demonstrated to increase vascular permeability [9]. AKI is a common manifestation of capillary leak syndrome. Intravascular volume depletion resulting from increased vascular permeability leads to pre-renal AKI. Corticosteroids have been shown to be effective in ameliorating the symptoms of drug-induced capillary leak syndrome [9].

9.3 Intrinsic Causes of AKI

9.3.1 Cast Nephropathy

Depending on the definition of renal insufficiency, approximately 15–40% of patients with multiple myeloma have renal insufficiency. Cast nephropathy is the most common pathogenesis of AKI and the most common histologic lesion in

multiple myeloma patients. In the normal state, free light chains (FLC) are filtered through the glomerulus, absorbed into the proximal tubular cells and then hydrolyzed. In multiple myeloma, the increased production of FLCs by neoplastic plasma cells overwhelms the reabsorption capacity of the proximal tubular cells, and excessive FLCs bind to Tamm-Horsfall protein in the distal tubule, causing tubular obstruction. Factors that promote intratubular cast formation include volume depletion, metabolic acidosis, non-steroidal anti-inflammatory drugs, loop diuretics, and radiocontrast media. There is a general correlation between the severity of renal insufficiency and patient survival. If treated early with anti-myeloma agents, cast nephropathy has the potential to be reversed. Treatment should be initiated promptly on diagnosis, since an early reduction in serum FLCs is associated with renal recovery [10]. Although the availability of new anti-myeloma agents such as bortezomib has improved patient survival, the prognosis of cast nephropathy is worse in dialysis-dependent patients than in dialysis-independent patients [11]. Intravenous fluid therapy should be provided to decrease light chain concentration in the urine. Urine alkalization may increase the solubility of FLCs. Extracorporeal methods such as plasmapheresis and high-cut hemodialysis may benefit patients with cast nephropathy, since these therapies can reduce serum FLC concentration. However, the effectiveness of these therapies remains a matter of debate, due to the relatively small sample sizes of the trials conducted to date. Further studies are warranted to study the role of plasmapheresis in conjunction with the new generation of anti-myeloma agents.

9.3.2 Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) remains a potentially life-threatening complication that occurs after the treatment of large or rapidly proliferating malignancies. The causes of TLS include not only hematological malignancies such as acute leukemia and aggressive lymphomas but also some solid malignancies such as germinoma, neuroblastoma, and small cell carcinoma of the lung. In recent years, with the advent of molecular target therapies, increasing numbers of TLS cases have been reported. TLS occurs when intracellular contents released into the extracellular space exceed the capacity of the body's homeostatic mechanisms. Elevated production of both uric acid from the catabolism of nucleic acids and phosphate makes it easy for uric acid crystals and calcium-phosphate crystals to precipitate in the tubules and leads to subsequent intraluminal renal tubular obstruction. In the current classification system of Cario and Bishop, TLS can be classified as laboratory or clinical TLS [12]. Laboratory TLS can be diagnosed when patients meet more than two of four criteria within 3 days before or 7 days after the initiation of chemotherapy: hyperuricemia (uric acid $\geq$8.0 mg/dL), hyperphosphatemia (phosphorus $\geq$8.0 mg/dL), hyperkalemia (potassium $\geq$6.0 mEq/dL), and hypocalcemia (corrected calcium $\leq$7.0 mg/dL). A 25% change from baseline is also acceptable. Clinical TLS is defined as the presence of laboratory TLS plus any one or more of

the following: increased serum creatinine concentration (≥1.5 times the upper limit of normal), cardiac arrhythmia/sudden death, or seizure. In the treatment of cancer, awareness of the risks for developing TLS is crucial. An expert panel has developed a TLS risk classification system in which malignancies are classified as associated with a low (<1% chance), intermediate (1–5% chance), or high risk (>5% chance) of developing TLS [13]. Risk severity is dependent on cancer type, extent of disease, induction therapy type, presence or absence of renal insufficiency, and serum levels of uric acid/potassium/phosphate. The strategies for TLS management consist of prophylaxis and treatment of established TLS. The prophylactic strategies mainly involve monitoring through electrolyte checks, intravenous hydration, and administration of hypouricemic agents (allopurinol or rasburicase). Rasburicase is an Aspergillus-derived recombinant urate oxidase. Use of rasburicase for prophylaxis is recommended in patients with high risk of developing TLS [13]. Despite appropriate preventive measures, some patients will eventually develop TLS. Patients who present with TLS should receive intensive supportive care consisting of continuous monitoring, treatment of electrolyte abnormalities, administration of rasburicase, and appropriate use of renal replacement therapy.

9.3.3 Lymphomatous Infiltration of the Kidney

AKI due to lymphomatous infiltration of the kidney (LIK) is a relatively rare complication of hematopoietic malignancies. Increased intra-renal pressure due to invading lymphomas leads to tubular and microvascular compression, which is considered to contribute to the impairment of renal function. Percutaneous kidney biopsy is important for diagnosis, yet prior to kidney biopsy the diagnosis of LIK is often unsuspected. In a published series of 55 kidney biopsies revealing the diagnosis of LIK, lymphoma was suspected prior to biopsy in only ten cases [14]. Most patients respond rapidly to chemotherapy, but they frequently relapse, and long-term patient survival is poor due to the fact that LIK is typically discovered at a late stage.

9.3.4 Cancer-Associated Thrombotic Microangiopathy

Malignancy is important in the differential diagnosis of thrombotic microangiopathy (TMA). Cancer-associated TMA may appear at any stage of the disease, from early in the course to after wide dissemination of the cancer [15]. Most cases of cancer-associated TMA have been associated with disseminated carcinoma, usually mucin-producing adenocarcinomas such as gastric, breast, and colorectal cancers [16]. At present, the pathogenesis of cancer-associated TMA is unknown. Prompt chemotherapeutic treatment of an underlying cancer is important in the management of TMA in these patients, but the prognosis of cancer-associated TMA is quite poor, since a majority of patients have widely disseminated cancer [16].

9.3.5 HCT-Associated TMA

HCT-associated TMA is considered to affect approximately 10–25% of hematopoietic stem cell transplantation recipients [17]. The kidney is the most commonly affected tissue, and the histologic features of HCT-associated TMA in the kidney include thickened capillary walls, fragmented erythrocytes, occluded vascular lumens, and endothelial separation with swelling, fibrin deposition, and necrosis [17]. The clinical presentation of HCT-associated TMA is often chronic kidney disease (CKD), but sometimes life-threatening AKI. The conditioning regimen, particularly the use of total body irradiation, is thought to be the primary cause of renal endothelial damage [18]. The prognosis of HCT-associated TMA is poor, with a high mortality rate of 50–75% [19]. Calcineurin inhibitors should be withdrawn immediately when HCT-associated TMA is suspected. When immunosuppression must be continued, alternative agents such as corticosteroids, MMF, azathioprine, or others are substituted. Plasma exchange is often employed as part of the management of HCT-associated TMA, but its role is largely questioned [19]. Limited reports exist on the benefits of therapeutic agents such as rituximab (a monoclonal antibody against CD20), daclizumab (a humanized monoclonal antibody to the α-chain of the IL-2 receptor), and defibrotide. Some recent studies have also reported therapeutic response to eculizumab, a monoclonal antibody that binds C5 and inhibits the formation of membrane attack complex/C5b-9 in patients with HCT-associated TMA [19]. Further studies are needed to establish treatment strategies for HCT-associated TMA.

9.3.6 Chemotherapy-Associated Kidney Injury

9.3.6.1 Acute Tubular Necrosis

Cisplatin, a platinum-based alkylating anti-neoplastic agent, induces dose-dependent acute tubular necrosis (ATN) in up to 20–30% of patients, which is generally seen after several days after treatment with cisplatin. During renal excretion, the drug is concentrated in the kidneys, and even non-toxic concentrations in the blood may lead to toxic levels in the kidneys. Cisplatin is absorbed into the renal tubular epithelial cells through passive diffusion and active transport mediated by renal transporters such as organic cation transporter 2 (OCT2), and more recently copper transport protein 1 (Ctr1), although the proportions of mediation contributed by these transporters remain unclear. No specific treatment for cisplatin-induced ATN exists, and the proposed treatment is primarily supportive, consisting of proper hydration and adjustment of electrolyte concentrations.

9.3.6.2 Crystal Nephropathy

Methotrexate (MTX) is an anti-folate agent used in the treatment of malignant and non-malignant disease. The etiology of MTX-induced renal dysfunction is mediated by the precipitation of MTX and its metabolites in the renal distal tubules and

direct tubular injury by the formation of oxygen radicals, particularly with high-dose intravenous MTX. The risk of MTX-induced nephrotoxicity is increased by low urinary pH and volume depletion. Treatment consists of adequate hydration, urinary alkalization, leukovorin rescue, and administration of glucarbidase. Leukovorin rescue should be initiated promptly, within 24–36 h of methotrexate therapy, to reverse MTX action and reduce cellular injury in non-malignant cells. Glucarbidase, a recombinant form of the bacterial enzyme carboxypeptidase G2 that hydrolyzes methotrexate and 7-OH-methotrexate to an inactive form, can rapidly lower serum MTX levels that remain unacceptably high despite adequate hydration and urinary alkalization. The 2017 consensus guideline provided recommendations for the use of glucarbidase in patients with high-dose MTX-induced AKI and delayed MTX clearance [20]. According to these recommendations, for an MTX infusion ≤24 h, if the 36-h serum MTX concentration is above 30 μM, the 42-h concentration is above 10 μM, or the 48-h concentration is above 5 μM, and the serum creatinine is significantly elevated relative to baseline measurement, glucarbidase may be indicated. After an MTX infusion of 36–42 h, glucarbidase may be indicated when the 48-h MTX concentration is above 5 μM. Administration of glucarpidase should optimally occur within 48–60 h from the start of the MTX infusion because life-threatening toxicities may not be preventable beyond this time point.

9.3.6.3 Chemotherapy-Associated TMA

Chemotherapeutic agents such as bevacizumab, sunitinib/sorafenib, and gemcitabine can cause TMA. Vascular endothelial growth factor (VEGF) acts as the central mediator of tumor angiogenesis, stimulating the growth of new blood vessels from nearby capillaries and allowing tumors to access oxygen and nutrients. Bevacizumab (an anti-VEGF monoclonal antibody) and sunitinib/sorafenib (inhibitors of VEGF receptor tyrosine kinases) retard the growth of tumor tissue by blocking VEGF signaling. VEGF is also a potent survival factor for endothelial cells during physiological angiogenesis. However, VEGF stimulates endothelial cells to generate nitric oxide and prostaglandin, which induce endothelial cell-dependent vasodilation in arterioles and venules. In addition, in the glomerulus, VEGF is also primarily produced by podocytes and binds to VEGF receptors in endothelial cells, maintaining the integrity of the filtration barrier. Therefore, blockage of VEGF can lead to hypertension from systemic vasoconstriction with capillary rarefaction as well as to proteinuria from damage to the glomerular filtration barrier. The development of hypertension has been suggested to predict a better tumor response to treatment with these anti-VEGF therapies [21–23]. Therefore, when hypertension develops, clinicians should continue anti-cancer therapy and control blood pressure with antihypertensive agents rather than withdrawing these agents, unless severe hypertension or nephrotic-range proteinuria develop. It should also be noted that the combinational use of bevacizumab and these kinase inhibitors could cause severe hypertension and life-threatening vascular/hematological complications [24, 25].

Gemcitabine, a pyrimidine antagonist, has also been associated with TMA. Gemcitabine-associated TMA is relatively rare, with a prevalence of 0.015–0.31% [26, 27], but its mortality rate ranges from 40 to 90%. Because of this high mortality rate, immediate discontinuation of gemcitabine is essential for the treatment of gemcitabine-associated TMA. Total drug dose and previous therapy with mitomycin-C are considered to be risk factors for gemcitabine-associated TMA [28].

9.3.6.4 Interferon-Associated Nephrotic Syndrome

Glomerular injury is a relatively uncommon presentation of drug-induced renal injury but may present as nephrotic syndrome with varying degrees of renal insufficiency. The most commonly used type of interferon (IFN) is IFN α, which is used to treat hepatitis C and B viruses and various malignancies. IFN β is used to treat hepatitis C and B viruses and multiple sclerosis, whereas IFN γ is used to treat chronic granulomatous disease. Treatment with IFN has been associated with nephrotic syndrome with histologic findings of minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS) not otherwise specified (FSGS-NOS), or collapsing FSGS (C-FSGS). The IFN that is most frequently associated with nephrotic syndrome is IFN α. A case series and another report by Markowitz et al. included 24 patients treated with IFN α, 5 patients treated with IFN β, and 3 patients treated with IFN γ (8 patients with MCD, 10 patients with FSGS-NOS, and 14 patients with C-FSGS). Although this is a relatively small number of cases, patients receiving IFN α were likely to develop nephrotic syndrome after a short duration of treatment (often months after the initiation of IFN therapy). In contrast, patients receiving IFN β and γ developed nephrotic syndrome after a prolonged course of interferon treatment (often 1–2 years after the initiation of interferon therapy). Nephrotic syndrome often went into partial or complete remission after discontinuation of interferon, although no remission was achieved in some patients.

9.3.6.5 Acute Interstitial Nephritis

Acute interstitial nephritis (AIN) can develop in connection with certain monoclonal antibodies. Programmed cell death 1 (PD-1), expressed on the surface of immune cells, activated T cells, B cells, natural killer T cells, monocytes, and dendritic cells, binds to programmed cell death ligand 1 (PD-L1), expressed in cancer cells. This binding leads to T-cell inactivation and protection of the tumor cells from destruction by the immune system. Nivolumab and pembrolizumab are PD-1-blocking monoclonal antibodies that directly block the interaction between PD-1 and PD-L1. Ipilimumab is a monoclonal antibody that exerts antitumor activity by targeting CTLA-4 and activating the immune system. A member of the Ig family, CTLA4 is expressed on CD4+ T-helper cell surfaces and transmits an inhibitory signal to T cells. Blocking CTLA-4 prevents this signal and improves antitumor response.

Cortazar et al. reported a case series of 12 patients with AIN with or without podocytopathy induced by the administration of nivolumab, pembrolizumab, and ipilimumab [29]. These checkpoint inhibitors (CPI) are believed to rescue the suppression of T cells, which allows activated T cells to migrate into the kidney. However, most patients who develop AIN are taking other concomitant drugs that may be involved in this disease's development, and it cannot be excluded that the synergistic effects between CPIs and concomitant drugs contribute to the development of kidney lesions. Whereas the onset of podocytopathy induced by administration of an anti-CTLA-4 antibody has been reported, at present, there are no reported cases of podocytopathy induced by administration of PD-1 antagonists. In the study reported by Cortazar et al. [29], after AKI was confirmed by kidney biopsy as AIN or podocytopathy, the implicated checkpoint inhibitor was discontinued and glucocorticoids were administered in 10 of the 12 patients, resulting in complete and partial improvement in renal function in 2 and 7 patients, respectively. Two patients with AIN who were not given corticosteroids showed no improvement in renal function. Only two patients were later re-challenged with their respective CPIs (pembrolizumab and ipilimumab) following improvement of AKI after steroid therapy; upon re-challenge, neither developed AKI. Re-challenge with CPIs may be reasonable if other potentially offending agents are withdrawn and AIN has resolved, although optimal dosing regimens and treatment durations remain unknown. Accumulation of more cases is needed to develop a proper management protocol for renal toxicities associated with CPIs.

9.3.7 Paraneoplastic Glomerulopathy

9.3.7.1 Solid Malignancy-Associated Membranous Nephropathy

Membranous nephropathy (MN) is the most commonly reported glomerular disease in patients with carcinoma. The overall prevalence of cancer in participants with MN has been reported to be 5–25%. The solid malignancies most frequently associated with MN are lung and gastrointestinal carcinomas. In 2009, Beck et al. identified the transmembrane glycoprotein M-type phospholipase A2 receptor (PLA2R) as the major target podocyte antigen involved in the majority of adult idiopathic MN cases [30]. They showed that IgG4 was the predominant subclass of anti-PLA2R antibodies co-localized with the PLA2R antigen with the subepithelial immune deposits in patients with idiopathic MN, whereas IgG1 and IgG2 are the prevailing subclasses in patients with solid malignancy-associated MN. Although it has been suggested that anti-PLA2R antibodies could be useful in distinguishing between idiopathic and malignancy-associated MN, it was recently reported that anti-PLA2R antibodies also exist in cancer-associated MN [31]. Thus the usefulness of anti-PLA2R antibodies remains controversial; at present, patients with MN without evident secondary cause should be screened for malignancy regardless of the presence of anti-PLA2R antibodies. More recently, thrombospondin type 1 domain-containing 7A (THSD7A) was identified as an additional antigen in

patients with MN [32]. However, the usefulness of anti-THSD7A antibodies for discrimination of cancer-associated MN is undetermined. It has been reported that patients with THSD7A-antibody positive MN have a high rate of developing cancer (8 of 40 MN patients) [33], though other studies have found that the coexistence of cancer was not high in patients with THSD7A-antibody positive MN [34]. Removal of the underlying cancer can lead to the amelioration of the symptoms of MN [35].

9.3.7.2 Hematologic Malignancy-Associated MCD

MCD is the most common paraneoplastic manifestation of Hodgkin's lymphoma, occurring in 0.4% of patients, and less commonly, in connection with other lymphoproliferative disorders as well as solid malignancies. MCD may result from immune cell dysfunction in Hodgkin's lymphoma that leads to the release of a glomerular permeability factor [36]. Lymphoma-associated MCD is frequently resistant to treatment with glucocorticoids and immunosuppressive agents [37]. Therefore, a poor response to the treatment of MCD with these agents should prompt an investigation for an underlying malignancy. Effective treatment of lymphoma is associated with the disappearance of MCD [37].

9.4 Post-renal Causes of AKI

9.4.1 Extra-renal Obstruction Due to Malignancies and Retroperitoneal Fibrosis

Post-renal causes should be considered in cancer patients presenting with AKI. Ureteric obstruction could be caused by a wide range of malignancies, most commonly gastrointestinal, urologic, and gynecologic malignancies. Retroperitoneal fibrosis, which is induced by radiation therapy of the abdomen and pelvis, or malignancies such as malignant lymphoma and a variety of solid tumors, can also cause post-renal AKI. Anuria raises suspicion for the diagnosis of obstruction; however, partial obstruction may lead to non-oliguric AKI. The diagnosis of obstruction can be confirmed with ultrasonography or computed tomography (CT) scan by the presence of hydronephrosis or hydroureter. It should be noted, however, that ureteric obstruction can present in the absence of hydronephrosis or hydroureter, in cases of retroperitoneal fibrosis or early obstruction by malignancies.

Treatment of post-renal AKI aims to relieve obstruction by percutaneous nephrostomy or ureteral stenting. Despite successful relief of the obstruction, however, patients often experience complications such as urinary tract infection and obstruction of nephrostomy tubes or stents. Recovery of renal function is dependent on the severity and duration of the obstruction. Overall patient survival is poor, which is reflected by the high frequency of malignancies at advanced stages.

9.5 Summary

This chapter reviewed the etiologies of AKI related to cancer and the management strategies for each type. Remarkable progress in anti-cancer therapy has lengthened survival times for cancer patients, and this has made renal disease a growing concern in this population. Cancer patients are at increased risk of developing AKI during cancer treatment. In the future, we must not only achieve a better understanding of the etiologies of AKI in cancer patients but also establish better strategies for treating cancer patients with CKD.

The numbers of cancer patients with CKD have increased for several reasons. First, in recent years, the interconnectedness of AKI and CKD has been emphasized, and it has been suggested that patients presenting with AKI have an increased risk of developing CKD [38]. As shown in the general population, cancer patients who have presented with AKI are also considered to have an increased risk of developing CKD. Second, recent advances in pre-dialysis and dialysis care have led to an increasing number of patients who survive CKD and are later diagnosed with cancer. The coexistence of CKD with cancer reduces the likelihood that patients will receive optimal anti-cancer treatment. It has been shown that a remarkable number of CKD patients are treated with potentially nephrotoxic agents or agents for which dosage must be adjusted [39]. Many chemotherapeutic agents are cleared by the kidney, which can lead to alterations in pharmacokinetics, elevated blood levels of the drugs, and increased toxicity in CKD patients. It is hoped that a better understanding of kidney complications in cancer patients will lead to improved treatment in these patients.

References

1. Christiansen CF, Johansen MB, Langeberg WJ, Fryzek JP, Sørensen HT. Incidence of acute kidney injury in cancer patients: a Danish population-based cohort study. Eur J Intern Med. 2011;22(4):399–406.
2. Soares M, et al. Prognosis of critically ill patients with cancer and acute renal dysfunction. J Clin Oncol. 2006;24(24):4003–10.
3. Salahudeen AK, et al. Incidence rate, clinical correlates, and outcomes of AKI in patients admitted to a comprehensive cancer center. Clin J Am Soc Nephrol. 2013;8(3):347–54.
4. Rosner MH, Dalkin AC. Electrolyte disorders associated with cancer. Adv Chronic Kidney Dis. 2014;21(1):7–17.
5. Coppell JA, et al. Hepatic veno-occlusive disease following stem cell transplantation: incidence, clinical course, and outcome. Biol Blood Marrow Transplant. 2010;16(2):157–68.
6. Parikh CR, Coca SG. Acute renal failure in hematopoietic cell transplantation. Kidney Int. 2006;69(3):430–5.
7. Richardson PG, et al. Phase 3 trial of defibrotide for the treatment of severe veno-occlusive disease and multi-organ failure. Blood. 2016;127(13):1656–65.
8. Rosenberg SA, et al. Observations on the systemic administration of autologous lymphokine-activated killer cells and recombinant interleukin-2 to patients with metastatic cancer. N Engl J Med. 1985;313(23):1485–92.

9. Rosenstein M, Ettinghausen SE, Rosenberg SA. Extravasation of intravascular fluid mediated by the systemic administration of recombinant interleukin 2. J Immunol. 1986;137(5):1735–42.
10. Hutchison CA, et al. Early reduction of serum-free light chains associates with renal recovery in myeloma kidney. J Am Soc Nephrol. 2011;22(6):1129–36.
11. Dimopoulos MA, et al. Bortezomib-based triplets are associated with a high probability of dialysis independence and rapid renal recovery in newly diagnosed myeloma patients with severe renal failure or those requiring dialysis. Am J Hematol. 2016;91(5):499–502.
12. Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. Br J Haematol. 2004;127(1):3–11.
13. Cairo MS, Coiffier B, Reiter A, Younes A, Panel TE. Recommendations for the evaluation of risk and prophylaxis of tumour lysis syndrome (TLS) in adults and children with malignant diseases: an expert TLS panel consensus. Br J Haematol. 2010;149(4):578–86.
14. Törnroth T, Heiro M, Marcussen N, Franssila K. Lymphomas diagnosed by percutaneous kidney biopsy. Am J Kidney Dis. 2003;42(5):960–71.
15. Copelovitch L, Kaplan BS. The thrombotic microangiopathies. Pediatr Nephrol. 2008;23(10):1761–7.
16. Lesesne JB, et al. Cancer-associated hemolytic-uremic syndrome: analysis of 85 cases from a national registry. J Clin Oncol. 1989;7(6):781–9.
17. Laskin BL, Goebel J, Davies SM, Jodele S. Small vessels, big trouble in the kidneys and beyond: hematopoietic stem cell transplantation-associated thrombotic microangiopathy. Blood. 2011;118(6):1452–62.
18. Humphreys BD, Soiffer RJ, Magee CC. Renal failure associated with cancer and its treatment: an update. J Am Soc Nephrol. 2005;16(1):151–61.
19. Gavriilaki E, Sakellari I, Anagnostopoulos A, Brodsky RA. Transplant-associated thrombotic microangiopathy: opening Pandora's box. Bone Marrow Transplant. 2017;52(10):1355–60.
20. Ramsey LB, et al. Consensus guideline for use of glucarpidase in patients with high-dose methotrexate induced acute kidney injury and delayed methotrexate clearance. Oncologist. 2018;23(1):52–61.
21. De Stefano A, Carlomagno C, Pepe S, Bianco R, De Placido S. Bevacizumab-related arterial hypertension as a predictive marker in metastatic colorectal cancer patients. Cancer Chemother Pharmacol. 2011;68(5):1207–13.
22. Rixe O, Billemont B, Izzedine H. Hypertension as a predictive factor of Sunitinib activity. Ann Oncol. 2007;18(6):1117.
23. Li Y, et al. Incidence and risk of sorafenib-induced hypertension: a systematic review and meta-analysis. J Clin Hypertens (Greenwich). 2014;16(3):177–85.
24. Feldman DR, et al. Phase I trial of bevacizumab plus escalated doses of sunitinib in patients with metastatic renal cell carcinoma. J Clin Oncol. 2009;27(9):1432–9.
25. Azad NS, et al. Combination targeted therapy with sorafenib and bevacizumab results in enhanced toxicity and antitumor activity. J Clin Oncol. 2008;26(22):3709–14.
26. Humphreys BD, et al. Gemcitabine-associated thrombotic microangiopathy. Cancer. 2004;100(12):2664–70.
27. Fung MC, et al. A review of hemolytic uremic syndrome in patients treated with gemcitabine therapy. Cancer. 1999;85(9):2023–32.
28. Perazella MA. Onco-nephrology: renal toxicities of chemotherapeutic agents. Clin J Am Soc Nephrol. 2012;7(10):1713–21.
29. Cortazar FB, et al. Clinicopathological features of acute kidney injury associated with immune checkpoint inhibitors. Kidney Int. 2016;90(3):638–47.
30. Beck LH, et al. M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. N Engl J Med. 2009;361(1):11–21.
31. Wang J, et al. Circulating antibodies against thrombospondin type-I domain-containing 7A in Chinese patients with idiopathic membranous nephropathy. Clin J Am Soc Nephrol. 2017;12(10):1642–51.
32. Tomas NM, et al. Thrombospondin type-1 domain-containing 7A in idiopathic membranous nephropathy. N Engl J Med. 2014;371(24):2277–87.

33. Hoxha E, et al. An indirect immunofluorescence method facilitates detection of thrombospondin type 1 domain-containing 7A-specific antibodies in membranous nephropathy. J Am Soc Nephrol. 2017;28(2):520–31.
34. Sharma SG, Larsen CP. Tissue staining for THSD7A in glomeruli correlates with serum antibodies in primary membranous nephropathy: a clinicopathological study. Mod Pathol. 2018;31(4):616–22.
35. Beauvais P, Vaudour G, Boccon Gibod L, Levy M. Membranous nephropathy associated with ovarian tumour in a young girl: recovery after removal. Eur J Pediatr. 1989;148(7):624–5.
36. Grimbert P, Audard V, Remy P, Lang P, Sahali D. Recent approaches to the pathogenesis of minimal-change nephrotic syndrome. Nephrol Dial Transplant. 2003;18(2):245–8.
37. Audard V, et al. Minimal change nephrotic syndrome and classical Hodgkin's lymphoma: report of 21 cases and review of the literature. Kidney Int. 2006;69(12):2251–60.
38. Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. Kidney Int. 2012;81(5):442–8.
39. Janus N, et al. Cancer and renal insufficiency results of the BIRMA study. Br J Cancer. 2010;103(12):1815–21.

Chapter 10
Community- and Hospital-Acquired Acute Kidney Injury

Sadudee Peerapornratana and Nattachai Srisawat

Abstract Community-acquired acute kidney injury (CA-AKI) has been found to be more common than hospital-acquired acute kidney injury (HA-AKI), even though the incidence is underestimated. Data comparing these two phenotypes of AKI are limited using various definitions. CA-AKI appears to be more common in male and younger patients. Preexisting chronic kidney disease is the most important risk factor for both CA- and HA-AKI. Difficulty in recognition of AKI in the community may lead to higher severity of CA-AKI compared to HA-AKI. Unlike HA-AKI, the causes of CA-AKI vary by geography, environment, socioeconomic status of patients, and level of hospital care. Interestingly, there are some unique spectrums of CA-AKI in the tropic areas. Despite the difference in epidemiologic profile between CA- and HA-AKI, the long-term outcomes are similar.

Keywords CA-AKI · HA-AKI · Epidemiology · Outcome

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10.1 Introduction

The concept of community- and hospital-acquired acute kidney injury (CA- and HA-AKI) has been mentioned in literature since 1980 [1–6]. However, there is no clear definition of the two terms as over time there have been improvements in defining AKI. Furthermore, most of the AKI data were derived from hospital-based studies and there are limited data on CA-AKI for which the prevalence is underestimated. The two terms differ not only in the place where AKI developed, but also in their epidemiology, etiologies, and outcomes. This chapter aims to compare community- and hospital-acquired AKI in every aspect.

10.2 Definitions

During the last few decades, the criteria for diagnosing and classifying AKI became more standardized as it evolved from RIFLE to KDIGO [7, 8]. These AKI definitions mainly focus on an acute increase in serum creatinine level and/or a decrease in urine output within a certain period and were used in defining CA-AKI and HA-AKI. In the hospital setting, we have well-recorded temporal changes in serum creatinine and/or urine output making KDIGO criteria feasible for identifying patients who develop AKI. Conversely, in the community setting, KDIGO is less applicable.

Timing of CA-AKI detection is an important issue that needs to be considered to make a diagnosis of AKI. In contrast to patients who develop AKI in the hospital, in which serum creatinine and urine output have been serially monitored, those who develop AKI in the community might be recognized and diagnosed in various settings (timing and places), either in their own community, at outpatient clinics, and at the emergency department or even a few days after hospitalization. Thus, variable definitions of CA-AKI have been used in the literature (Fig. 10.1). In most studies, patients are considered to have CA-AKI when the admission serum creatinine is elevated and meet the diagnostic criteria of AKI (either by RIFLE, AKIN, or KDIGO). Some studies considered patients as having CA-AKI by using data collected in the first 48 hours after hospital admission [9, 10]. Some studies, for a more sophisticated adjudication of CA-AKI, used the temporal change in the magnitude of serum creatinine during hospitalization [11, 12]. For HA-AKI, the definition used also varies across studies. Table 10.1 summarizes the various definitions of CA-AKI and HA-AKI, which have been proposed in the literature.

10.3 Epidemiology of CA-AKI and HA-AKI

The worldwide-pooled incidence rate of AKI is 21% [13]. However, this estimate is mainly derived from HA-AKI population in high-income countries setting. It does not reflect the exact incidence of AKI, particularly in the community

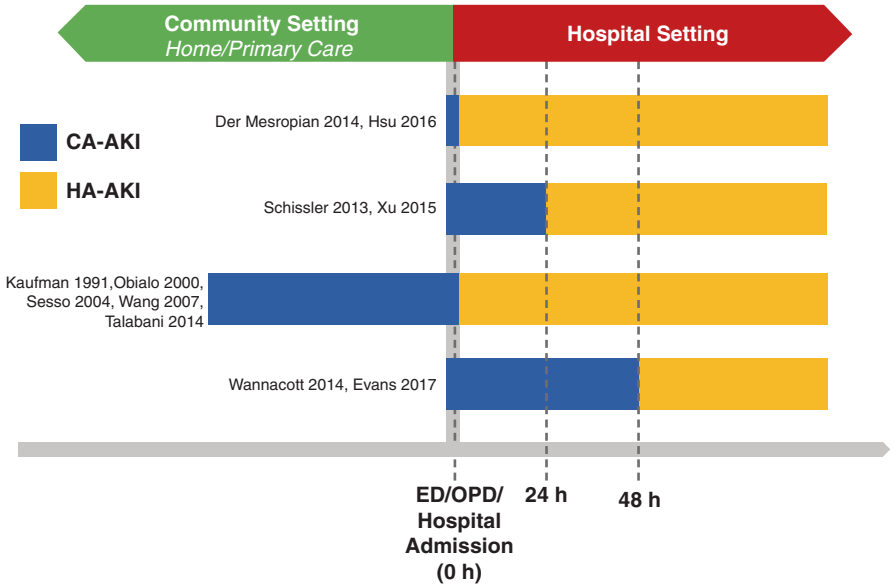

Fig. 10.1 Variable timing of CA-AKI diagnosis used in the literature. CA-AKI has been diagnosed either before or up to 48 h after hospital admission

setting and in low-income countries. Only 7 out of the 147 studies in this meta-analysis focused on CA-AKI which showed the incidence rate of 8.3% for CA-AKI [13].

10.4 High-Income Countries

Over a 17-month period, Kaufman et al. prospectively screened patients admitted to a single veteran affairs hospital in Boston having acute elevations in serum creatinine (>2 mg/dL) and found that the incidence of CA-AKI was 1% of all hospital admissions [6]. Other retrospective studies in the United States, using different definitions, identified a larger number of patients with CA-AKI than HA-AKI [11, 14–16]. They found that the incidence of CA-AKI was 0.7–0.8% of all hospital admissions, about three times more prevalent than HA-AKI (Table 10.1). Liano et al. performed a 9-month prospective population-based study in Madrid covering over four million people and reported that 60% of AKI patients were recognized on admission (CA-AKI) while the remaining 40% developed AKI during hospitalization (HA-AKI) [5]. Wonnacott et al. reported an incidence of 4.3% for CA-AKI compared to 2.1% for HA-AKI from two general hospitals in the UK [9].

Table 10.1 Epidemiology and definition of CA-AKI and HA-AKI

Study	Country	Type of study	Study period	Source population	Definition of CA-AKI and HA-AKI (criteria used)	Number of AKI cases	Incidence of AKI in hospital admission (%)			% of patients with AKI	
							Total	CA-AKI	HA-AKI	CA-AKI	HA-AKI
Kaufman, 1991 [6]	USA	Prospective (single center)	17 months	All hospital admissions	CA-ARF: screening sCr >2 mg/dL and acute elevation in sCr occurring outside hospital	100	1	1	NA	100	NA
Liano, 1996 [5]	Spain	Prospective (multicenter)	9 months	200,464 hospital admissions	ARF: sudden rise in sCr to >177 μmol/L (2 mg/dL) was found in patients with normal renal function, or the sudden rise (≥50%) was observed in patients with previous mild-to-moderate chronic renal failure	748	0.4	N/A	N/A	60	40
Obialo, 2000 [14]	USA	Retrospective cohort (single center)	3 years (1994–1996)	Patients diagnosed with ARF at hospital discharge	CA-ARF: ARF developed outside the hospital and diagnosed at hospital admission HA-ARF: ARF developed during hospitalization by non-renal–related problems	100	0.7	0.55	0.15	79	21

Sesso, 2004 [48]	Brazil	Prospective cohort (single center)	3 years (1999–2002)	Patients diagnosed with ARF at admission	ARF: a creatinine level >1.4 mg/dL for men or >1.3 mg/dL for women CA-ARF: ARF developed outside the hospital and diagnosed at hospital admission HA-ARF: ARF developed during hospitalization by non-renal–related problems	325	N/A	N/A	N/A	52.6	47.4
Wang, 2007 [24]	China	Retrospective cohort (single center)	10 years (1994–2003)	Patients with ARF by ICD-9 codes	CA-ARF: ARF developed outside the hospital HA-ARF: ARF developed during hospitalization by non-renal–related problems	205	N/A	N/A	N/A	59.5	40.5
Schissler, 2013 [15]	USA	Retrospective cohort (single center)	7 years (1999–2007)	50,204 hospitalized patients	CA-AKI: the admission sCr was elevated to meet AKI criteria HA-AKI: AKI that occurred at 24 h or longer after hospitalization (RIFLE)	422	0.8	0.6	0.2	79.4	20.6
Wonnacott, 2014 [9]	UK	Retrospective cohort (multicenter)	6 months (2011–2012)	15,976 hospitalized patients	CA-AKI: the first sCr within 48 h of admission meet the AKI criteria (AKIN)	1020	6.4	4.3	2.1	67.3	32.7
Der Mesropian, 2014 [16]	USA	Retrospective cohort (multicenter)	2 years (2004–2005)	All hospital admissions	CA-AKI: AKI at hospital admission HA-AKI: AKI that occurred during the hospitalization (RIFLE)	718	N/A	N/A	N/A	78.0	22.0

(continued)

Table 10.1 (continued)

Study	Country	Type of study	Study period	Source population	Definition of CA-AKI and HA-AKI (criteria used)	Number of AKI cases	Incidence of AKI in hospital admission (%)			% of patients with AKI	
							Total	CA-AKI	HA-AKI	CA-AKI	HA-AKI
Talabani, 2014 [23]	UK	Retrospective cross-sectional (single center)	1 month (2009)	31,591 patients having sCr measurement in the communities	CA-AKI: AKI by KDIGO criteria identified by blood collected at community setting (either an acute hospital assessment ward, the hospital outpatient department, or requested by the general practice)	230	N/A	N/A	N/A	100	N/A
Warnock, 2016 [11]	USA	Retrospective cohort (multicenter)	4 years (2009–2013)	82,403 hospitalized patients	HA-AKI: the minimum sCr preceding the peak sCr, and an increased sCr above the AKI threshold Transient HA-AKI (THA-AKI): the peak preceding the minimum sCr, with a significant decrease in sCr	28,720	35	25 (THA-AKI)	10	70.5 (THA-AKI)	29.5
Stucker, 2017 [26]	Switzerland	Prospective cohort (single center)	8 weeks (2013)	8464 emergency department admissions	CA-AKI: CA-ACKI (community-acquired acute on chronic kidney injury): baseline eGFR <60 mL/min/1.73 m^2 with acute rise of sCr (KDIGO)	445	5.3	5.3	N/A	N/A	N/A
Yang, 2015 [18]	China	Retrospective, cross-sectional (nationwide)	2 months (2013)	2,223,230 hospitalized patients	AKI by KDIGO criteria	7604	0.99	N/A	N/A	54.4	45.6

Xu, 2015 [19]	China	Retrospective (multicenter)	1 year (2013)	659,945 hospitalized patients	CA-AKI: meet one of the followings (1) patient was admitted with AKI according to diagnosis code; (2) sCr change on the first day of admission met the KDIGO definition; and (3) sCr on admission was ≥1.4 mg/dL in men or ≥1.1 mg/dL in women and ≥1.5 fold of the minimal sCr level during hospitalization HA-AKI: patients who developed AKI but did not meet CA-AKI criteria	14,985	11.6	2.5	9.1	30.4	69.6
Hsu, 2016 [47]	Taiwan	Retrospective (multicenter)	5 years (2010–2014)	734,340 hospital admissions	CA-AKI: only index sCr measured in the emergency department HA-AKI: the highest measured sCr during hospitalization increased at least 1.5 times above admission value RIFLE	11,542	1.7	N/A	N/A	54.5	26.9

(continued)

Table 10.1 (continued)

Study	Country	Type of study	Study period	Source population	Definition of CA-AKI and HA-AKI (criteria used)	Number of AKI cases	Incidence of AKI in hospital admission (%)			% of patients with AKI	
							Total	CA-AKI	HA-AKI	CA-AKI	HA-AKI
Wang, 2017 [12]	China	Retrospective, cross-sectional (multicenter)	2 months (2013)	374,286 hospital admissions	CA-AKI: the patient met any of the following criteria (KDIGO): (1) an increased sCr level at admission and a trend of decreasing sCr levels during the hospital stay; or (2) an increased sCr level at admission and an sCr level that continued to increase or remained at a high level during the hospital stay, with preadmission sCr values establishing the existence of AKI; or (3) normal kidney function upon admission with sCr levels that began to increase and AKI that could be defined within 2 days after hospitalization combined with causal factors that were determined (by the nephrologists among the investigators) to be present prior to admission based on review of medical records	4136	2.0	1.1	0.9	54.4	45.6

Evans, 2017 [10]	Malawi	Prospective (single center)	3 months	All hospital admissions	CA-AKI: AKI (KDIGO) that is detected at or within 48 h of hospital admission	892	17.2	17.2	NA	100	NA
Srisawat (unpublished)	Thailand	Prospective (multicenter)	12 months	5006 ICU admissions	CA-AKI: AKI that developed within the first day of ICU admission HA-AKI: AKI that developed after 48 h of ICU admission (KDIGO)	2471	50.2	37.3	12.9	74.3	25.7

10.5 Low- and Middle-Income Countries

Data on CA-AKI from low- and middle-income countries are scant and heterogeneous. The studies use different definitions of AKI and are primarily from single center from different regions or from large academic hospitals which tend to specifically focus on a high-risk population (e.g., critically ill patient, sepsis, undergoing cardiac surgery) [13, 17]. Due to this variability in study designs, the incidence of CA-AKI in these countries is underestimated. Data from a recent cross-sectional nationwide survey in China, the largest developing country which covered over 2.2 million hospitalized adult patients, found a rate of AKI of 1% [18]. Of these AKI patients, 50.5 and 65.8% were CA-AKI diagnosed in academic hospitals and in local hospitals, respectively [18]. Another large study in China of 659,945 hospitalized adults reported the incidence of CA-AKI was 2.5% as compared to 9.1% for HA-AKI [19].

The epidemiology in low- and middle-income countries is different from the high-income ones. The largest prospective observational study from Southeast Asia by Srisawat et al. included 5006 patients from 17 ICUs across Thailand and reported that 74.3% of ICU AKI was community acquired (37.3% of ICU patients), while 25.7% was acquired in the ICU (12.9% of ICU patients) (unpublished data). However, this report could not provide the true incidence of CA-AKI because the data collection started from ICU admission, not hospital admission.

The prevalence of AKI in low- and middle-income regions is underestimated. AKI data from rural areas in Asia, South America, and Africa are sparse. Some of these regions still lack or have insufficient monitoring of serum creatinine in hospitalized patients [17, 20]. Although the available data suggest a high prevalence of CA-AKI in these areas, the true magnitude is unknown. A recent prospective study from Malawi, a low-income and resource-poor area in Africa, reported an incidence of CA-AKI of 17.2% of all medical admissions, and about 60% of these AKI cases were HIV-infected and more likely to have severe AKI [10]. A systematic review from sub-Saharan African countries of 1,403 adult patients found that 80% of AKI cases were community acquired and about 70% required dialysis [21].

10.6 Demographic Differences Between CA-AKI and HA-AKI

In general, the mean age of AKI patients ranges between 50 and 75 years [22], and patients with CA-AKI are significantly older than those without AKI [23]. Some studies also showed that patients with CA-AKI are younger than those with HA-AKI [9, 24]. However, the age distribution of patients with CA-AKI is markedly different between high-income and low- and middle-income countries (Table 10.2). In high-income countries, the AKI population is predominantly older, while in the low- and middle-income countries AKI generally affects the young. A prospective study from

Table 10.2 Characteristics of CA-AKI and HA-AKI

	CA-AKI	HA-AKI
Epidemiologic data	Limited	Excellent
Age	High-income countries: elder Low-middle income: younger	Elder
Gender	Male predominance in low- and middle-income countries	No predominance
Risk factors	Preexisting CKD Male gender Diuretic used	Preexisting CKD Other medical comorbidities are more common
Recognition	High-income countries: good recognition in primary care and outpatient clinic Low-middle income: non-recognition or under-recognition	Standard recognition in hospital
Etiologies	High-income countries: similar with HA-AKI Low-middle income or tropical areas: diarrhea, tropical infection, exogenous toxins (from animals and plants), obstetric complication are common	Sepsis, hypovolemia, drug-associated
Severity	More severe at presentation	Less severe at presentation
ICU and hospital LOS	Shorter	Longer
Short-term outcome	Lower in-hospital mortality (high in-hospital mortality in low-income countries due to lack of resources and delayed access to optimal care)	Higher in-hospital mortality
Long-term outcome (ESRD and death up to 3 years)	Similar	Similar
Nephrology referral	Higher	Lower
Prevention	More preventable	Difficult to prevent

Malawi reported a median age of 41 years (range 30–52 years) [10], which is consistent with a study from India where the average age was 40 years [25].

In the high-income countries, some data suggested there is no gender difference in the prevalence of CA-AKI or HA-AKI while other studies suggested AKI affects males more than females. In the low- and middle-income countries, there is a higher male-to-female ratio [10, 25].

In both high-income and low- and middle-income countries, patients with CA-AKI have more severe AKI than those with HA-AKI. Roughly one third of patients with CA-AKI have preexisting CKD [9, 26], but the underlying CKD is not associated with developing more severe AKI [15]. Patients with CA-AKI tend to have a lower rate of stage 1 and 2 (or Risk and Injury) AKI and a higher rate of stage 3 (or Failure) AKI compared to those with HA-AKI [9, 10, 15, 16, 19, 22]. A study from Malawi found that 60% of CA-AKI patients were classified as stage 3 [10] while a study from UK found that two thirds of the CA-AKI patients were classified

as stage 1 AKI and only 10% as stage 3 AKI [23]. This difference can be attributed to the difficulty in recognizing AKI patients in the community setting especially, since AKI has no obvious signs or symptoms.

10.7 Difference in Recognition Patterns Between CA-AKI and HA-AKI

Most of the CA-AKI is detected in the hospital after patients seek medical attention due to other issues and often they get diagnosed with severe AKI.

Early recognition of AKI is challenging even in the high-income countries where facilities and resources are available for AKI diagnosis. Several studies reported different incidence rates of CA-AKI identified in the primary care setting [23, 27–29]. In a recent UK study, about half (48.2%) of the CA-AKI was diagnosed in the community (35.6% in the primary care and 12.6% following a visit to the hospital outpatient clinic) and another half was identified in the hospital [23]. The median time from AKI identification to hospital admission was 33 days for stage 1, 12 days for stage 2, and 1 day for stage 3 ($p < 0.05$) with a median length of stay of 2, 4, and 7 days, respectively ($p < 0.05$) [27]. Moreover, Barton et al. found that patients identified as having stage 1 AKI in the primary care setting were not having their serum creatinine levels measured within 14 days of assessment (49%) [27]. Inadequate monitoring of renal function in the primary care setting could lead to poor outcomes.

Delayed access to hospital care and differences in socioeconomic status of patients result in late diagnosis of AKI. A recent nationwide survey from China reported a non-recognition rate of AKI of about 74% [18]. Other low- and middle-income countries have been considered as having a high rate of non-recognition as well [17]. The prevalence of AKI in these regions has been underreported and should to be addressed by public health organizations and healthcare professionals in order to improve the diagnosis of AKI and consequently patient outcomes.

Despite access to better diagnostic tools, even in the hospital setting early recognition of AKI could be improved. In a single center study from Switzerland, Stucker and colleague found that AKI was mentioned in 53.1% of the medical records within the emergency department and 46% of patients with stage 1 and 88% of patients with stage 3 were identified by the physician in charge. Adequate work-up for AKI was performed in 57% of patients [26].

10.8 Comparison of Risk Factors of CA-AKI and HA-AKI

In terms of underlying comorbidities, results from recently published studies are not consistent. Patients with AKI share common underlying medical conditions such as older age, diabetes mellitus, hypertension, preexisting CKD, and coronary heart

disease. However, medical comorbidities are more common among patients with HA-AKI. Patients with CA-AKI have less hypertension, diabetes mellitus, chronic heart failure, chronic kidney disease, and coronary heart disease [9, 15, 16]. However, a study from China found that preexisting CKD is a major risk factor for both CA-AKI and HA-AKI [19]. One study in patients with preexisting CKD reported that males and use of diuretics (not ACEIs or ARBs) were risk factors for CA-AKI [26]. Concurrent medical conditions such as community-acquired pneumonia might also be associated with an increased risk of CA-AKI [30].

10.9 Specific Etiologies of CA-AKI

The spectrum of AKI is variable across the world and depends on different factors in each region, such as geography, ecology, socioeconomic status, and the level of hospital care [31, 32]. In high-income countries, AKI patients are usually older and have more comorbidities [31], while in low- and middle-income countries, the causes of AKI vary depending on the region and level of care. The etiology of AKI in tertiary hospitals is similar across regions, but in rural areas AKI is usually community acquired and can be attributed to infectious diseases, diarrheal syndromes, toxins, herbal medicines, or obstetric complications [31, 32].

The common causes of HA-AKI were sepsis, renal hypoperfusion, and nephrotoxic drugs (antibiotics, contrast media), but each area has different etiologies [15, 17, 20]. On the other hand, patterns of CA-AKI are different between high-income and low- and middle-income countries. In the United States, prerenal azotemia (e.g., gastrointestinal diseases or poor oral intake), drug-induced AKI (e.g., nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin converting enzyme inhibitors (ACEI), and diuretics), pigmented or crystal-induced nephropathy, and urinary tract obstruction are common causes of CA-AKI [14, 15]. Also, nephrotoxicity from prescription drugs such as antibiotics and over-the-counter painkillers become more common. A recent study by Rennie et al. found a 16% increase in the incidence of AKI between 2008 and 2012, and in the same period the use of sulfonamides, trimethoprim, and nitrofurantoin increased by 47% [33]. Many large epidemiologic studies and meta-analyses showed an association between the use of NSAIDS and the risk of developing CA-AKI [34–39].

In the low- and middle-income countries, CA-AKI has unique characteristics in each region. In China, intrinsic renal disease is the most common cause of CA-AKI (70%) according to a large cohort study [24]. However, a large Chinese national survey found that prerenal azotemia (49%) and nephrotoxic drugs are the most common causes of CA-AKI followed by intrinsic renal disease and urinary tract obstruction [12]. Antimicrobial agents, NSAIDs, and herbal medicine are the most common types of nephrotoxic drugs in China [18, 19]. Toxicity from traditional or herbal medicine is an important cause of CA-AKI across Asian countries due to the unique and distinct cultural behavior [17].

Tropical countries have a unique and broader spectrum of AKI due to the difference in ecological and socioeconomic factors from other parts of the world [32]. Few studies reported on the epidemiology of AKI in the tropics and identified an array of factors associated with AKI. Vector-borne infections such as malaria, dengue, scrub typhus, leptospirosis, hanta hemorrhagic fever, and melioidosis are common causes for AKI (Table 10.3) [17, 32]. Exogenous toxins (plant-derived, animal-derived, and chemical toxins) such as traditional or herbal medicines, certain species of mushrooms (direct tubular toxicity and hypovolemia), djenkol beans (intratubular obstruction and acute tubular necrosis), star fruit juice, poisonous snake bites, and bee and wasp stings are also commonly found in the tropical regions [17, 32]. Extremely hot summer temperatures can cause heat strokes which often lead to AKI-related complications. Suffering from natural disasters such as

Table 10.3 Etiologies of CA-AKI in the tropics [32]

Infections
Malaria
Dengue fever
Scrub typhus
Leptospirosis
Hanta hemorrhagic fever with renal syndrome
Melioidosis
Diarrheal diseases (*E. coli*, *E. histolytica*, *Shigella*, cholera, viral gastroenteritis)
Exogenous toxins
Herbal medicines
Impila food plants
Djenkol beans
Mushroom
Snake bites
Wasp, hornet, and bee stings
Jellyfish sting
Spider bite
Scorpion sting
Carp gallbladder or bile
Chemical nephrotoxins
Ethylene glycol
N,N′-dimethyl-4,4′-bipyridinium dichloride
Ethylene dibromide
Copper sulfate
Chromic acid
Environmental factors
Heat stroke
Natural disasters
Other causes
Obstetric complications
Intravascular hemolysis (G-6-PD deficiency)

earthquakes, landslides, floods, typhoons, and tsunamis are often accompanied by AKI. Rhabdomyolysis is a common cause of AKI after victims are trapped in collapsed buildings [40, 41]. Even though obstetric AKI has been eliminated in the high-income countries due to advances in the health care system and socioeconomic status [42], pregnancy-related AKI is still problematic in the tropics due to suboptimal antenatal care, out-of-hospital delivery, and unsafe abortion practices [17, 32].

Over time the etiology of CA-AKI has changed in the low- and middle-income countries. Prakash et al. retrospectively observed the change in the epidemiology of CA-AKI in India over 26 years and found that diarrhea-related AKI, obstructive uropathy, and obstetric-related AKI significantly decreased since 1996, while malaria-, sepsis-, and liver disease-related AKI increased [25]. In endemic areas, AKI can seriously complicate malarial infection with mortality rates reaching 45%. In India, up to 13% of CA-AKI cases are related to malaria (*Plasmodium falciparum* or *Plasmodium vivax*) [43]. This is a reminder that infections are still the leading cause of AKI in tropical areas. Leptospirosis is another common infectious disease that causes AKI in tropical and subtropical countries such as Thailand, Singapore, India, and Brazil [44, 45]. AKI occurred in 88% of patients with leptospirosis of which 55% had stage 3 AKI [45]. In sub-Saharan Africa, the majority of CA-AKI cases are caused by sepsis and hypoperfusion followed by nephrotoxic tenofovir-based antiretroviral drugs and NSAIDs [10].

The epidemiology of drug-related AKI has also changed over time. Antibiotics used to be the most common cause for AKI and popular over-the-counter painkillers NSAIDs and ACEIs are still a common cause for CA-AKI, but recent chemotherapeutic and antiviral drugs have emerged and became novel causes of CA-AKI [25].

10.10 Comparison of Outcomes Between CA-AKI and HA-AKI

10.10.1 Short-Term Outcomes

10.10.1.1 Renal Outcomes

Patients with CA-AKI have worse renal function at admission than those with HA-AKI [15]. Once hospitalized, patients with CA-AKI had a slightly higher or similar rate of dialysis requirement as those with HA-AKI [19, 22], which could be explained by the more severe stage of AKI found in this population. The rate of renal recovery at hospital discharge differs between studies. One study found that serum creatinine at discharge was not significantly different between CA-AKI and HA-AKI [15] while another study found that the mean serum creatinine at discharge was significantly higher in patients with CA-AKI [9]. AKI management affects the chance of renal recovery. Talabani et al. found that only 58% of patients with CA-AKI had complete renal recovery at 3 months [23], and patients who were admitted to the hospital had a higher rate of complete renal recovery at 3 months

than those who were managed as outpatients [23]. Hospital admission was also associated with higher rate of renal recovery at 90 days [29].

Follow up with a nephrologist after an AKI episode is an important step in achieving better outcomes. A recent study from Canada reported that within 1 year after discharge, only 24% of patients hospitalized with AKI saw a nephrologist and this included 18% of patients who required dialysis during hospitalization with a trend toward lower rates of follow-up over more recent years of the study [46]. Another study reported that only 8% of patients hospitalized with AKI were referred to a nephrologist after discharge [9]. Patients with CA-AKI were more likely to be referred to a nephrologist than patients with HA-AKI (10.3% vs. 4.2%, respectively) [9]. These findings suggest that an increase in awareness of the long-term risks associated with AKI and the proper steps in the follow-up care is crucial among non-nephrology physicians.

10.10.1.2 Morbidity and Mortality (Less Than 3 Months)

CA-AKI is associated with a lower rate of ICU stay and requirement of mechanical ventilation [15, 22] and a significantly shorter length of hospital stay than HA-AKI [9, 22]. Patients with HA-AKI are more likely to suffer from multiple morbidities, such as respiratory failure, pneumonia, and sepsis, and to require an ICU stay [15, 19]. For CA-AKI, and increase in AKI stage was associated with an increased incidence of myocardial infarction, urinary tract infection, sepsis, and ICU monitoring, whereas for HA-AKI, an increase in AKI stage was only associated with an increased incidence of pneumonia [15].

Most of the studies comparing CA-AKI and HA-AKI are retrospective and derived from high-income countries. A worldwide-pooled meta-analysis found an AKI-associated mortality rate of about 22% at less than 3 months and 32% between 3 and 6 months [13]. The mortality rate of CA-AKI was reported at 32.8% [13]. A study in the United States found significantly higher in-hospital mortality for HA-AKI than CA-AKI (33.7% vs 11.5%) [15]. In a UK study, the 3-month mortality in patients with CA-AKI was 16.5% and was related to the severity of AKI [23]. The large cohort studies conducted in China and Taiwan also reported significantly higher in-hospital mortality in HA-AKI compared to CA-AKI (10.6% vs. 4.7% and 51.6% vs. 26.1%, respectively) [19, 47]. In a Thai cohort study, ICU and hospital mortality were also higher in HA-AKI compared to CA-AKI (40.3% vs. 31.0% and 53.8% vs. 38.1%, respectively) (unpublished data). A recent meta-analysis confirmed that CA-AKI had significantly lower in-hospital mortality (OR 2.79; 95% CI, 2.18–3.56) which was similar across high-income and low- and middle-income countries [22]. These findings are a reminder that despite CA-AKI being associated with more severe AKI than HA-AKI, in-hospital mortality is lower in this population. This emphasizes the difference in in-hospital management between CA-AKI and HA-AKI including ICU transfers and the intensity of monitoring. Patients with CA-AKI tend to be monitored and treated more aggressively which might ultimately lead to better outcomes. However, this

meta-analysis did not include data from low-income developing countries. In these countries, the in-hospital mortality of CA-AKI is still very high (about 50%) which reflects the AKI severity and lack of resources to manage the underlying conditions, particularly severe sepsis. Mortality could reach 80–90% in areas with poor access to dialysis [10, 21].

One study reported that the 3-month mortality rate in CA-AKI patients was 16.5% and was related to the severity of AKI suffered during hospitalization. 69% of patients who died at 3 months had stage 2 or 3 AKI compared to only 39% of those who survived. Mortality at 3 months was not different between those with preexisting CKD and those without. A short-term mortality difference was not observed when comparing patients who were admitted to the hospital to those who were managed in the primary care (15% vs. 17%) [23]. But another study found that hospital admission for AKI treatment was associated with significantly reduced 90-day mortality in stage 3 AKI compared to those treated in the primary care setting (27% in in-hospital treatment vs. 65% in outpatient management) [27]. Wonnacott et al. reported that the rate of hospital readmission within 6 months after discharge did not differ between CA-AKI and HA-AKI [9].

10.10.2 Long-Term Outcomes

10.10.2.1 Renal Outcomes

AKI is a strong risk factor for developing CKD particularly in patients with preexisting kidney disease. Few studies reported the long-term outcomes after an episode of CA-AKI. Serum creatinine at 1 year follow-up was not different between CA-AKI and HA-AKI [15]. Wonnacott et al. reported a similar rate of new CKD or CKD progression in those with preexisting CKD at 14 months after discharge in patients with CA-AKI compared to those with HA-AKI (39.1% vs. 33.6%, $p = 0.24$) [9]. The change in eGFR over 14 months did not differ between the two groups (−30 vs. −28.8 mL/min/1.73 m^2, $p = 0.72$) [9]. Der Mesropian et al. followed patients with CA-AKI and HA-AKI for 3 years and found no different outcomes in terms of doubling of serum creatinine and progression to ESRD [16]. AKI management also has an impact on long-term renal outcomes. Patients not admitted to the hospital within 7 days of AKI development are associated with higher rate of progression to chronic dialysis at 5 years compared to those treated early in the hospital [29].

10.10.2.2 Long-Term Mortality (More Than 1 Year)

At 14-month follow-up, patients with CA-AKI still had significantly lower mortality rate compared to those with HA-AKI (45.0% vs. 63.1%) [9]. The mortality at 3 years following CA-AKI was 45% compared to 15.7% in the age- and

sex-matched non-AKI patients [23]. The mortality at 3 years was also associated with the severity of AKI during hospitalization with 94% mortality in patients with CA-AKI stage 2 or 3 and 13% for those with stage 1 [23]. Another study showed no difference in 3-year mortality in patients with CA-AKI [16].

10.11 Conclusion

Based on limited and heterogeneous data, CA-AKI can be considered as a distinct phenotype of AKI carrying different epidemiology, etiologies, and outcomes compared to HA-AKI. Definition of CA-AKI and HA-AKI is needed to be standardized for universal use. Prevention and early recognition of AKI in community setting is still challenging for clinicians particularly in rural area. Future research in this field should be focused in these issues as well.

References

1. Hou SH, Bushinsky DA, Wish JB, Cohen JJ, Harrington JT. Hospital-acquired renal insufficiency: a prospective study. Am J Med. 1983;74(2):243–8.
2. Shusterman N, Strom BL, Murray TG, Morrison G, West SL, Maislin G. Risk factors and outcome of hospital-acquired acute renal failure. Clinical epidemiologic study. Am J Med. 1987;83(1):65–71.
3. Brivet FG, Kleinknecht DJ, Loirat P, Landais PJ. Acute renal failure in intensive care units—causes, outcome, and prognostic factors of hospital mortality; a prospective, multicenter study. French Study Group on Acute Renal Failure. Crit Care Med. 1996;24(2):192–8.
4. Feest TG, Round A, Hamad S. Incidence of severe acute renal failure in adults: results of a community based study. BMJ. 1993;306(6876):481–3.
5. Liano F, Pascual J. Epidemiology of acute renal failure: a prospective, multicenter, community-based study. Madrid Acute Renal Failure Study Group. Kidney Int. 1996;50(3):811–8.
6. Kaufman J, Dhakal M, Patel B, Hamburger R. Community-acquired acute renal failure. Am J Kidney Dis. 1991;17(2):191–8.
7. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P, Acute Dialysis Quality Initiative W. Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute dialysis Quality Initiative (ADQI) Group. Crit Care. 2004;8(4):R204–12.
8. Kidney disease: improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012;2:1–138.
9. Wonnacott A, Meran S, Amphlett B, Talabani B, Phillips A. Epidemiology and outcomes in community-acquired versus hospital-acquired AKI. Clin J Am Soc Nephrol. 2014;9(6):1007–14.
10. Evans RD, Hemmila U, Craik A, Mtekateka M, Hamilton F, Kawale Z, et al. Incidence, aetiology and outcome of community-acquired acute kidney injury in medical admissions in Malawi. BMC Nephrol. 2017;18(1):21.
11. Warnock DG, Powell TC, Siew ED, Donnelly JP, Wang HE, Mehta RL. Serum creatinine trajectories for community-versus hospital-acquired acute kidney injury. Nephron. 2016;134(3):177–82.
12. Wang Y, Wang J, Su T, Qu Z, Zhao M, Yang L, et al. Community-acquired acute kidney injury: a nationwide survey in China. Am J Kidney Dis. 2017;69(5):647–57.

13. Susantitaphong P, Cruz DN, Cerda J, Abulfaraj M, Alqahtani F, Koulouridis I, et al. World incidence of AKI: a meta-analysis. Clin J Am Soc Nephrol. 2013;8(9):1482–93.
14. Obialo CI, Okonofua EC, Tayade AS, Riley LJ. Epidemiology of de novo acute renal failure in hospitalized African Americans: comparing community-acquired vs hospital-acquired disease. Arch Intern Med. 2000;160(9):1309–13.
15. Schissler MM, Zaidi S, Kumar H, Deo D, Brier ME, McLeish KR. Characteristics and outcomes in community-acquired versus hospital-acquired acute kidney injury. Nephrology (Carlton). 2013;18(3):183–7.
16. Der Mesropian PJ, Kalamaras JS, Eisele G, Phelps KR, Asif A, Mathew RO. Long-term outcomes of community-acquired versus hospital-acquired acute kidney injury: a retrospective analysis. Clin Nephrol. 2014;81(3):174–84.
17. Yang L. Acute kidney injury in Asia. Kidney Dis (Basel). 2016;2(3):95–102.
18. Yang L, Xing G, Wang L, Wu Y, Li S, Xu G, et al. Acute kidney injury in China: a cross-sectional survey. Lancet. 2015;386(10002):1465–71.
19. Xu X, Nie S, Liu Z, Chen C, Xu G, Zha Y, et al. Epidemiology and clinical correlates of AKI in Chinese hospitalized adults. Clin J Am Soc Nephrol. 2015;10(9):1510–8.
20. Bouchard J, Mehta RL. Acute kidney injury in Western countries. Kidney Dis (Basel). 2016;2(3):103–10.
21. Olowu WA, Niang A, Osafo C, Ashuntantang G, Arogundade FA, Porter J, et al. Outcomes of acute kidney injury in children and adults in sub-Saharan Africa: a systematic review. Lancet Glob Health. 2016;4(4):e242–50.
22. Inokuchi R, Hara Y, Yasuda H, Itami N, Terada Y, Doi K. Differences in characteristics and outcomes between community- and hospital-acquired acute kidney injury: a systematic review and meta-analysis. Clin Nephrol. 2017;88(10):167–82.
23. Talabani B, Zouwail S, Pyart RD, Meran S, Riley SG, Phillips AO. Epidemiology and outcome of community-acquired acute kidney injury. Nephrology (Carlton). 2014;19(5):282–7.
24. Wang Y, Cui Z, Fan M. Hospital-acquired and community-acquired acute renal failure in hospitalized Chinese: a ten-year review. Ren Fail. 2007;29(2):163–8.
25. Prakash J, Singh TB, Ghosh B, Malhotra V, Rathore SS, Vohra R, et al. Changing epidemiology of community-acquired acute kidney injury in developing countries: analysis of 2405 cases in 26 years from eastern India. Clin Kidney J. 2013;6(2):150–5.
26. Stucker F, Ponte B, De la Fuente V, Alves C, Rutschmann O, Carballo S, et al. Risk factors for community-acquired acute kidney injury in patients with and without chronic kidney injury and impact of its initial management on prognosis: a prospective observational study. BMC Nephrol. 2017;18(1):380.
27. Barton AL, Mallard AS, Parry RG. One year's observational study of acute kidney injury incidence in primary care; frequency of follow-up serum creatinine and mortality risk. Nephron. 2015;130(3):175–81.
28. Hobbs H, Bassett P, Wheeler T, Bedford M, Irving J, Stevens PE, et al. Do acute elevations of serum creatinine in primary care engender an increased mortality risk? BMC Nephrol. 2014;15:206.
29. Sawhney S, Fluck N, Fraser SD, Marks A, Prescott GJ, Roderick PJ, et al. KDIGO-based acute kidney injury criteria operate differently in hospitals and the community-findings from a large population cohort. Nephrol Dial Transplant. 2016;31(6):922–9.
30. Akram AR, Singanayagam A, Choudhury G, Mandal P, Chalmers JD, Hill AT. Incidence and prognostic implications of acute kidney injury on admission in patients with community-acquired pneumonia. Chest. 2010;138(4):825–32.
31. Mehta RL, Cerda J, Burdmann EA, Tonelli M, Garcia-Garcia G, Jha V, et al. International society of nephrology's 0by25 initiative for acute kidney injury (zero preventable deaths by 2025): a human rights case for nephrology. Lancet. 2015;385(9987):2616–43.
32. Jha V, Parameswaran S. Community-acquired acute kidney injury in tropical countries. Nat Rev Nephrol. 2013;9(5):278–90.
33. Rennie TJW, De Souza N, Donnan PT, Marwick CA, Davey P, Dreischulte T, et al. Risk of acute kidney injury following community prescription of antibiotics: self-controlled case series. Nephrol Dial Transplant. 2019;34(11):1910–6.

34. Griffin MR, Yared A, Ray WA. Nonsteroidal antiinflammatory drugs and acute renal failure in elderly persons. Am J Epidemiol. 2000;151(5):488–96.
35. Huerta C, Castellsague J, Varas-Lorenzo C, Garcia Rodriguez LA. Nonsteroidal anti-inflammatory drugs and risk of ARF in the general population. Am J Kidney Dis. 2005;45(3):531–9.
36. Lapi F, Azoulay L, Yin H, Nessim SJ, Suissa S. Concurrent use of diuretics, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers with non-steroidal anti-inflammatory drugs and risk of acute kidney injury: nested case-control study. BMJ. 2013;346:e8525.
37. Dreischulte T, Morales DR, Bell S, Guthrie B. Combined use of nonsteroidal anti-inflammatory drugs with diuretics and/or renin-angiotensin system inhibitors in the community increases the risk of acute kidney injury. Kidney Int. 2015;88(2):396–403.
38. Chou CI, Shih CJ, Chen YT, Ou SM, Yang CY, Kuo SC, et al. Adverse effects of oral nonselective and cyclooxygenase-2-selective NSAIDs on hospitalization for acute kidney injury: a nested case-control cohort study. Medicine (Baltimore). 2016;95(9):e2645.
39. Zhang X, Donnan PT, Bell S, Guthrie B. Non-steroidal anti-inflammatory drug induced acute kidney injury in the community dwelling general population and people with chronic kidney disease: systematic review and meta-analysis. BMC Nephrol. 2017;18(1):256.
40. Sever MS, Lameire N, Van Biesen W, Vanholder R. Disaster nephrology: a new concept for an old problem. Clin Kidney J. 2015;8(3):300–9.
41. Gibney RT, Sever MS, Vanholder RC. Disaster nephrology: crush injury and beyond. Kidney Int. 2014;85(5):1049–57.
42. Gurrieri C, Garovic VD, Gullo A, Bojanic K, Sprung J, Narr BJ, et al. Kidney injury during pregnancy: associated comorbid conditions and outcomes. Arch Gynecol Obstet. 2012;286(3):567–73.
43. Prakash J, Gupta A, Kumar O, Rout SB, Malhotra V, Srivastava PK. Acute renal failure in falciparum malaria—increasing prevalence in some areas of India—a need for awareness. Nephrol Dial Transplant. 1996;11(12):2414–6.
44. Sitprija V. Renal dysfunction in leptospirosis: a view from the tropics. Nat Clin Pract Nephrol. 2006;2(12):658–9.
45. Teles F, de Mendonca Uchoa JV, Mirelli Barreto Mendonca D, Falcao Pedrosa Costa A. Acute kidney injury in leptospirosis: the Kidney Disease Improving Global Outcomes (KDIGO) criteria and mortality. Clin Nephrol. 2016;86 (2016)(12):303–9.
46. Karsanji DJ, Pannu N, Manns BJ, Hemmelgarn BR, Tan Z, Jindal K, et al. Disparity between nephrologists' opinions and contemporary practices for community follow-up after AKI hospitalization. Clin J Am Soc Nephrol. 2017;12(11):1753–61.
47. Hsu CN, Lee CT, Su CH, Wang YC, Chen HL, Chuang JH, et al. Incidence, outcomes, and risk factors of community-acquired and hospital-acquired acute kidney injury: a retrospective cohort study. Medicine (Baltimore). 2016;95(19):e3674.
48. Sesso R, Roque A, Vicioso B, Stella S. Prognosis of ARF in hospitalized elderly patients. Am J Kidney Dis. 2004;44(3):410–9.

Part II
Complication of AKI

Chapter 11
Complication of Homeostasis (Electrolytes and Acid-Base)

Atsuko Uehara and Yugo Shibagaki

Abstract Patients who develop acute kidney injury (AKI) are at a great risk of both electrolyte abnormalities and acid-base disorders, which can be complicated and progressive because of the acute deterioration of kidney function and the impact of renal replacement therapy. Thus, we should recognize the significance of these disorders and tackle them accordingly. Among various acid-base disorders and electrolyte abnormalities, we discuss metabolic acidosis, metabolic alkalosis, hyperkalemia, hypokalemia, hypocalcemia, hypercalcemia, and hyperphosphatemia, all of which are frequently encountered in the setting of AKI and can significantly influence morbidity and mortality.

Keywords Metabolic acidosis · Metabolic alkalosis · Hyperkalemia
Hypokalemia · Hypocalcemia · Hypercalcemia · Hyperphosphatemia

11.1 Introduction

Acute kidney injury (AKI) can significantly influence mortality. The in-hospital mortality rate of patients with AKI requiring dialysis was more than 50% in patients admitted to the intensive care unit (ICU) [1].

Before renal replacement therapy (RRT) was routinely used, patients died of electrolyte abnormalities such as hyperkalemia, complications from uremia such as pericarditis or upper gastrointestinal bleeding, or respiratory failure from volume overload [2]. Presently, these "traditional" complications of AKI can be managed by initiating RRT; thus, death from one of these complications has become an unusual phenomenon [3].

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However, this does not imply that these complications should be neglected because electrolyte abnormalities and acid-base disorders can become fatal when treatment is delayed and even RRT itself can aggravate or cause these problems. Thus, we should recognize the importance of these disorders and manage them in a timely manner.

The characteristic of electrolyte abnormalities and acid-base disorders complicated with AKI (and chronic kidney disease) is that patients can easily present with both extremes of the disorders, namely metabolic alkalosis as well as metabolic acidosis, or hypokalemia and hypercalcemia as well as hyperkalemia and hypocalcemia.

Both hypokalemia and hyperkalemia can lead to fatal arrhythmia or paralysis including the respiratory muscles. Severe acidemia (generally, pH < 7.20) can cause a reduction in cardiac contractility, unresponsiveness to vasopressors, and fatal arrhythmia. Severe alkalemia can cause seizures, vasoconstriction leading to ischemia, and respiratory depression. Abnormalities in serum calcium and phosphorus levels, which are not routinely checked, are also observed in patients with AKI. Hypocalcemia is extremely frequent in hospitalized patients (up to 88%) and correlates with the severity of illness, which can be assessed by Acute Physiology and Chronic Health Evaluation II scores. The presence of AKI is also associated with decreased calcium levels [4]. Profound hypocalcemia can lead to hemodynamic instability and fatal arrhythmia. Hypercalcemia and hyperphosphatemia are also common in patients with AKI because urinary clearance decreases along with reduced glomerular filtration rate (GFR). Hypercalcemia causes reduced consciousness and AKI. Hyperphosphatemia can cause hypocalcemia and acute phosphate nephropathy [5].

11.2 Metabolic Acidosis

11.2.1 Pathophysiology

In the setting of AKI, the ability of the kidney to produce ammonium at the proximal tubules and to excrete protons at the distal tubules is deteriorated, contributing to a normal anion gap (AG) or non-gap metabolic acidosis. As kidney dysfunction worsens, the retention of anions including phosphate, sulfate, and some poorly characterized organic anions takes places, leading to an elevated AG or simply AG metabolic acidosis. In addition to AKI itself, patients with sepsis, hypoxemia, and hemodynamic instability caused by organ ischemia are at a high risk of developing lactic acidosis. This type of lactic acidosis caused by local or systemic decreases in oxygen delivery can lead to the rapid production and accumulation of lactate; this is also known as type A lactic acidosis.

When AKI is complicated by shock, large amounts of intravenous solution and vasopressors are needed rapidly. There is abundant evidence to indicate that a

massive isotonic saline solution decreases the serum bicarbonate concentration, leading to hyperchloremic or non-gap acidosis [6–8].

Although rare, use of drugs and other types of intoxications can cause AKI and metabolic acidosis. For example, metformin used in the treatment of diabetes mellitus has been associated with lactic acidosis. The risk factors for this adverse event are a low GFR and overdose. Lactic acidosis and subsequent hypotension can lead to hemodynamic instability and to AKI, which is fatal in up to 50% of cases [9]. Intoxication with ethylene glycol, a major component of antifreeze, causes severe AG metabolic acidosis by producing toxic metabolites such as oxalate. Calcium oxalate crystals are deposited in the lumen and tubular cells, resulting in tubular necrosis and anuric AKI [10].

Irrespective of how severely the kidney is damaged and how severely its ability to excrete protons is deteriorated, respiratory compensation quickly occurs as long as lung ventilation is normal. When respiratory compensation functions normally, serum pH does not decrease below 7.2 when the serum bicarbonate level is above 5–10 mEq/L; therefore, in the presence of severe acidemia (pH < 7.2) with a bicarbonate level above 5–10 mEq/L, we should also consider the presence of ventilatory failure (lung problems or reduced consciousness).

11.2.2 Clinical Consequences

Severe acidemia (pH < 7.15–7.2) can depress cardiac contractility, blunt the response to catecholamines, and decrease peripheral vascular resistance, leading to hemodynamic instability [11]. Severe acidemia in critically ill patients is associated with a high mortality rate of up to 57% [12].

11.2.3 Treatment

Lactic acidosis associated with tissue hypoxemia may induce cardiogenic shock and severe sepsis. These require urgent recognition and cause-specific treatment.

In case of hemodynamic compromise, vasopressors should be administered as needed. Caution is required as acidemia blunts the response to catecholamines; therefore, the required dose should be considered accordingly.

In patients with a decrease in the extracellular fluid (ECF) volume or volume depletion, crystalloid solutions are administered considering indices such as central volume pressure. However, in the setting of AKI, even a little bit of excess fluid administration can easily cause fluid overload and subsequent organ damage. Thus, we need to pay continuous attention to ECF volume monitoring while administering the solution and regulate the amount of fluid administered to prevent over-hydration.

Whether the isotonic saline solution (0.9% NaCl) or balanced solution (Ringer's solution with lactate and Plasma-Lyte with acetate and gluconate) is appropriate as a means of resuscitation fluid therapy remains controversial. When massive solutions need to be administered, isotonic saline can cause non-gap acidosis and coagulopathy; thus, balanced solutions are recommended.

Oxygen delivery to tissues is determined by the cardiac output, regional blood flow, hemoglobin concentration, and partial pressure of oxygen (PO_2). Thus, for restoring tissue perfusion, red cell transfusions should be performed as needed and the inspired oxygen concentration should be regulated to maintain an adequate PO_2. If hypercapnia is present, which worsens acidemia, assisted ventilation may also be required.

Measures targeting the causes of lactic acidosis should also be initiated. Such measures include the treatment of sepsis with antibiotic agents, management of arrhythmia, coronary intervention for acute myocardial infarction, surgery for tissue ischemia, and dialysis for the removal of drug toxins [11].

As mentioned above, if severe metabolic acidosis (pH < 7.15–7.2) is complicated with hemodynamic instability that is unresponsive to catecholamines, therapy with intravenous sodium bicarbonate is considered. This severe and deleterious condition caused by metabolic acidosis is often experienced in the setting of type A lactic acidosis. Ketoacidosis and acidosis due to renal failure itself are not progressive, and urgent base administration is not demanded in such cases. However, if AKI is present in addition to critically ill conditions, the intrinsic ability of the kidney to regenerate bicarbonate is deteriorated, thus requiring extrinsic base administration.

Base administration increases serum pH level, but it remains elusive whether it can lead to hemodynamic stability and decrease mortality. Moreover, there are several adverse effects of bicarbonate infusion: volume overload, decrease in the concentration of ionized calcium, hypernatremia, carbon dioxide retention especially in the setting of decreased ventilation, overshoot alkalosis, and paradoxical intracellular acidification [13]

Jaber et al. reported the results of a randomized controlled trial in which they assigned patients from the ICU with serum pH levels of 7.20 or less to treatment with sodium bicarbonate or to no bicarbonate infusion [14]. The primary outcome was a composite of death by day 28 and the presence of at least one organ failure at day 7; no difference in this outcome was observed between the bicarbonate group and the control group. However, in a subgroup analysis, patients with Acute Kidney Injury Network scores of 2–3, the primary outcome, and the need for RRT occurred less frequently in the bicarbonate group than in the control group. In evaluating the results of this study, we should recognize that RRT itself did infuse alkali to the patients because alkali-containing dialysate is used during RRT.

Nonetheless, RRT is sometimes more appealing than bicarbonate infusion because RRT allows a better control of serum osmolality, ionized calcium level, and ECF volume. RRT is more invasive than bicarbonate infusion; therefore, we cannot conclude which method is best.

11.3 Metabolic Alkalosis

11.3.1 Pathophysiology

Considering the fact that a decrease in renal function results in a decrease in acid excretion from the urine leading to metabolic acidosis, it makes sense that metabolic alkalosis in AKI is related to the cause of AKI itself, not the result of AKI. In other words, metabolic alkalosis can be seen in prerenal AKI caused by volume reduction (i.e., chloride depletion) or diuretic use, AKI caused by hypertensive crisis, and AKI caused by calcium alkali syndrome in patients who take calcium or magnesium supplements.

When metabolic alkalosis is seen, initiation and maintenance factors should be investigated, respectively. In most cases, metabolic alkalosis is initiated by excess base administration, proton loss from the gastrointestinal tract, or chloride depletion from the kidney or gastrointestinal tract. In critically ill patients, bicarbonate substances, whose metabolism generate bicarbonate (e.g., lactate, citrate), are often administered at a greater rate than metabolic protons. This situation occurs when sodium bicarbonate is administered to manage metabolic acidosis, balance solutions are administered to stabilize hemodynamic instability, alkali-containing dialysate is used during RRT, or a massive transfusion containing citrate is administered. In elderly patients with a reduced GFR, calcium- or magnesium-containing drugs, which are mostly alkalis, are often used to treat gastric ulcers, constipation, and osteoporosis. The accumulation of these drugs can lead to metabolic alkalosis and AKI due to hypercalcemia and hypermagnesemia. Proton and chloride loss from the gastrointestinal tract can be detected in patients who vomit, but in critically ill patients, it can be noticed through nasogastric tube drainage, leading to metabolic alkalosis, especially when a large amount is drained. Moreover, patients who have stoma or short bowel syndrome after surgery tend to suffer from metabolic alkalosis when the amount of chloride-rich fluid and gastrointestinal secretion increases; chloride loss from the kidney can also result from the use of loop diuretics or thiazide.

Maintenance factors of metabolic alkalosis include chloride depletion, volume depletion stimulating renal tubular sodium reabsorption, potassium depletion, and a decline in GFR levels. Metabolic alkalosis itself causes the GFR to decline, forming a vicious cycle. In the kidney, pendrin (Cl/HCO3 exchanger) located in the luminal side of β intercalated cells of the collecting duct is responsible for excess bicarbonate excretion. In chloride depletion, this exchanger does not function, maintaining metabolic alkalosis. When volume depletion is sensed and the renin-angiotensin-aldosterone system is activated, aldosterone stimulates proton secretion from the collecting tubule and angiotensin II stimulates Na/K ATPase and the Na/H exchanger of the proximal tubule, both working as a maintenance factor of metabolic alkalosis. Profound hypokalemia ($K < 2$ mEq/L) upregulates H/K ATPase in the intercalated

cells of the collecting duct, maintaining metabolic alkalosis. The GFR determines the amount of bicarbonate filtered; thus, GFR decline correlates with a decrease in net bicarbonate excretion. In AKI patients whose GFR is nearly zero, bicarbonate excretion does not occur. In other words, AKI patients who are RRT-dependent are predisposed to metabolic alkalosis as well as metabolic acidosis.

11.3.2 Clinical Consequences

Signs and symptoms of metabolic alkalosis are non-specific. Most of them are caused by decreases in ionized calcium levels that occur as increased pH causing plasma proteins to bind calcium more avidly. Signs of hypocalcemia are mentioned below, but they are primarily those of enhanced neuromuscular activation (Chvostek and Trousseau signs). Hypokalemia, which often accompanies metabolic alkalosis, is caused by the proton and potassium transcellular exchange or potassium loss from urine or the gastrointestinal tract. When it becomes severe, muscle weakness follows.

In metabolic alkalosis, respiratory compensation (reduced ventilation) takes place, leading to hypercapnia and hypoxemia. In addition, alkalemia shifts the oxygen dissociation curve to the left, causing organ ischemia.

In profound alkalemia, when bicarbonate levels increase to more than 50 mEq/L, confusion, seizure, and coma can be seen. These central nervous symptoms can be caused by a combination of hypocalcemia, hypokalemia, carbon dioxide narcosis, and brain ischemia due to hypoventilation, all of which are caused by metabolic alkalosis [15].

11.3.3 Treatment

During emergency where an increased pH may be life threatening, rapid reduction in systemic pH through ventilation control is required. In this clinical condition, intubation, sedation, and controlled hypoventilation with a mechanical ventilator are often lifesaving.

The treatment of metabolic alkalosis includes a correction of the underlying disease state. Removal of the initiating factors should be considered such as the withdrawal of base and/or diuretic. To remove the maintenance factors, such as chloride depletion, volume depletion, and potassium depletion, saline administration and/or KCl administration can be considered. Chloride-rich solutions such as an amino acid solution for liver failure can also be used [16]. This solution can be useful especially in the setting of volume overload as the volume of the solution required to correct alkalemia is much less than the volume of normal saline. When the amount of drainage from the gastrointestinal tract is in such a way that the loss of HCl cannot be controlled, H2 blockers and proton pump inhibitors are reported to be effective in decreasing the concentration of chloride [17].

When the GFR decline is caused by prerenal AKI, chloride administration can enhance bicarbonate excretion via pendrin, leading to the correction of metabolic alkalosis. On the other hand, when the GFR decline leads to anuric AKI, metabolic alkalosis can be refractory and sometimes requires RRT; however, we should be cautious in using RRT as the dialysate contains a large amount alkali, which may aggravate metabolic alkalosis. In such cases, the use of hemofiltration instead of hemodialysis may be considered.

Metabolic alkalosis can be complicated in diseases with volume overload, such as heart failure and nephrotic syndrome. In these cases, the use of a high-dose loop diuretic can exacerbate metabolic alkalosis; thus, acetazolamide and spironolactone may be effective [18]. Caution is required with acetazolamide as it can worsen hypokalemia.

11.4 Hyperkalemia

11.4.1 Pathophysiology

Potassium excretion takes place mainly in the kidney, and patients with AKI are at a high risk of hyperkalemia.

The etiologies of hyperkalemia include an excess in potassium intake, potassium shifting from the intracellular to the extracellular space, and a decrease in renal potassium excretion. Of these, reduced renal excretion is the most frequent.

Antihypertensive drugs such as ACE inhibitors and angiotensin receptor blockers can cause hyperkalemia, especially when patients develop AKI. Rhabdomyolysis and tumor lysis syndrome can cause progressive hyperkalemia due to continuous cell destruction as well as AKI due to phosphate calcium deposition and urate crystal deposition.

Metabolic acidosis, non-gap acidosis in particular, can cause hyperkalemia by shifting potassium from the intracellular to the extracellular space in exchange of protons.

11.4.2 Clinical Consequences

The signs and symptoms of hyperkalemia are non-specific. Hyperkalemia can cause an abnormality in neuromuscular conduction, leading to abnormal cardiac muscle conduction (arrhythmia). In profound hyperkalemia, skeletal muscle abnormalities, such as muscle weakness and paralysis, as well as smooth muscle abnormalities, such as ileus, can be identified.

Electrocardiogram (ECG) changes including the tenting of T waves, widening of the QRS complex, a loss of P waves (loss of sinus rhythm, leading to subsequent

junctional rhythm and bradycardia), and ventricular tachycardia and fibrillation can be detected in hyperkalemia. When identifying ECG changes, immediate and aggressive therapy is required to prevent a fatal outcome.

The relationship between serum potassium concentration and ECG manifestations is less precise. A patient whose serum potassium level was more than 9 mEq/L was reported to show no ECG abnormality. It is noteworthy that the absence of ECG changes cannot rule out potentially severe hyperkalemia [19].

11.4.3 Treatment

The presence of profound ECG changes such as bradycardia, widening of the QRS complex, ventricular tachycardia, and ventricular fibrillation indicates that emergent treatment is required. To stabilize excitable membranes, cardiac tissues in particular, intravenous calcium is administered. For patients on digoxin, calcium should be administered as a slow drip so as to not cause digoxin intoxication. Its effect lasts only for 60 min; thus, if the ECG changes persist, repeat calcium administration should be considered. Following calcium therapy (or at the same time), a treatment of immediate effect, which shifts potassium into cells, to lower serum potassium concentration should be initiated. The intravenous administration of regular insulin with glucose effectively and rapidly lowers the serum potassium concentration. If patients are hyperglycemic, glucose administration is unnecessary and insulin alone should be administered. It lowers the serum potassium concentration by approximately 0.5–1.0 mEq/L. The effect of insulin lasts for approximately 6 h; therefore, during this period, treatment to remove potassium from the body should be initiated. However, if this strategy is not effective, continuous insulin and glucose administration should be considered. Further, if insulin is not effective, it may indicate that endogenous production of *K* is occurring, which may prompt us to search for a massive destruction of cells such as in case of intrabody bleeding or tumor lysis, rhabdomyolysis, and massive necrosis of organs/tissues. Loop diuretics and/or isotonic saline are effective in increasing the excretion of potassium in urine. If the ECF volume is increased, the administration of isotonic saline should be avoided. In the setting of anuric AKI, loop diuretics might not increase urine output and turn out to be ineffective. It is worth noting that as the GFR declines, the diuretic effect of diuretics diminishes. To judge whether a loop diuretic is effective, ceiling doses of furosemide (100–200 mg) should be administered intravenously. Patients who fail to respond to a high dose of intravenous furosemide are regarded as refractory. In such cases, RRT should be considered.

The need for RRT is determined by two factors. One is the cause of AKI that results in hyperkalemia, and the other is the urine output. Prerenal AKI caused by volume depletion and postrenal AKI caused by urinary tract obstruction can be reversible once appropriate treatments are initiated, and as filtration improves and urine output increases, serum potassium concentration decreases in most cases. However, in case of anuric AKI or in case where potassium can be released from an

endogenous source (within cells), as in tumor lysis syndrome, rhabdomyolysis, and intra-abdominal bleeding, hyperkalemia can often be progressive and refractory with the treatments mentioned above, requiring RRT. Intermittent hemodialysis (IHD) is effective in removing potassium from the body, but as 98% of the total potassium distributes in the intracellular space, potassium shifting from the intracellular space to the extracellular space occurs, leading to rebound hyperkalemia after IHD. Thus, in the case of a progressive disease such as rhabdomyolysis and tumor lysis syndrome, continuous RRT (CRRT) after IHD should be considered. In addition, CRRT can be the first choice when patients are hemodynamically unstable.

The cation-exchanger resin sodium polystyrene is administered orally to increase gastrointestinal potassium excretion. Its onset of action is slow, approximately 2–4 h, which limits its use during an emergency. However, a novel oral drug, sodium zirconium cyclosilicate (ZS-9), has been described to be efficient for the emergent treatment of severe hyperkalemia. There is an article reporting that in patients with a serum potassium concentration of more than 6.0 mEq/L, 10 g of ZS-9 decreases the serum potassium concentration by 0.4 mEq/L after 1 h and by 0.7 mEq/L after 4 h, with 80% of the patients achieving a serum potassium concentration of under 6.0 mEq/L [20].

11.5 Hypokalemia

11.5.1 Pathophysiology

In AKI patients, not only hyperkalemia but also hypokalemia can develop. Considering that a decline in renal function results in a decrease in potassium excretion from urine, leading to hyperkalemia, hypokalemia with AKI should prompt us to determine the specific causes of AKI. These causes include the use of diuretics, hypertensive crisis, and drug toxicity that damages the renal tubules.

When the amount of urine increases after the use of chronic diuretics, release of urinary tract obstruction, or the recovery of acute tubular necrosis, potassium excretion by urine increases, leading to hypokalemia. Drugs that induce AKI, such as aminoglycosides, cisplatin, and amphotericin B, all of which can cause tubule damage, can result in hypokalemia [21–23]. When patients are on CRRT for several days, serum potassium concentration decreases to the level of that of dialysate, leading to hypokalemia [24]. Extrarenal potassium loss results from diarrhea, and hypokalemia due to potassium shifting from the extracellular space to the intracellular space includes refeeding syndrome caused by insulin release and acute catecholamine release, as seen in acute myocardial infarction. It is worth noting that hypomagnesemia is one of the causes that stimulate renal potassium loss, thus leading to refractory hypokalemia. The above-mentioned causes of hypokalemia can often cause hypomagnesemia. Thus, serum magnesium level should be routinely checked whenever hypokalemia is present.

11.5.2 Clinical Consequences

Clinical manifestations of hypokalemia include muscle weakness, frank paralysis, and rhabdomyolysis, and if it progresses, it can lead to respiratory failure due to weakness in the diaphragmatic muscle and to fatal arrhythmia.

Previously healthy patients can survive mild hypokalemia, but it is reported that patients with an ischemic heart disease are at a high risk of fatal arrhythmia [25].

Characteristic ECG changes in hypokalemia include the presence of prominent U waves, depression of ST segments, flattening of T waves, and prolongation of QT segments. When hypokalemia progresses, the paroxysmal ventricular complex and Torsades de pointes, which can be fatal, are seen; these are especially accompanied by hypomagnesemia. When patients are symptomatic or ECG changes are noticed, aggressive therapy is required to prevent a fatal outcome.

11.5.3 Treatment

Potassium can be supplemented by KCl, aspartate potassium, or gluconate potassium. Among these types of potassium supplementation, KCl is the most useful in increasing the serum potassium concentration for two reasons [26]. One reason is that chloride does not cross the cell membrane easily, so by accompanying potassium, it is more likely to stay within the extracellular space. Another is that metabolic alkalosis, often complicated with hypokalemia, makes the hypokalemia refractory, and KCl is neutral; compared with serum (pH 7.4), it is rather acidic; thus, it can improve metabolic alkalosis.

When there are emergent signs and symptoms such as fatal arrhythmia and respiratory failure or when patients cannot take KCl orally because of unconsciousness and ileus, intravenous KCl is given. Oral KCl is employed for mild-to-moderate hypokalemia, and its onset of action is 30 min, leading to a rapid increase in serum potassium concentration to avoid overcorrection of hypokalemia.

When hypokalemia is mild to moderate (3.0–3.5 mEq/L), 60–80 mEq of oral KCl is recommended to be administered daily, and when hypokalemia is severe (<3.0 mEq/L), 40 mEq of oral KCl is recommended to be administered every 3–4 h, three times a day. Intravenous KCl administration may injure veins; thus, when the concentration of KCl reaches above 40 mEq/L, administration should be performed via the central venous route. Faster rates may lead to cardiac dysrhythmia, and intravenous KCl should be administered at a rate of no more than 20 mEq/h. In the case of an emergency, intravenous KCl can be administered at a rate of 40–100 mEq/h via the central venous route, but it requires ECG monitoring to avoid overcorrection and dysrhythmia. Hypokalemic patients with AKI and with hypokalemia caused by potassium shifting from the extracellular space to the intracellular space are at a

high risk of overcorrection. Therefore, the dose of KCl administration should be reduced by 50%, or frequent monitoring of serum potassium concentration, such as every 2–4 h, should be considered [27].

11.6 Hypocalcemia

11.6.1 Pathophysiology

A similar abnormality in calcium and phosphorus metabolism in chronic kidney disease (CKD) patients is also seen in AKI patients. In other words, hypocalcemia, hyperphosphatemia, hyperparathyroidism, a decrease in the 1,25-vitamin D level, an increase in the fibroblast growth factor (FGF)-23 level, and decreased klotho expression in the kidney are noticed [28].

Hypocalcemia has been reported to be frequently complicated in AKI patients [29]. Multiple etiologies have been proposed to account for this finding. These include the decreased renal synthesis of 1,25-vitamin D, hyperphosphatemia, retention of phosphorus that sequesters calcium, skeletal resistance to parathyroid hormone (PTH), upregulation of the calcium-sensing receptor, and accumulation of intracellular calcium. In addition, hypomagnesemia is known to cause hypocalcemia due to decreased PTH secretion and increased PTH resistance [30, 31].

Two methods are available in routine clinical practice for the assessment of circulating calcium levels: total serum calcium and plasma ionized calcium (iCa). iCa is considered the gold standard assessment of physiologically relevant free calcium levels in circulation because total serum calcium measurements assess both biologically active (around 45%) and biologically inactive (around 55%) calcium. The latter is bound to albumin and other organic and inorganic anions such as sulfate, phosphate, and citrate [32]. Clinicians tend to prefer total serum calcium levels because the measurement of iCa levels is more cumbersome: the samples must be drawn in a heparinized syringe, transported on ice, and processed immediately. The alternative index to assess iCa using total serum calcium levels is albumin-corrected calcium. Although a different formula for correction [total calcium + (4.0—albumin) × 0.8] is used in Europe and the United States, Payne's formula is commonly used for its simplicity. Payne's formula is shown as follows: total calcium + (4.0 − albumin).

Although there is a report assessing the association of serum total calcium and albumin-corrected calcium with mortality in patients undergoing maintenance dialysis, there have been no reports comparing serum total calcium and albumin-corrected calcium among AKI patients [33]. However, both serum total calcium and albumin-corrected calcium cannot be an appropriate index to assess iCa in AKI patients because there are several factors that might change the total calcium besides

albumin, such as acid-base disorders, hyperphosphatemia, and citrate load due to massive transfusion and CRRT [34–36]. Hence, when assessing hypocalcemia, signs and symptoms of hypocalcemia are as important as total calcium and albumin-corrected calcium.

11.6.2 Clinical Consequences

Symptoms of hypocalcemia are primarily those of enhanced neuromuscular activation. Tetany, seizure, and Chvostek and Trousseau signs are seen. In AKI patients, hemodynamic instability and arrhythmia tend to be a problem. Hypocalcemia can lead to a decrease in systemic vascular resistance and cardiac contractility, causing hypotension. An ECG change noticed in hypocalcemia is the prolongation of the QT segments, and it can cause fatal arrhythmia such as Torsades de pointes. Hypocalcemia is an independent predictor of increased mortality in the ICU. However, hypocalcemia must be severe (iCa < 0.8 mmol/L). Few reports mentioned the relationships between hypocalcemia and mortality in AKI patients [37].

11.6.3 Treatment

Treatment varies depending on the degree of hypocalcemia. In life-threatening circumstances, such as seizures, tetany, hypotension, or cardiac arrhythmias, intravenous calcium should be used. Magnesium deficits must first be corrected, as treatment with only calcium supplementation will be ineffective. In AKI patients, hyperphosphatemia is often complicated; thus, calcium administration might exacerbate the deposition of calcium phosphate in tissues, leading to worsening of AKI. In addition, calcium administration might cause hypocalcemia overcorrection, leading to hypercalcemia. Thus, during the supplementation of calcium, frequent calcium level monitoring should be performed.

11.7 Hypercalcemia

11.7.1 Pathophysiology

Hypercalcemia results in polyuria that leads to the depletion of ECF volume and decreased renal blood flow, leading to AKI. In addition, chronic hypercalcemia can cause nephrocalcinosis and/or urolithiasis, which is also a cause of AKI. The causes of hypercalcemia vary between inpatients and outpatients. In outpatients, hypercalcemia can be largely due to primary hyperparathyroidism and calcium or vitamin D

excess in patients with reduced kidney function (such as the elderly, those with existing CKD, or those using nonsteroidal anti-inflammatory drugs), known as calcium-alkali syndrome. In calcium-alkali syndrome, metabolic alkalosis aggravates the already reduced kidney function. In comparison, in inpatients, hypercalcemia can be caused by malignancy producing a PTH-related protein, malignancy with osteolytic bone metastases, myeloma, and immobilization. In these settings, prerenal AKI, postrenal AKI, or drug-induced AKI is associated with the status of the patient and the therapy for underlying diseases.

11.7.2 Clinical Consequences

Mild hypercalcemia is often asymptomatic, but when it becomes severe, it is associated with prominent neurological and gastrointestinal manifestations. As mentioned above, severe hypercalcemia can cause AKI. Central nervous system symptoms range from malaise and deterioration of cognitive function to confusion, coma, and seizures. Gastrointestinal manifestations are related to decreased gastrointestinal motility that results in the loss of appetite, nausea, vomiting, constipation, and ulcers. Hypercalcemia decreases the expression of aquaporin channels, resulting in polyuria and polydipsia.

11.7.3 Treatment

The treatment of hypercalcemia is directed at increasing renal excretion and blocking bone resorption. The former includes saline administration to increase the ECF volume and the subsequent use of loop diuretics. However, loop diuretics can exacerbate volume depletion, and their effect is reported only in case reports. Thus, the routine use of loop diuretics cannot be recommended [38]. In case of volume overload or anuric AKI, hypercalcemia can be refractory; thus, hemodialysis may be indicated. To block bone resorption, calcitonin, bisphosphonate, and denosumab are used. Calcitonin acts within a few hours, and the serum calcium concentration is reduced by 1–2 mg/dL. However, its downside is the tachyphylaxis that develops with repeated use. Bisphosphonates have a long duration of action (weeks), but their advantage is that they have a slow onset of action (48–72 h). Denosumab is a novel agent registered for the treatment of osteoporosis and malignancy-induced hypercalcemia. It is a monoclonal antibody acting against the receptor activator of the nuclear factor-κ B ligand that inhibits osteoclast activity. The mechanism is unclear, but in patients with decreased GFR, denosumab is known to cause persistent and refractory hypocalcemia, so when denosumab is used, dose reduction and/or close monitoring of calcium level should be considered [39].

11.8 Hyperphosphatemia

11.8.1 Pathophysiology

In AKI patients, hyperphosphatemia results from decreased renal phosphate excretion. In addition, phosphorus can be released from an endogenous source (within cells), as in tumor lysis syndrome, hemolysis, or rhabdomyolysis. Although it is rare, in lactic acidosis and diabetic ketoacidosis, phosphorus shifts from the intracellular space to the extracellular space, leading to hyperphosphatemia [40, 41]. Although hyperphosphatemia is a frequent complication of AKI, hypophosphatemia is extremely common in AKI patients who have undergone CRRT.

11.8.2 Clinical Consequences

Chronic hyperphosphatemia seen in CKD patients causes vascular calcification, and it is related to increased mortality [42]. However, symptoms of acute hyperphosphatemia seen in AKI patients are related to hypocalcemia. When the calcium-phosphorus product concentration exceeds a certain limit, calcium starts to deposit in soft tissues and the concentration of serum calcium drops. Moreover, hyperphosphatemia in inpatients presents a risk of AKI, and hyperphosphatemia in AKI patients is related to short-term mortality [43, 44]. The mechanism of AKI caused by hyperphosphatemia is acute phosphate nephropathy. Calcium phosphate deposits within the tubules, inside tubule cells, and in the interstitium, leading to AKI. Thus far, acute phosphate nephropathy caused by tumor lysis syndrome and oral sodium phosphate bowel purgative has been reported [5, 45].

11.8.3 Treatment

In AKI patients requiring RRT, hyperphosphatemia is often normalized within several days [46]. For AKI patients who do not need RRT, treatment options for hyperphosphatemia are limited to phosphate binders and dietary phosphorus restriction. Mild asymptomatic hyperphosphatemia does not require prompt treatment in most cases.

References

1. Uchino S, Bellomo R, Morimatsu H, et al. Continuous renal replacement therapy: a worldwide practice survey. The beginning and ending supportive therapy for the kidney (B.E.S.T. kidney) investigators. Intensive Care Med. 2007;33(9):1563–70.
2. Thadhani R, Pascual M, Bonventre JV. Acute renal failure. N Engl J Med. 1996;334(22):1448–60.

3. Faubel S, Shah PB. Immediate consequences of acute kidney injury: the impact of traditional and nontraditional complications on mortality in acute kidney injury. Adv Chronic Kidney Dis. 2016;23(3):179–85.
4. Zivin JR, Gooley T, Zager RA, et al. Hypocalcemia: a pervasive metabolic abnormality in the critically ill. Am J Kidney Dis. 2001;37(4):689–98.
5. Boles JM, Dutel JL, Briere J, et al. Acute renal failure caused by extreme hyperphosphatemia after chemotherapy of an acute lymphoblastic leukemia. Cancer. 1984;53(11):2425–9.
6. Shaw AD, Bagshaw SM, Goldstein SL, et al. Major complications, mortality, and resource utilization after open abdominal surgery: 0.9% saline compared to Plasma-Lyte. Ann Surg. 2012;255(5):821–9.
7. Yunos NM, Bellomo R, Hegarty C, et al. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. JAMA. 2012;308(15):1566–72.
8. Gennari FJ. Intravenous fluid therapy: saline versus mixed electrolyte and organic anion solutions. Am J Kidney Dis. 2013;62(1):20–2.
9. Regolisti G, Antoniotti R, Fani F, et al. Treatment of metformin intoxication complicated by lactic acidosis and acute kidney injury: the role of prolonged intermittent hemodialysis. Am J Kidney Dis. 2017;70(2):290–6.
10. Ting SM, Ching I, Nair H, et al. Early and late presentations of ethylene glycol poisoning. Am J Kidney Dis. 2009;53(6):1091–7.
11. Kraut JA, Madias NE. Lactic acidosis. N Engl J Med. 2014;371(24):2309–19.
12. Jung B, Rimmele T, Le Goff C, et al. Severe metabolic or mixed acidemia on intensive care unit admission: incidence, prognosis and administration of buffer therapy. A prospective, multiple-center study. Crit Care. 2011;15(5):R238. https://doi.org/10.1186/cc10487.
13. Kraut JA, Madias NE. Sodium bicarbonate for severe metabolic acidaemia. Lancet. 2018;392(10141):3–4.
14. Jaber S, Paugam C, Futier E. Sodium bicarbonate therapy for patients with severe metabolic acidaemia in the intensive care unit (BICAR-ICU): a multicentre, open-label, randomised controlled, phase 3 trial. Lancet. 2018;392(10141):31–40.
15. Huber L, Gennari FJ. Severe metabolic alkalosis in a hemodialysis patient. Am J Kidney Dis. 2011;58(1):144–9.
16. Ryuge A, Matsui K, Shibagaki Y. Hyponatremic chloride-depletion metabolic alkalosis successfully treated with high cation-gap amino acid. Intern Med. 2016;55(13):1765–7.
17. Jacobi J, Schnellhardt S, Opgenoorth M, et al. Severe metabolic alkalosis and recurrent acute on chronic kidney injury in a patient with Crohn's disease. BMC Nephrol. 2010;11:6. https://doi.org/10.1186/1471-2369-11-6.
18. Peixoto AJ, Alpern RJ. Treatment of severe metabolic alkalosis in a patient with congestive heart failure. Am J Kidney Dis. 2013;61(5):822–7.
19. Szerlip HM, Weiss J, Singer I. Profound hyperkalemia without electrocardiographic manifestations. Am J Kidney Dis. 1986;7(6):461–5.
20. Kosiborod M, Peacock WF, Packham DK. Sodium zirconium cyclosilicate for urgent therapy of severe hyperkalemia. N Engl J Med. 2015;372(16):1577–8.
21. Alexandridis G, Liberopoulos E, Elisaf M. Aminoglycoside-induced reversible tubular dysfunction. Pharmacology. 2003;67(3):118–20.
22. Blachley JD, Hill JB. Renal and electrolyte disturbances associated with cisplatin. Ann Intern Med. 1981;95(5):628–32.
23. Zietse R, Zoutendijk R, Hoorn EJ. Fluid, electrolyte and acid-base disorders associated with antibiotic therapy. Nat Rev Nephrol. 2009;5(4):193–202.
24. Yessayan L, Yee J, Frinak S, et al. Continuous renal replacement therapy for the management of acid-base and electrolyte imbalances in acute kidney injury. Adv Chronic Kidney Dis. 2016;23(3):203–10.
25. Goyal A, Spertus JA, Gosch K, et al. Serum potassium levels and mortality in acute myocardial infarction. JAMA. 2012;307(2):157–64.

26. Villamil MF, Deland EC, Henney RP, et al. Anion effects on cation movements during correction of potassium depletion. Am J Physiol. 1975;229(1):161–6.
27. Asmar A, Mohandas R, Wingo CS. A physiologic-based approach to the treatment of a patient with hypokalemia. Am J Kidney Dis. 2012;60(3):492–7.
28. Christov M, Neyra JA, Gupta S, et al. Fibroblast growth factor 23 and klotho in AKI. Semin Nephrol. 2019;39(1):57–75.
29. Leaf DE, Siew ED, Eisenga MF, et al. Fibroblast growth factor 23 associates with death in critically ill patients. Clin J Am Soc Nephrol. 2018;13(4):531–41.
30. Vetter T, Lohse MJ. Magnesium and the parathyroid. Curr Opin Nephrol Hypertens. 2002;11(4):403–10.
31. Freitag JJ, Martin KJ, Conrades MB, et al. Evidence for skeletal resistance to parathyroid hormone in magnesium deficiency. Studies in isolated perfused bone. J Clin Invest. 1979;64(5):1238–44.
32. Leaf DE, Christov M. Dysregulated mineral metabolism in AKI. Semin Nephrol. 2019;39(1):41–56.
33. Rivara MB, Ravel V, Kalantar-Zadeh K, et al. Uncorrected and albumin-corrected calcium, phosphorus, and mortality in patients undergoing maintenance dialysis. J Am Soc Nephrol. 2015;26(7):1671–81.
34. Oberleithner H, Greger R, Lang F. The effect of respiratory and metabolic acid-base changes on ionized calcium concentration: in vivo and in vitro experiments in man and rat. Eur J Clin Invest. 1982;12(6):451–5.
35. Ladenson JH, Lewis JW, McDonald JM, et al. Relationship of free and total calcium in hypercalcemic conditions. J Clin Endocrinol Metab. 1979;48(3):393–7.
36. Dzik WH, Kirkley SA. Citrate toxicity during massive blood transfusion. Transfus Med Rev. 1988;2(2):76–94.
37. Afshinnia F, Belanger K, Palevsky PM, et al. Effect of ionized serum calcium on outcomes in acute kidney injury needing renal replacement therapy: secondary analysis of the acute renal failure trial network study. Ren Fail. 2013;35(10):1310–8.
38. LeGrand SB, Leskuski D, Zama I. Narrative review: furosemide for hypercalcemia: an unproven yet common practice. Ann Intern Med. 2008;149(4):259–63.
39. Uehara A, Yazawa M, Kawata A, et al. Denosumab for treatment of immobilization-related hypercalcemia in a patient with end-stage renal disease. CEN Case Rep. 2017;6(1):111–4.
40. O'Connor LR, Klein KL, Bethune JE. Hyperphosphatemia in lactic acidosis. N Engl J Med. 1977;297(13):707–9.
41. Kebler R, McDonald FD, Cadnapaphornchai P. Dynamic changes in serum phosphorus levels in diabetic ketoacidosis. Am J Med. 1985;79(5):571–6.
42. Block GA, Klassen PS, Lazarus JM, et al. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. J Am Soc Nephrol. 2004;15(8):2208–18.
43. Thongprayoon C, Cheungpasitporn W, Mao MA, et al. Admission hyperphosphatemia increases the risk of acute kidney injury in hospitalized patients. J Nephrol. 2018;31(2):241–7.
44. Jung SY, Kwon J, Park S, et al. Phosphate is a potential biomarker of disease severity and predicts adverse outcomes in acute kidney injury patients undergoing continuous renal replacement therapy. PLoS One. 2018;13(2):e0191290. https://doi.org/10.1371/journal.pone.0191290.
45. Markowitz GS, Stokes MB, Radhakrishnan J, et al. Acute phosphate nephropathy following oral sodium phosphate bowel purgative: an underrecognized cause of chronic renal failure. J Am Soc Nephrol. 2005;16(11):3389–96.
46. Tan HK, Bellomo R, M'Pis DA, et al. Phosphatemic control during acute renal failure: intermittent hemodialysis versus continuous hemodiafiltration. Int J Artif Organs. 2001;24(4):186–91.

Chapter 12
Volume Overload and Pulmonary Complications

Masashi Tada, Hiroki Hayashi, Naotake Tsuboi, and Yukio Yuzawa

Abstract Acute kidney injury (AKI) has been shown to be associated with unfavorable outcomes in patients with concurrent acute lung injury (ALI). ALI related to AKI was originally called "uremic lung," and these conditions are currently also related to cardiac and noncardiac pulmonary edema. However, lung injuries, as well as mechanical ventilation used to treat respiratory failure, have been shown to induce AKI. Experimental evidences in animal models with AKI or ALI have demonstrated the tight and bidirectional interactions between kidney and lung injury and shown many structural and functional similarities. To date, the molecular mechanisms of the kidney–lung interaction have been shown to involve a number of inflammatory mediators and receptors, channels/transporters for water or electrolytes, and leukocytes. Thus, kidney–lung crosstalk is commonly present in certain pathological states and is clinically recognized as a critical condition requiring intensive management. In this chapter, we discuss the pathogenic and mechanistic associations of AKI with lung injury.

Keywords Acute lung injury · Alveolar epithelial cell · Interleukin-6 · Mechanical ventilation · Pulmonary edema

12.1 Introduction

Many studies have evaluated kidney injury-related lung injury, also known as "uremic lung," since its discovery in the 1930s [1]. Until the 1950s, volume overload was thought to be the only cause of pulmonary edema associated with acute kidney injury (AKI) [2]; however, noncardiogenic pulmonary edema has recently been recognized as another clinical form of AKI-induced lung injury [3].

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In clinical practice, AKI, which is observed in 20% of hospitalized patients [4] and in 30–50% of patients in the intensive care unit (ICU) [5], is a critical medical condition associated with a high mortality rate. Therefore, nephrologists frequently receive consultations for patients with AKI from other clinical departments. The overall mortality rates for patients with severe AKI who require renal replacement therapy [6] and those who are admitted to the ICU [7, 8] have been shown to reach 33% and more than 50%, respectively. Moreover, patients with AKI often have extended durations of hospitalization by twofold compared with that in patients without AKI [9, 10]. Multiple studies have shown that AKI is an independent risk factor determining patient mortality, even when the severity is mild [11–17]. Multi-organ failure, not uremia or volume overload, has been shown to be the major cause of AKI-related death; therefore, injuries in various remote organs, including the heart, lung, and brain, occurring with or after AKI are considered adverse prognostic factors [18].

Inflammatory mediators derived from injured kidneys easily spread to remote organs. In particular, lungs, which contain abundant capillary blood vessels and are the location of most of systemic blood circulation, are highly susceptible to inflammatory mediators derived from extrapulmonary organs [19]. In addition, the tight interactions between the lungs and kidneys can be explained by structural and functional similarities as 1. apical and basolateral cell polarity, and distributions and types of channels/transporters for water or electrolytes between alveolar and tubular epithelial cells 2. lung/kidney crosstalk to maintain vascular tension, erythropoietin production, and balances in fluid, electrolytes, and acid–base under health conditions 3. organ reactivity for pathological stimuli under diseased conditions, including activation of the renin-angiotensin-aldosterone system (RAAS), inappropriate secretion of antidiuretic hormone, multi-organ failure complicated with ischemic injury, pulmonary, and renal vasculitis involving activated immune cells [20–22].

12.2 Proposed Mechanism of Remote Organ Injury from Injured Kidneys

The mechanisms of AKI-related remote organ injury have been investigated in animal models of ischemia-reperfusion injury (IRI) and bilateral nephrectomy. In an IRI model, inflammatory mediators stimulated by renal injury are involved in local injury to the kidneys, and also induce systemic innate immunity, including Toll-like receptors and the complement pathway, enhance production of oxygen radicals, promote organ-specific chemokine production, and activate neutrophils and macrophages. These inflammatory responses, together with the subsequent induction of acquired immunity involving T and B lymphocytes and cell apoptosis, finally cause physiological dysfunction in corresponding organs [23].

12.3 Pathogenesis of AKI-Related Acute Lung Injury (ALI)

Mechanical ventilation is an independent predictor of patient prognosis and is required in patients with AKI twice as frequently as in patients without AKI [16, 24]. Moreover, mechanical ventilation is more frequent in patients with AKI requiring renal replacement therapy [16]. The mortality rate of patients with AKI under mechanical ventilation is significantly increased to 81% compared with that (29%) in patients with AKI who do not require mechanical ventilation [25].

AKI involves kidney tissue injury and subsequent renal dysfunction. Systemic accumulation of various excretions and metabolites via kidney dysfunction potentially influences the entire organ system. Once kidney dysfunction occurs, several uremic toxins, which should have been eliminated from circulation, accumulate and directly injure the lungs [21, 23], subsequently resulting in enhancement of vascular permeability, inflammatory cell infiltration, and oxidative stress in the lungs [26]. The lungs are composed of abundant capillaries and are highly susceptible to chemical and inflammatory mediators, which can induce pulmonary damage [19, 27]. During the development of major clinical conditions associated with AKI, including respiratory or cardiac dysfunction requiring the mechanical ventilation, sepsis, and immunodeficiency, the kidneys regulate inflammatory activity; in particular, the renal tubular epithelium plays important roles. Renal tubular epithelial cells are the main target cells injured in AKI and produce inflammatory mediators involved in both local and systemic inflammation [21]. In addition to renal cell-derived inflammatory mediators (e.g., cytokines and chemokines), renal cell damage-related factors, including cell debris, microstructures, DNA, RNA, and microRNA, systemically affect remote organs, such as the lungs.

Pulmonary edema, a major pulmonary manifestation related to AKI, can be categorized as cardiogenic or noncardiogenic according to its pathogenesis [23].

12.3.1 Cardiogenic Pulmonary Edema

Renal dysfunction induced by AKI increases capillary hydrostatic pressure secondary to excess fluid volume and results in pulmonary edema and subsequent respiratory failure [28]. In pediatric nephrology, pediatric patients with end-stage kidney disease (ESKD) under strict management of fluid volume by peritoneal dialysis exhibit 25% shorter mechanical ventilation periods after cardiac surgery compared with those in patients with volume overload [29]. Excess volume overload in patients with AKI is generally accepted as a major risk factor increasing mortality [30]. Indeed, in an observational study of sepsis patients in the ICU, higher mortality (odds ratio: 2.07) was found in patients with excess volume overload than in those without volume overload [31]. Notably, cardiogenic pulmonary edema can occur in patients with normal and deteriorated cardiac functions. Cardiogenic pulmonary edema physiologically elevates jugular and central venous pressure, and

presents bilateral enhancement of pulmonary marking and congestion in X-ray images. Administration of diuretics in patients with residual renal function and extracorporeal ultrafiltration in those with ESKD are effective for alleviation of disease symptoms [23].

12.3.2 Noncardiogenic Pulmonary Edema

Noncardiogenic pulmonary edema is initiated by cell damage in the pulmonary capillary endothelium. Inflammatory mediators promote the recruitment of leukocytes into pulmonary alveoli to initiate local inflammation, and pulmonary alveoli are then filled with flowing fluid directly from pulmonary capillaries to the interstitium. Protein-rich fluid is often observed as eosinophilic material on lung histology in cases of noncardiogenic pulmonary edema. In histological analysis, autopsied lung specimens with noncardiogenic pulmonary edema exhibit extravasation of inflammatory cells and hyaline membrane formation in the alveoli [23, 27]. In a prior study of 66 autopsy cases with uremic lung complicated with AKI, hyaline membrane formation was observed in all cases without overload of systemic fluid volume [32]. Elevation of central venous pressure and pulmonary capillary wedge pressure was not evident by the assessment of cardiac function in noncardiogenic pulmonary edema [33]; however, bilateral enhancement of pulmonary marking and congestion were observed on chest X-ray images. Therefore, chest X-ray was not sufficient for discrimination of cardiogenic pulmonary edema from noncardiogenic pulmonary edema.

AKI has been shown to affect the pulmonary microenvironment by increasing inflammatory mediators and vascular hyperpermeability, enhancing leukocyte recruitment, and altering alveolar expression of sodium/water channels or transporters, significantly affecting the onset of ALI [34]. In practice, patients with AKI often present with cardiogenic and noncardiogenic pulmonary edema, which both aggravate respiratory function.

12.4 Experimental Evidence in Animal Models with Ischemic AKI and Bilateral Nephrectomy

Lung injury following AKI has been observed in animal models of both ischemic AKI and bilateral nephrectomy. Lung injury mediated by ischemic AKI results in neutrophil accumulation and upregulation of inflammatory proteins and genes. Pulmonary neutrophil accumulation is observable at 1–2 h [35], peaks at 4–8 h [35–37], and returns to baseline at 24–36 h following the onset of AKI [35]. Neutrophil migration occurs mainly in pulmonary alveoli, forming the center of inflammatory processes in AKI-mediated lung injury [38]. Upregulation of inflammatory mediators, including tumor necrosis factor (TNF)-α [36, 37],

interleukin (IL)-8 (known as macrophage inflammatory protein-2 in mice) [35, 39–41], and TNF receptor 1 (TNFR1) [42], as well as activation of inflammation-related signaling pathways (e.g., nuclear factor-kappa B [NF-κB]) [36, 42] and enhanced expression of intercellular adhesion molecule-1 [34, 36, 37] support leukocyte recruitment to the pulmonary vascular endothelium and have been observed in animal models of lung injury following ischemic AKI. Anti-inflammatory compounds or antibodies targeting inflammatory signaling molecules, including p38 mitogen-activated protein kinase (CNI-1493) [43], melanocyte-stimulating hormone (MSH) [36], IL-6 [35], IL-10 [39], IL-8 [41], dexmedetomidine [37], high mobility group protein B1 (HMGB1) [44], Toll-like receptor 4 (TLR4) [44], NF-κB [42], and TNFα (etanercept) [42], have been shown to ameliorate lung injury in animal models with ischemic AKI and bilateral nephrectomy.

Pulmonary edema is also experimentally observed in animal models with ischemic AKI and bilateral nephrectomy [36, 37, 45]. Among pulmonary molecules playing important roles in fluid clearance in the lungs, reductions in the alveolar sodium channel [46], pulmonary Na-K ATPase [46], and pulmonary aquaporin 1 [45] and 5 [46] have been observed in AKI-related pulmonary edema, indicating the involvement of these targets in the pathogenesis of this disease.

Various inflammatory mediators and leukocytes, such as IL-6, IL-8, TNF, NF-κB, TNFR1, caspase-3, HMGB1, neutrophils and T lymphocytes, have been shown to be involved in AKI-related ALI in animal models and biological samples from patients (Table 12.1). Among these targets, IL-6, TNFR1, and caspase-3 have been extensively investigated in order to clarify their roles in the pathogenesis of ALI.

Table 12.1 Inflammatory mediators and leukocytes involved in AKI-related ALI (from [23])

Mediators	Evidence	Proposed mechanism
IL-6	Serum IL-6 levels are elevated within 2 h after AKI in mouse and human AKI [47] Serum IL-6 elevation is involved in prolonged mechanical ventilation in AKI [47] AKI increases the expressions of IL-6-related inflammatory signaling molecules in the lungs [36] Mice treated with monoclonal anti-IL-6 antibodies and deficient in IL-6 show reduced inflammation and capillary vascular permeability in the lungs [35] Intravenous administration of IL-6 into IL-6-deficient mice induces pulmonary inflammation [41]	Circulating IL-6 promotes IL-8 production from pulmonary vascular endothelial cells
IL-8	Serum IL-8 levels are elevated within 2 h after AKI in mouse and human AKI [47] Elevated serum IL-8 is a prognostic factor for prolonged mechanical ventilation in AKI [47] Pulmonary IL-8 is increased in AKI model mice [35, 44] Mice treated with monoclonal anti-IL-8 antibodies and deficient in IL-8 receptor show mild pulmonary inflammation [41]	Elevated IL-8, a strong chemoattractant for neutrophils) in lungs following AKI, promotes pulmonary neutrophil accumulation to injure pulmonary tissues

(continued)

Table 12.1 (continued)

Mediators	Evidence	Proposed mechanism
NF-κB	The NF-κB pathway is activated in lungs with AKI [36, 42] Mice treated with α-MSH show reduced NF-κB activation and mild pulmonary inflammation in AKI [36] Mice treated with an NF-κB inhibitor show amelioration of AKI-related pulmonary edema associated with reduced apoptosis [42]	NF-κB-mediated pulmonary inflammation and apoptosis of alveolar endothelial cells promote pulmonary tissue injury and induce noncardiac pulmonary edema
TNFR1- and caspase-3-related apoptosis	Serum TNFα is elevated within 2 h after the induction of ischemic AKI in mice [44] Pulmonary TNFR1 is increased in mice with AKI [55] Multiple genes of signaling molecules downstream from TNFR1 are expressed in murine lungs with AKI [55] Increased pulmonary cell apoptosis after AKI [55] Caspase-3 activation is increased in lungs with AKI, and caspase inhibition ameliorates pulmonary edema after AKI [55] Inhibition of TNFα reduces pulmonary apoptosis and edema associated with impaired NF-κB activation [42] Mice deficient in TNFR1 show caspase-3 activation and apoptosis in lungs with AKI [55]	Circulating TNFα binds TNFR1 on pulmonary vascular endothelial cells to promote noncardiac pulmonary edema through activation of the NF-κB/caspase-3 pathway
TLR4 and HMGB1	Plasma HMGB1 is elevated within 6 h after AKI in mice [44] Mice treated with anti-HMGB1 antibodies show reduced pulmonary edema associated with downregulation of TNFα, IL-8, and IL-1β and with increased neutrophil accumulation in the lungs after induction of AKI [44] Mice with impaired TLR4 responses show amelioration of pulmonary edema; reduced TNFα, IL-8, and IL-1β expression, and increased neutrophil accumulation in the lungs in bilateral nephrectomy or bilateral ischemic AKI [44]	Circulating HMGB1 partially activates TLR4 to induce pulmonary inflammation and neutrophil accumulation, resulting in noncardiac pulmonary edema
Neutrophils	Pulmonary accumulation of esterase$^+$ leukocytes in parallel with the elevation of pulmonary myeloperoxidase (MPO) activity started at 4 h after ischemic AKI [36] Systemic administration of IL-10 before bilateral nephrectomy in mice ameliorates pulmonary neutrophil infiltration in accordance with reductions in pulmonary MPO activity and MIP-2 [39] Uremic mice with AKI show significant protection from ALI in a murine two-hit model consisting of AKI and subsequent ALI initiated by intratracheal HCl instillation. Reconstitution experiments, in which uremic neutrophils were injected into ALI mice with neutrophil depletion, showed improved oxygenation in a murine HCl-induced ALI model. Attenuation of pulmonary recruitment of uremic neutrophils is associated with altered surface expression of L-selectin [57]	Neutrophils recruited to the lungs after AKI initiate ALI by secreting chemical mediators. Uremia in AKI attenuates neutrophil-dependent ALI and exerts anti-inflammatory effect by the reduction of pulmonary neutrophil recruitment

Table 12.1 (continued)

Mediators	Evidence	Proposed mechanism
T lymphocytes	T lymphocytes are recruited to the lungs within 24 h after AKI [58] Mice lacking T lymphocytes exhibit mild pulmonary edema associated with reduced caspase-3 activation in lungs [58] Reconstitution of T lymphocytes in mice deficient in T cells induces pulmonary edema associated with enhanced caspase-3 activation in the lungs [58]	Pulmonary T lymphocytes recruited within 24 h after AKI onset promote noncardiac pulmonary edema though caspase-3-dependent alveolar endothelial cells

12.4.1 IL-6

Elevation of IL-6 in patient serum can predict AKI progression under various clinical conditions, including after coronary artery bypass grafting (CABG) [47], sepsis [48], and ALI [49]. Increased serum IL-6 within 2 h after manifestation of postoperative AKI for CABG is prognostic factor for prolonged withdrawal of mechanical ventilation and correlates with mortality in patients complicated with AKI and ALI [23]. Amelioration of ALI by IL-6 inhibition has been observed in animal models of AKI. IL-6 deficiency or neutralization by monoclonal anti-IL-6 antibodies in mice impairs AKI-mediated pulmonary inflammation, exudative changes in pulmonary capillaries, and IL-6 concentrations in the serum and lungs. In contrast, intravenous administration of recombinant IL-6 successfully induces pulmonary inflammation in IL-6-deficient mice with AKI [41]; however, comparable treatment in to the mouse trachea does not result in pulmonary inflammation in wild-type or AKI model animals [50]. Moreover, high levels of IL-6 in circulation, but low levels of IL-6 in bronchoalveolar lavage fluid (BALF), in AKI mice are related to the pathogenesis of AKI-related ALI owing to the dominant role of IL-6 in circulation rather than the lungs. The mechanism through which circulating IL-6 affects ALI is thought to involve the molecular complex of circulating IL-6 and its soluble receptor associating with gp130 on capillary endothelial cells, resulting in activating signals, which then increase the local production of pulmonary IL-8 to promote neutrophil recruitment and finally initiate pulmonary inflammation (Fig. 12.1) [23, 41]. In contrast to the positive effects of circulating IL-6 on lung tissue injury observed in IRI and bilateral nephrectomy in mice, ALI involves the anti-inflammatory and protective roles of pulmonary IL-6, which is directly mediated by mechanical ventilation or intratracheal administration of lipopolysaccharide [23].

AKI accelerates renal and extrarenal production of other cytokines with IL-6, and renal dysfunction further increases cytokine concentrations in circulation via impaired clearance. These two processes collectively increase circulating inflammatory cytokines to exacerbate ALI by forming a vicious cycle [23]. Experimental findings have shown that cytokine mRNAs or proteins derived from kidneys with ischemic or toxic tissue injury can be observed in circulation, whereas circulating IL-6 is elevated in bilateral nephrectomized mice; these findings indicate that

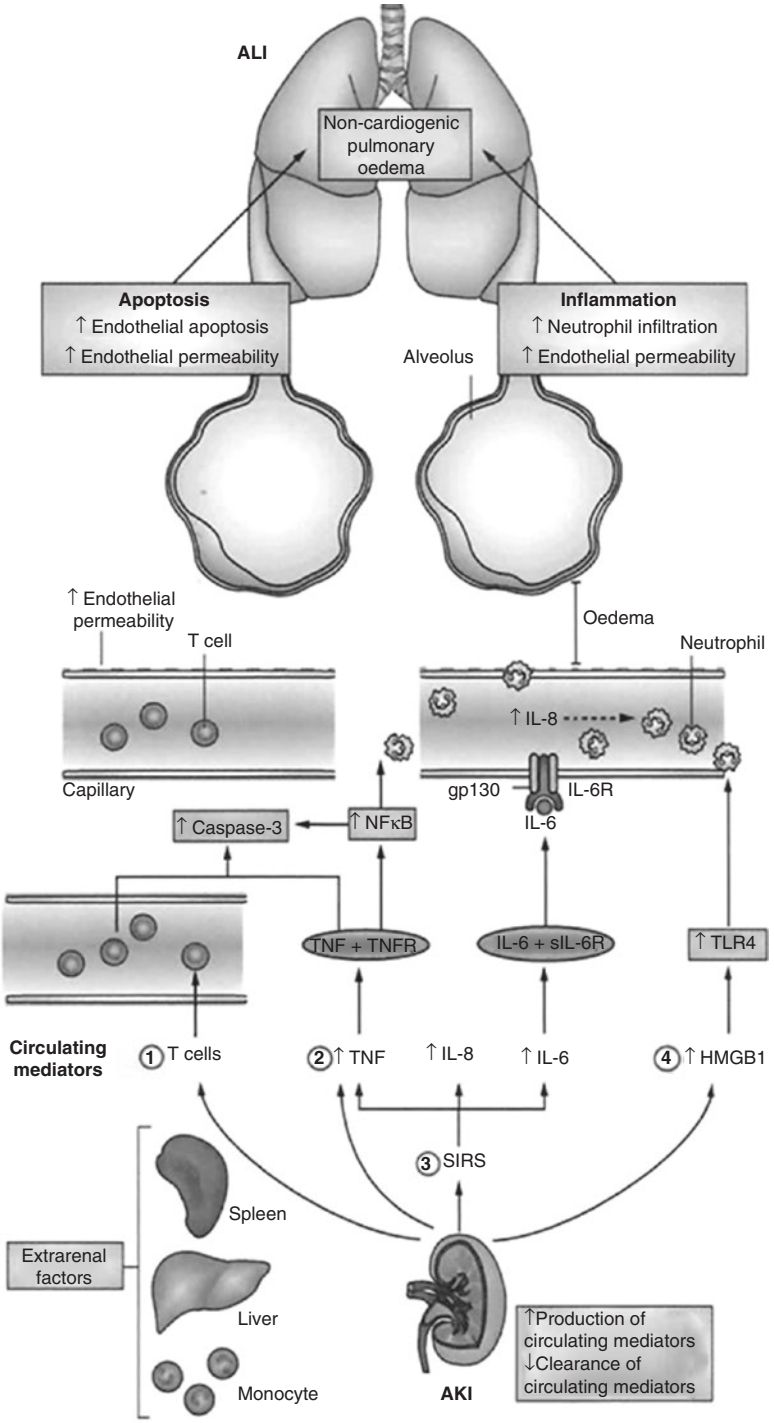

Fig. 12.1 Pathological cascade from AKI to ALI (from [23])

enhanced production in extrarenal organs or cells, including the spleen, liver, and macrophages, and impaired clearance in renal dysfunction are involved in cytokine upregulation in AKI [23]. Bilateral nephrectomized mice exhibit high concentrations of IL-6 after intravenous injection, highlighting the importance of clearance in the upregulation of inflammatory cytokines in AKI [51]. IL-6 is re-absorbed and metabolized in the proximal tubule following glomerular filtration in the kidneys. The concentration of exogenous IL-6 was increased in AKI model mice with ischemia-mediated tubular injury following intravenous administration, but was not increased in mice with pre-renal azotemia after furosemide administration (no tubular injury), indicating that proximal tubular injury in AKI affects serum IL-6 levels [52].

12.4.2 IL-8

IL-8, a chemokine secreted from neutrophils, has been intensively studied in patients and animal models with ALI, AKI, and AKI-related ALI. Clinical studies in patients with ALI have revealed that elevated IL-8 in circulation and BALF is a predictor of patient mortality [53]. Elevated IL-8 in circulation is also a predictor of patient mortality in AKI [54], and circulating IL-8 levels at 2 h after AKI onset are significantly associated with prolongation of mechanical ventilation [47]. The involvement of IL-8 in AKI-related ALI was further supported by experimental evidence demonstrating that mice with antibody-dependent neutralization of IL-8 and deficiencies in the IL-8 receptor were resistant to AKI-related ALI [40].

12.4.2.1 TNFR1- and Caspase-3-Dependent Apoptosis

Programmed cell death (apoptosis) is known to have pathogenic roles in AKI-related ALI [23]. Pulmonary gene analysis after ALI has demonstrated that the expression levels of many genes related to apoptosis pathways are increased. Moreover, histological assessment of ALI lungs has revealed that pulmonary apoptosis occurs initially in capillary endothelial cells, not in alveolar epithelial cells, at 24 h after the onset of AKI [55]. Furthermore, animals with pharmaceutical inhibition of the total caspase pathway, TNF inhibition by etanercept, or TNFR1 downregulation exhibit significant reductions in pulmonary apoptosis and protein contents in the BALF [55, 56]. Therefore, these findings collectively demonstrated that destruction of alveolar barrier function followed by TNFR1- and caspase-3-dependent apoptosis in capillary endothelial cells initiate noncardiogenic pulmonary edema in AKI.

12.4.3 Neutrophils

Depletion of circulating neutrophils attenuates ALI induced by intratracheal exposure to HCl, suggesting that neutrophils may have important roles in pulmonary injury in a murine ALI model [57]. Pulmonary accumulation of neutrophils after

ischemic AKI or bilateral nephrectomy has been demonstrated [36, 39]. Moreover, administration of the anti-inflammatory cytokine IL-10 before bilateral nephrectomy ameliorates pulmonary neutrophil infiltration in accordance with reductions in pulmonary myeloperoxidase activity (a biochemical marker of neutrophils) and the chemokine macrophage inflammatory protein 2 (a neutrophil chemoattractant and functional homolog of human IL-8 in mice) [39]. In contrast, the presence of AKI prior to HCl exposure and reconstitution of bone marrow-derived neutrophils from bilateral nephrectomized mice into ALI mice with neutrophil depletion results in improved oxygenation in a murine HCl-induced ALI model, suggesting that uremic neutrophils may be the primary mediators for attenuating ALI. Additionally, uremic conditions suppress pulmonary recruitment of neutrophils by inducing alterations in the surface expression of L-selectin [57]. Therefore, the roles of neutrophils in AKI-mediated ALI are still controversial.

12.4.4 T Lymphocytes

T cells are involved in the pathogenesis of AKI-related ALI. T-cell-deficient mice, lacking pulmonary T-cell recruitment as normally observed at 24 h after AKI onset in wild-type animals, exhibit impaired pulmonary caspase-3 activity and amelioration of pulmonary edema, indicating that capillary endothelial cell apoptosis mediated by T cells via a caspase-3-dependent mechanism leads to noncardiogenic pulmonary edema [58].

12.4.5 Sodium/Water Channels or Transporters

Type I alveolar epithelial cells expressing aquaporin 5 (AQP5) on the apical side and Na/K ATPase on the basal side and type I cells expressing epithelial sodium channels (ENaCs) on the apical side and Na/K ATPase on basal side are responsible for sodium and water transport from alveolar cavities to pulmonary capillaries [59]. Rats with bilateral nephrectomy or bilateral renal IRI show downregulation of ENaC, Na/K-ATPase, and AQP5 in alveolar epithelial cells at 48 h after AKI [46]. Because these features were not remarkable in unilateral renal IRI, elevated uremic toxin in renal dysfunction, rather than ischemia-related oxidative stress, has been proposed to cause alterations involving sodium/water channels. Thus, AKI, even at the initial phase, has been shown to exacerbate ALI by influencing the expression levels of sodium and water channels. Moreover, in clinical practice, Na/K-ATPase has emerged as an important therapeutic target for pulmonary edema in ALI [60].

12.5 Pulmonary Complications with AKI Are Associated with Patient Mortality

The incidence of pulmonary complications requiring mechanical ventilation is increased by twofold in patients with AKI compared with that in patients without AKI [5]. In accordance with the high frequency of mechanical ventilation, the mortality rate in patients with AKI is also increased to 80% among patients who require mechanical ventilation compared with 26% among those who do not require mechanical ventilation [18].

Previous studies focusing on the clinical mode leading to renal dysfunction have shown increased mortality in patients with AKI (61–63% compared with 36–46% in those with ESKD) [5, 18]. Moreover, increased mortality may result from the higher frequency of mechanical ventilation in patients with AKI because of the higher susceptibility to noncardiac pulmonary edema caused by systemic inflammation and because cardiac pulmonary edema is a common comorbidity in patients with AKI [5, 18].

12.6 Pathogenesis of ALI-Mediated AKI

ALI caused directly by pneumonia and pulmonary hemorrhage or indirectly by noninfectious inflammation [21] have been shown to induce AKI. Circulating inflammatory mediators produced in injured lungs [21, 22, 26] or pulmonary acidosis in ventilatory disturbance [27] influence renal insufficiency. Because of the large oxygen consumption observed in Henle loops and proximal tubules, kidneys are highly susceptible to hypoxia [26]. Additionally, because of the ALI- mediated impairment of the renal autoregulatory system, which prevents the kidneys from experiencing ischemic conditions, hypoxia in ALI reduces renal blood flow, thereby leading to renal insufficiency. Additionally, CO_2 accumulation in ALI decreases renal blood flow directly through renal vasoconstriction via activation of RAAS and indirectly through CO_2-mediated systemic vasodilatation [21, 26, 27]. Impairment of glomerular filtration has been documented in cases with CO_2 accumulation caused by sustained pulmonary insufficiency [21, 23].

12.7 Mechanical Ventilation in AKI-Related ALI

Contrary to the beneficial roles of mechanical ventilation in ALI, mechanical ventilation has harmful effects on the development of AKI [21]. In addition to dysregulation of renal vascular tension by ALI-mediated inflammatory mediators from injured lungs, mechanical ventilation increases AKI risk and mortality in patients with ALI [27]. Modulation of systemic hemodynamics and central venous pressure by mechanical ventilation may deteriorate renal function [26]. Additionally, increased

afterload in the right side of heart induced by decreased cardiac output under mechanical ventilation results in reduced glomerular filtration, and inhibition of atrial natriuretic peptide production by the sympathetic nervous system following mechanical ventilation results in severe hypoxia and accelerates RAAS [20–22, 26]. Angiotensin II-induced RAAS activation in response to hypoxia and noradrenaline induced by CO_2 accumulation play important roles as vasoconstrictors to increase renal vascular resistance [20, 26].

12.7.1 Involvement of Positive Pressure Ventilation in Renal Hemodynamics

An ARDS network study comparing respiratory care following positive pressure ventilation with conventional (12 mL/kg) and low tidal volume (6 mL/kg) showed that the latter significantly reduces renal dysfunction and improves mortality caused by ARDS [61]. This suggests that ventilation using high positive endoexpiratory pressure followed by increased intrathoracic pressure results in decreased cardiac output owing to reduced cardiac venous return impairs renal blood flow and glomerular filtration rate (GFR).

12.7.2 Involvement of Positive Pressure Ventilation in the Neuroendocrine System

Positive pressure ventilation induces neuroendocrine dysregulation, including hyperactivity of the sympathetic nervous system, activation of the RAAS, hypersecretion of vasopressin, and reduced production of atrial natriuretic peptide. These changes promote the shift of intrarenal blood flow from the cortex to the medulla, resulting in decreased renal blood flow and GFR [62]. In addition, ALI-mediated severe hypoxia and hypercapnia also decrease renal blood flow through the elevation of angiotensin II, endothelin, and norepinephrine in circulation.

12.7.3 Involvement of Lung-Derived Inflammatory Mediators in AKI

ALI is a type of acute inflammation-related injury mediated by various cytokines/chemokines in pulmonary alveoli and capillaries. In particular, pulmonary overdistension, repetitive alveolar collapse (atelectrauma), and biotrauma by respiratory care with a high ventilation volume promote the productions of various chemokines, including IL-6, IL-8, TNFα, monocyte chemoattractant protein-1, and nitric oxide synthase [63, 64].

12.8 Association of Other Pulmonary Disorders with Kidney Injury

12.8.1 Chronic Obstructive Pulmonary Disease (COPD)

Patients with COPD with low levels of uremic nitrogen exhibit favorable maintenance of serum pH and rapid improvement of the acid–base imbalance in response to initiation of noninvasive mechanical ventilation. In contrast, patients with COPD plus ESKD, whose renal adaptive abilities against CO_2 accumulation are highly impaired, easily progress to acidosis [21]. Because of the impairment of sodium excretion function by chronic reduction of renal blood flow, patients with COPD are predisposed to systemic fluid retention and subsequent pulmonary congestion to induce pulmonary hypertension and right-side cardiac insufficiency [21, 22]. During acute exacerbation of COPD, enhanced noradrenaline production via activation of the sympathetic nervous system following additional CO_2 accumulation results in further renal vasocontraction and reduced renal blood flow. Moreover, elevation of intra-abdominal pressure in COPD blocks venous blood flow, resulting in renal congestion and promoting a vicious cycle to further elevate intra-abdominal pressure.

12.8.2 Obstructive Sleep Apnea

Nocturnal hypoxia reduces glomerular filtration and increases the risk of atherosclerosis, hypertension, and cardiovascular diseases [65]. Renal hypoxia, increased inflammatory mediators, and sympathetic nervous system activation mediate sleep apnea and synergistically deteriorate renal function. Moreover, elevate blood pressure following the activation of the sympathetic nervous system and RAAS, induction of systemic inflammation and oxidative stress, and dysfunction of the vascular endothelium in sleep apnea promote chronic kidney diseases [20, 22, 65, 66]. Sleep apnea, which occurs in approximately 50% of patients with chronic kidney disease and ESKD, is currently recognized as a risk factor for the further deterioration of renal function and for cardiovascular diseases [65].

12.9 Conclusion

In addition to the conventional paradigm of AKI-related “cardiogenic” pulmonary edema, the concept of “noncardiogenic” pulmonary edema has emerged as an alternative mechanism involved in AKI-related ALI. Increased levels of cytokines, chemokines, and uremic toxins cause apoptosis in the pulmonary capillary endothelium, further promoting chemokine production, hypervascular permeability, pulmonary leukocyte accumulation, and noncardiogenic edema. During or after these processes, reduction of sodium/water channels, including ENaCs,

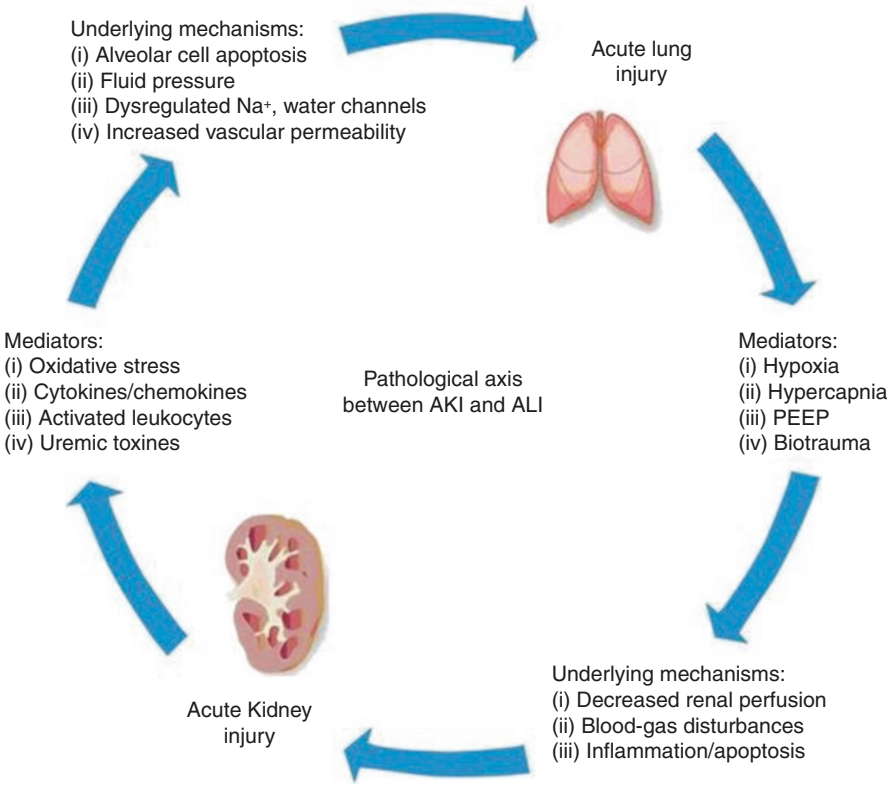

Fig. 12.2 Pathophysiology of lung–kidney crosstalk (from [56])

Na/K-ATPase, and AQP5, further accelerates noncardiogenic pulmonary edema. Moreover, both ALI-mediated hypoxia/hypercapnia and conventional positive pressure ventilation disrupt renal blood flow and promote renal ischemia or induce renal inflammation. These pathogenic factors in lungs and kidneys alternately interact and form the vicious cycle of AKI-related ALI (Fig. 12.2).

References

1. Roubier C, Plaichau M. Sur certains aspects radiographisues de l'oedemepulmonaire chez les cardiorenauxazotemiques. Arch Med-chir de l'app Respire. 1934;9:189.
2. Depass SW, Jacobson HG, Poppel MH, Stein J. Pulmonary congestion and edema in uremia. J Am Med Assoc. 1956;162(1):5–9.
3. Alwall N, Lunderquist A, Olsson O. Uremic lung, wet lung. Nord Med. 1953;49(6):211–4.
4. Uchino S, Bellomo R, Goldsmith D, Bates S, Ronco C. An assessment of the RIFLE criteria for acute renal failure in hospitalized patients. Crit Care Med. 2006;34(7):1913–7.
5. Star RA. Treatment of acute renal failure. Kidney Int. 1998;54(6):1817–31.

6. Xue JL, Daniels F, Star RA, Kimmel PL, Eggers PW, Molitoris BA, et al. Incidence and mortality of acute renal failure in Medicare beneficiaries, 1992 to 2001. J Am Soc Nephrol. 2006;17(4):1135–42.
7. Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M, Tan I, et al. Continuous renal replacement therapy: a worldwide practice survey. The beginning and ending supportive therapy for the kidney (B.E.S.T. kidney) investigators. Intensive Care Med. 2007;33(9):1563–70.
8. Network VNARFT, Palevsky PM, Zhang JH, O'Connor TZ, Chertow GM, Crowley ST, et al. Intensity of renal support in critically ill patients with acute kidney injury. N Engl J Med. 2008;359(1):7–20.
9. Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. J Am Soc Nephrol. 2005;16(11):3365–70.
10. Liangos O, Wald R, O'Bell JW, Price L, Pereira BJ, Jaber BL. Epidemiology and outcomes of acute renal failure in hospitalized patients: a national survey. Clin J Am Soc Nephrol. 2006;1(1):43–51.
11. Levy EM, Viscoli CM, Horwitz RI. The effect of acute renal failure on mortality. A cohort analysis. JAMA. 1996;275(19):1489–94.
12. Bates DW, Su L, Yu DT, Chertow GM, Seger DL, Gomes DR, et al. Mortality and costs of acute renal failure associated with amphotericin B therapy. Clin Infect Dis. 2001;32(5):686–93.
13. Chertow GM, Levy EM, Hammermeister KE, Grover F, Daley J. Independent association between acute renal failure and mortality following cardiac surgery. Am J Med. 1998;104(4):343–8.
14. Lassnigg A, Schmidlin D, Mouhieddine M, Bachmann LM, Druml W, Bauer P, et al. Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic surgery: a prospective cohort study. J Am Soc Nephrol. 2004;15(6):1597–605.
15. Parikh CR, McSweeney PA, Korular D, Ecder T, Merouani A, Taylor J, et al. Renal dysfunction in allogeneic hematopoietic cell transplantation. Kidney Int. 2002;62(2):566–73.
16. Metnitz PG, Krenn CG, Steltzer H, Lang T, Ploder J, Lenz K, et al. Effect of acute renal failure requiring renal replacement therapy on outcome in critically ill patients. Crit Care Med. 2002;30(9):2051–8.
17. du Cheyron D, Bouchet B, Parienti JJ, Ramakers M, Charbonneau P. The attributable mortality of acute renal failure in critically ill patients with liver cirrhosis. Intensive Care Med. 2005;31(12):1693–9.
18. Scheel PJ, Liu M, Rabb H. Uremic lung: new insights into a forgotten condition. Kidney Int. 2008;74(7):849–51.
19. Floege J, Uhlig S. Kidney calling lung and call back: how organs talk to each other. Nephrol Dial Transplant. 2010;25(1):32–4.
20. Ricci Z, Ronco C. Pulmonary/renal interaction. Curr Opin Crit Care. 2010;16(1):13–8.
21. Husain-Syed F, Slutsky AS, Ronco C. Lung-kidney cross-talk in the critically ill patient. Am J Respir Crit Care Med. 2016;194(4):402–14.
22. Visconti L, Santoro D, Cernaro V, Buemi M, Lacquaniti A. Kidney-lung connections in acute and chronic diseases: current perspectives. J Nephrol. 2016;29(3):341–8.
23. Faubel S, Edelstein CL. Mechanisms and mediators of lung injury after acute kidney injury. Nat Rev Nephrol. 2016;12(1):48–60.
24. Waikar SS, Liu KD, Chertow GM. The incidence and prognostic significance of acute kidney injury. Curr Opin Nephrol Hypertens. 2007;16(3):227–36.
25. Chertow GM, Christiansen CL, Cleary PD, Munro C, Lazarus JM. Prognostic stratification in critically ill patients with acute renal failure requiring dialysis. Arch Intern Med. 1995;155(14):1505–11.
26. Basu RK, Wheeler DS. Kidney-lung cross-talk and acute kidney injury. Pediatr Nephrol. 2013;28(12):2239–48.
27. Doi K, Ishizu T, Fujita T, Noiri E. Lung injury following acute kidney injury: kidney-lung crosstalk. Clin Exp Nephrol. 2011;15(4):464–70.

28. Frank HA, Seligman AM, Fine J. Further experiences with peritoneal irrigation for acuter renal failure including a description of modifications in method. Ann Surg. 1948;128(3):561–608.
29. Vieira JM Jr, Castro I, Curvello-Neto A, Demarzo S, Caruso P, Pastore L Jr, et al. Effect of acute kidney injury on weaning from mechanical ventilation in critically ill patients. Crit Care Med. 2007;35(1):184–91.
30. Payen D, de Pont AC, Sakr Y, Spies C, Reinhart K, Vincent JL, et al. A positive fluid balance is associated with a worse outcome in patients with acute renal failure. Crit Care. 2008;12(3):R74.
31. Bouchard J, Soroko SB, Chertow GM, Himmelfarb J, Ikizler TA, Paganini EP, et al. Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. Kidney Int. 2009;76(4):422–7.
32. Bleyl U, Sander E, Schindler T. The pathology and biology of uremic pneumonitis. Intensive Care Med. 1981;7(4):193–202.
33. Matthay MA, Ware LB, Zimmerman GA. The acute respiratory distress syndrome. J Clin Invest. 2012;122(8):2731–40.
34. Feltes CM, Hassoun HT, Lie ML, Cheadle C, Rabb H. Pulmonary endothelial cell activation during experimental acute kidney injury. Shock. 2011;36(2):170–6.
35. Klein CL, Hoke TS, Fang WF, Altmann CJ, Douglas IS, Faubel S. Interleukin-6 mediates lung injury following ischemic acute kidney injury or bilateral nephrectomy. Kidney Int. 2008;74(7):901–9.
36. Deng J, Hu X, Yuen PS, Star RA. Alpha-melanocyte-stimulating hormone inhibits lung injury after renal ischemia/reperfusion. Am J Respir Crit Care Med. 2004;169(6):749–56.
37. Gu J, Chen J, Xia P, Tao G, Zhao H, Ma D. Dexmedetomidine attenuates remote lung injury induced by renal ischemia-reperfusion in mice. Acta Anaesthesiol Scand. 2011;55(10):1272–8.
38. Lee WL, Downey GP. Neutrophil activation and acute lung injury. Curr Opin Crit Care. 2001;7(1):1–7.
39. Hoke TS, Douglas IS, Klein CL, He Z, Fang W, Thurman JM, et al. Acute renal failure after bilateral nephrectomy is associated with cytokine-mediated pulmonary injury. J Am Soc Nephrol. 2007;18(1):155–64.
40. Andres-Hernando A, Altmann C, Ahuja N, Lanaspa MA, Nemenoff R, He Z, et al. Splenectomy exacerbates lung injury after ischemic acute kidney injury in mice. Am J Physiol Renal Physiol. 2011;301(4):F907–16.
41. Ahuja N, Andres-Hernando A, Altmann C, Bhargava R, Bacalja J, Webb RG, et al. Circulating IL-6 mediates lung injury via CXCL1 production after acute kidney injury in mice. Am J Physiol Renal Physiol. 2012;303(6):F864–72.
42. White LE, Santora RJ, Cui Y, Moore FA, Hassoun HT. TNFR1-dependent pulmonary apoptosis during ischemic acute kidney injury. Am J Physiol Lung Cell Mol Physiol. 2012;303(5):L449–59.
43. Kramer AA, Postler G, Salhab KF, Mendez C, Carey LC, Rabb H. Renal ischemia/reperfusion leads to macrophage-mediated increase in pulmonary vascular permeability. Kidney Int. 1999;55(6):2362–7.
44. Doi K, Ishizu T, Tsukamoto-Sumida M, Hiruma T, Yamashita T, Ogasawara E, et al. The high-mobility group protein B1-Toll-like receptor 4 pathway contributes to the acute lung injury induced by bilateral nephrectomy. Kidney Int. 2014;86(2):316–26.
45. Ma T, Liu Z. Functions of aquaporin 1 and alpha-epithelial Na+ channel in rat acute lung injury induced by acute ischemic kidney injury. Int Urol Nephrol. 2013;45(4):1187–96.
46. Rabb H, Wang Z, Nemoto T, Hotchkiss J, Yokota N, Soleimani M. Acute renal failure leads to dysregulation of lung salt and water channels. Kidney Int. 2003;63(2):600–6.
47. Liu KD, Altmann C, Smits G, Krawczeski CD, Edelstein CL, Devarajan P, et al. Serum interleukin-6 and interleukin-8 are early biomarkers of acute kidney injury and predict prolonged mechanical ventilation in children undergoing cardiac surgery: a case-control study. Crit Care. 2009;13(4):R104.
48. Chawla LS, Seneff MG, Nelson DR, Williams M, Levy H, Kimmel PL, et al. Elevated plasma concentrations of IL-6 and elevated APACHE II score predict acute kidney injury in patients with severe sepsis. Clin J Am Soc Nephrol. 2007;2(1):22–30.

49. Liu KD, Glidden DV, Eisner MD, Parsons PE, Ware LB, Wheeler A, et al. Predictive and pathogenetic value of plasma biomarkers for acute kidney injury in patients with acute lung injury. Crit Care Med. 2007;35(12):2755–61.
50. Bhargava R, Janssen W, Altmann C, Andres-Hernando A, Okamura K, Vandivier RW, et al. Intratracheal IL-6 protects against lung inflammation in direct, but not indirect, causes of acute lung injury in mice. PLoS One. 2013;8(5):e61405.
51. Andres-Hernando A, Dursun B, Altmann C, Ahuja N, He Z, Bhargava R, et al. Cytokine production increases and cytokine clearance decreases in mice with bilateral nephrectomy. Nephrol Dial Transplant. 2012;27(12):4339–47.
52. Dennen P, Altmann C, Kaufman J, Klein CL, Andres-Hernando A, Ahuja NH, et al. Urine interleukin-6 is an early biomarker of acute kidney injury in children undergoing cardiac surgery. Crit Care. 2010;14(5):R181.
53. Meduri GU, Kohler G, Headley S, Tolley E, Stentz F, Postlethwaite A. Inflammatory cytokines in the BAL of patients with ARDS. Persistent elevation over time predicts poor outcome. Chest. 1995;108(5):1303–14.
54. Simmons EM, Himmelfarb J, Sezer MT, Chertow GM, Mehta RL, Paganini EP, et al. Plasma cytokine levels predict mortality in patients with acute renal failure. Kidney Int. 2004;65(4):1357–65.
55. Hassoun HT, Lie ML, Grigoryev DN, Liu M, Tuder RM, Rabb H. Kidney ischemia-reperfusion injury induces caspase-dependent pulmonary apoptosis. Am J Physiol Renal Physiol. 2009;297(1):F125–37.
56. White LE, Hassoun HT. Inflammatory mechanisms of organ crosstalk during ischemic acute kidney injury. Int J Nephrol. 2012;2012:505197.
57. Zarbock A, Schmolke M, Spieker T, Jurk K, Van Aken H, Singbartl K. Acute uremia but not renal inflammation attenuates aseptic acute lung injury: a critical role for uremic neutrophils. J Am Soc Nephrol. 2006;17(11):3124–31.
58. Lie ML, White LE, Santora RJ, Park JM, Rabb H, Hassoun HT. Lung T lymphocyte trafficking and activation during ischemic acute kidney injury. J Immunol. 2012;189(6):2843–51.
59. Liu KD, Matthay MA. Advances in critical care for the nephrologist: acute lung injury/ARDS. Clin J Am Soc Nephrol. 2008;3(2):578–86.
60. Vadasz I, Raviv S, Sznajder JI. Alveolar epithelium and Na, K-ATPase in acute lung injury. Intensive Care Med. 2007;33(7):1243–51.
61. Acute Respiratory Distress Syndrome N, Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, et al. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000;342(18):1301–8.
62. Rodrigo R, Trujillo S, Bosco C. Biochemical and ultrastructural lung damage induced by rhabdomyolysis in the rat. Exp Biol Med (Maywood). 2006;231(8):1430–8.
63. Ranieri VM, Giunta F, Suter PM, Slutsky AS. Mechanical ventilation as a mediator of multisystem organ failure in acute respiratory distress syndrome. JAMA. 2000;284(1):43–4.
64. Kuiper JW, Vaschetto R, Della Corte F, Plotz FB, Groeneveld AB. Bench-to-bedside review: ventilation-induced renal injury through systemic mediator release—just theory or a causal relationship? Crit Care. 2011;15(4):228.
65. Nicholl DDM, Ahmed SB, Loewen AHS, Hemmelgarn BR, Sola DY, Beecroft JM, et al. Declining kidney function increases the prevalence of sleep apnea and nocturnal hypoxia. Chest. 2012;141(6):1422–30.
66. Sakaguchi Y, Hatta T, Hayashi T, Shoji T, Suzuki A, Tomida K, et al. Association of nocturnal hypoxemia with progression of CKD. Clin J Am Soc Nephrol. 2013;8(9):1502–7.

Part III
Prevention and Management of AKI

Chapter 13
Prophylaxis and Management of Acute Kidney Injury

Yasuhiro Komatsu

Abstract AKI is associated with increase of morbidity and mortality. Whenever AKI is suspected, diagnostic approach and management to preserve or recover kidney function should be employed. No specific treatment for AKI is established except for certain glomerular or vascular diseases. Thus, general principles of treatment of AKI are, firstly, treatment for underlying disease, secondly, maintenance of renal blood flow and perfusion to preserve kidney function and recovery, third, supportive treatment for electrolyte disorders and uremic syndrome, fourth, renal replacement therapy when needed. Optimization of volume status by fluid therapy using crystalloids is the first step to maintain renal perfusion, while volume overload should be avoided by meticulous monitoring of volume status. Prevention and treatment for specific conditions are also described.

Keywords Acute kidney injury · Fluid therapy · Volume overload · Renal replacement therapy · Hepatorenal syndrome · Cardiorenal syndrome

13.1 Introduction

AKI is a syndrome which presents an abrupt decrease in kidney function due to heterogenous disorders. Prompt treatment results in recovery in majority of cases; however, delay in diagnosis and management can lead to prolonged decrease of kidney function requiring renal replacement therapy or progress to chronic kidney disease. AKI is associated with increase of morbidity and mortality. Whenever seeing patients with decrease of urine output or increase of serum creatinine, a diagnosis of AKI should be suspected, and diagnostic approach and management to preserve or recover kidney function should be employed.

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Table 13.1 Risk factors and predicting score [1]

	Risk factors
Cardiac surgery	Age, preoperative renal dysfunction, duration of cardiopulmonary bypass
Liver transplantation	MELD score (perioperative model for end-stage liver disease), intraoperative blood transfusion volume, intraoperative hypotension, the use of vasopressors
Heart failure	Aging, renal impairment, cardiac dysfunction
Sepsis	Pre-existing renal dysfunction, aging, use of renin–angiotensin–aldosterone system inhibitors

AKI is classified into prerenal, renal, and postrenal AKI [1–4]. Prerenal AKI is defined as hemodynamically mediated kidney dysfunction that is rapidly reversible after normalization of renal perfusion [4]. Renal hypoperfusion can occur either due to a generalized decrease in tissue perfusion or selective renal ischemia. Kidney structure in prerenal AKI is preserved, but if left untreated, it can progress to renal AKI. Renal AKI is a state where GFR is reduced due to structural abnormalities of kidney, and includes vascular, glomerular, and tubule-interstitial diseases. Postrenal AKI or obstructive nephropathy occurs when obstruction occurs in the urinary tract. Once urinary obstruction is removed, recovery and post-obstruction diuresis are observed. If untreated, obstructive nephropathy leads to irreversible tubulointerstitial fibrosis. In this section, prevention and management of prerenal and renal AKI will be discussed.

After AKI is established, specific treatment is limited and recovery takes time, prevention is important. First, assess the risk of AKI, and monitor serum creatinine and urine volume for high-risk patients. Risk factors for AKI is shown in Table 13.1 [1]. For high-risk patients, monitor the volume status, avoid the use of nephrotoxic drugs, and adjust the dosage as needed. For patients identified as high risk, detailed information and meticulous monitoring during peri-operation period are required. Prevention and management for specific conditions are described in the following section.

13.2 Prevention and Treatment: General Principle

No specific treatment for AKI is available except for certain rapidly progressive glomerulonephritis or thrombotic microangiopathy. Thus, general principles of treatment of AKI are, firstly, treatment for underlying disease, secondly, maintenance of renal blood flow and perfusion to preserve kidney function and recovery, third, supportive treatment for electrolyte disorders and uremic syndrome, fourth, renal replacement therapy when needed.

Fluid therapy is main strategy for restoration and maintenance of renal perfusion and recovery of kidney function. Various studies have been conducted concerning when, which, and how much fluid to be administered [5–9]. Conversely, studies have also found that excessive fluid administration exacerbates kidney injury

through renal and organ congestion, and is associated with poor outcome [10–14]. Diuretic use may worsen kidney injury and needs to be used with caution.

Pharmacological treatment to prevent and recover AKI includes low dose dopamine, hANP, endothelin inhibitors, loop diuretics, prostaglandin analogues, antioxidants, and IGF1 [1–3]. Animal studies and some case studies have shown their effectiveness, although no standard pharmacological treatment has been established yet.

13.3 Treatment for Prerenal AKI

Prerenal AKI is defined as hemodynamically mediated kidney dysfunction that is rapidly reversible following normalization of renal perfusion. Besides simple hypovolemia where extracellular volume is depleted, prerenal AKI can occur among patients without hypovolemia or with extracellular volume overload, such as sepsis, post-surgery, heart failure, or liver cirrhosis. In the early phase of AKI, treatment and recovery of underlying disease often leads to recovery from AKI. In cases where treatment for underlying disease is difficult, delay for treatment may lead to acute tubular necrosis. In this section, general management for prerenal AKI is described, followed by description for special conditions.

13.3.1 Fluid Therapy: Maintenance of Effective Arterial Blood Volume to Preserve Renal Perfusion

Restoration of EABV to increase cardiac output and maintain renal perfusion is important for prevention and treatment for AKI. On the contrary, excessive fluid administration deteriorates kidney injury and outcome.

For patients without obvious fluid overload, or when prerenal AKI cannot be excluded, volume challenge of 300–500 mL of fluid administered in 30–60 min, while monitoring urine volume is often used. In oliguric AKI, initial target will be 0.5 mL/kg/h, which is diagnostic criteria for AKI stage 1 in KDIGO criteria. Note that urine volume is a marker of hemodynamics, and achieving optimal urine volume per se is not the goal of treatment. Diuretics should not be used before assessment of volume status. Aim of diuretics is to excrete excessive sodium and water, and not to achieve hourly urine volume. Diuretic use for prerenal AKI with true volume depletion causes further decrease of renal perfusion and exacerbates kidney injury. Once fluid therapy restores effective arterial blood volume, withhold further fluid administration or avoid diuretic use even when target urine volume is not achieved.

The optimal composition of fluids for hypovolemic prerenal AKI is controversial and depends on the source of fluid loss and associated electrolyte disturbance.

Colloids, such as albumin, hydroxyethyl starches (HESs), and gelatins, contain oncotic macromolecules that largely remain in the intravascular space and are expected to have more effective in expanding intravascular volume; however, recent data shows that their volume expanding effect compared to crystalloids is modest, with colloid-to-crystalloid ratio in the range of 1:11–1:1.4 [5, 6].

Colloids Versus Crystalloids for the Resuscitation of the Critically ill (CRISTAL) examined the effect of colloids and crystalloids on 2800 ICU patients with hypovolemic shock. There was no difference in RRT requirement or mortality at 28 days [15]. Among colloid solutions, HES is reported to have increased risk of developing AKI requiring RRT. Gelatin-based colloid induces osmotic nephrosis-induced AKI. Survival rate and risk of RRT do not differ between those who received albumin and crystalloid. Following these findings, current guidelines do not support the routine use of colloids in volume resuscitation in hypovolemia and sepsis [1, 2].

Crystalloids can be divided to normal saline (0.9% sodium chloride) and buffered solution. 0.9% sodium chloride is "normal" regarding to its sodium concentration of 154 mEq/L. "Plasma water" sodium concentration is around 152 mEq/L, whereas "plasma" sodium concentration is 140 mEq/L. Sodium concentration of most buffer solution is 130–140 mEq/L, which is lower than "plasma water" sodium concentration. However, 0.9% sodium chloride is not "normal" in that its higher chloride concentration and its pH of below 6.0. Administration of normal saline does not affect plasma concentration of either chloride or bicarbonate as long as the administered volume is less than 1 L, while it can cause hyperchloremia or metabolic acidosis if massive amount is administered [16]. Hyperchloremia can induce renal vasoconstriction, reduction in renal cortical tissue perfusion and glomerular filtration, and longer period of fluid retention [17–19].

Various clinical trials were conducted to compare the effectiveness of normal saline and buffered solution among critical care patients. SPLIT (Saline versus Plasma-Lyte 148 for ICU Fluid Therapy) randomized 2278 ICU patients to either Plasma-Lyte 148 or 0.9% saline. There was no significant difference in the proportion of patients with moderate to severe AKI [20]. SMART investigators conducted cluster-randomized study including five ICU and 15,802 patients to determine a major adverse kidney event within 30 days, between those who received normal saline or balanced crystalloids. They found a significant reduction in the risk of major adverse kidney event (MAKE) within 30 days in the group of patients treated with buffered solution [21]. In SALT-ED trial, which included 13,347 non-critically-ill patients admitted to the hospital from the emergency department, initial fluid resuscitation with balanced crystalloids does not reduce duration of hospitalization when compared to the isotonic crystalloid, normal saline. However, balanced crystalloid use is associated with a reduction in major kidney-related events [22].

Studies to date indicate that crystalloids are the solution of choice for intravascular fluid resuscitation of hypovolemic patients; the evidence against isotonic saline over balanced solution is not robust, but it may be prudent to use buffered solutions for patients at risk of AKI who do not have hypochloremia [9, 23]. For patients with hypovolemia and hypochloremia, normal saline would be preferred.

In prerenal AKI, renal function recovers shortly after the return of renal blood flow and renal perfusion; however, delay in renal perfusion recovery leads to renal AKI, and renal recovery takes several days to weeks even after renal blood flow and perfusion return. After the initial fluid resuscitation, fluid therapy needs to be adjusted to avoid volume overload.

Observational studies showed that positive fluid balance is associated with increased morality in AKI and those receiving renal replacement therapy [10, 11]. Fluid overload is associated with an increased risk for 90-day mortality in critically ill patients with renal replacement therapy [11]. Excessive fluid administration is associated with development of AKI. The plausible mechanism includes the intrarenal compartment syndrome, venous congestion, or increased renal oxygen demand for sodium reabsorption [9, 24, 25]. Fluids should be administered until intravascular hypovolemia has been corrected, and the minimum amount of intravenous fluid required to maintain perfusion and systemic oxygen delivery should be administered [9]. For patients who have fluid overload due to the fluid therapy, discontinue fluid therapy and fluid removal by diuretic therapy or renal replacement therapy needs to be conducted [25]. Decreasing the dose or discontinue the use of medication which decreases renal blood flow, such as ACE inhibitors or NSAIDs, are also important.

Determining how much volume to administer and how to assess the volume status is challenging. Various invasive and non-invasive techniques, such as passive leg raise (PLR) test, ultrasonography, and echocardiography, can assess volume status based on the response to the fluid challenge. For patients who are not on ventilators and blood pressure monitoring is available via arterial line, PLR test is simple and reliable [26, 27].

No criteria to discontinue aggressive fluid therapy is established; monitor the sign of any fluid overload. Increase of CVP after fluid challenge can be a marker of discontinuation of fluid therapy.

Blood pressure is essential for organ perfusion, and maintaining the optimal blood pressure is important for prevention and management of AKI.

13.3.2 Vasopressors

Maintaining optimal blood pressure is critical for prevention and management of AKI, although “optimal” blood pressure target varies. “Normotensive ischemic AKI” signifies the condition where AKI develops without an overt severe hypotensive episode, mainly due to renal susceptibility to the lower blood pressure [28]. Factors increasing susceptibility to renal hypoperfusion include failure to decrease arteriolar resistance, failures to increase efferent arteriolar resistance or renal-artery stenosis, as is often seen among elderly patients with hypertension or chronic kidney disease. Clinicians need to assess whether AKI patients are in low-perfusion state or with any susceptibility factors. When assessing blood pressure, patients’

current and usual blood pressure need to be taken into account. For these patients, blood pressure that is on the lower end of the normal range should be increased by correction of any hypovolemia, by dose reduction or discontinuation of antihypertensive medication.

Optimal target of blood pressure management differs in certain situations such as intracranial hemorrhage patients and dissecting aneurism patients who require strict blood pressure management. For those patients, discussion between surgeons and nephrologist is needed.

Once circulating blood volume is restored, vasoactive medication can correct hemodynamic instability. KDIGO guideline recommends the use of vasopressors in conjunction with fluids in patients with vasomotor shock with, or at risk for, AKI. Generally, noradrenalin is the selection of choice as vasopressors for AKI patients with shock. Low dose dopamine had once been expected to increase renal perfusion and diuresis, but studies did not show superiority over noradrenalin as for mortality or risk of AKI, and use of dopamine was associated with a greater number of adverse events [29–31].

13.4 Prevention and Treatment for Specific Conditions

13.4.1 Sepsis

For septic AKI, restoration of tissue perfusion and optimization of hemodynamic status are key management strategy; however, the pathogenesis of septic AKI is complex, and includes macro and micro-circulatory alteration and dysregulated inflammatory response [32]. In sepsis, body fluid distribution and hemodynamics change dynamically during treatment, and can be divided into our phases, namely, rescue (or salvage), optimization, stabilization, and de-escalation [33, 34]. The fluid management strategy needs to be tailored depending on patients' condition and duration of phases.

In 2001, EGDT (early goal-directed therapy) is proposed as therapeutic strategy in the early stage of AKI [35], which is comprised of early identification of high-risk patients, appropriate cultures, source control, and administration of appropriate antibiotics. Achieving a MAP of 65 mmHg, central venous pressure of 8–12 mmHg, aiming for urine output of at least 0.5 mL/kg/h and a Scvo2 of 70% or higher were recommended. Three randomized control trials which examined the effectiveness of EGDT, ProCESS (Protocol-Based Care for Early Septic Shock), ARISE (Australasian Resuscitation in Sepsis Evaluation), and ProMISe (Protocolized Management in Sepsis), reported that patients randomized to receive EGDT compared to usual care or to less invasive alternative hemodynamic resuscitation protocols did not show the improvement of survival, and need for RRT is greater among those who received larger amount of fluid [36–38]. These studies do not deny the need for fluid resuscitation in the early phase of sepsis, but alert the harm of

excessive fluid therapy. Kidney is encapsulated by renal capsule, and excessive fluid administration or increased central venous pressure is associated with worse patient outcome including exacerbation of kidney injury [12, 13].

Fluid therapy administered within 6 h of presentation covers the rescue and optimization phases. Sufficient fluid should be administered to stabilize sepsis-induced tissue hypoperfusion for lifesaving and organ rescue purposes. To avoid excessive fluid, boluses should be administered at patient presentation and then fluid responsiveness should be evaluated within a few hours [39]. Once effective arterial blood volume is achieved, or if fluid therapy for certain duration is not effective for blood pressure management, avoid further fluid administration and use vasopressors to achieve adequate blood pressure. In stabilization phase, fluid administration aims to supplement ongoing physiological fluid loss, and adjust even or negative balance. In de-escalation phase, aim of treatment is to normalize the fluid status.

13.4.2 Heart Failure

Cardiac and kidney function are often interdependent, and worsening of cardiac function deteriorates kidney function and vice versa. The coexistence of renal and cardiac disease is defined as cardiorenal syndrome (CRS) [40, 41]. CRS is classified into five subtypes, and CRS type 1 denotes acute heart failure leading to AKI. Acute worsening of heart function leading to acute kidney injury (AKI) is currently defined as CRS type 1. In cardiology literature, "worsening of renal function" instead of AKI is often used, although no established definition of WRF exists.

Pathophysiology of AKI during AHF includes hemodynamic and neurohormonal activation, venous congestion, and nephrotoxic medications. Renin–angiotensin–aldosterone system, sympathetic nervous system, and non-osmotic arginine vasopressin release are stimulated, which are the neurohormonal adaptive mechanisms to conserve salt-water retention, but also lead to worsening of heart failure. Venous congestion is the most important hemodynamic factor driving WRF in decompensated patients with advanced heart failure. The mechanism of impairment of kidney function is the increased pressure in renal veins which is back transmitted by the increased CVP. RBF is determined by the abdominal perfusion pressure which is inversely related to intra-abdominal pressure (IAP). The normal IAP is <5–7 mmHg, but venous congestion or massive ascites increases IAP [42].

Management of AKI among patients with heart failure is complex; cessation of ACE inhibitors or ARB may decrease serum creatinine while it exacerbates renal function and patient outcome in the long run. High dose diuretic use is associated with poor outcome among AKI patients, while diuretics remain the cornerstone of therapy among patients with congestion, and can improve GFR by reducing renal venous pressure [43, 44]. The Renal Association and British Society for Heart Failure published national guidance on the use of RAAS inhibitors in patients with heart failure. Key management principle for patients with heart failure is to compare

renal function with baseline renal function, assess fluid status, interpret blood pressure in the context of usual values, reduce or withdraw RAASI if symptomatic hypotension or severe hyperkalemia develops [45]. Among hospitalized AKI patients, treatment with ACEI or ARB is associated with a lower risk of death [46]. During initiation and titration of RAAS inhibitors, increase in serum creatine by less than 30% is acceptable. Judgement to stop RAAS inhibitors can be acceptable if serum creatinine increase more than 30% in patients with chronic heart failure due to preserved left ventricular ejection fraction (HFpEF), and over 50% among those with chronic heart failure due to reduced left ventricular ejection fraction (HFrEF) [47].

13.4.3 Cardiac Surgery

Acute kidney injury is the major complication of cardiac surgery with incidence of 5–42% [48]. Cardiac surgery has the unique characteristics in which use of cardiopulmonary bypass, aorta cross-clamping, high volume of blood products, and high doses of exogenous vasopressors are common. Multiple factors contribute to the development of AKI, including renal hypoperfusion, ischemia-reperfusion injury, neurohormonal activation, inflammation, oxidative stress, nephrotoxins, and mechanical factors [49].

The management of cardiac surgery-associated AKI includes identification of high-risk patients, early diagnosis, monitoring of renal function and volume status, and preventive and therapeutic interventions. Preventive strategies include discontinuation of nephrotoxic agents, optimization of blood glycemic control, close monitoring of serum creatinine level and urine output, and maintenance of hemodynamic stability. Nephrotoxic agents such as non-steroidal anti-inflammatory agents, aminoglycoside antibiotics, or radiocontrast agents should be avoided in perioperative period. Many patients are on ACE inhibitors or ARBs treatment, and controversy exists whether to continue or discontinue its use. General consensus is to discontinue their use in perioperative period, but after perioperative period and patients become stable, we should consider restarting ACE inhibitors or ARBs for long-term benefit.

Several pharmaceutical preventive strategies have been studied including statins, fenoldopam, nesiritide (beta-type natriuretic peptides), and intravenous bicarbonate. Statins have anti-oxidative and anti-inflammatory effect, which favors prophylactic effect of AKI. Intravenous bicarbonate induces urinary alkalinization which has anti-oxidative and anti-inflammatory effect, reducing complement activation and preventing hemoglobin-induced pigment nephropathy. Fenoldopam, a selective dopamine D1 receptor agonist, has vasodilatation and inhibition of renal tubular sodium reabsorption. Efficacy of these interventions on the prevention and improvement of patient outcome remains to be studied.

Remote ischemic preconditioning (RIPC) therapy is another strategy to prevent renal damage by ischemia. RIPC induces brief transient episodes of ischemia at a site remote from vital organs before vital organs are exposed to prolonged periods of ischemia and reperfusion. Effects of RIPC on cardiac surgery-associated AKI is variable, and the 2017 Cochrane review concluded that RIPCS led to little or no difference in serum creatinine levels, the incidence of adverse effects, probability of death, and the incidence of AKI [50].

13.4.4 Hepatorenal Syndrome

AKI is a frequent complication among patients with advanced hepatic cirrhosis. All types of AKI can occur in patients with cirrhosis including (1) prerenal AKI, (2) the hepatorenal syndrome-type AKI (HRS-AKI), (3) intrinsic causes such as acute tubular necrosis, and (4) postrenal causes [51]. Hepatorenal syndrome (HRS) is a unique form of AKI developing in patients with end-stage liver disease, which is defined as a potentially reversible deterioration of renal function unresponsive to volume resuscitation, caused by renal vasoconstriction in the absence of alternative identifiable causes. Recently, the ICA proposed a new definition and diagnostic criteria for HRS-AKI, and the diagnosis of HRS-AKI should be based on revised ICA criteria.

The cause of AKI should be investigated as soon as possible, to prevent AKI progression. Diuretics and/or beta-blockers as well as other drugs that could be associated with the occurrence of AKI such as vasodilators, NSAIDs, and nephrotoxic drugs should be immediately stopped. Volume replacement should be used in accordance with the cause and severity of fluid losses. EASL Clinical Practice Guidelines recommend to use 20% albumin solution at the dose of 1 g of albumin/kg of body weight (with a maximum of 100 g of albumin) for two consecutive days in case of no obvious cause of AKI, AKI stage >1A, or infection-induced AKI. In patients with AKI and tense ascites, therapeutic paracentesis should be associated with albumin infusion even when a low volume of ascetic fluid is removed.

EASL clinical practice guidelines recommend the use of vasoconstrictors and albumin in all patients meeting the current definition of AKI-HRS stage >1A. Terlipressin, vasopressin analogue, is the first-line pharmacologic option for the treatment of HRS-AKI; however, noradrenalin can be used in countries where terlipressin is not available. The limitation of noradrenalin is that it requires a central venous line. Albumin solution (20%) should be used at the dose 20–40 g/day. Adverse events related to terlipressin or noradrenaline include ischemic and cardiovascular events, and a careful clinical screening including electrocardiogram is recommended before starting the treatment. In cases of recurrence of HRS-AKI upon treatment cessation, a repeat course of therapy should be given [51].

13.4.5 Treatment for Renal AKI

Specific therapy for renal AKI due to acute vasculitis and acute glomerular disease is available and should be tailored based on clinical presentation and biopsy findings. Therapeutic strategies include corticosteroids, alkylating agents, rituximab, and plasmapheresis depending on the primary cause of the disease. Plasma exchange is effective in the treatment of sporadic TTP and possibly sporadic HUS in adults, whereas postdiarrheal HUS in children can be managed conservatively without plasma exchange. Eculizumab, a humanized monoclonal antibody to complement factor 5, inhibits terminal complement activation and can be used for the treatment of nondiarrheal (complement-mediated) HUS unresponsive to plasma exchange [52, 53].

Acute interstitial nephritis is a relatively common cause of AKI and is caused by infections, medications, or immune disorders. Among AKI patients, AIN develops frequently due to an allergic response to a medication, including antibiotics, NSAIDs, and diuretics. Discontinuation of the offending mediation is the first step of treatment; if discontinuation is not effective, use of corticosteroid can be treatment option. One potential regimen consists of the intravenous administration of methylprednisolone (250–500 mg/day) for 3–4 days followed by oral prednisone at a dose of 1 mg/kg/day tapered over 8–12 weeks [54].

13.5 Non-dialytic Supportive Therapy for AKI

13.5.1 Volume Overload

Theoretically, loop diuretics can protect kidney by reducing active sodium transport, decreasing the oxygen consumption, and reducing renal congestion. However, a meta-analysis of multiple clinical studies on loop diuretics for the treatment of AKI could not establish a reduction of in-hospital mortality or the requirement for renal replacement therapy [55]. Bagshaw et al. conducted a meta-analysis of 62 studies and reported that loop diuretics were not associated with improved mortality or an accelerated rate of independence from RRT. They also reported that the diuretic treatment was associated with a shorter duration of RRT, shorter time to spontaneous decline in serum creatinine levels, and increased urine output [47]. Currently, the evidence for a beneficial effect on renal function is lacking, and KDIGO guideline and Japanese Society of Nephrology guidelines do not recommend diuretic use for preventive and treatment purpose of AKI [1, 2, 56].

The loop diuretics can be used for the management of volume overload, but not for the treatment of oliguria. The loop diuretics enter the urine primarily by tubular secretion in the proximal tubule; the dose needs to be increased in patients with renal impairment in whom proximal tubular secretion is reduced [57]. When starting furosemide, reasonable approach is to start with 40–80 mg of intravenous (IV)

furosemide and assess for response. If urine output does not increase within 2 h of IV furosemide, dose can be doubled, up to 200 mg in a single dose of IV furosemide. Tolvaptan, vasopressin antagonists, has been used for treatment for heart failure. Its cost is expensive, and when used, meticulous monitoring for serum sodium concentration is required, and the amount of sodium excreted in the urine is lower compared to that of furosemide. Vasopressin antagonism can be used in acutely decompensated patients with clinical hyponatremia who are refractory to escalating doses of loop diuretics and adjunctive thiazide therapy [58].

Principles for diuretic use for patients with heart failure are different. Priority is achieving clinical euvolemia rather than transient rise of serum creatinine, and high doses of diuretics are needed. Prescription strategy includes combination therapy with loop and thiazide or continuous administration. For patients refractory to diuretics therapy, fluid removal by ultrafiltration can be another option.

13.5.2 Hyperkalemia

Management strategy for hyperkalemia in AKI patients depends on the severity, symptoms, underlying condition and rapidity of progression of hyperkalemia, and response to medical management including diuretic therapy. Progressing hyperkalemia seen in patients with crash syndrome and rhabdomyolysis or symptomatic severe hyperkalemia is life-threatening and demands urgent treatment including renal replacement therapy. Hyperkalemia management includes cardiac protection, shifting potassium into cells, removing potassium from the body, monitoring serum potassium and blood glucose, and prevention of recurrence (Table 13.2) [59–61].

Mild hyperkalemia (<5.5 mEq/L) usually can be managed by restriction of potassium intake including potassium containing infusions and the discontinuation of potassium-sparing diuretics or renin–angiotensin system inhibitors. For moderate

Table 13.2 Management of hyperkalemia

Treatment	Dosage and route	Onset of action	Duration of effect
Calcium gluconate (8.5%)	10–20 mL i.v. over 5 min	1–3 min	30–60 min
Glucose and insulin	50 mL of 50% DW Regular insulin 10 unit i.v. over 15–30 min	15–30 min	4–6 h
Sodium bicarbonate	50–100 mL i.v. over 5–10 min	15–30 min	1–2 h
Furosemide	20–80 mg i.v.	15–30 min	6 h
Cation exchange resin	15–30 g, oral	1–2 h	4–6 h
Dialysis	Hemodialysis Peritoneal dialysis with frequent exchange	Within minutes	

hyperkalemia (5.5–6.5 mEq/L), use of a potassium-binding resin or loop diuretics can be considered to enhance potassium excretion by gastrointestinal route or kidney. For severe hyperkalemia, especially those who have electrocardiographic manifestations, emergent treatment to decrease serum potassium level is indicated, which includes intravenous administration of calcium, insulin and glucose, or sodium bicarbonate. Calcium antagonizes the cardiac and neuromuscular effects of hyperkalemia. Insulin promotes potassium entry into cells and lowers serum potassium concentration. Sodium bicarbonate can stimulate potassium entry into the intracellular compartment in patients with acidosis. Sodium bicarbonate lowers serum potassium concentration by enhancing tubular potassium excretion as well. Dose, time, and duration of action are shown in table.

Medical management is often sufficient for patients with mild hyperkalemia due to reversible causes (hypovolemic prerenal AKI or use of renin–angiotensin system inhibitors). Dialysis is indicated for severe hyperkalemia refractory to medical management or hyperkalemia due to rhabdomyolysis, compartment syndrome, tumor lysis syndrome, in whom continued release is foreseen.

Hemodialysis is the selection of choice to remove potassium rapidly and efficiently. Continuous renal replacement therapy is often selected for hemodynamically unstable patients, but its efficiency for potassium removal is low, and is not suitable for emergent therapy. Peritoneal dialysis effectively removes potassium, and sometimes results in hypokalemia if frequent, rapid exchange is applied. Jackson et al. reported a case of hyperkalemic cardiac arrest successfully treated with peritoneal dialysis. Rapid exchanges of peritoneal dialysis solution, 8 L input and 7.5 L output in an hour decreased serum potassium from 9.8 to 4.3 mEq/L [62, 63].

13.5.3 Metabolic Acidosis

Acidosis is associated with many adverse hemodynamic, respiratory, cerebral, and metabolic adverse effects, although association does not indicate causation [64]. Conversely, acidosis can protect myocardial and hepatic cells during hypoxia in animal experiment [65, 66].

Treatment principles are identifying and treating underlying cause, with meticulous review of clinical circumstances and drug therapy. The indication and use of bicarbonate buffer for treatment of metabolic acidosis is controversial; general consensus is to administer sodium bicarbonate only when pH is below 7.10–7.20 and serum HCO3 concentration is below 10–15 mEq/L. When administering sodium bicarbonate, monitor the plasma sodium concentration and blood gas analysis since bicarbonate administration could cause hypernatremia, an increase in the partial pressure of carbon dioxide (pCO_2) among patients with ventilatory compromise.

Renal replacement therapy is indicated for metabolic acidosis among AKI patients with oliguria or volume overload. Administration of isotonic sodium

bicarbonate solution and simultaneous fluid removal by renal replacement therapy can effectively administer sodium bicarbonate without the risk of sodium or volume overload; however, whether correction of metabolic acidosis by renal replacement therapy and isotonic sodium bicarbonate infusion has clinical benefit as for patient outcome remains to be studied.

13.5.4 Nutrition

Providing adequate nutrition is key element of disease management including AKI; however, the specific efficacy of nutritional support for AKI has not been demonstrated [67, 68]. This may be because nutritional requirements for patients with AKI varies according to the severity and nature of underlying disease rather than AKI per se. JSN AKI guideline suggests that the administration of caloric and protein as nutritional support for AKI treatment be tailored to the severity and the underlying disease. For severe AKI, enteral nutrition is recommended whenever possible. Enteral nutrition is preferred over intravenous, parenteral nutrition for intestinal mucosal maintenance, bacterial translocation, and the prevention of organ dysfunction. Meta-analysis of studies involving critically ill patients, including AKI, has shown that the initiation of enteral nutrition within 24 h of ICU admission significantly reduced the mortality and the incidence of infectious complications, and shortened the length of hospital stay [69–72], although negative results have also been reported [1].

KDIGO guideline suggests total energy intake of 20–30 kcal/kg/day for patients with any stage of AKI. Timeframe to achieve this target energy provision is controversial. Permissive underfeeding suggests to initiate energy provision with 500 kcal/day or one fourth of target energy for the first week, which is minimal requirement to maintain intestinal function. Recent study reported that provision of 70% of resting energy consumption is associated with reduction of mortality among ICU patients [73].

Protein energy wasting is common among critically ill patients with AKI; protein restriction for the prevention or delay of RRT is not recommended. Suggested protein goals by KDIGO guideline are: 0.8–1 g/kg/day in non-catabolic AKI patients without need for dialysis, 1–1.5 g/kg/day in patients with AKI on RRT, and up to maximum of 1.7 g/kg/day in patients on continuous renal replacement therapy (CRRT) and in hypercatabolic patients.

During CRRT, commercially available dialysates and replacement fluids in Japan can cause hypokalemia and hypophosphatemia. Patients with AKI or CKD who presents hyperkalemia, hyperphosphatemia, or hypermagnesemia before the initiation of RRT can develop severe hypokalemia, hypophosphatemia, or hypomagnesemia if they are treated on CRRT without appropriate supplementation of potassium, phosphate, or magnesium. Monitoring and appropriate supplementation of these essential minerals are key component of standard care.

No robust study has shown optimal glycemic control target for AKI. Both hypoglycemia and hyperglycemia are associated with increased morbidity and mortality. As is described in JSN guidelines, the initiation of inulin control at a plasma glucose level ≥180 mg/dL and the setting of target plasma glucose level of 144–180 mg/dL is reasonable suggestion for patients with severe AKI [2, 74, 75].

13.5.5 Medication Dosage Adjustment

For patients with AKI, medication should be reviewed thoroughly to eliminate the potential cause, risk, contributory factor for AKI, to reduce adverse events, and to ensure that doses of prescribed medication are appropriate for the patient's level of renal function.

Dose adjustment for patients with AKI is complex; dose reduction is required for drugs which are excreted by the kidney, while dose increase may be considered when volume of distribution is expanded due to fluid overload or capillary leak [76, 77]. Drug dosing adjustment information provided by pharmaceutical companies is derived mainly from studies in chronic kidney disease patients whose renal function is relatively stable. Furthermore, estimating GFR for drug dosing is also problematic for patients with AKI, since most eGFR formula, such as Cockcroft-Gault, MDRD equation, and CKD-EPI, are derived from conditions where the serum creatinine is at steady state. In the early phase of AKI when GFR decreases rapidly, eGFR equations will overestimate GFR, whereas it may underestimate GFR in recovery phase of AKI when GFR increases.

In 2010, KDIGO held a conference to investigate the issues on drug dosage adjustment for patients with acute or chronic kidney disease [78]. They recommend larger loading doses to avoid subtherapeutic responses due to the achievement of lower than desired serum concentrations, since the volume of distribution of several medications is dramatically increased in the presence of AKI. This is especially true for hydrophilic antibiotics, including b-lactams, cephalosporins, and penems, and the administration of aggressive loading doses (25–50% greater than normal) is highly recommended. They also recommend therapeutic drug monitoring be utilized for those medications where serum drug concentrations can be obtained in a clinically relevant time frame. For those medications where therapeutic drug monitoring is not possible, close monitoring of drug PD may prove to be a useful surrogate. Drug dosage adjustment for AKI patients on intermittent dialysis or CRRT is different from that for ESRD patients. The existing maintenance dosing recommendations for ESRD patients receiving HD often result in the achievement of subtherapeutic concentrations and treatment failures for patients with severe AKI requiring RRT. Readers are advised to refer KDIGO recommendation to guide prescription strategy.

References

1. Doi K, Nishida O, Shigematsu T, et al. The Japanese clinical practice guideline for acute kidney injury 2016. Clin Exp Nephrol. 2018;22:985–1045.
2. Kidney Disease: Improving Global Outcomes (KDIGO). KDIGO 2012 clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012;2:1–138.
3. Moore PK, Hsu RK, Liu KD. Management of acute kidney injury: core curriculum 2018. Am J Kidney Dis. 2018;71(1):136–48.
4. Sharfuddin AA, Weisbord SD, Palevsky PM, Molitoris BA. Acute kidney injury. In: Brenner and Rector's the kidney, vol. 2. 10th ed; 2016. p. 958–1011.e19. https://doi.org/10.1016/B978-1-4557-4836-5.00031-X.
5. Ostermann M, Liu K, Kashani K. Fluid management in acute kidney injury. Chest. 2019;156(3):594–603.
6. Perner A, Prowle J, Joannidis M, et al. Fluid management in acute kidney injury. Intensive Care Med. 2017;43(6):807–15.
7. Gibson JL, Nesbit ID. Fluid management. Surgery. 2016;34:60–5.
8. Brown RM, Semler MW. Fluid management in sepsis. J Intensive Care Med. 2019;34(5):364–73.
9. Finfer S, Myburgh J, Bellomo R. Intravenous fluid therapy in critically ill adults. Nat Rev Nephrol. 2018;14(9):541–57.
10. Teixeira C, Garzotto F, Piccinni P, et al. Fluid balance and urine volume are independent predictors of mortality in acute kidney injury. Crit Care. 2013;17:R14. https://doi.org/10.1186/cc12484.
11. Vaara ST, Korhonen A-M, Kaukonen K-M, et al. Fluid overload is associated with an increased risk for 90-day mortality in critically ill patients with renal replacement therapy: data from the prospective FINNAKI study. Crit Care. 2012;16(5):R197.
12. Teixeira C, Garzotto F, Piccinni P, et al. Fluid balance and urine volume are independent predictors of mortality in acute kidney injury. Crit Care. 2013;17(1):R14.
13. Bouchard J, Soroko SB, Chertow GM, et al. Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. Kidney Int. 2009;76(4):422–7.
14. Legrand M, Dupuis C, Simon C, et al. Association between systemic hemodynamics and septic acute kidney injury in critically ill patients: a retrospective observational study. Crit Care. 2013;17:R278.
15. Annane D, Siami S, Jaber S, et al. Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock: the CRISTAL randomized trial. JAMA. 2013;310:1809–17.
16. Kawano K. Introduction to Fluid Therapy. 2nd Ed. p.39, Kinpodo, 1995 (Japanese).
17. Wilcox CS. Regulation of renal blood flow by plasma chloride. J Clin Invest. 1983;71(3):726–35.
18. Bullivant EM, Wilcox CS, Welch WJ. Intrarenal vasoconstriction during hyperchloremia: role of thromboxane. Am J Phys. 1989;256(1 pt 2):F152–7.
19. Chowdhury AH, Cox EF, Francis ST, Lobo DN. A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and plasma-Lyte® 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. Ann Surg. 2012;256(1):18–24.
20. Young P, Bailey M, Beasley R, et al. Effect of a buffered crystalloid solution vs saline on acute kidney injury among patients in the intensive care unit: the SPLIT randomized clinical trial. JAMA. 2015;314(16):1701–10.
21. Semler MW, Self WH, Wanderer JP, et al. Balanced crystalloids versus saline in critically ill adults. N Engl J Med. 2018;378(9):829–39.

22. Self WH, Semler MW, Wanderer JP, et al. SALT-ED Investigators. Balanced crystalloids versus saline in noncritically ill adults. N Engl J Med. 2018;378(9):819–28.
23. Prowle JR, Echeverri JE, Ligabo EV, Ronco C, Bellomo R. Fluid balance and acute kidney injury. Nat Rev Nephrol. 2010;6(2):107–15.
24. Skytte Larsson J, Bragadottir G, Krumbholz V, et al. Effects of acute plasma volume expansion on renal perfusion, filtration, and oxygenation after cardiac surgery: a randomized study on crystalloid vs colloi. Br J Anaesth. 2015;115(5):736–42.
25. Rosner MH, Ostermann M, Murugan R, et al. Indications and management of mechanical fluid removal in critical illness. Br J Anaesth. 2014;113(5):764–71.
26. Cherpanath TG, Hirsch A, Geerts BF, et al. Predicting fluid responsiveness by passive leg raising: a systematic review and meta-analysis of 23 clinical trials. Crit Care Med. 2016;44(5):981–91.
27. Monnet X, Marik P, Teboul JL. Passive leg raising for predicting fluid responsiveness: a systematic review and meta-analysis. Intensive Care Med. 2016;42(12):1935–47.
28. Abuelo JG. Normotensive ischemic acute renal failure. N Engl J Med. 2007;357:797–805.
29. Friedrich JO, Adhikari N, Herridge MS, Beyene J. Meta-analysis: low-dose dopamine increases urine output but does not prevent renal dysfunction or death. Ann Intern Med. 2005;142(7):510–24.
30. Kellum JA, Decker JM. Use of dopamine in acute renal failure: a meta-analysis. Crit Care Med. 2001;29(8):1526–31.
31. De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med. 2010;362(9):779–89.
32. Post EH, Kellum JA, Vincent JL. Renal perfusion in sepsis: from macro- to microcirculation. Kidney Int. 2017;91:45–60.
33. Hoste EA, Maitland K, Brudney CS, Mehta R, Vincent JL, Yates D, Kellum JA, Mythen MG, Shaw AD, ADQI XII Investigators Group. Four phases of intravenous fluid therapy: a conceptual model. Br J Anaesth. 2014;113(5):740–7.
34. Hayakawa K. Aggressive fluid management in the critically ill: pro. J Intensive Care. 2019;7:9.
35. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early goal directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001;345:1368–77.
36. Process Investigators, Yealy DM, Kellum JA, Huang DT, Barnato AE, Weissfeld LA, et al. A randomized trial of protocol-based care for early septic shock. N Engl J Med. 2014;370(18):1683–93.
37. ARISE Investigators, Anzics Clinical Trials Group, Peake SL, Delaney A, Bailey M, Bellomo R, Cameron PA, et al. Goal-directed resuscitation for patients with early septic shock. N Engl J Med. 2014;371(16):1496–506.
38. Mouncey PR, Osborn TM, Power GS, Harrison DA, Sadique MZ, Grieve RD, et al. Trial of early, goal-directed resuscitation for septic shock. N Engl J Med. 2015;372(14):1301–11.
39. Godin M, Murray P, Mehta RL. Clinical approach to the patient with AKI and sepsis. Semin Nephrol. 2015;35(1):12–22.
40. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. J Am Coll Cardiol. 2008;52(19):1527–39.
41. Rangaswami J, Bhalla V, Blair JEA, Chang TI, Costa S, Lentine KL, et al. Cardiorenal syndrome: classification, pathophysiology, diagnosis, and treatment strategies: a scientific statement from the American Heart Association. Circulation. 2019;139(16):e840–e87.
42. Mullens W, Abrahams Z, Skouri HN, et al. Elevated intra-abdominal pressure in acute decompensated heart failure: a potential contributor to renal function? J Am Coll Cardiol. 2008;51(3):300–6.
43. Bagshaw SM, Delaney A, Haase M, et al. Loop diuretics in the management of acute renal failure: a systematic review and meta-analysis. Crit Care Resusc. 2008;9:60–8.
44. Ellison DH, Felker GM. Diuretic treatment in heart failure. N Engl J Med. 2017;377:1964–75.
45. Clark AL, Kalra PR, Petrie MC, et al. Change in renal function associated with drug treatment in heart failure: national guidance. Heart. 2019;105:904–10.

46. Brar Y, Ye F, James MT, et al. Association of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use with outcomes after acute kidney injury. JAMA Intern Med. 2018;178:1681.
47. Hobson CE, et al. Acute kidney injury is associated with increased long-term morality after cardiothoracic surgery. Circulation. 2009;119:2444–5.
48. Wang Y, Bellomo R. Cardiac surgery-associated acute kidney injury: risk factors, pathophysiology and treatment. Nat Rev Nephrol. 2017;13:697–711.
49. O'Neal JB, Shaw AD, Billings FT IV. Acute kidney injury following cardiac surgery: current understanding and future directions. Crit Care. 2016;20:187.
50. Menting TP, et al. Ischaemic preconditioning for the reduction of renal ischaemia reperfusion injury. Cochrane Database Syst Rev. 2017;3:CD010777.
51. Angeli P, Bernardi M, Villanueva C, et al. European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol. 2018;69:406–60.
52. von Baeyer H. Plasmapheresis in thrombotic microangiopathy associated syndromes: review of outcome data derived from clinical trials and open studies. Ther Apher. 2002;6:320–8.
53. Alamartine E, Maillard N. Therapeutic plasma exchange in nephrology. Where it applies? Transfusion and apheresis. Science. 2019;58(3):262–5.
54. Gonzalez E, Gutierrez E, Galeano C, et al. Early steroid treatment improves the recovery of renal function in patients with drug-induced acute interstitial nephritis. Kidney Int. 2008;73:940–6.
55. Ho KM, Sheridan DJ. Meta-analysis of frusemide to prevent or treat acute renal failure. BMJ. 2006;333:420.
56. Karajala V, Mansour W, Kellum JA. Diuretics in acute kidney injury. Minerva Anestesiol. 2009;75:251–7.
57. Brater DC. Diuretic therapy. N Engl J Med. 1998;339:387.
58. Gunderson EG, Lillyblad MP, Fine M, et al. Tolvaptan for volume management in heart failure. Pharmacotherapy. 2019;39(4):473–85.
59. UK Renal Association. Treatment of acute hyperkalaemia in adults. Clinicalpractice guidelines. London: UK Renal Association; 2014.
60. Truhlá A, Deakin CD, Soar J. European resuscitation council guidelines for resuscitation 2015: section 4. Cardiac arrest in special circumstances. Resuscitation. 2015;95:148–201.
61. Bianchi S, Aucella F, De Nicola L, et al. Management of hyperkalemia in patients with kidney disease: a position paper endorsed by the Italian Society of Nephrology. J Nephrol. 2019;32:499–516.
62. Jackson MA, Lodwick R, Hutchinson SG. Hyperkalaemic cardiac arrest successfully treated with peritoneal dialysis. BMJ. 1996;312(7041):1289–90.
63. Roseman DA, Schechter-Perkins EM, Bhatia JS. Treatment of life-threatening hyperkalemia with peritoneal dialysis in the ED. Am J Emerg Med. 2015;33(3):473.e3–5.
64. Morris CG, Low J. Metabolic acidosis in the critically ill: part 2. Causes and treatment. Anaesthesia. 2008;63:396–411.
65. Bonventre JV, Cheung JY. Effects of metabolic acidosis on viability of cells exposed to anoxia. Am J Physiol. 1985;249:C149–59.
66. Right G, Kingston MA, Ross IS. Role of metabolic acidosis on cardiac mechanical performance during severe acute hypoxia and reoxygenation is small and transient. Cardiovasc Res. 1995;29:611–5.
67. Cano N, Fiaccadori E, Tesinsky P, et al. ESPEN guidelines on enteral nutrition: adult renal failure. Clin Nutr. 2006;25:295–310.
68. Li Y, Tang X, Zhang J, et al. Nutritional support for acute kidney injury. Cochrane Database Syst Rev. 2012;(8):CD005426.
69. Marik PE, Zaloga GP. Early enteral nutrition in acutely ill patients: a systematic review. Crit Care Med. 2001;29:2264–70.
70. Heyland DK, Dhaliwal R, Drover JW, Gramlich L, Dodek P. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. JPEN J Parenter Enteral Nutr. 2003;27:355–73.

71. Doig GS, Heighes PT, Simpson F, Sweetman EA. Early enteral nutrition reduces mortality in trauma patients requiring intensive care: a meta-analysis of randomised controlled trials. Injury. 2011;42:50–6.
72. Bost RB, Tjan DH, van Zanten AR. Timing of (supplemental) parenteral nutrition in critically ill patients: a systematic review. Ann Intensive Care. 2014;4:31.
73. Zusman O, Theilla M, Cohen J, et al. Resting energy expenditure, calorie and protein consumption in critically ill patients: a retrospective cohort study. Crit Care. 2016;20(1):367.
74. Finfer S, Liu B, Chittock DR, et al. Hypoglycemia and risk of death in critically ill patients. N Engl J Med. 2012;367:1108–18.
75. Fiaccadori E, Sabatino A, Morabito S, et al. Hyper/hypoglycemia and acute kidney injury in critically ill patients. Clin Nutr. 2016;35:317–21.
76. Roberts DM, Sevatos J, Carland JE, et al. Clinical pharmacokinetics in kidney disease: application to rational design of dosing regimens. Clin J Am Soc Nephrol. 2018;13:1254–63.
77. NHS. Guidelines for medicines optimisation in patients with acute kidney injury. 2016. https://www.thinkkidneys.nhs.uk/aki/wp-content/uploads/sites/2/2016/03/Guidelines-for-Medicines-optimisation-in-patients-with-AKI-final.pdf. Accessed 16 Aug 2019.
78. Matzke GR, Aronoff GR, Atkinson AJ Jr, et al. Drug dosing consideration in patients with acute and chronic kidney disease—a clinical update from kidney disease: improving global outcomes (KDIGO). Kidney Int. 2011;80:1122–37.

Chapter 14
Postrenal AKI

Naoya Nagaya and Shigeo Horie

Abstract Postrenal acute kidney injury (AKI) is a condition in which renal function is compromised due to urinary tract obstruction (UTO). UTO can occur at any site in the urinary tract, including the upper (renal pelvis, ureter) and lower urinary tract (bladder, prostate, urethra). In addition, UTO may be acute or chronic, partial or complete, unilateral, or bilateral. Postrenal AKI commonly results from obstructions in the renal pelvis, the ureters, bladder, and urethra, but it can also be caused by unilateral UTO alone, especially in patients with anatomic or functional nephropathy in a solitary kidney. Primary disorders that are associated with UTO include benign prostatic hypertrophy, urologic malignancies, urinary calculi, retroperitoneal fibrosis, and blood clot. Neurogenic bladder is a functional urinary tract dysfunction that might predispose an individual to UTO. Early diagnosis of UTO and treatment providing relief of the obstruction by either transurethral stenting or percutaneous nephrostomy (PCN) is critical to preserving, improving, or restoring renal function. An untreated or suboptimally treated UTO increases the risk of urinary tract infection (UTI), sepsis and end-stage renal disease (ESRD). Among cancer patients, renal function may improve with the initiation of anticancer therapy, although urologic intervention, such as ureteral stenting and urinary catheters, is often required in cases of treatment-resistant cancers. This chapter describes the causes, diagnosis, treatment, and prognosis of UTO causing acute renal injury.

Keywords Acute renal injury · Postrenal acute kidney injury · Urinary tract obstruction · Transurethral stenting · Percutaneous nephrostomy · Hydronephrosis

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14.1 Epidemiology

Urinary tract obstruction (UTO) is frequently encountered in daily urologic practice and is an important cause of acute kidney injury (AKI) [1]. UTO is relatively more common in men than in women, especially elderly men who are at increased risk for benign prostatic hyperplasia. UTO should always be considered in the cancer patient with AKI because postrenal AKI is more likely to occur in cancer patients than in healthy individuals [2]. Causes of UTO vary notably by patient age. Congenital anatomic abnormalities, such as urethral valves or stricture and stenosis at the ureterovesical or ureteropelvic junction, account for most UTO cases in pediatric patients [3]. Urinary calculi are a major cause of UTO in young adult patients. Prostatic hypertrophy or carcinoma, retroperitoneal or pelvic tumors, and urinary calculi are among the major causes of UTO in the elderly [4].

14.2 Etiology

14.2.1 Anatomical Classification

Understanding the anatomy of the urinary tract is important because UTO can occur at any point along the urinary tract. The kidneys and the ureters are retroperitoneal organs located in the retroperitoneum. The bladder is located in the subperitoneal space. Each kidney contains 10–20 renal pyramids, which are formed by the collecting tubules and collecting ducts. Urine is excreted into the calyces from the renal papilla at the tip of the renal pyramid. Each renal papilla secretes urine into the minor calyces, which connect to the major calyces. The major calyces join the renal pelvis and the ureters. Each ureter moves downward in the retroperitoneum and passes posteriorly through the bladder to the base of the bladder. In both men and women, there are three physiologic ureteral stenoses: the ureteropelvic junction, the intersection of the common iliac artery, and the vesicoureteral junction. Ureteral calculi are more likely to be incarcerated in a physiologic stricture. The urethra, which arises from the bladder neck, lies just below the ureteral orifice and is surrounded by the prostate. The male urethra is 18–20 cm long and is longer than 3–4 cm in women [5]. The different types of UTO are categorized according to the location of the obstacle.

14.2.1.1 Obstruction of the Kidney, Renal Pelvis, or Ureter

Obstruction of the upper urinary tract can develop due to a variety of causes, which may include: urinary calculi; transitional cell carcinoma; extrinsic compression of the urinary outflow tract from primary malignancies, lymphadenopathy or

retroperitoneal fibrosis; blood clot; and fungal balls [6]. Upper UTO can result in diffuse calyceal dilation or hydronephrosis and is, in most cases, unilateral. Besides urologic malignancies, upper UTO is common in gynecologic cancers such as uterine and ovarian cancer and in gastrointestinal cancers such as gastric, pancreatic, colorectal, and rectal cancers, which include direct invasion, lymph node metastases, retroperitoneal dissemination, and Douglas' pouch metastases. Inflammatory strictures following irradiation may also cause upper UTO [7]. Postrenal AKI during pregnancy due to ureteral obstruction is rare and its risk increases with twin pregnancy, polyhydramnios, nephropathy in a solitary kidney, and urinary calculi [8]. Occlusion of the ureteral stent may lead to recurrent hydronephrosis.

14.2.1.2 Bladder and Urethral Obstruction

Cancer in the bladder can lead to obstruction in one or both ureters, or in the orifices of the ureter. Further, lower UTO (e.g., due to neurogenic bladder or prostatic hypertrophy) may contribute to elevated upper urinary tract pressure and development of postrenal AKI (Table 14.1).

Table 14.1 The causes of UTO are categorized according to the location of the obstacle

Anatomical site	Causes
Kidney, renal pelvis, and ureter	Stones
	Tumor (urothelial cancer, extrinsic tumors)
	Lymphadenopathy
	Retroperitoneal fibrosis
	Blood clot
	Infection, fungus balls
	Pregnancy
	Urethral obstruction in the transplanted kidney
	Obstructed stent
	Vesicoureteral reflux, ureteropelvic junction (UPJ) stenosis
	Postoperative ureteral stricture, postradiation ureteral stricture
Bladder and urethral	Stones
	Tumor (urothelial cancer, extrinsic tumors)
	Neurogenic bladder
	Prostatic hypertrophy
	Pelvic organ prolapse
	Urethral stricture (iatrogenic, bacteria urethritis, trauma)
	Blood clot

14.2.1.3 Ureteral Obstruction in the Transplanted Kidney

Approximately, 2% of renal transplant patients are at risk of developing UTO within 6 months after transplantation [9]. Persistent elevation of serum creatinine remains the mainstay serologic marker used for detecting renal dysfunction, including AKI. Ureteral obstruction is typically caused by strictures due to ischemia. A vesicoureteral anastomosis is the most common site of ischemia [10]. Hydronephrosis (or calyceal dilation) is usually detected on ultrasonography. Obstruction of the urinary tract in a kidney-transplanted patient often requires emergency surgical intervention.

Other possible causes of ureteral obstruction include blood clots, renal ischemia, and calculi in the donor's kidney. In addition to ultrasonography and computed tomography (CT), urography of the renal fistula (antegrade) or the bladder (retrograde) is often considered to correctly diagnose obstruction. In nonobstructive cases, renal scintigraphy may be helpful.

14.3 Clinical Findings

A patient's past medical history, current health status, and risk factors can be used to aid the diagnosis of postrenal AKI. The presence or absence of clinical symptoms, especially pain, depends on the location of the obstruction, the degree of obstruction (i.e., partial or complete), and the progression rate of the obstruction. Other commonly reported signs and symptoms include pain, fever, decreased urine output, weight gain, edema, hypertension, hematuria, increased serum creatinine, hyperkalemia, and metabolic acidosis.

14.3.1 Pain/Fever

Pain in postrenal AKI patients frequently manifests as with lower abdominal or flank pain. Careful percussion of the kidney, which involves tapping over the costovertebral angle, can be used to determine whether the pain is present. Acute UTO does not always cause pain. Pain tends to co-occur in patients with bladder distention, secondary infection, and renal calculi or masses. While pain suggests renal calculi, acute tubular necrosis, or infection requiring further evaluation, hydronephrosis alone is almost always asymptomatic. In cases of complete acute obstruction, such as those caused by ureteral stones, patients experiencing renal or ureteral colic may present with severe pain. However, pain may not be common in patients with UTO due to external ureteral compression as the course of obstruction is generally gradual. Co-occurring symptoms of lower abdominal pain and urinary urgency suggest lower UTO. Further, fever may be present in patients with pyelonephritis due to UTO.

14.3.2 Decreased Urine Output

Oliguria and anuria are the main symptoms of AKI. Anuria, defined by a marked decrease in urine production with less than 100 mL of urine output per day, may result from complete bilateral ureteral obstruction or complete urethral obstruction. Even in the absence of anuria, the partial obstruction may cause AKI. Care must be taken because normal urinary output and polyuria may occur even if patients have UTO.

Due to tubular damage, polyuria may occur despite decreased glomerular filtration rate (GFR) because the tubules retain salt and impair the ability to concentrate urine [11, 12]. Decreased urine output due to urethral obstruction is defined as urinary retention, which is different from oliguria and anuria. Obstruction in the urethra can cause bladder distention and overflow incontinence, which frequently manifests as frequency, urgency, and nocturia. Palpation of the lower abdomen can detect the presence of an enlarged bladder. The residual urine volume can be easily measured by an abdominal ultrasound.

14.3.3 Hypertension

Hypertension may result from the retention of salt and water due to oliguria or, in some cases, from activation of the renin–angiotensin system. Reflex vasoconstriction of the afferent glomerular capillaries in the obstructed kidney can result in the activation of the renin–angiotensin system [13]. In patients with hypertension due to fluid retention, renal function improves with the recovery of urine volume.

14.4 Laboratory Findings

14.4.1 Blood Tests

Creatinine is used as an index of GFR because it is cleared by the kidneys with minimal tubular reabsorption and secretion. Renal function decreases with serum creatinine. Unilateral UTO alone does not typically increase serum creatinine because serum creatinine may increase when the GFR falls below 50% of normal. In the presence of chronic renal disease, unilateral UTO can lead to an increase in serum creatinine. Although uncommon, increased creatinine levels can give rise to an incidental finding of UTO. If UTO persists and left untreated, it can lead to hyperkalemia and renal tubular acidosis [14].

14.4.2 Urinalysis

Hematuria may not occur in the presence of UTO, but it is often present when a calculus or tumor is the underlying mechanism of obstruction. If urinary retention occurs in the renal pelvis due to complete obstruction of the urinary tract, pyuria may not be present even if clinical findings suggest pyelonephritis. Serum creatinine is a suboptimal marker for AKI. On the contrary, urine biomarkers, such as urinary neutrophil gelatinase-associated lipocalin (NGAL) and liver type fatty acid-binding protein (L-FABP), are considered to be useful for the early and accurate diagnosis of AKI [15, 16].

14.5 Diagnosis

Early detection of acute renal failure is critical to prevent treatment delay and eventual irreversible renal damage. The presence of tumor infiltration or compression should always be considered, though benign conditions cannot be ruled out [2]. Such benign conditions may include upper UTO such as calculi or pyeloureteric junction stenosis with unilateral hydronephrosis, and lower UTO such as bladder dysfunction or prostatic hypertrophy with bilateral hydronephrosis. When postrenal AKI is suspected based on the clinical symptoms and medical history, imaging studies should be performed to detect UTO.

14.5.1 Ultrasonography

Ultrasonography is a safe and relatively inexpensive procedure for diagnosing hydronephrosis and urinary retention [17]. Although ultrasonography is used to delineate hydronephrosis in the evaluation of obstructive uropathy, it is not always sensitive and specific. A study demonstrated that ultrasonography detection of hydronephrosis had a sensitivity of 72.6% and a specificity of 73.3%, defining hydronephrosis on CT as the criterion standard [18].

14.5.2 CT

CT has proven to be useful for detecting anatomic abnormalities that cannot be adequately visualized by ultrasonography [19]. CT should be always considered, especially if obstructive renal calculi are suspected. If external compression of the urinary tract by a tumor is suspected, CT urography with contrast can be used to determine the site of the obstruction.

14.5.3 Magnetic Resonance Urography (MRU)

MRU enables a more detailed visualization of the urinary tract. It can also be used in patients with impaired renal function and it does not emit damaging ionizing radiation. For these reasons, MRI is especially useful for pregnant patients. Although urinary calculi are poorly visualized by MRI, MRI should be considered when CT and ultrasonography provide inadequate diagnostic information [20, 21].

14.5.4 Urography

Intravenous urography (IVU) is performed using conventional X-ray after the intravenous administration of a contrast agent, which is excreted through the urinary tract as part of the urine. Visualization of narrowing of the urinary tract or dilation of the upper urinary tract is possible with the IVU, but a definitive diagnosis of extra-urinary tract diseases is often difficult to establish. In recent years, CT and MRI have replaced IVU due to the significant diagnostic information provided by these advanced imaging modalities [22]. Retrograde pyelography (RP) is also an X-ray examination of the upper urinary tract using a cystoscope to insert a catheter into the renal pelvis and ureters and injecting a radiopaque dye. RP is also usually performed during a ureteral stent placement procedure.

14.5.5 Classification of Hydronephrosis

Hydronephrosis can be classified in several ways, with the three-stage system (mild, moderate and severe; Emergency Ultrasound Imaging Criteria 2014) being the most commonly used. Moderate hydronephrosis is characterized by the fusion of the calyces arranged in a pattern reminiscent of a bear's paw. In cases of severe hydronephrosis, there is thinning of the renal parenchyma. Mild hydronephrosis refers to any dilation of the renal pelvis that does not belong to the moderate or severe categories.

14.5.6 Differential Diagnosis

There is evidence to suggest that clinical symptoms (e.g., anuria, back pain) and history of urological obstruction (e.g., due to cancer) are risk factors of postrenal AKI. However, anuria is not necessarily caused by postrenal AKI. Acute renal failure due to prerenal or renal failure also causes anuria.

Detection of hydronephrosis is important in the diagnosis of postrenal AKI, but attention should be paid to other clinical manifestations that may appear similar to hydronephrosis. The differential diagnosis of hydronephrosis includes peripelvic cysts, extrarenal pelvis, and dilated renal veins. Peripelvic cysts can be distinguished from hydronephrosis because they are dilated lymphatics in the renal pelvis, and neither the minor calyces nor the proximal ureters are dilated. An extrarenal pelvis is a localized dilation of the ureters, often with dilation of the major calyces; however, the minor calyces and other ureters are not enlarged. Dilated veins usually branch laterally in the kidneys and extend into the vena cava, and they can be distinguished from the renal pelvis by Doppler ultrasonography, which reveals the presence of blood flow.

14.6 Treatment Method

For postrenal AKI due to UTO, the initial goal of treatment is to establish urine flow. Either a transvesically placed stents or an ultrasound-guided PCN can be the emergency procedure of choice to achieve urine flow. In patients with bilateral hydronephrosis, these procedures are often performed on the side of the kidney, which is considered to have a better renal function. A bilateral nephrostomy or ureteral stenting is performed if both kidneys are symptomatic or if chemotherapy for cancer is being considered in the future. An ileal conduit urinary diversion and bilateral ureterocutaneostomy are considered treatment options when a favorable long-term prognosis is anticipated and the discomfort associated with urination is expected to be significant. Conversely, if the prognosis is determined to be poor, there is an option to follow the natural disease course without ensuring urine flow. In a study involving patients with renal failure associated with cancer who underwent PCN, poor prognostic factors were identified to be serum albumin before nephrostomy (3 g/dL or less), degree of hydronephrosis (grade 1 or 2), and the number of events related to malignant dissemination (3 or more) [23]. The presence of two or more of these poor prognostic factors was associated with a 2% survival rate at 6 months, whereas the absence of these poor prognostic factors was associated with a 69% survival rate. Ureteral stenting and PCN could potentially impair the patient's quality of life by inducing irritative urinary symptoms, pain, and the need for replacement [24]. Therefore, the physician needs to be aware of these risks before deciding on treatment. If the urethral obstruction is identified as the cause of postrenal AKI, urethral stenting, or cystostomy may be necessary.

14.6.1 Ureteric Stenting

The ureteral stent insertion was developed by Zimskind and colleagues in 1967 [25]. Using a cystoscope, the procedure involves: insertion of a guidewire through the ureteral orifice on the hydronephrotic side; the advancement of the tip of the

ureteral stent into the renal pelvis; and placement of a ureteral stent between the renal pelvis and the bladder. The most common complications associated with ureteral stents are pain and urinary irritation, with 70% of patients reporting the use of any analgesic within 7 days after insertion [26]. Because of the narrow internal foramen and occlusion of the stent over time, stents are usually replaced in 3–4 months. Metal stents have recently become available, enabling stent dwell time to be longer than before with ureteral stents. The main advantage of ureteral stents is that there is no change in body image; however, the disadvantage is difficulty in assessing stent occlusion and the eventual delay in stent replacement. Further, ureteral stenting may be not appropriate for patients in whom cystoscopy is a challenging procedure, such as those with external UTO associated with a pelvic or retroperitoneal tumor [27].

14.6.2 PCN

PCN, which was first reported by Goodwin and colleagues in 1955 [28], is a procedure that involves the placement of a percutaneous nephrostomy catheter under ultrasound guidance. Associated complications may include renal calculi, bleeding, infection, and organ damage. Bleeding during insertion has a 2–4% risk of necessitating transfusion [29]. The probability of pleural injury at insertion is less than 0.1–0.2% [30]. Direct visualization of the renal fistula with the injection of radiopaque dye can help determine the site of obstruction. Hemorrhage may result in filling defects caused by blood clots in the renal pelvis, obstructed urinary, and no improvement in renal function. While PCN is technically easier to implement compared with ureteral stents [31], it is more likely to result in poorer patient quality of life.

14.6.3 Ileal Conduit Urinary Diversion and Ureterocutaneous Fistula

A ureterocutaneous fistula or an ileal conduit urinary diversion may be applied in a patient with favorable long-term prognosis after a nephrostomy is created in an acute phase. In addition, there is the option of creating an ileal conduit urinary diversion or ureterocutaneous fistula in advance for patients with increased risk of UTO from bladder invasion associated with cancer or hematuria associated with growing bladder cancer. Because an invasive surgery under general anesthesia is required for these procedures, careful consultation with the patient and family about treatment decisions is important and necessary.

14.7 Mechanisms and Prognosis of Postrenal AKI

The marked thinning of the renal cortex on ultrasonography indicates severe and irreversible renal disease. Renal function recovery usually occurs in the first 7 or 10 days after the UTO has been relieved [32]. Patients with severe renal insufficiency may require several weeks of dialysis for adequate renal function [33]. Complete or prolonged partial UTO increases the risk of tubular atrophy, interstitial fibrosis, and, ultimately, irreversible renal damage [34].

The mechanisms by which UTO causes irreversible renal damage and atrophy are not fully understood. Continuous glomerular filtration following an obstruction could lead to an increase of pressure proximal to the obstruction in the renal pelvis [35], which also causes dilation of the renal pelvis. The pressure increase is transmitted to the proximal tubule, counteracting the high intraglomerular pressure that promotes glomerular filtration, thereby causing decreased GFR. UTO also affects renal blood flow. Increased tubular pressure causes secondary constriction of the renal vasculature, leading to marked glomerular hypovolemia [35]. Decreased renal perfusion could result in a chronic decrease in GFR. An experimental study in rats has shown that 15% of renal nephrons underwent irreversible damage after only 24 h of UTO [36]. As GFR decreases, the high intraluminal pressure reduces and normalizes steadily [37]. Prolonged glomerular ischemia also affects the renin–angiotensin system [38].

Obstructed kidney releases substances that attract monocytes and macrophages [35]. By stimulating the production of NF-kB, angiotensin II induces the chemotaxis of macrophages that produce reactive oxygen species and TNF-α [39]. These infiltrating cells also release TGF-β, other cytokines, and proteases that contribute to tubular damage and fibrosis [40]. TGF-β promotes epithelial–mesenchymal transition in tubular epithelial cells, leading to the production of stress fibers by fibroblasts and the deposition of extracellular matrix [41]. Renin also binds directly to the renin receptor and is believed to stimulate the production of TGF-β through extracellular signal-regulated kinase [42]. As such, tubular damage that occurs in UTO may be caused initially by increased intraluminal pressure and later by atrophy induced by ischemia and/or inflammation [43].

The prognosis of renal function depends on the severity and duration of obstruction [44]. Biomarkers predicting progression from postrenal AKI to CKD are not yet established. Serum creatinine is one of the candidate biomarkers. Serum creatinine levels in the setting of acute renal damage have been reported to be associated with progression to ESRD [45]. Biomarkers of inflammation, C-reactive protein and TNF receptor 2, have been associated with early deterioration in renal function in CKD; however, the usefulness of these markers in predicting CKD following postrenal AKI needs to be clarified [46]. KIM-1 (Kidney Injury Molecular-1), a protein expressed and induced in proximal tubular epithelial cells during the process of repairing and regenerating tubular damage, is expected to be a diagnostic and prognostic marker for acute and chronic renal damage [47].

References

1. Lam AQ, Humphreys BD. Onco-nephrology: AKI in the cancer patient. Clin J Am Soc Nephrol. 2012;7(10):1692–700.
2. Humphreys BD, Soiffer RJ, Magee CC. Renal failure associated with cancer and its treatment: an update. J Am Soc Nephrol. 2005;16(1):151–61.
3. Caiulo VA, Caiulo S, Gargasole C, Chiriaco G, Latini G, Cataldi L, Mele G. Ultrasound mass screening for congenital anomalies of the kidney and urinary tract. Pediatr Nephrol. 2012;27(6):949–53.
4. Lameire N, Van Biesen W, Vanholder R. Acute renal failure. Lancet. 2005;365(9457):417–30.
5. Abelson B, Sun D, Que L, Nebel RA, Baker D, Popiel P, Amundsen CL, Chai T, Close C, DiSanto M, Fraser MO, Kielb SJ, Kuchel G, Mueller ER, Palmer MH, Parker-Autry C, Wolfe AJ, Damaser MS. Sex differences in lower urinary tract biology and physiology. Biol Sex Differ. 2018;9(1):45.
6. Seker KG, Eksi M, Colakoglu Y, Yenice MG, Akbay FG, Tugcu V, Simsek A. A rare cause of acute post renal failure: retroperitoneal fibrosis. Arch Ital Urol Androl. 2017;89(4):301–4.
7. Makris K, Spanou L. Acute kidney injury: definition, pathophysiology and clinical phenotypes. Clin Biochem Rev. 2016;37(2):85–98.
8. Jim B, Garovic VD. Acute kidney injury in pregnancy. Semin Nephrol. 2017;37(4):378–85.
9. Inci MF, Ozkan F, See TC, Tatli S. Renal transplant complications: diagnostic and therapeutic role of radiology. Can Assoc Radiol J. 2014;65(3):242–52.
10. Mano R, Golan S, Holland R, Livne PM, Lifshitz DA. Retrograde endoureterotomy for persistent ureterovesical anastomotic strictures in renal transplant kidneys after failed antegrade balloon dilation. Urology. 2012;80(2):255–9.
11. Klahr S. Pathophysiology of obstructive nephropathy. Kidney Int. 1983;23(2):414–26.
12. Hwang SJ, Haas M, Harris HW Jr, Silva P, Yalla S, Sullivan MR, Otuechere G, Kashgarian M, Zeidel ML. Transport defects of rabbit medullary thick ascending limb cells in obstructive nephropathy. J Clin Invest. 1993;91(1):21–8.
13. Weidmann P, Beretta-Piccoli C, Hirsch D, Reubi FC, Massry SG. Curable hypertension with unilateral hydronephrosis. Studies on the role of circulating renin. Ann Intern Med. 1977;87(4):437–40.
14. Batlle DC, Arruda JA, Kurtzman NA. Hyperkalemic distal renal tubular acidosis associated with obstructive uropathy. N Engl J Med. 1981;304(7):373–80.
15. Singer E, Elger A, Elitok S, Kettritz R, Nickolas TL, Barasch J, Luft FC, Schmidt-Ott KM. Urinary neutrophil gelatinase-associated lipocalin distinguishes pre-renal from intrinsic renal failure and predicts outcomes. Kidney Int. 2011;80(4):405–14.
16. Matsui K, Kamijo-Ikemori A, Hara M, Sugaya T, Kodama T, Fujitani S, Taira Y, Yasuda T, Kimura K. Clinical significance of tubular and podocyte biomarkers in acute kidney injury. Clin Exp Nephrol. 2011;15(2):220–5.
17. Licurse A, Kim MC, Dziura J, Forman HP, Formica RN, Makarov DV, Parikh CR, Gross CP. Renal ultrasonography in the evaluation of acute kidney injury: developing a risk stratification framework. Arch Intern Med. 2010;170(21):1900–7.
18. Herbst MK, Rosenberg G, Daniels B, Gross CP, Singh D, Molinaro AM, Luty S, Moore CL. Effect of provider experience on clinician-performed ultrasonography for hydronephrosis in patients with suspected renal colic. Ann Emerg Med. 2014;64(3):269–76.
19. Denker B, Robles-Osorio ML, Sabath E. Recent advances in diagnosis and treatment of acute kidney injury in patients with cancer. Eur J Intern Med. 2011;22(4):348–54.
20. Masselli G, Derchi L, McHugo J, Rockall A, Vock P, Weston M, Spencer J. Acute abdominal and pelvic pain in pregnancy: ESUR recommendations. Eur Radiol. 2013;23(12):3485–500.
21. Semins MJ, Feng Z, Trock B, Bohlman M, Hosek W, Matlaga BR. Evaluation of acute renal colic: a comparison of non-contrast CT versus 3-T non-contrast HASTE MR urography. Urolithiasis. 2013;41(1):43–6.

22. Hiorns MP. Imaging of the urinary tract: the role of CT and MRI. Pediatr Nephrol. 2011;26(1):59–68.
23. Ishioka J, Kageyama Y, Inoue M, Higashi Y, Kihara K. Prognostic model for predicting survival after palliative urinary diversion for ureteral obstruction: analysis of 140 cases. J Urol. 2008;180(2):618–21. discussion 621.
24. Monsky WL, Molloy C, Jin B, Nolan T, Fernando D, Loh S, Li CS. Quality-of-life assessment after palliative interventions to manage malignant ureteral obstruction. Cardiovasc Intervent Radiol. 2013;36(5):1355–63.
25. Zimskind PD, Fetter TR, Wilkerson JL. Clinical use of long-term indwelling silicone rubber ureteral splints inserted cystoscopically. J Urol. 1967;97(5):840–4.
26. Giannarini G, Keeley FX Jr, Valent F, Manassero F, Mogorovich A, Autorino R, Selli C. Predictors of morbidity in patients with indwelling ureteric stents: results of a prospective study using the validated Ureteric Stent Symptoms Questionnaire. BJU Int. 2011;107(4):648–54.
27. Chitale SV, Scott-Barrett S, Ho ET, Burgess NA. The management of ureteric obstruction secondary to malignant pelvic disease. Clin Radiol. 2002;57(12):1118–21.
28. Goodwin WE, Casey WC, Woolf W. Percutaneous trocar (needle) nephrostomy in hydronephrosis. J Am Med Assoc. 1955;157(11):891–4.
29. Hausegger KA, Portugaller HR. Percutaneous nephrostomy and antegrade ureteral stenting: technique-indications-complications. Eur Radiol. 2006;16(9):2016–30.
30. Farrell TA, Hicks ME. A review of radiologically guided percutaneous nephrostomies in 303 patients. J Vasc Interv Radiol. 1997;8(5):769–74.
31. Ku JH, Lee SW, Jeon HG, Kim HH, Oh SJ. Percutaneous nephrostomy versus indwelling ureteral stents in the management of extrinsic ureteral obstruction in advanced malignancies: are there differences? Urology. 2004;64(5):895–9.
32. Green J, Vardy Y, Munichor M, Better OS. Extreme unilateral hydronephrosis with normal glomerular filtration rate: physiological studies in a case of obstructive uropathy. J Urol. 1986;136(2):361–5.
33. Cohen EP, Sobrero M, Roxe DM, Levin ML. Reversibility of long-standing urinary tract obstruction requiring long-term dialysis. Arch Intern Med. 1992;152(1):177–9.
34. Sacks SH, Aparicio SA, Bevan A, Oliver DO, Will EJ, Davison AM. Late renal failure due to prostatic outflow obstruction: a preventable disease. BMJ. 1989;298(6667):156–9.
35. Klahr S. New insights into the consequences and mechanisms of renal impairment in obstructive nephropathy. Am J Kidney Dis. 1991;18(6):689–99.
36. Bander SJ, Buerkert JE, Martin D, Klahr S. Long-term effects of 24-hr unilateral ureteral obstruction on renal function in the rat. Kidney Int. 1985;28(4):614–20.
37. Gaudio KM, Siegel NJ, Hayslett JP, Kashgarian M. Renal perfusion and intratubular pressure during ureteral occlusion in the rat. Am J Phys. 1980;238(3):F205–9.
38. Dal Canton A, Stanziale R, Corradi A, Andreucci VE, Migone L. Effects of acute ureteral obstruction on glomerular hemodynamics in rat kidney. Kidney Int. 1977;12(6):403–11.
39. Chevalier RL, Forbes MS, Thornhill BA. Ureteral obstruction as a model of renal interstitial fibrosis and obstructive nephropathy. Kidney Int. 2009;75(11):1145–52.
40. Schreiner GF, Kohan DE. Regulation of renal transport processes and hemodynamics by macrophages and lymphocytes. Am J Phys. 1990;258(4 Pt 2):F761–7.
41. Lopez-Hernandez FJ, Lopez-Novoa JM. Role of TGF-beta in chronic kidney disease: an integration of tubular, glomerular and vascular effects. Cell Tissue Res. 2012;347(1):141–54.
42. Huang Y, Wongamorntham S, Kasting J, McQuillan D, Owens RT, Yu L, Noble NA, Border W. Renin increases mesangial cell transforming growth factor-beta1 and matrix proteins through receptor-mediated, angiotensin II-independent mechanisms. Kidney Int. 2006;69(1):105–13.
43. Tanner GA, Evan AP. Glomerular and proximal tubular morphology after single nephron obstruction. Kidney Int. 1989;36(6):1050–60.
44. Better OS, Arieff AI, Massry SG, Kleeman CR, Maxwell MH. Studies on renal function after relief of complete unilateral ureteral obstruction of three months' duration in man. Am J Med. 1973;54(2):234–40.

45. Chawla LS, Amdur RL, Amodeo S, Kimmel PL, Palant CE. The severity of acute kidney injury predicts progression to chronic kidney disease. Kidney Int. 2011;79(12):1361–9.
46. Tonelli M, Sacks F, Pfeffer M, Jhangri GS, Curhan G. Biomarkers of inflammation and progression of chronic kidney disease. Kidney Int. 2005;68(1):237–45.
47. Sabbisetti VS, Waikar SS, Antoine DJ, Smiles A, Wang C, Ravisankar A, Ito K, Sharma S, Ramadesikan S, Lee M, Briskin R, De Jager PL, Ngo TT, Radlinski M, Dear JW, Park KB, Betensky R, Krolewski AS, Bonventre JV. Blood kidney injury molecule-1 is a biomarker of acute and chronic kidney injury and predicts progression to ESRD in type I diabetes. J Am Soc Nephrol. 2014;25(10):2177–86.

Chapter 15
Acute Kidney Injury in Intensive Care Medicine

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Abstract Acute kidney injury (AKI) is one of the most serious complications in intensive care unit. The major etiologies of AKI in intensive care are post-cardiac surgery and sepsis. Although post-cardiac surgery AKI will worsen the outcomes, mild and transient AKI are frequently observed especially in the scheduled surgery patient. On the other hand, better therapeutics against septic AKI are urgently required because sepsis and AKI synergistically worsen the outcomes of critically ill patients. To overcome this problem, evidence accumulation is necessary for building the foundation for developing novel septic AKI treatments. This chapter provides a summary of updated evidence regarding septic AKI in intensive care medicine.

Keywords Acute kidney injury · Sepsis · Epidemiology · Adsorption · Endotoxin adsorption

15.1 Acute Kidney Injury

Acute kidney injury (AKI) is a syndrome caused by an abrupt loss of kidney function. A recent definition of AKI by the Kidney Disease: Improving Global Outcomes (KDIGO) includes the following: (1) an increase in serum creatinine level by 0.3 mg/dL within 48 h; (2) an increase in serum creatinine level to 1.5 times from the baseline, which is known or presumed to have occurred within the prior 7 days; or (3) urine volume of <0.5 mL/kg/h for 6 h [1]. This standardized definition allows for the identification of AKI in different patient populations. Although many clinical studies reported AKI to be associated with poor outcomes, the outcomes vary by clinical phenotypes, such as community-acquired AKI versus hospital-acquired AKI [2]. Previous studies evaluating hospital-acquired AKI, particularly

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in intensive care unit (ICU) settings, have reported sepsis or septic shock to be the most common cause of AKI [3, 4]. In fact, 45–70% of all AKI cases are associated with sepsis in ICUs [5–7].

15.2 Sepsis

Sepsis is a syndrome characterized by systemic inflammation triggered by an infection. In 2016, the third international consensus definitions for sepsis and septic shock (Sepsis-3) were proposed [8]. According to these most recent definitions, sepsis is recognized as a life-threatening organ dysfunction caused by dysregulated host response to infection. AKI is one of the most frequently observed organ dysfunctions among sepsis cases, and septic AKI is associated with poor outcomes, including in-hospital mortality and a longer duration of hospitalization [4]. Septic AKI is associated with a higher mortality rate than both non-septic AKI and septic non-AKI, suggesting negative synergistic worsening effect of sepsis and AKI [5].

15.3 Septic AKI

According to the assumed pathophysiology of septic AKI, AKI is a syndrome with a broad spectrum of etiologies, including ischemia and/or hypoxia, inflammation, and direct tissue injury by nephrotoxins. These different etiologies may simultaneously contribute to the development of AKI. Depending on different clinical settings, such as post-cardiac surgery, low output syndrome in heart failure, contrast media exposure, and sepsis, the pathophysiology and clinical features of AKI will vary. As described above, sepsis is associated with the most severe AKI phenotype among different etiologies. Based on previous basic research using different animal models [9], several pathophysiological mechanisms for sepsis-induced AKI have been proposed (Table 15.1). Notably, considering the complexity of sepsis and AKI, a single mechanism cannot explain all clinical features of septic AKI. In this chapter, we summarize the current evidence regarding the epidemiology of septic AKI reported especially from Asian countries and provide a brief review of treatments against septic AKI.

15.4 Prevalence of AKI

In 2013, Susantitaphong and colleagues from the Acute Kidney Injury Advisory Group of the American Society of Nephrology conducted a meta-analysis to estimate the worldwide epidemiology of AKI [10]. In 2015, an updated

Table 15.1 Pathophysiological mechanisms of septic AKI

Pro-inflammatory state
Complement and coagulation activation
Protease activation (heparan sulfate, elastase)
Free radical formation
Pro-inflammatory cytokine production (IL-1, IL-6, IL-18, TNF-α)
Cell activation (neutrophil, macrophage, platelet, endothelial cell)
Anti-inflammatory state
Anti-inflammatory cytokine (IL-10)
Reduced phagocytosis and chemotaxis
Deranged immune function (lymphocyte apoptosis)
Dysregulation of microcirculation
Vasodilation-induced glomerular hypoperfusion
Abnormal blood flow within the peritubular capillary network

TNF tumor necrosis factor

meta-analysis, adding 313 new reports, was conducted by Mehta and colleagues for the International Society of Nephrology's 0by25 initiative in 2015 [11]. This updated meta-analysis included more than 77 million individuals. The pooled incidence of AKI in Asian regions was reported as follows: eastern Asia, 19.4%; southern Asia, 7.5%; southeastern Asia, 31.0%; and central Asia, 9.0%. Thus, the heterogeneity of different ethnicities, economics, and social and climate circumstances across Asian regions should be considered. Many studies conducted in developed Asian countries, such as Japan, Korea, Taiwan, Singapore, and Hong Kong, have reported the incidence of hospital-acquired AKI, particularly in ICU settings. As described above, sepsis is widely recognized as one of the most frequent causes of AKI in ICU settings [5–7].

Recently, the ISN Acute Kidney Failure 0by25 China Consortium conducted a nationwide survey of hospitalized individuals and evaluated the clinical features of hospital- and community-acquired AKI [12, 13]. This large cohort study revealed that the characteristics of community-acquired AKI in China were heterogenous, which varied by region, and were associated with environmental, economic, and medical resources. The complication of sepsis in hospital- and community-acquired AKI was 7.2% and 5.7%, respectively ($p < 0.01$). The Taiwan Consortium for Acute Kidney Injury and Renal Diseases also conducted a survey in combination with the ISN's 0by25 initiative survey [14]. Approximately 80% of enrolled patients were treated in ICUs, and the sepsis was the major contributing factor to AKI (52%). In total, 62 of 201 patients with AKI were treated by dialysis, and dialysis-requiring AKI was associated with a mortality rate of 29%.

15.5 Dialysis-Requiring AKI

Dialysis-requiring AKI (AKI-D) is the most severe type of AKI and is associated with the highest mortality rate. A retrospective cohort study using data from the Nationwide Inpatient Sample, the United States' nationally representative database of hospitalizations, has revealed that in-hospital mortality was significantly higher for AKI-D (22%) than for non-AKI-D (2%) [15]. Another nationwide retrospective study from Denmark has reported that 1-year mortality for AKI-D was 57% [16]. We previously conducted a nationwide retrospective analysis on AKI-D with data extracted from the Japanese Diagnosis Procedure Combination database for 2011 [17]. From a cohort of critically ill adult patients treated in ICUs, we identified 6478 patients with AKI treated with continuous renal replacement therapy (CRRT) out of 165,815 ICU patients (3.9%). The overall in-hospital mortality rate among the CRRT-treated AKI patients was 50.6%, and this rate increased to 51.7% when the cause of AKI was sepsis. Two Japanese studies with smaller cohorts have also reported mortality rates of AKI-D complicated with sepsis. In the first study, Yasuda and colleagues have evaluated 242 patients with AKI-D and have reported that sepsis (34%), cardiac shock (23%), and major surgery (12%) were the main contributing factors for AKI. Among these etiologies, sepsis was associated with the highest mortality rate (62%) [18]. In the second study, Nagata and colleagues have evaluated 343 patients with AKI-D treated with CRRT in ICUs [19]. They have reported that 49% of the enrolled patients had sepsis or septic shock as a contributing factor for AKI. Although the disease severity of septic AKI was higher than that of non-septic AKI, there was no difference in mortality between these two groups. However, because AKI-D is the most severe type of AKI, the effect of sepsis on mortality might not have been detected in this small sample size.

15.6 Pharmacological Treatment Against Septic AKI

Although a number of studies have elucidated the basic mechanisms underlying AKI and have reported several promising drugs against this condition [20–23], such findings have still not been successfully implemented in a clinical setting. A similar difficulty has been recognized regarding research on sepsis. In addition to inflammation and immunological dysregulation, several different mechanisms have been reported to contribute to sepsis, such as complement activation, hypoxic injury, and endothelial dysfunction [24–26]. Despite the critical knowledge provided by basic research, no specific drugs capable of significantly improving outcomes of patients with sepsis are currently available for clinical use.

15.7 Renal Replacement Therapy Initiation

Renal replacement therapy (RRT) is a definitive treatment for AKI. Emergent RRT initiation is necessary when life-threatening changes in fluids, electrolytes, or the acid-base balance occur. The decision to initiate RRT for severe AKI without such "absolute indications" is likely to be subjective owing to a lack of robust evidence. Two recent randomized controlled trials conducted in Europe (the AKIKI and ELAIN studies) have revealed discrepant results [27, 28]. In the AKIKI study, there was no significant difference between the early- and delayed-strategy groups in terms of 60-day mortality. Conversely, in the ELAIN study, there was significantly reduced 90-day mortality, recovered renal function, shorter duration of RRT, and reduced length of hospital stay in the early RRT initiation group. Differences in trial design are thought to explain these discrepant results [29, 30]. In 2018, the result of the IDEAL-ICU study was published [31]. This study assigned the patients with septic shock who had severe AKI to an early strategy for the initiation of RRT and a delayed strategy. There was no significant difference in overall mortality at 90 days between these two groups. In addition to patient characteristics and disease severity, the wide variation in clinical practice should be acknowledged for explaining this controversy. Therefore, both observational and interventional studies regarding RRT initiation timing will help to design larger multicenter randomized trials that can provide a more definitive conclusion on this issue.

15.8 Removal of Inflammatory Mediators

Because the remarkable elevation of many inflammatory mediators in the blood has been demonstrated in septic AKI, the removal of these substances via RRT technique is expected to improve the outcomes of septic AKI. There are several different ways to remove inflammatory mediators via RRT techniques, including high volume hemofiltration (HVHF), high cutoff (HCO) hemofiltration, plasma filtration, and adsorption. HCO hemofiltration using a polyflux hemofilter with a cutoff point of approximately 60 KD significantly reduces blood cytokine levels in patients with septic AKI; however, a remarkable albumin loss was also observed [32, 33]. HVHF reportedly decreased vasopressor requirements in human septic shock [34]. Despite preliminary data showing promising results, a multicenter randomized trial (the IVOIRE study) failed to demonstrate the advantages of HVHF for improving mortality in patients suffering from septic shock [35]. A recent systematic review that of four randomized controlled trials did not observe any advantage of HVHF on mortality in adults with severe sepsis and septic shock [36].

Cytokine removal with adsorption is another method to reduce cytokine blood levels via RRT technique. Cytokine removal with continuous hemodiafiltration

(CHDF) using a poly(methyl methacrylate) (PMMA) membrane hemofilter, which has a high cytokine-adsorbing capacity, has been primarily investigated in Japan [37]. IL-6 and high-mobility group box 1 (HMGB1) removal via PMMA is superior to that via cellulose acetate and polysulfone membranes [38, 39]. A clinical study with historical control showed better hemodynamics, urinary output, and survival rates for PMMA-CHDF than for polyacrylonitrile hemofilter-CHDF, which does not have cytokine-adsorbing capacity [40]. AN69 filter is known to have a high-adsorption capacity. Haase and colleagues have reported that high-adsorption continuous hemofiltration with AN69 is more effective than that with standard filter for decreasing pressor requirements and blood cytokine levels in patients suffering from septic shock [41]. In pigs under experimental septic shock, AN69ST (surface treated) filter has been shown to possess enhanced adsorption properties for removing cytokines and other humoral mediators [42]. This filter has recently been approved for clinical usage in Japan on the basis of results of a clinical trial [43]. A retrospective observational study using a Japanese health insurance claim database analyzed 2469 ICU patients and observed significant associations between AN69ST membrane usage and lower in-hospital mortality and a shorter length of ICU stay [44].

15.9 Endotoxin Adsorption Therapy Against Septic AKI

Endotoxin (lipopolysaccharide; LPS), a component of the Gram-negative bacterial cell wall, is recognized as the most potent microbial mediator in the pathogenesis of sepsis. Endotoxin plays a crucial role in triggering the overreaction of the immunological defense system in sepsis. Sepsis induces changes in systemic hemodynamics that evolve from an early hyperdynamic (“warm shock”) state to a late hypodynamic (“cold shock”) state. Similar hemodynamic changes have been reported after a large endotoxin injection [45]. These results support the notion that it is not the bacterial infection but rather the endotoxin that directly contributes to the pathophysiology of septic shock.

It has been demonstrated that PMX-B has both antibacterial and antiendotoxin properties. PMX-B can bind to lipid A located in the active center of endotoxin and neutralize its activity. Removal of circulating endotoxin via hemoperfusion through an immobilized PMX-B column (i.e., direct hemoperfusion with PMX-B column; PMX-DHP) is a technique developed in Japan. An extracorporeal device (Toraymyxin PMX-F; Toray, Tokyo, Japan) is used wherein the PMX-B is grafted on sorbent material and is able to provide the selective removal of circulating endotoxin. This device is clinically available in several countries in Europe and Asia. The use of this extracorporeal cartridge avoids the adverse side effects, such as nephrotoxicity and neurotoxicity, associated with the systemic administration of PMX-B.

Although endotoxin removal appears to be a promising strategy for treating sepsis caused by a Gram-negative bacterial infection, recent large multicenter randomized trials have observed no beneficial effect of PMX-DHP. A recent French

clinical trial (the ABDOMIX study) examined the effect of PMX therapy in 243 patients suffering from septic shock following an emergency surgery for peritonitis. Results showed no significant difference in 28-day mortality between the PMX and control groups [46]. Another large clinical trial conducted in North America (the EUPHRATES study) enrolled 450 patients suffering from septic shock. Polymyxin B hemoperfusion was not associated with a significant difference in mortality at 28 days among all participants or in the population with a MODS of more than 9 [47]. Post-hoc analysis of the EUPHRATES trial for the 194 patients with endotoxin activity assay (EAA) ≥ 0.6–0.89 [48] who completed two treatments showed some partial responses regarding mean arterial pressure, ventilator-free days, and mortality [49].

15.10 Evidence on PMX-DHP from Japan

Although PMX-DHP was developed in Japan, there are no randomized trials of PMX-DHP in Japan. However, several observational studies using big data have been conducted in Japan. We conducted two retrospective observational studies using data of inpatients from the Japanese National Claims Database (Table 15.2). The first study involved 590 propensity score-matched pairs, with and without postoperative PMX-DHP for the perforation of the lower gastrointestinal tract. This study found no benefit of PMX on survival, with the 28-day mortality of 17.1% and 16.3% in the PMX and control groups, respectively [50]. In contrast, the second study found a significant survival benefit of PMX-DHP for patients suffering from septic shock, who were started on CRRT for AKI. In particular, the 28-day mortality rate was 40.2% (393/978) in the PMX group, and 46.8% (458/978) in the control group (P = 0.003). Logistic regression analysis revealed a significant association between the use of PMX and decreased 28-day mortality [51]. Taken together, these

Table 15.2 Japanese observational studies on PMX-DHP using data from the Japanese National Claims Database

Author	Year	Patients	Inclusion	Exclusion	PMX-DHP 28-day mortality	Control 28-day mortality
Iwagami et al.	2014	Perforation of lower GI tract	Lower GI perforation, abdominal surgery, and pressor use on day 0	Death at day 0 or 1, PMX-DHP on day 2~	17% (103/597)	17% (105/597)
Iwagami et al.	2016	Severe AKI requiring CRRT	Sepsis, CRRT in ICU, pressor use on day 0	ESRD (chronic HD), cardiogenic s/o, IRRT before CRRT, PMX-DHP on day 2~	41% (542/1325)	47% (628/1325)

discrepant results suggest that it is the necessary to identify the populations sufficiently ill to response to PMX-DHP. In particular, patients with septic AKI requiring RRT may be a good target for PMX-DHP. Another Japanese observational study was conducted using the Japan Septic Disseminated Intravascular Coagulation (JSEPTIC DIC) study database. This study demonstrated that in-hospital mortality was significantly lower in the PMX-DHP group than in the control group (32.8% vs. 41.2%, $P = 0.042$) [52]. Notably, the evaluated population in this study showed a relatively high mortality rate that ranged from 30% to 40%.

15.11 Conclusion

This chapter summarizes the updated evidence regarding septic AKI in intensive care medicine. Considering the complexity and heterogeneous disease characteristics of both AKI and sepsis, it is difficult to identify the precise mechanisms underlying septic AKI, which makes it challenging to develop novel therapeutics against this condition.

Conflict of Interest None.

References

1. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012;2:138.
2. Inokuchi R, Hara Y, Yasuda H, Itami N, Terada Y, Doi K. Differences in characteristics and outcomes between community- and hospital-acquired acute kidney injury: a systematic review and meta-analysis. Clin Nephrol. 2017;88:167–82.
3. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, et al. Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA. 2005;294:813–8.
4. Bagshaw SM, George C, Bellomo R. Early acute kidney injury and sepsis: a multicentre evaluation. Crit Care. 2008;12:R47.
5. Neveu H, Kleinknecht D, Brivet F, Loirat P, Landais P. Prognostic factors in acute renal failure due to sepsis. Results of a prospective multicentre study. The French Study Group on Acute Renal Failure. Nephrol Dial Transplant. 1996;11:293–9.
6. Silvester W, Bellomo R, Cole L. Epidemiology, management, and outcome of severe acute renal failure of critical illness in Australia. Crit Care Med. 2001;29:1910–5.
7. Bagshaw SM, Laupland KB, Doig CJ, Mortis G, Fick GH, Mucenski M, et al. Prognosis for long-term survival and renal recovery in critically ill patients with severe acute renal failure: a population-based study. Crit Care. 2005;9:R700–9.
8. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315:801–10.
9. Doi K, Leelahavanichkul A, Yuen PS, Star RA. Animal models of sepsis and sepsis-induced kidney injury. J Clin Invest. 2009;119:2868–78.
10. Susantitaphong P, Cruz DN, Cerda J, Abulfaraj M, Alqahtani F, Koulouridis I, et al. World incidence of AKI: a meta-analysis. Clin J Am Soc Nephrol. 2013;8:1482–93.

11. Mehta RL, Cerda J, Burdmann EA, Tonelli M, Garcia-Garcia G, Jha V, et al. International Society of Nephrology's 0by25 initiative for acute kidney injury (zero preventable deaths by 2025): a human rights case for nephrology. Lancet. 2015;385:2616–43.
12. Yang L, Xing G, Wang L, Wu Y, Li S, Xu G, et al. Acute kidney injury in China: a cross-sectional survey. Lancet. 2015;386:1465–71.
13. Wang Y, Wang J, Su T, Qu Z, Zhao M, Yang L. Community-acquired acute kidney injury: a nationwide survey in China. Am J Kidney Dis. 2017;69:647–57.
14. Pan HC, Wu PC, Wu VC, Yang YF, Huang TM, Shiao CC, et al. A nationwide survey of clinical characteristics, management, and outcomes of acute kidney injury (AKI)—patients with and without preexisting chronic kidney disease have different prognoses. Medicine. 2016;95:e4987.
15. Hsu RK, McCulloch CE, Heung M, Saran R, Shahinian VB, Pavkov ME, et al. Exploring potential reasons for the temporal trend in dialysis-requiring AKI in the United States. Clin J Am Soc Nephrol. 2016;11:14–20.
16. Carlson N, Hommel K, Olesen JB, Soja AM, Vilsboll T, Kamper AL, et al. Trends in one-year outcomes of dialysis-requiring acute kidney injury in Denmark 2005-2012: a population-based nationwide study. PLoS One. 2016;11:e0159944.
17. Iwagami M, Yasunaga H, Noiri E, Horiguchi H, Fushimi K, Matsubara T, et al. Current state of continuous renal replacement therapy for acute kidney injury in Japanese intensive care units in 2011: analysis of a national administrative database. Nephrol Dial Transplant. 2015;30:988–95.
18. Yasuda H, Kato A, Fujigaki Y, Hishida A. Incidence and clinical outcomes of acute kidney injury requiring renal replacement therapy in Japan. Ther Apher Dial. 2010;14:541–6.
19. Nagata I, Uchino S, Tokuhira N, Ohnuma T, Namba Y, Katayama S, et al. Sepsis may not be a risk factor for mortality in patients with acute kidney injury treated with continuous renal replacement therapy. J Crit Care. 2015;30:998–1002.
20. Jo SK, Rosner MH, Okusa MD. Pharmacologic treatment of acute kidney injury: why drugs haven't worked and what is on the horizon. Clin J Am Soc Nephrol. 2007;2:356–65.
21. Zarjou A, Agarwal A. Sepsis and acute kidney injury. J Am Soc Nephrol. 2011;22:999–1006.
22. Sharfuddin AA, Molitoris BA. Pathophysiology of ischemic acute kidney injury. Nat Rev Nephrol. 2011;7:189–200.
23. Bonventre JV, Yang L. Cellular pathophysiology of ischemic acute kidney injury. J Clin Invest. 2011;121:4210–21.
24. Ward PA. New approaches to the study of sepsis. EMBO Mol Med. 2012;4:1234–43.
25. Huet O, Dupic L, Harrois A, Duranteau J. Oxidative stress and endothelial dysfunction during sepsis. Front Biosci (Landmark Ed). 2011;16:1986–95.
26. Lee WL, Slutsky AS. Sepsis and endothelial permeability. N Engl J Med. 2010;363:689–91.
27. Gaudry S, Hajage D, Schortgen F, Martin-Lefevre L, Pons B, Boulet E, et al. Initiation strategies for renal-replacement therapy in the intensive care unit. N Engl J Med. 2016;375:122–33.
28. Zarbock A, Kellum JA, Schmidt C, Van Aken H, Wempe C, Pavenstadt H, et al. Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: the ELAIN randomized clinical trial. JAMA. 2016;315:2190–9.
29. Bagshaw SM, Lamontagne F, Joannidis M, Wald R. When to start renal replacement therapy in critically ill patients with acute kidney injury: comment on AKIKI and ELAIN. Crit Care. 2016;20:245.
30. Komaru Y, Doi K. Early or delayed initiation of renal replacement therapy for critically ill patients-do we know the right time? J Thorac Dis. 2016;8:E1006–9.
31. Barbar SD, Clere-Jehl R, Bourredjem A, Hernu R, Montini F, Bruyere R, et al. Timing of renal-replacement therapy in patients with acute kidney injury and Sepsis. N Engl J Med. 2018;379:1431–42.
32. Morgera S, Slowinski T, Melzer C, Sobottke V, Vargas-Hein O, Volk T, et al. Renal replacement therapy with high-cutoff hemofilters: impact of convection and diffusion on cytokine clearances and protein status. Am J Kidney Dis. 2004;43:444–53.

33. Morgera S, Haase M, Kuss T, Vargas-Hein O, Zuckermann-Becker H, Melzer C, et al. Pilot study on the effects of high cutoff hemofiltration on the need for norepinephrine in septic patients with acute renal failure. Crit Care Med. 2006;34:2099–104.
34. Cole L, Bellomo R, Journois D, Davenport P, Baldwin I, Tipping P. High-volume haemofiltration in human septic shock. Intensive Care Med. 2001;27:978–86.
35. Joannes-Boyau O, Honore PM, Perez P, Bagshaw SM, Grand H, Canivet JL, et al. High-volume versus standard-volume haemofiltration for septic shock patients with acute kidney injury (IVOIRE study): a multicentre randomized controlled trial. Intensive Care Med. 2013;39:1535–46.
36. Borthwick EM, Hill CJ, Rabindranath KS, Maxwell AP, McAuley DF, Blackwood B. High-volume haemofiltration for sepsis in adults. Cochrane Database Syst Rev. 2017;1:CD008075.
37. Hirasawa H, Oda S, Nakamura M, Watanabe E, Shiga H, Matsuda K. Continuous hemodiafiltration with a cytokine-adsorbing hemofilter for sepsis. Blood Purif. 2012;34:164–70.
38. Hirasawa H, Oda S, Matsuda K. Continuous hemodiafiltration with cytokine-adsorbing hemofilter in the treatment of severe sepsis and septic shock. Contrib Nephrol. 2007;156:365–70.
39. Yumoto M, Nishida O, Moriyama K, Shimomura Y, Nakamura T, Kuriyama N, et al. In vitro evaluation of high mobility group box 1 protein removal with various membranes for continuous hemofiltration. Ther Apher Dial. 2011;15:385–93.
40. Matsuda K, Moriguchi T, Harii N, Goto J. Comparison of efficacy between continuous hemodiafiltration with a PMMA membrane hemofilter and a PAN membrane hemofilter in the treatment of a patient with septic acute renal failure. Transfus Apher Sci. 2009;40:49–53.
41. Haase M, Silvester W, Uchino S, Goldsmith D, Davenport P, Tipping P, et al. A pilot study of high-adsorption hemofiltration in human septic shock. Int J Artif Organs. 2007;30:108–17.
42. Rimmele T, Assadi A, Cattenoz M, Desebbe O, Lambert C, Boselli E, et al. High-volume haemofiltration with a new haemofiltration membrane having enhanced adsorption properties in septic pigs. Nephrol Dial Transplant. 2009;24:421–7.
43. Shiga H, Hirasawa H, Nishida O, Oda S, Nakamura M, Mashiko K, et al. Continuous hemodiafiltration with a cytokine-adsorbing hemofilter in patients with septic shock: a preliminary report. Blood Purif. 2014;38:211–8.
44. Doi K, Iwagami M, Yoshida E, Marshall MR. Associations of polyethylenimine-coated AN69ST membrane in continuous renal replacement therapy with the intensive care outcomes: observations from a claims database from Japan. Blood Purif. 2017;44:184–92.
45. Taveira da Silva AM, Kaulbach HC, Chuidian FS, Lambert DR, Suffredini AF, Danner RL. Brief report: shock and multiple-organ dysfunction after self-administration of Salmonella endotoxin. N Engl J Med. 1993;328:1457–60.
46. Payen DM, Guilhot J, Launey Y, Lukaszewicz AC, Kaaki M, Veber B, et al. Early use of polymyxin B hemoperfusion in patients with septic shock due to peritonitis: a multicenter randomized control trial. Intensive Care Med. 2015;41:975–84.
47. Dellinger RP, Bagshaw SM, Antonelli M, Foster DM, Klein DJ, Marshall JC, et al. Effect of targeted polymyxin B hemoperfusion on 28-day mortality in patients with septic shock and elevated endotoxin level: the EUPHRATES randomized clinical trial. JAMA. 2018;320:1455–63.
48. Marshall JC, Walker PM, Foster DM, Harris D, Ribeiro M, Paice J, et al. Measurement of endotoxin activity in critically ill patients using whole blood neutrophil dependent chemiluminescence. Crit Care. 2002;6:342–8.
49. Klein DJ, Foster D, Walker PM, Bagshaw SM, Mekonnen H, Antonelli M. Polymyxin B hemoperfusion in endotoxemic septic shock patients without extreme endotoxemia: a post hoc analysis of the EUPHRATES trial. Intensive Care Med. 2018;44:2205–12.
50. Iwagami M, Yasunaga H, Doi K, Horiguchi H, Fushimi K, Matsubara T, et al. Postoperative polymyxin B hemoperfusion and mortality in patients with abdominal septic shock: a propensity-matched analysis. Crit Care Med. 2014;42:1187–93.
51. Iwagami M, Yasunaga H, Noiri E, Horiguchi H, Fushimi K, Matsubara T, et al. Potential survival benefit of polymyxin B hemoperfusion in septic shock patients on continuous renal replacement therapy: a propensity-matched analysis. Blood Purif. 2016;42:9–17.
52. Nakamura Y, Kitamura T, Kiyomi F, Hayakawa M, Hoshino K, Kawano Y, et al. Potential survival benefit of polymyxin B hemoperfusion in patients with septic shock: a propensity-matched cohort study. Crit Care. 2017;21:134.

Chapter 16
Nondialytic Supportive Management of AKI

Hiroyuki Yamada

Abstract Acute kidney injury (AKI) is associated with serious complications such as lethal arrhythmia, lung edema, and electrolyte disorder. For the management of AKI, it is imperative to identify and remove the cause of AKI. Also, it is essential to create a non-damaging environment for kidneys such as non-nephrotoxic drugs, appropriate intravascular volume, and drug dose adjustment. So far, many randomized controlled trials have examined the AKI prevention or treatment effect of various interventions, e.g., dopamine, diuretics, and natriuretic peptide. While most of those interventions did not have a decisive impact on clinical practices, some of them can be beneficial in a limited situation. Further research is expected in this field.

Keywords Acute kidney injury · AKI · Nondialytic management · AKI management

16.1 Introduction

Acute kidney injury (AKI) is a common comorbidity in critically ill patients and is associated with unfavorable clinical outcomes [1]. To fight with AKI, it is essential to early make an appropriate intervention for patients with developed AKI or at-risk AKI [2]. This chapter reviews the general management of AKI and the therapeutic interventions except for renal replacement therapy (RRT).

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16.2 General Management of AKI

16.2.1 Identifying the Cause of AKI

One of the reasons for the poor prognosis is that AKI causes various complications. In particular, hypervolemia, electrolyte abnormalities, and acid–base balance disturbance are life-threatening conditions, because they induce lethal arrhythmia, decompensated heart failure, or cold shock. Therefore, after finding AKI patients, what to do first is to evaluate the severity with KDIGO AKI criteria and the existence of fatal complications [3]. If the complications are difficult to immediately control with pharmaceutical interventions immediately, you should not hesitate to apply RRT to the patients.

16.2.2 Resolution of Cause and Monitoring

The next important task for AKI management is to resolve the cause of AKI. Although the below sections of this chapter mention additional pharmacotherapy for AKI, it is needless to say that the direct intervention against the cause of AKI is more important than any medication. For example, when there is a possibility of rapidly progressive glomerulonephritis in some patients, it is necessary to consult nephrologists and consider the administration of immunosuppressors. If the patient has a typical symptom of drug-induced kidney injury, such as rash, arthralgias, and eosinophilia, it is essential to check whether the patient took the suspected drugs or not (Table 16.1) [4]. Therefore, we need to identify the reason why the patients developed AKI or were at risk of AKI. For the detail of the cause of AKI, please refer to Part I, Chap. 2.

In tandem with the resolution of the cause, we also need to monitor serum creatinine and urine output intermittently and carefully. Although the frequency and duration of monitoring are dependent on patient risk, exposure, and clinical course, to prevent further damage, it is important to grasp the speed of AKI development. Also, it could be helpful for the expectation of the future clinical course and prognosis.

16.2.3 Maintaining Renal Perfusion

Generally, to recover the injured kidney, it is indispensable to create non-damaging environments for the kidney. As mentioned in the previous chapter, hypovolemia and hypotension induce pre-renal injury, and hypervolemia also increases the risk of respiratory failure. Therefore, it is vital to carefully manage the total fluid balance

Table 16.1 Common medications associated with acute kidney injury

Pathoetiology		Medication	Treatment
Prerenal injury		Diuretics, NSAIDs, ACE inhibitors, calcineurin inhibitor (ciclosporin, tacrolimus), radiocontrast media, interleukin-2, vasodilators (hydralazine, calcium-channel blockers, minoxidil, diazoxide)	Suspend or discontinue medication, volume replacement as clinically indicated
Intrinsic renal injury	Thrombotic microangiopathy	Calcineurin inhibitor (ciclosporin, tacrolimus), conjugated estrogens, quinine, 5-fluorouracil, ticlopidine, clopidogrel, valaciclovir, gemcitabine, bleomycin	Discontinue medication, supportive care, plasmapheresis if indicated
	Cholesterol emboli	Heparin, warfarin, streptokinase	Discontinue medication, supportive care, plasmapheresis if indicated
	Tubular toxicity	Aminoglycosides, radiocontrast media, cisplatin, nedaplatin, methoxyflurane, outdated tetracycline, amphotericin B, cephaloridine, streptozocin, tacrolimus, carbamazepine, mithramycin, quinolones, foscarnet, pentamidine, intravenous gammaglobulin, fosfamide, zoledronate, cidofovir, adefovir, tenofovir, mannitol, dextran, hydroxyethylstarch	Drug discontinuation, supportive care
	Rhabdomyolysis	Lovastatin, ethanol, codeine, barbiturates, diazepam	Drug discontinuation, supportive care
	Severe hemolysis	Quinine, quinidine, sulfonamides, hydralazine, triamterene, nitrofurantoin, mephenytoin	Drug discontinuation, supportive care
	Immune-mediated interstitial inflammation	Penicillin, methicillin ampicillin, rifampin, sulfonamides, thiazides, cimetidine, phenytoin, allopurinol, cephalosporins, cytosine arabinoside, furosemide, interferon, NSAIDs, ciprofloxacin, clarithromycin, telithromycin, rofecoxib, pantoprazole, omeprazole, atazanavir	Discontinue medication, supportive care
	Glomerulonephropathy	Gold, penicillamine, captopril, NSAIDs, lithium, mefenamate, fenoprofen, mercury, interferon-α, pamidronate, fenclofenac, tolmetin, foscarnet	Discontinue medication, supportive care

(continued)

Table 16.1 (continued)

Pathoetiology		Medication	Treatment
Obstruction	Intratubular: crystalluria and/or renal lithiasis	Aciclovir, methotrexate, sulfanilamide, triamterene, indinavir, foscarnet, ganciclovir	Discontinue medication, supportive care
	Ureteral; secondary to retroperitoneal fibrosis	Methysergide, ergotamine, dihydroergotamine, methyldopa, pindolol, hydralazine, atenolol	Discontinue medication, decompress ureteral obstruction by intrarenal stenting or percutaneous nephrostomy

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of patients with at-risk AKI and developed AKI. Now, there are various methods for assessing the intravascular volume, e.g., physical examination, sonography, stroke volume variation, and passive leg raising. By making the most of them, the intravascular volume of those patients should be kept to normovolemia. Additionally, if the oliguria is not responsive to fluid resuscitation or diuretics, RRT should be taken into consideration.

Monitoring blood pressure is also essential for renal protection or recovery. If the hypotension is refractory to fluid resuscitation, the administration of vasopressors such as noradrenaline and vasopressin should be initiated. As some guidelines about sepsis recommend, mean arterial pressure (MAP) should be targeted to more than 65 mmHg [5, 6]. In particular, patients with chronic hypertension sometimes require higher MAP to maintain autoregulation of renal blood flow [7]. Indeed, a recent RCT indicated that higher target MAP for septic shock patients with chronic hypertension significantly reduced the incidence of doubling in serum creatinine and RRT requirements [8]. Therefore, the target MAP should be adjusted depending on the clinical course and the medical history of every patient.

16.2.4 Checking Nephrotoxic Drug and Dose Adjustment

Treatments for critically ill patients often require the administration of many kinds of drugs. Unfortunately, some of the commonly used drugs in the acute phase of severe illness contain some nephrotoxic agents. Therefore, these drugs might induce further damage against injured kidney. If possible, it is desirable not to administer nephrotoxic agents and to consider alternative drugs. For instance, NSAIDs should not be the first choice antipyretic for AKI patients, because NSAIDs are one of the

Table 16.2 Injection drug which requires dose adjustment (or cessation) for acute kidney injury in ICU

	Generic name
Antiarrhythmic	Cibenzoline, disopyramide, flecainide, mexiletine, pilsicainide, procainamide
Antibiotics	Most of antibiotics need dose adjustment in AKI, except azithromycin, ceftriaxone, chloramphenicol, clindamycin, minocycline, tigecycline
Antifungals	Amphotericin b, fluconazole, fosfluconazole, voriconazole
Antiepileptics	Phenobarbital
Antivirals	Acyclovir, foscarnet, gancyclovir
Cardiotonic	Digoxin, milrinone
Hemostatic	Tranexamic acid
H2-blocker	Cimetidine, nizatidine, famotidine, ranitidine, rozatidine
Immunosuppressant	Cyclosporine, gusperimus, tacrolimus
NSAIDs	Flurbiprofen, sulpyrine
Opioid	Morphine

NSAIDs nonsteroidal anti-inflammatory drugs

major reasons for drug-induced kidney injury. As some studies indicated that acetaminophen is relatively safer for kidneys than NSAIDs, alternative drugs should be taken into consideration [9]. Meanwhile, it is sometimes unavoidable to administer some of the drugs which might induce renal failure. In such a case, it needs adjusting the dose of those medications, depending on the remaining renal function. Table 16.2 lists the commonly used injection drugs in the intensive care unit (ICU) which requires dose adjustment for AKI patients.

16.3 Pharmacological and Non-pharmacological Interventions

16.3.1 Diuretics

Since volume overload is one of the major symptoms of AKI, physicians need to use diuretics effectively for the management of total fluid balance. Furosemide is one of the widely used diuretics in many clinical situations. It inhibits the sodium reabsorption and exerts a diuretic effect by inhibiting the Na-K-2Cl co-transporter in the thick ascending limb of the loop of Henle. Besides, furosemide also has some theoretical background on the positive effect of AKI. Some experimental data showed that furosemide might improve the oxygen supply and demand balance by inhibiting Na-K-Cl2 co-transporter activity and increasing prostaglandin production and blood flow [10, 11]. Furthermore, ensuring a diuretic effect, loop diuretics can prevent the nephron obstruction induced by cell shedding [12].

Based on the above hypothesis, many clinical scientists performed an RCT and examined the effect of furosemide for AKI. Ho et al. synthesized the results of RCTs comparing furosemide with placebo [13]. In their analysis, the administration of furosemide did not improve the induction of RRT (Risk Ratio [RR] = 1.02, [0.90–1.16], $P = 0.73$) and mortality rate (RR = 1.12, [0.93–1.34], $P = 0.23$) for patients with at-risk AKI and developed AKI. After the meta-analysis, Bagshaw et al. conducted a further RCT for developed AKI patients comparing furosemide with 0.9% saline placebo [14]. This RCT also did not indicate the positive effect of furosemide in the rate of kidney recovery (29.7% vs. 42.9%, $P = 0.3$) and RRT (27.0% vs. 28.6%, $P = 0.8$). These results imply that furosemide should not be routinely administered for the management of AKI.

On the other hand, as furosemide occasionally makes it possible to increase urine output of oliguric AKI patients. It could help to correct fluid overload and electrolyte imbalance. Therefore, although these clinical trials provided strong evidence against the efficacy of furosemide, the recent AKI guidelines did not deny the administration of furosemide only for correcting total fluid imbalance and electrolyte abnormalities [3, 15, 16].

Mannitol is also a commonly used diuretic in many clinical situations, e.g., neurosurgery or severe brain infarction. As some clinical trials indicated the positive effect of AKI, Yang et al. synthesized the results of the RCTs comparing mannitol with placebo for patients at-risk of AKI [17]. Their analysis did not demonstrate evident effectiveness for the prevention of AKI. In subsequent RCTs, the mannitol groups also failed to exhibit significant improvement in their RRT requirements [18].

16.3.2 Dopamine

Once, low-dose dopamine was widely used as a renoprotective vasopressor [19, 20]. Preceding basic research also indicated a positive effect of low-dose dopamine. These researches demonstrated that when dopamine is administered at a dose of <5 μg/kg/min for healthy persons, it causes renovascular dilatation and natriuresis, [21–23]. Indeed, the recent meta-analysis which was performed by Friedrich et al. showed that urine output and creatinine clearance were increased only on day 1 of dopamine administration [24].

However, this effect of low-dose dopamine does not continue during the whole period of administration. The recent meta-analysis demonstrated that since two days after the start of the administration, the urine output and creatinine clearance were not significantly higher in low-dose dopamine group [24]. Besides, this meta-analysis did not show a positive effect on a hard outcome such as the induction rate of RRT and mortality rate [24]. Likewise, some new RCTs of low-dose dopamine also did not report the improvement of hard outcomes [25, 26]. Furthermore, using a physiological approach, Lauschke et al. indicated that low-dose dopamine could

worsen renal perfusion in patients with developed AKI [27]. From the above clinical and physiological analysis, the recent AKI guidelines recommended not using low-dose dopamine for the prevention and treatment of AKI [3, 15, 16].

In terms of the treatment of septic shock, which is one of the leading causes of AKI, dopamine administration is associated with a greater mortality rate and a high incidence of severe adverse events [28]. The recent guidelines for sepsis also recommend against using dopamine as a first-choice drug of vasopressors [5, 6]. Hence, the use of low-dose dopamine should be suggested just only for patients with absolute or relative bradycardia [5, 29].

16.3.3 Fenoldopam

Fenoldopam is a dopamine agonist that causes peripheral vasodilation via stimulation of dopamine 1 receptors [30]. In the kidney, it induces the decrease in renal vascular resistance accompanied by increases in renal blood flow and glomerular filtration rate and increases in sodium excretion and urine volume [31]. Therefore, as it could be theoretically effective for the prevention and treatment of AKI, some RCTs were performed to examine the effect.

Regarding the prevention effect of fenoldopam, so far, four meta-analyses were reported [32–35]. The most recent meta-analysis focused on cardiac surgery patients and analyzed the data of 1107 adult patients from 7 RCTs. It indicated that the use of fenoldopam reduced the incidence of AKI (RR = 0.42, [0.26–0.69], $P = 0.0006$). However, it exhibited a higher rate of hypotension (RR = 1.76, [1.29–2.39], $P = 0.0003$) [35]. Also, it did not significantly reduce the RRT requirement or hospital mortality [35]. Meanwhile, the previous meta-analysis included not only cardiac surgery but also major surgery such as liver transplant and nephrectomy [34]. This meta-analysis also showed that fenoldopam had no beneficial impact on RRT requirements (OR = 0.27, [0.06–1.19], $P = 0.11$) and hospital mortality (OR = 1.0, [0.14–7.37], $P = 0.60$) although it could reduce the incidence of postoperative AKI (OR = 0.46, [0.27–0.79], $P = 0.004$) [34]. Hence, these meta-analyses did not strongly support the use of fenoldopam for the prevention of AKI.

On the other hand, the treatment effect of fenoldopam for developed AKI patients was also evaluated in two multicenter RCTs [36, 37]. Tumlin et al. conducted a first multicenter RCT for the patients with developed AKI whose serum creatinine level increased to 50% greater than admission levels within 24 h [36]. They randomly assigned 155 ICU patients to receive fenoldopam or placebo. They could not show the significant difference between two groups in the incidence of RRT requirement (16.25% vs. 25.3%, $P = 0.163$) and 21-day mortality rate (13.8% vs. 25.3%, $P = 0.068$) [36]. Bove et al. also examined the treatment effect of fenoldopam, performing an RCT with much larger sample size; 667 early AKI patients admitted to ICU after cardiac surgery [37]. Likewise, they could not demonstrate the beneficial effect of the administration for the RRT rate (20.4% vs. 18.2%, $P = 0.47$) and 30-day mortality rate (23.1% vs. 22.5%, $P = 0.86$) [36].

Indeed, KDIGO AKI guidelines did not recommend using fenoldopam for the management of AKI [3]. After the issuance of the guideline, the recent meta-analysis and RCT also showed the uselessness of fenoldopam for AKI prevention and treatment [34, 35, 37].

16.3.4 Natriuretic Peptide

Natriuretic peptides, atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), are endogenous hormones that the heart releases in response to myocardial stretch [38]. By guanylyl cyclase A receptor activation, natriuretic peptides induce pleiotropic actions, such as natriuresis, vasodilation, and suppression of circulating renin, angiotensin II, and aldosterone [38, 39]. Since the pharmacological effects of these natriuretic peptides could be effective in a variety of cardiovascular diseases, the administration of ANP (carperitide in Japan) and BNP (nesiritide in the USA) has been approved for the management of heart failure [40]. Besides, these pharmacological effect could also be beneficial for AKI. Therefore, to elucidate the therapeutic impact on AKI, many RCTs have been performed until now.

Regarding ANP, at first, some RCTs for patients with acute renal failure were conducted in the 1990s [41–43]. As in these RCTs, the dose of ANP was relatively high (0.08–0.20 ng/kg/min), the cases of accidental hypotension were significantly larger in the ANP administration group. Also, these results did not demonstrate a decisive improvement of hard outcomes such as mortality rate and reduction in RRT. Hence, to prevent the accidental hypotension, the recent RCTs have focused on low-dose of ANP ($\leq$0.05 ng/kg/min). Yamada et al. performed a meta-analysis about the renal-protective effect of low-dose ANP for AKI [44]. Their meta-analysis showed that low-dose ANP significantly decreased the incidence of AKI (RR = 0.51, [0.36–0.72], $P = 0.0001$) and RRT requirements (RR = 0.17, [0.04–0.64], $P = 0.009$) for patients at risk of AKI. In addition, low-dose ANP also reduced RRT requirements for patients with developed AKI (RR = 0.17, [0.04–0.64], $P = 0.009$). However, they also advocated that those results were not conclusive, because the risk of bias in most of the included studies is not low, and the sample size was not enough for demonstrating the positive effect.

Meanwhile, as for BNP, some meta-analysis for decompensated heart failure patients examined the effectiveness of kidney-associated outcomes [45–47]. In the most recent meta-analysis for the comparison between nesiritide and control treatment, including 38,064 patients from 22 RCTs, the mortality rate was not improved in the nesiritide group (RR = 1.04, [0.79–1.38], $P = 0.76$) [47]. Also, there was no significant difference between the two groups in terms of the need for dialysis, serum creatinine, and creatinine clearance. Furthermore, the risk ratio of hypotension and bradycardia was significantly higher in the nesiritide group. Unfortunately, this analysis did not demonstrate the efficacy and safety of nesiritide for decompensated heart failure patients.

The effect of nesiritide for cardiovascular surgery patients has also been examined. Mitaka et al. performed a meta-analysis about the effect for these patients [48]. Although their results showed that nesiritide infusion significantly reduced the length of ICU stay and hospital stay, the renal outcome such as RRT requirements or dialysis survival rate was not reported due to insufficient data. After the publication of this analysis, Costello et al. newly reported the result of his RCT for Fontan surgery patients [18]. There does not appear to be the difference between the nesiritide group and the placebo group in terms of RRT requirements or a threefold increase in serum creatinine.

Considering the results of these clinical trials, it is not sufficiently clarified whether natriuretic peptides could be useful in the management of AKI or not.

16.3.5 Remote Ischemic Preconditioning

Remote ischemic preconditioning (RIPC) is a non-pharmacological approach induced by several cycles of transient nonlethal ischemia and reperfusion to one remote organ or tissue [49]. This method is performed by simply inflating and deflating a standard blood-pressure cuff placed on the upper arm or thigh to induce transient ischemia and reperfusion [50]. Although the molecular mechanism of RIPC is not entirely understood, many clinical trials investigated the efficacy of various organs because of non-invasiveness and low cost of the intervention [51].

The prevention effect for AKI of this intervention was also evaluated in many RCTs [51]. Menting et al. conducted a meta-analysis and synthesized the results of these RCTs which examined kidney-associated outcomes [52]. Their analysis did not demonstrate the positive effect of RIPC for RRT requirements (RR = 3.47, [0.55–21.76], $P = 0.70$) and that the AKI prevention effect of RIPC was not slightly significant (RR = 0.76, [0.57–1.00], $P = 0.05$). After the meta-analysis, the two large RCTs reported the effect of RIPC [53, 54]. In both studies, there were no significant differences in RRT requirements between RIPC and the control group. Meanwhile, while in the study of Kim et al. RIPC significantly reduced the incidence of AKI (30% vs. 48%, $P = 0.023$), Song et al. reported that RIPC did not decrease the incidence of AKI (16% vs. 19%, $P = 0.47$). From these results, RIPC has little possibility of reducing the RRT requirement. Also, the effect of RIPC on the incidence of AKI remains controversial.

16.3.6 Statin

Since statin is called HMG-CoA reductase inhibitors, it could downregulate the LDL-cholesterol production and has been widely used for primary or secondary prevention of cardiovascular diseases [55]. Also, as some experimental studies showed that statin has anti-inflammatory, antioxidant, and antithrombotic effects,

many RCTs were conducted to investigate whether the stain is not effective for AKI management or not [56]. Particularly, regarding the prevention effect for cardiovascular surgery patients, three large RCTs for cardiac surgery patients were published in 2016 [57–59]. Neither of these RCTs indicated the prevention effect of statin for cardiac surgery-associated AKI (CSA-AKI). After that, some meta-analyses which included these RCTs have been also published [60, 61]. These analyses did not demonstrate that the perioperative administration of statin in cardiac surgery reduced the incidence of CSA-AKI.

On the other hand, as for the prevention effect of statin for contrast-induced nephropathy (CIN), many RCTs have also been published until now since Zhang reported a first RCT comparing statin with placebo [62]. Wang et al. synthesized the data of these RCTs and analyzed the effect of statin for CIN with trial sequential analysis [63]. This analysis showed that the incidence of CIN in the statin group was significantly lower than the control group (RR = 0.46, [0.36–0.58], $P < 0.00001$), and that trial sequential analysis also supported the synthesized results. Likewise, Marenzi et al. did a subgroup analysis only for acute coronary syndrome (ACS) patients [64]. Their analysis indicated that statin could significantly reduce the incidence of CIN even for ACS patients (RR = 0.37, [0.25–0.55], $P < 0.00001$). Now, as some new RCTs which examine the efficacy of statin for ACS patients are currently underway (ClinicalTrials.gov identifier: NCT03526367, NCT01870804), further research is expected.

References

1. Murugan R, Kellum JA. Acute kidney injury: what's the prognosis? Nat Rev Nephrol. 2011;7(4):209–17.
2. Mohsenin V. Practical approach to detection and management of acute kidney injury in critically ill patient. J Intensive Care. 2017;5:57.
3. Group KAW. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012;2:1–138.
4. Choudhury D, Ahmed Z. Drug-associated renal dysfunction and injury. Nat Clin Pract Nephrol. 2006;2(2):80–91.
5. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med. 2017;43(3):304–77.
6. Nishida O, Ogura H, Egi M, Fujishima S, Hayashi Y, Iba T, Imaizumi H, Inoue S, Kakihana Y, Kotani J, et al. The Japanese clinical practice guidelines for management of sepsis and septic shock 2016 (J-SSCG 2016). J Intensive Care. 2018;6:7.
7. Post EH, Vincent JL. Renal autoregulation and blood pressure management in circulatory shock. Crit Care. 2018;22(1):81.
8. Asfar P, Meziani F, Hamel J-F, Grelon F, Megarbane B, Anguel N, Mira J-P, Dequin P-F, Gergaud S, Weiss N, et al. High versus low blood-pressure target in patients with septic shock. N Engl J Med. 2014;370(17):1583–93.
9. Hiragi S, Yamada H, Tsukamoto T, Yoshida K, Kondo N, Matsubara T, Yanagita M, Tamura H, Kuroda T. Acetaminophen administration and the risk of acute kidney injury: a self-controlled case series study. Clin Epidemiol. 2018;10:265–76.

10. Janssen BJ, Struyker-Boudier HA, Smits JF. Acute arteriolar vasoconstriction following furosemide in conscious spontaneously hypertensive rats. Eur J Pharmacol. 1989;170(1–2):1–9.
11. Gerber JG, Nies AS. Furosemide-induced vasodilation: importance of the state of hydration and filtration. Kidney Int. 1980;18(4):454–9.
12. Kantariia VA, Timirbulatov RA, Dvoinikova EV. [Mechanism of the therapeutic effect of furosemide and mannitol in hemorrhagic shock and developing acute renal insufficiency]. Farmakol Toksikol. 1979;42(1):47–51.
13. Ho KM, Power BM. Benefits and risks of furosemide in acute kidney injury. Anaesthesia. 2010;65(3):283–93.
14. Bagshaw SM, Gibney RTN, Kruger P, Hassan I, McAlister FA, Bellomo R. The effect of low-dose furosemide in critically ill patients with early acute kidney injury: a pilot randomized blinded controlled trial (the SPARK study). J Crit Care. 2017;42:138–46.
15. National Institute for Health and Clinical Excellence: Guidance. NICE clinical guideline 169: acute kidney injury: prevention, detection and management of acute kidney injury up to the point of renal replacement therapy; 2013.
16. Doi K, Nishida O, Shigematsu T, Sadahiro T, Itami N, Iseki K, Yuzawa Y, Okada H, Koya D, Kiyomoto H, et al. The Japanese clinical practice guideline for acute kidney injury 2016. J Intensive Care. 2018;6:48.
17. Yang B, Xu J, Xu F, Zou Z, Ye C, Mei C, Mao Z. Intravascular administration of mannitol for acute kidney injury prevention: a systematic review and meta-analysis. PLoS One. 2014;9(1):e85029.
18. Costello JM, Dunbar-Masterson C, Allan CK, Gauvreau K, Newburger JW, McGowan FX Jr, Wessel DL, Mayer JE Jr, Salvin JW, Dionne RE, et al. Impact of empiric nesiritide or milrinone infusion on early postoperative recovery after Fontan surgery: a randomized, double-blind, placebo-controlled trial. Circ Heart Fail. 2014;7(4):596–604.
19. Denton MD, Chertow GM, Brady HR. "Renal-dose" dopamine for the treatment of acute renal failure: scientific rationale, experimental studies and clinical trials. Kidney Int. 1996;50(1):4–14.
20. Pichler M, Kleinberger G, Kotzaurek R, Pall H, Szeless S. [Clinical results with dopamine in acute renal failure (author's transl)]. Wien Klin Wochenschr. 1976;88(2):72–74.
21. Steinhausen M, Weis S, Fleming J, Dussel R, Parekh N. Responses of in vivo renal microvessels to dopamine. Kidney Int. 1986;30(3):361–70.
22. Olsen NV, Hansen JM, Ladefoged SD, Fogh-Andersen N, Leyssac PP. Renal tubular reabsorption of sodium and water during infusion of low-dose dopamine in normal man. Clin Sci (Lond). 1990;78(5):503–7.
23. Carcoana OV, Hines RL. Is renal dose dopamine protective or therapeutic? Yes. Crit Care Clin. 1996;12(3):677–85.
24. Friedrich JO, Adhikari N, Herridge MS, Beyene J. Meta-analysis: low-dose dopamine increases urine output but does not prevent renal dysfunction or death. Ann Intern Med. 2005;142(7):510–24.
25. Schmoelz M, Schelling G, Dunker M, Irlbeck M. Comparison of systemic and renal effects of dopexamine and dopamine in norepinephrine-treated septic shock. J Cardiothorac Vasc Anesth. 2006;20(2):173–8.
26. Triposkiadis FK, Butler J, Karayannis G, Starling RC, Filippatos G, Wolski K, Parissis J, Parisis C, Rovithis D, Koutrakis K, et al. Efficacy and safety of high dose versus low dose furosemide with or without dopamine infusion: the dopamine in acute decompensated heart failure II (DAD-HF II) trial. Int J Cardiol. 2014;172(1):115–21.
27. Lauschke A, Teichgraber UK, Frei U, Eckardt KU. 'Low-dose' dopamine worsens renal perfusion in patients with acute renal failure. Kidney Int. 2006;69(9):1669–74.
28. De Backer D, Aldecoa C, Njimi H, Vincent JL. Dopamine versus norepinephrine in the treatment of septic shock: a meta-analysis*. Crit Care Med. 2012;40(3):725–30.
29. Link Mark S, Berkow Lauren C, Kudenchuk Peter J, Halperin Henry R, Hess Erik P, Moitra Vivek K, Neumar Robert W, O'Neil Brian J, Paxton James H, Silvers Scott M, et al. Part 7: adult advanced cardiovascular life support. Circulation. 2015;132(18_suppl_2):S444–64.

30. Brogden RN, Markham A. Fenoldopam: a review of its pharmacodynamic and pharmacokinetic properties and intravenous clinical potential in the management of hypertensive urgencies and emergencies. Drugs. 1997;54(4):634–50.
31. Singer I, Epstein M. Potential of dopamine A-1 agonists in the management of acute renal failure. Am J Kidney Dis. 1998;31(5):743–55.
32. Zangrillo A, Biondi-Zoccai GG, Frati E, Covello RD, Cabrini L, Guarracino F, Ruggeri L, Bove T, Bignami E, Landoni G. Fenoldopam and acute renal failure in cardiac surgery: a meta-analysis of randomized placebo-controlled trials. J Cardiothorac Vasc Anesth. 2012;26(3):407–13.
33. Landoni G, Biondi-Zoccai GG, Tumlin JA, Bove T, De Luca M, Calabro MG, Ranucci M, Zangrillo A. Beneficial impact of fenoldopam in critically ill patients with or at risk for acute renal failure: a meta-analysis of randomized clinical trials. Am J Kidney Dis. 2007;49(1):56–68.
34. Gillies MA, Kakar V, Parker RJ, Honore PM, Ostermann M. Fenoldopam to prevent acute kidney injury after major surgery-a systematic review and meta-analysis. Crit Care. 2015;19:449.
35. Sun H, Xie Q, Peng Z. Does fenoldopam protect kidney in cardiac surgery? A systemic review and meta-analysis with trial sequential analysis. Shock. 2019;52(3):326–33.
36. Tumlin JA, Finkel KW, Murray PT, Samuels J, Cotsonis G, Shaw AD. Fenoldopam mesylate in early acute tubular necrosis: a randomized, double-blind, placebo-controlled clinical trial. Am J Kidney Dis. 2005;46(1):26–34.
37. Bove T, Zangrillo A, Guarracino F, Alvaro G, Persi B, Maglioni E, Galdieri N, Comis M, Caramelli F, Pasero DC, et al. Effect of fenoldopam on use of renal replacement therapy among patients with acute kidney injury after cardiac surgery: a randomized clinical trial. JAMA. 2014;312(21):2244–53.
38. Potter LR, Abbey-Hosch S, Dickey DM. Natriuretic peptides, their receptors, and cyclic guanosine monophosphate-dependent signaling functions. Endocr Rev. 2006;27(1):47–72.
39. Kuwahara K, Nakao K. Regulation and significance of atrial and brain natriuretic peptides as cardiac hormones. Endocr J. 2010;57(7):555–65.
40. Boerrigter G, Burnett JC Jr. Natriuretic peptides renal protective after all? J Am Coll Cardiol. 2011;58(9):904–6.
41. Rahman SN, Kim GE, Mathew AS, Goldberg CA, Allgren R, Schrier RW, Conger JD. Effects of atrial natriuretic peptide in clinical acute renal failure. Kidney Int. 1994;45(6):1731–8.
42. Allgren RL, Marbury TC, Rahman SN, Weisberg LS, Fenves AZ, Lafayette RA, Sweet RM, Genter FC, Kurnik BR, Conger JD, et al. Anaritide in acute tubular necrosis. Auriculin Anaritide Acute Renal Failure Study Group. N Engl J Med. 1997;336(12):828–34.
43. Lewis J, Salem MM, Chertow GM, Weisberg LS, McGrew F, Marbury TC, Allgren RL. Atrial natriuretic factor in oliguric acute renal failure. Anaritide Acute Renal Failure Study Group. Am J Kidney Dis. 2000;36(4):767–74.
44. Yamada H, Doi K, Tsukamoto T, Kiyomoto H, Yamashita K, Yanagita M, Terada Y, Mori K. Low-dose atrial natriuretic peptide for prevention or treatment of acute kidney injury: a systematic review and meta-analysis. Crit Care. 2019;23(1):41.
45. Sackner-Bernstein JD, Kowalski M, Fox M, Aaronson K. Short-term risk of death after treatment with nesiritide for decompensated heart failure: a pooled analysis of randomized controlled trials. JAMA. 2005;293(15):1900–5.
46. Xiong B, Wang C, Yao Y, Huang Y, Tan J, Cao Y, Zou Y, Huang J. The dose-dependent effect of nesiritide on renal function in patients with acute decompensated heart failure: a systematic review and meta-analysis of randomized controlled trials. PLoS One. 2015;10(6):e0131326.
47. Gong B, Wu Z, Li Z. Efficacy and safety of nesiritide in patients with decompensated heart failure: a meta-analysis of randomised trials. BMJ Open. 2016;6(1):e008545.
48. Mitaka C, Kudo T, Haraguchi G, Tomita M. Cardiovascular and renal effects of carperitide and nesiritide in cardiovascular surgery patients: a systematic review and meta-analysis. Crit Care. 2011;15(5):R258.
49. Zhou CC, Yao WT, Ge YZ, Xu LW, Wu R, Gao XF, Song KW, Jiang XM, Wang M, Huang WJ, et al. Remote ischemic conditioning for the prevention of contrast-induced acute kidney

injury in patients undergoing intravascular contrast administration: a meta-analysis and trial sequential analysis of 16 randomized controlled trials. Oncotarget. 2017;8(45):79323–36.
50. Hausenloy DJ, Candilio L, Evans R, Ariti C, Jenkins DP, Kolvekar S, Knight R, Kunst G, Laing C, Nicholas J, et al. Remote ischemic preconditioning and outcomes of cardiac surgery. N Engl J Med. 2015;373(15):1408–17.
51. Le Page S, Prunier F. Remote ischemic conditioning: current clinical perspectives. J Cardiol. 2015;66(2):91–6.
52. Menting TP, Wever KE, Ozdemir-van Brunschot DM, Van der Vliet DJ, Rovers MM, Warle MC. Ischaemic preconditioning for the reduction of renal ischaemia reperfusion injury. Cochrane Database Syst Rev. 2017;3:CD010777.
53. Kim TK, Min JJ, Cho YJ, Hausenloy DJ, Ahn H, Kim KH, Hwang HY, Hong DM, Jeon Y. Effects of delayed remote ischemic preconditioning on peri-operative myocardial injury in patients undergoing cardiac surgery—a randomized controlled trial. Int J Cardiol. 2017;227:511–5.
54. Song JW, Lee WK, Lee S, Shim JK, Kim HJ, Kwak YL. Remote ischaemic conditioning for prevention of acute kidney injury after valvular heart surgery: a randomised controlled trial. Br J Anaesth. 2018;121(5):1034–40.
55. Diamantis E, Troupis T, Mazarakis A, Kyriakos G, Diamanti S, Troupis G, Skandalakis P. Primary and secondary prevention of acute coronary syndromes: the role of the statins. Recent Adv Cardiovasc Drug Discov. 2014;9(2):97–105.
56. Jain MK, Ridker PM. Anti-inflammatory effects of statins: clinical evidence and basic mechanisms. Nat Rev Drug Discov. 2005;4(12):977–87.
57. Park JH, Shim JK, Song JW, Soh S, Kwak YL. Effect of atorvastatin on the incidence of acute kidney injury following valvular heart surgery: a randomized, placebo-controlled trial. Intensive Care Med. 2016;42(9):1398–407.
58. Billings FT, Hendricks PA, Schildcrout JS, Shi Y, Petracek MR, Byrne JG, Brown NJ. High-dose perioperative atorvastatin and acute kidney injury following cardiac surgery: a randomized clinical trial. JAMA. 2016;315(9):877–88.
59. Zheng Z, Jayaram R, Jiang L, Emberson J, Zhao Y, Li Q, Du J, Guarguagli S, Hill M, Chen Z, et al. Perioperative rosuvastatin in cardiac surgery. N Engl J Med. 2016;374(18):1744–53.
60. Zhao BC, Shen P, Liu KX. Perioperative statins do not prevent acute kidney injury after cardiac surgery: a meta-analysis of randomized controlled trials. J Cardiothorac Vasc Anesth. 2017;31(6):2086–92.
61. Xiong B, Nie D, Cao Y, Zou Y, Yao Y, Qian J, Rong S, Huang J. Preoperative statin treatment for the prevention of acute kidney injury in patients undergoing cardiac surgery: a meta-analysis of randomised controlled trials. Heart Lung Circ. 2017;26(11):1200–7.
62. Toso A, Maioli M, Leoncini M, Gallopin M, Tedeschi D, Micheletti C, Manzone C, Amato M, Bellandi F. Usefulness of atorvastatin (80 mg) in prevention of contrast-induced nephropathy in patients with chronic renal disease. Am J Cardiol. 2010;105(3):288–92.
63. Wang N, Qian P, Yan TD, Phan K. Periprocedural effects of statins on the incidence of contrast-induced acute kidney injury: a systematic review and trial sequential analysis. Int J Cardiol. 2016;206:143–52.
64. Marenzi G, Cosentino N, Werba JP, Tedesco CC, Veglia F, Bartorelli AL. A meta-analysis of randomized controlled trials on statins for the prevention of contrast-induced acute kidney injury in patients with and without acute coronary syndromes. Int J Cardiol. 2015;183:47–53.

Chapter 17
Renal Replacement Therapy in AKI

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Abstract Acute kidney injury (AKI) has become a global problem in the developing countries as well as the developed countries in recent years. AKI has been rapidly increasing during the past few decades. However, the incidence of AKI varies in previous studies depending on the definitions of AKI and patients' demographics. AKI, particularly among patients with severe AKI requiring renal replacement therapy (RRT), is associated with high mortality and morbidity. Moreover, the survivors of AKI are at increased risk of progression to chronic kidney disease and end-stage renal disease even if AKI is recovered completely. Despite significant advances in RRT technology, the mortality of AKI requiring RRT is over 50% in the intensive care unit (ICU). Although RRT is a mainstay strategy for critically ill patients with AKI, there still remains several controversial issues with respect to RRT for AKI.

Keywords Acute kidney injury · Dose · Modality · Renal replacement therapy
Dialysis membrane

17.1 Introduction

Acute kidney injury (AKI) is one of the most serious and well-recognized complications among hospitalized patients, especially in the intensive care unit (ICU). Despite significant advances in critical care medicine, the mortality rate of patients with AKI remains unacceptably high, particularly among critically ill patients with AKI severe enough to require renal replacement therapy (RRT) in the ICU. The

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incidence of AKI in ICU settings has been increasing globally during the past few decades along with population aging. Critically ill patients requiring RRT account for 1.0–13.5% of patients in ICU settings [1–10] (Fig. 17.1). Moreover, the mortality rates of patients with AKI are three or four times higher than those of patients without AKI [1–9, 11–16]. High mortality of critically ill patients with AKI requiring RRT might be partially attributable to the fact that no specific pharmacological therapy for AKI has been established. RRT plays a pivotal role in patients with severe AKI. However, several issues of RRT for AKI remain unresolved (Table 17.1). Although some consensus has been reached on the RRT dose and modality in

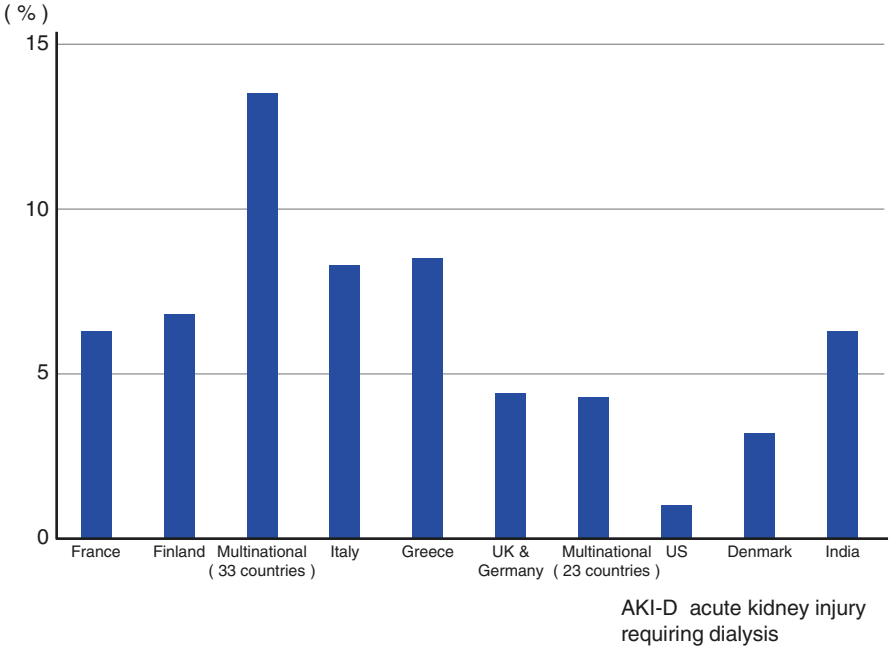

Fig. 17.1 The incidence of AKI-D in the ICU setting. *AKI-D* acute kidney injury requiring dialysis

Table 17.1 The controversial issues regarding RRT for AKI

1. Timing of initiation and discontinuation of RRT
2. Modality and mode of RRT:CRRT or IRRT or SLED, HD or HF or HDF or PD
3. Intensity (dose) of RRT
4. Dialysis membranes for RRT
5. Anticoagulants for RRT
6. Dialysate and replacement fluid for RRT

RRT renal replacement therapy, *AKI* acute kidney injury, *CRRT* continuous renal replacement therapy, *IRRT* intermittent renal replacement therapy, *SLED* sustained low-efficiency dialysis, *HD* hemodialysis, *HF* hemofiltration, *HDF* hemodiafiltration, *PD* peritoneal dialysis

patients with AKI requiring RRT, the optimal timing for initiation of RRT is still controversial. Little evidence or consensus exists regarding the idea that early initiation of RRT in patients with AKI improves both patient and renal outcomes.

17.2 When to Start and Stop RRT in Critically Ill Patients with AKI

Many studies have been performed to examine the optimal timing of initiation of RRT in patients with severe AKI [17–26]. However, there is insufficient evidence to recommend early initiation of RRT for AKI in critically ill patients. Although early initiation of RRT in patients with AKI has several advantages, it also has a few shortcomings. RRT in critically ill patients at an early stage could make it easier for physicians to manage acid–base homeostasis, electrolyte abnormalities, and fluid overload. However, early initiation of RRT in patients with AKI might expose such patients to unnecessary RRT and RRT-related complications. Even the latest high-quality randomized controlled trial (RCT), the Initiation of Dialysis Early Versus Delayed in the Intensive Care Unit (IDEAL-ICU) trial conducted in France, failed to show reduced mortality in patients with AKI and sepsis who underwent early versus delayed initiation of RRT [27]. In total, 488 patients with septic shock and severe AKI were randomly assigned to either the early-strategy group (initiation of RRT within 12 h after documentation of failure stage of RIFLE criteria) or the delayed-strategy group (initiation of RRT at 48 h after the diagnosis of AKI if hyperkalemia, metabolic acidosis, and fluid overload had not occurred). This trial showed no significant difference in 90-day all-cause mortality between the two groups (58% in the early-strategy group vs. 54% in the delayed-strategy group, $p = 0.38$). In the delayed-strategy group, 70 of 242 patients (29%) did not receive RRT because their renal function improved. Several other RCTs and meta-analysis have also investigated the ideal timing for initiation of RRT in critically ill patients with AKI. In 2016, two large RCTs were conducted to examine whether early initiation of RRT in patients with AKI reduces mortality. However, the two RCTs produced conflicting results [25, 26]. The Early Versus Late Initiation of Renal Replacement Therapy In Critically Ill Patients With Acute Kidney Injury (ELAIN) trial was a single-center RCT conducted in Germany [25]. This trial examined 231 critically ill patients with AKI. The 231 patients were randomly assigned to either early initiation of RRT (within 8 h of meeting Kidney Disease: Improving Global Outcomes [KDIGO] stage 2 criteria, $n = 112$) or delayed initiation of RRT (within 12 h of meeting KDIGO stage 3 criteria or if absolute indications for RRT were met, $n = 119$). Early initiation of RRT significantly improved 90-day mortality compared with delayed initiation of RRT (44 of 112 patients [39.3%] in the early group vs. 65 of 119 patients [54.7%] in the delayed group, $p = 0.03$). In contrast, the Artificial Kidney Initiation in Kidney Injury (AKIKI) trial was a multicenter trial conducted in France that evaluated the timing of RRT in patients with AKI [26].

In total, 620 patients with AKI were randomized to either the early-strategy group (initiation of RRT within 6 h of meeting KDIGO stage 3 criteria, $n = 311$) or delayed-strategy group (initiation of RRT if at least one of the following criteria was met: blood urea nitrogen level of >112 mg/dL, serum potassium level of >6 mmol/L, pH of <7.15, acute pulmonary edema due to fluid overload, or oliguria or anuria lasting for >72 h after randomization; $n = 308$). This trial showed no significant difference in 60-day mortality between the early-strategy and delayed-strategy groups (48.5% vs. 49.7%, respectively; $p = 0.79$). However, the post hoc analysis revealed that the 60-day mortality rate was lowest (37.1%) among the patients in the delayed-strategy group who required no RRT. The highest mortality rate (61.8%) was found among the patients in the delayed-strategy group who received RRT. In 2017, eight meta-analyses were conducted to evaluate the optimal timing of RRT in patients with AKI [28–35]. The meta-analyses that included only RCTs showed no significant mortality-related benefit of early initiation of RRT in patients with AKI compared with late initiation of RRT. Among meta-analyses that included non-randomized trials, early initiation of RRT in critically ill patients with AKI was associated with significantly lower mortality compared with late initiation of RRT. The Japanese clinical practice guideline for AKI was published in December 2016 [36]. In this guideline, early initiation of RRT in patients with AKI was not recommended, and when to start RRT for AKI should be decided under consideration of clinical symptoms and disease conditions. The superiority of early over late RRT in patients with AKI still remains controversial. The severity of injury and the clinical condition, not the timing of the initiation of RRT, may affect the mortality rate and renal recovery of patients with AKI. The largest multinational, multicenter RCT is currently ongoing. The Standard versus Accelerated Initiation of Renal Replacement Therapy in Acute Kidney Injury (STARRT-AKI) trial is being conducted to investigate whether accelerated initiation of RRT for AKI improves patient survival and renal outcomes [37]. This trial may provide new evidence of the optimal timing of RRT in critically ill patients with AKI.

Although several trials have examined when to start RRT in patients with AKI, few studies have showed the optimal timing for discontinuation of RRT or ideal biomarkers with which to predict sufficient renal recovery. No RCTs have investigated when or how to stop RRT in patients with AKI. It is widely accepted that the decisions regarding weaning of RRT or changing the RRT modality in patients with AKI are influenced by patient-related factors (hemodynamic instability, fluid overload), biomarkers (serum creatinine, blood urea nitrogen, serum potassium, novel biomarkers), and urine output. Only five observational studies have examined the significant predictors of successful discontinuation of RRT in patients with AKI requiring RRT [38–43]. In the first study, Wu et al. investigated 304 postoperative patients with AKI undergoing RRT in Taiwan. Successful discontinuation of RRT was defined as cessation of RRT for at least 30 days [38]. In total, 64 (21.1%) patients were successfully weaned from RRT. The multivariate logistic regression analysis identified the following factors as independent predictors for restarting RRT within 30 days: a longer duration of RRT (odds ratio [OR], 1.06; 95% confidence interval [CI], 1.02–1.10; $p = 0.005$), a higher sequential organ failure

assessment score (OR, 1.44; 95% CI, 1.13–1.83; $p = 0.003$), oliguria (urine output of <100 mL per 8 h) (OR, 4.17; 95% CI, 1.07–16.13; $p = 0.039$), and age of >65 years (OR, 6.35; 95% CI, 1.61–24.99; $p = 0.008$). Uchino et al. conducted a post hoc analysis of a prospective multicenter observational study (BEST Kidney study) evaluating 529 patients with AKI who survived initial therapy among 529 patients treated with continuous RRT (CRRT) [39]. In total, 313 patients were successfully weaned from CRRT and required no RRT for at least 7 days (defined as the success group). In contrast, the remaining 216 patients were defined as the repeat-RRT group. Patients in the success group had lower urea and creatinine concentrations and a higher urine output at discontinuation of RRT. The authors concluded that urine output was the most important predictor of successful discontinuation of CRRT. In the most recent study, Raurich et al. identified factors associated with successful weaning of CRRT for patients with AKI requiring CRRT [42]. Of 86 patients with AKI, 67 (77.9%) were successfully weaned from CRRT and 19 (22.1%) failed. The multivariate logistic regression analysis revealed that the factors associated with successful weaning of CRRT were female sex (OR, 5.1; 95% CI, 1.6–17.8; $p = 0.01$) and 6 h-urine output after CRRT cessation (OR, 1.014; 95% CI, 1.008–102; $p < 0.001$). At present, most nephrologists and intensivists believe that urine output is the most important predictor of successful cessation of RRT in patients with AKI. However, multicenter RCTs are needed to determine the optimal timing of discontinuation of RRT for patients with AKI requiring RRT.

17.3 Dose of RRT in Patients with AKI

The optimal dose of RRT in patients with AKI has been investigated during the past few decades. Ronco et al. first examined whether three different doses in patients with AKI requiring continuous veno-venous hemofiltration (CVVHF) were associated with mortality and renal recovery [44]. In total, 425 patients with AKI at a single center in Italy were randomized to 3 groups according to the CVVHF filtration rate (20, 35, or 45 mL/kg/h). The survival rate at 15 days after discontinuation of CVVHF in the 20-, 35-, and 45-mL/kg/h groups was 41%, 57%, and 58%, respectively. The survival rates in the high-dose group (45 mL/kg/h) and intermediate-dose group (35 mL/kg/h) were significantly higher than that in the low-dose group (20 mL/kg/h) ($p = 0.007$, $p = 0.0013$). No significant difference in the survival rate was found between the high- and intermediate-dose groups. Since this study, a CRRT dose of >35 mL/kg/h has been recommended for critically ill patients with AKI. Additionally, since the study by Ronco et al., several RCTs gave compared high- and low-dose CRRT among patients with AKI [45–47]. These studies produced conflicting results, and the small numbers of patients were insufficiently powerful to prove the superiority of a high dose over a low dose in CRRT. Therefore, a larger RCT is needed to determine the effect of high-dose CRRT on survival.

The two largest RCTs evaluating the RRT dose in patients with AKI were published [48, 49] in 2008 and 2009. In 2008, the Veterans Affairs/National Institutes of

Health Acute Renal Failure Trial Network (ATN) study was conducted in the United States [48]. This trial randomly assigned critically ill patients with AKI to either intensive therapy (n = 563) or less intensive therapy (n = 561). In the intensive therapy, continuous veno-venous hemodiafiltration (CVVHDF) was performed at a CRRT dose of 35 mL/kg/h or sustained low-efficiency dialysis (SLED) was performed six times per week when patients were hemodynamically unstable. Intermittent HD (IHD) was performed if the patients were hemodynamically stable. In contrast, in the less intensive therapy, CVVHDF was administered at 20 mL/kg/h along with the performance of SLED and IHD three times per week. The intensive therapy did not lead to an improvement in 60-day mortality compared with the less intensive therapy (53.6% vs. 51.5%, respectively; OR, 1.09; 95% CI, 0.86–1.4; p = 0.47). In 2009, the Randomized Evaluation of Normal versus Augmented Level (RENAL) Renal Replacement Therapy Study was conducted in Australia and New Zealand [49]. In total, 1508 critically ill patients with AKI were randomly assigned to post-CVVHDF at an effluent flow of either 40 mL/kg/h (higher-intensity therapy, n = 747) or 25 mL/kg/h (lower-intensity therapy, n = 761). This study also showed a no significant difference in 90-day mortality between the higher- and lower-intensity groups. The 90-day mortality rate was the same (44.7%) in the two groups (OR, 1.00; 95% CI, 0.81–1.23; p = 0.99). Two large RCTs failed to show an effect of high-dose CRRT on mortality compared with low-dose CRRT. From the abovementioned results, the KDIGO clinical guideline for AKI recommends that the delivered dose of CRRT in patients with AKI should be 20–25 mL/kg/h [50]. Several systematic reviews and meta-analyses have examined the effects of the intensity of RRT on mortality and renal recovery in critically ill patients with AKI [51–55]. No significant difference in mortality was seen between higher-intensity RRT and standard-intensity RRT. However, with respect to renal recovery, the latest meta-analysis showed that higher-intensity RRT was associated with less RRT independence by day 28 compared with the standard-intensity group (70.3% vs. 75.3%, respectively; p = 0.03) using individual patient data [55]. Two recent RCTs were performed to determine whether more higher-volume CRRT improves mortality in patients with septic AKI compared with conventional-dose CRRT [56, 57]. The IVOIRE study was conducted in France, Belgium, and the Netherlands [56]. In total, 140 critically ill patients with septic AKI were randomized to receive either high-volume hemofiltration at a dose of 70 mL/kg/h or standard-volume hemofiltration at a dose of 35 mL/kg/h. High-volume hemofiltration did not significantly reduce mortality at 28 days compared with standard-volume hemofiltration (37.9% vs. 40.8%, respectively; p = 0.94). Park et al. compared the conventional dose (40 mL/kg/h) with a high dose (80 mL/kg/h) among 212 patients with septic AKI requiring CVVHDF [57]. High-dose CVVHDF did not significantly reduce 28-day mortality (hazard ratio [HR], 1.02; 95% CI, 0.73–1.43; p = 0.9) compared with conventional-dose CVVHDF.

Unlike the international dose of CRRT for patients with AKI, the Japanese standard dose is much lower at 600–800 mL/h (approximately 10–13 mL/kg/h), which is only about half of the international dose (Table 17.2). However, no RCT has shown that the Japanese dose for CRRT is associated with higher mortality of

Table 17.2 Standard mode of RRT in Japan

	CHDF	IDH	SLED
Blood flow rate (mL/min)	80–100	200–250	100–200
Dialysate flow rate	500 mL/h	500 mL/min	200–300 mL/min
Replacement flow rate (mL/min)	200–300 mL/h		
Treatment period (h)	24	4–5	6–10

RRT renal replacement therapy, *CHDF* continuous hemodiafiltration, *IHD* intermittent hemodialysis, *SLED* sustained low-efficiency dialysis

patients with AKI in comparison with the international CRRT dose. Only two retrospective observational studies demonstrated that even very-low-dose CRRT in Japan did not increase the mortality of critically ill patients with AKI [58, 59].

17.4 Large Variations in CRRT Dose

Wide variations exist in the delivered dose and prescribed dose of CRRT for patients with AKI. In several RCTs evaluating the relationships between the CRRT dose and mortality of patients with AKI, more than 80% of the prescribed dose was delivered on average [44, 46–49]. In the DO-RE-MI (DOse REsponse Multicentre International collaborative initiative) study, the median delivered dose was 27.1 mL/kg/h (interquartile range [IQR], 22.1–33.9) in the CRRT group [60]. The median prescribed dose, however, was 34.3 mL/kg/h (IQR, 27.3–42.9) with approximately 20% loss of the delivered dose. This loss was mainly attributable to treatment downtime. The most common causes of downtime were clotting of the circuit (74%), vascular access problems (11%), and clinical reasons (10%). Moreover, Claure-Del Granado et al. analyzed the prescribed versus delivered dose in 52 critically ill patients with AKI requiring pre-dilution CVVHDF [61]. The delivered CRRT dose was 72.8% of the prescribed CRRT dose. The leading cause of CRRT downtime was filter clotting. According to the KDIGO clinical practice guideline for AKI, the prescribed CRRT dose must be within 25–30 mL/kg/h to achieve a delivered CRRT dose of 20–25 mL/kg/h [50].

17.5 RRT Modality for AKI

Three RRT modalities (CRRT, intermittent RRT [IRRT], and hybrid forms of RRT such as SLED) are available for the treatment of AKI in critically ill patients in the ICU. HD removes solutes by diffusion, HF removes them by convection, and HDF removes them by both methods. To date, several RCTs have assessed the effect of RRT modalities on clinical outcomes [62–76]. The largest RCT, which was conducted in France, compared the effect of CRRT and IRRT on survival rates in critically ill patients with AKI [70]. In total, 360 patients with AKI requiring RRT were

randomly assigned to receive either IHD or CVVHDF. No significant difference in 60-day survival was observed between the two RRT modalities. The CONVINT (CONtinuous Vs. INTermittent RRT on the outcome of critically ill patients with ARF trial), which was the most recent RCT to compare CVVH (n = 122) and IHD (n = 128), showed no significant difference in 14-day survival after the end of RRT between the CVVHF group (43.9%) and IHD group (39.5%) (OR for patients in IHD group, 0.84; 95% CI, 0.49–1.41; p = 0.50) [76]. The limitations of these RCTs comparing CRRT and IRRT in terms of mortality were that the numbers of patients were small and most RCTs had a short follow-up period. Three larger retrospective studies evaluated the superiority of CRRT over IRRT with respect to mortality and RRT dependence [77–79]. A Swedish study (n = 2202) of the impact of CRRT and IRRT on RRT dependence showed that the use of CRRT was associated with a significantly lower incidence of RRT dependence at 90 days [77]. However, no significant differences in mortality were observed between the two treated groups. Wald et al. performed a retrospective propensity score-matched cohort study examining the association between the RRT modality and long-term kidney function among patients with AKI [78]. The median follow-up period was 3.1 years in the CRRT group and 3.2 years in the IRRT group. The risk of chronic dialysis was significantly lower in the CRRT than IRRT group (HR, 0.75; 95% CI, 0.65–0.87). All-cause mortality was similar between the two groups (CRRT vs. IRRT: HR, 1.02; 95% CI, 0.91–1.14). The most recent large retrospective study (n = 58,635) conducted in France assessed the influence of the RRT modality on renal recovery at hospital discharge [79]. IRRT significantly reduced the rate of renal recovery at hospital discharge (OR, 0.910; 95% CI, 0.834–0.992; p = 0.0327). Moreover, several meta-analyses have compared CRRT with IRRT in terms of mortality and RRT dependence in patients with AKI [80–88]. A Cochrane systematic review evaluating 15 RCTs demonstrated no significant differences between patients treated with CRRT and IRRT in terms of either hospital mortality (relative risk [RR], 1.01; 95% CI, 0.92–1.12) or ICU mortality (RR, 1.06; 95% CI, 0.90–1.26) [82]. Zhang et al. performed a meta-analysis of 7 RCTs (n = 533) and 10 observational studies (n = 675) that compared extended daily dialysis (EDD) versus CRRT for the treatment of AKI [87]. The seven RCTs showed no difference in mortality (RR, 0.90; 95% CI, 0.74–1.11; p = 0.3). However, EDD was associated with significantly lower morality than CRRT in the 10 observational studies. The most recent systematic review and meta-analysis (performed in 2017), which included 21 studies (n = 5015; 16 RCTs and 5 prospective cohort studies), compared CRRT with IHD/SLED in terms of mortality, dialysis dependence, and length of hospital and ICU stays [88]. Hospital mortality and dialysis dependence were analyzed from the RCTs. RRT modality was not associated with in-hospital mortality (CRRT vs. IHD: RR, 1.00; 95% CI, 0.92–1.09 and CRRT vs. SLED: RR, 1.23; 95% CI, 1.00–1.51) or dialysis dependence (CRRT vs. IHD: RR, 0.90; 95% CI, 0.59–1.38 and CRRT vs. SLED: RR, 1.15; 95% CI, 0.67–1.99). In this way, no modality of RRT has shown definitive superiority over the others in terms of survival benefit and dialysis dependence. At present, it is widely accepted that CRRT is preferable over IRRT for the treatment of AKI in critically ill patients with hemodynamic instability (KDIGO guideline

2012). For hemodynamically stable patients with AKI in Japan, RRT may be used by either CRRT or IRRT according to the Japanese Clinical Practice Guideline for AKI 2016 [36]. However, CRRT is preferable for patients with hemodynamic instability. Numerous studies have investigated the effect of different modalities of RRT in patients with AKI on mortality and RRT dependence. In contrast, no RCTs have examined the differences in clinical outcomes of patients with AKI among the three modes of RRT (HDF, HF, and HD). Evidence is not sufficient to recommend the use of one RRT mode over another in patients with AKI severe enough to require RRT. Several RCTs have compared two of the three modes of RRT in terms of morality and renal recovery in patients with AKI [89–92]. A systematic review and meta-analysis including 19 RCTs showed no significant effect of HF on mortality or RRT dependence compared with HD [93]. The filter lifetime is well known to be shorter in patients treated with HF than HD. Additionally, although both HF and HD have the same effect on the removal of small-molecular-weight solutes, HF has the advantage of removing of larger-molecular-weight solutes such as toxic inflammatory cytokines. A multinational epidemiological survey (BEST kidney study) showed that CVVHF (52.8%) was the most commonly used modality in patients with AKI, followed by CVVHDF (34%) and CVVHD (13.1%) among 54 ICUs in 23 countries [94].

Peritoneal dialysis (PD) was commonly used for the treatment of AKI in the 1980s. However, CRRT has become the most standard treatment strategy in patients with AKI worldwide since the 1990s. In Brazil, an RCT comparing high-volume PD with daily HD showed no significant differences in mortality or renal recovery between the two treatments [95]. Moreover, a systematic review of 24 studies (n = 1556 patients) showed no significant differences in mortality between PD and extracorporeal blood purification; however, most studies (19/24) were conducted in low-resource regions [96]. At present, PD is usually used for AKI in developing countries because of its lower cost and technical simplicity.

17.6 What Dialysis Membrane Should Be Used for RRT in Patients with AKI?

Dialysis membranes are classified as either biocompatible dialysis membranes (BCMs) or bioincompatible dialysis membranes (BICMs). In Japan, BCMs (polymethyl methacrylate [PMMA], polyacrylonitrile [PAN], polysulfone [PS], cellulose triacetate [CTA], polyethersulfone [PES], polyarylethersulfone [PAES], ethylene vinyl alcohol [EVAL], polyester polymer alloy [PEPA], and polyethyleniminecoated polyacrylonitrile [AN69ST]) have commonly been used for RRT in both patients with AKI and those with end-stage kidney disease. Only six RCTs have demonstrated the survival benefit of each dialysis membrane on mortality in patients with AKI [97–102]. These RCTs compared BCMs with BICMs. Among these RCTs, most involved patients treated with IRRT, not CRRT. In the first study, Schiffl et al. examined the differences in mortality and renal recovery in postoperative

patients with AKI who were treated with regenerated cellulose (Cuprophan) versus PAN [97]. No significant differences were observed between the two groups. A meta-analysis by the Cochrane collaboration that included 10 RCTs (n = 1100) evaluated the differences in mortality and renal recovery between patients treated with a BCM (synthetic polymeric membrane, n = 575) and BICM (regenerated cellulose, n = 525) [103]. No significant differences were seen in mortality (RR, 0.93; 95% CI, 0.81–1.07) or renal recovery (RR, 1.09; 95% CI, 0.90–1.31). Well-designed RCTs comparing various BCMs in the treatment of RRT for AKI are needed. According to a recent study, the removal of inflammatory cytokines, which play pivotal roles in the pathophysiology of septic shock and septic AKI, is expected to lead to improvement in mortality [104]. PMMA and AN69ST are well-known cytokine-adsorbing hemofilters (CAHs). Several observational studies have evaluated the survival benefit in patients with septic shock treated with CAH-CHDF [105–108]. Shiga et al. showed that the 28-day survival rate was 73.5% (predicted 28-day survival of 20.3%) among patients with septic AKI treated with CAH-CHDF (AN69ST) in a prospective multicenter study [107]. In addition, a significant decrease in the blood interleukin-6 level compared with baseline was observed after 3, 12, 24, 48, and 72 h of treatment.

17.7 Conclusion

AKI is one of the most serious and life-threatening complications during hospitalization because of patients' increasing age and increasing prevalence of risk factors for AKI. Though RRT for AKI has been progressing on an annual basis during the past few decades, several issues of RRT in patients with AKI remain to be resolved. Further studies clarifying the epidemiology and pathophysiology of AKI worldwide are required to improve the mortality and comorbidity in patients with AKI, especially those requiring RRT.

References

1. Clećh C, Gonzalez F, Lautrette A, Nguile-Makao M, Garrouste-Orgeas M, Jamali S, et al. Multiple-center evaluation of mortality associated with acute kidney injury in critically ill patients: a competing risks analysis. Crit Care. 2011;15:R128.
2. Vaara ST, Pettilä V, Reinikainen M, Kaukonen KM. Population-based incidence, mortality and quality of life in critically ill patients treated with renal replacement therapy: nationwide retrospective cohort study in finish intensive care units. Crit Care. 2011;16:R13.
3. Hoste EA, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med. 2015;41:1411–23.
4. Piccinni P, Cruz DN, Gramaticopolo S, Garzotto F, Santo MD, Aneloni G, et al. Prospective multicenter study on epidemiology of acute kidney injury in the ICU: a critical care nephrology Italian collaborative effort (NEFROINT). Minerva Anestesiol. 2011;77:1072–83.

5. Andrikos E, Tseke P, Balafa O, Cruz DN, Tsinta A, Androulaki M, et al. Epidemiology of acute renal failure in ICUs: a multi-center prospective study. Blood Purif. 2009;28:239–44.
6. Ostermmann M, Chang RWS. Acute kidney injury in the intensive care unit according to RIFLE. Crit Care Med. 2007;35:1837–43.
7. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, et al. Acute renal failure in critically ill patients. JAMA. 2005;294:813–8.
8. Thakar CV, Christianson A, Freyberg R, Almenoff P, Render ML. Incidence and outcomes of acute kidney injury in intensive care units: a veterans administration study. Crit Care Med. 2009;37:2552–8.
9. Gammelager H, Christiansen CF, Johansen MB, Tønnesen E, Jespersen B, Sørensen HT, et al. One-year mortality among Danish intensive care patients with acute kidney injury: a cohort study. Crit Care. 2012;16:R124.
10. Korula S, Balakishnan S, Sundar S, Paul V, Balagopal A. Acute kidney injury-incidence, prognostic factors, and outcome of patients in an intensive care unit in a tertiary center: a prospective observational study. Indian J Crit Care Med. 2016;20:332–6.
11. Kashani K, Shao M, Li G, Wiliiams AW, Rule AD, Kremers WK, et al. No increase in the incidence of acute kidney injury in a population-based annual temporal trends epidemiology study. Kidney Int. 2017;92:721–8.
12. Hoste EAJ, Clermont G, Kersten A, Venkatarman R, Angus DC, Bacquer DD, et al. RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. Crit Care. 2006;10:R73.
13. Bagshaw SM, George C, Bellomo R. Changes in the incidence and outcome for early acute kidney injury in a cohort of Australian intensive care units. Crit Care. 2007;11:R68.
14. Bagshaw SM, George C, Dinu I, Bellomo R. A multi-centre evaluation of the RIFLE criteria for early acute kidney injury in critically ill patients. Nephrol Dial Transplant. 2008;23:1203–10.
15. Medve L, Antek C, Paloczi B, Kocsi S, Gartner B, Marjanek Z, Bencsik G, et al. Epidemiology of acute kidney injury in Hungarian intensive care units: a multicenter, prospective, observational study. BMC Nephrol. 2011;12:43.
16. Joannidis M, Metnitz B, Bauer P, Schusterschitz N, Moreno R, Druml W, et al. Acute kidney injury in critically ill patients classified by AKIN versus RIFLE using the SAPS 3 database. Intensive Care Med. 2009;35:1692–702.
17. Pursnani ML, Hazra DK, Singh B, Pandey DN. Early haemodialysis in acute tubular necrosis. J Assoc Physicians India. 1997;45:850–2.
18. Bouman CS, Oudemans-Van Straaten HM, Tijssen JG, Zandstra DF, Kesescioglu J. Effects of early high-volume continuous venovenous hemofiltration on survival and recovery of renal function in intensive care patients with acute renal failure: a prospective, randomized trial. Crit Care Med. 2002;30:2205–11.
19. Durmaz I, Yagdi T, Calkavur T, Mahmudov R, Apaydin AZ, Posacioglu H, et al. Prophylactic dialysis in patients with renal dysfunction undergoing on-pump coronary artery bypass surgery. Ann Thorac Surg. 2003;75:859–64.
20. Sugahara S, Suzuki H. Early start on continuous hemodialysis therapy improves survival rate in patients with acute renal failure following coronary bypass surgery. Hemodial Int. 2004;8:320–5.
21. Payen D, Mateo J, Cavaillon JM, Fraisse F, Floriot C, Vicaut E, et al. Impact of continuous venovenous hemofiltration on organ failure during the early phase of severe sepsis: a randomized controlled trial. Crit Care Med. 2009;37:803–10.
22. Jamale TE, Hase NK, Kulkarni M, Pradeep KJ, Keskar V, Jawale S, et al. Earlier-start versus usual-start dialysis in patients with community-acquired acute kidney injury: a randomized controlled trial. Am J Kidney Dis. 2013;62:1116–21.
23. Combes A, Bréchot N, Amour J, Cozic N, Lebreton G, Guidon C, et al. Early high-volume hemofiltration versus standard care for postcardiac surgery shock (the HEROICS study). Am J Respir Crit Care Med. 2015;192:1179–90.

24. Wald R, Adhikari NK, Smith OM, Weir MA, Pope K, Cohen A, et al. Comparison of standard and accelerated initiation of renal replacement therapy in acute kidney injury. Kidney Int. 2015;88:897–904.
25. Gaudry S, Hajage D, Schortgen F, Martin-Lefevre L, Pons B, Boulet E, et al. Initiation strategies for renal replacement therapy in the intensive care unit. N Engl J Med. 2016;375:122–33.
26. Zarbock A, Kellum JA, Schmidt C, Aken HV, Wempe C, Pavenstädt H, et al. Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury. The ELAIN randomized clinical trial. JAMA. 2016;315:2190–9.
27. Barbar SD, Clere-Jehl R, Bourredjem A, Herno R, Bruyère MR, Lebert C, et al. Timing do renal-replacement therapy in patients with acute kidney injury and sepsis. N Engl J Med. 2018;379:1431–42.
28. Wang C, Lv LS, Huang H, Guan J, Ye Z, Li S, et al. Initiation time of renal replacement therapy on patients with acute kidney injury: a systematic review and meta-analysis of 8179 participants. Nephrology (Carlton). 2017;22:7–18.
29. Bhatt GC, Das RR. Early versus late initiation of renal replacement therapy in patients with acute kidney injury-a systematic review & meta-analysis of randomized controlled trials. BMC Nephrol. 2017;18:78.
30. Feng YM, Yang Y, Han XL, Zhang F, Wan D, Guo R. The effect of early versus late initiation of real replacement therapy in patients with acute kidney injury: a meta-analysis. PLoS One. 2017;12:e0174158.
31. Luo K, Fu S, Fang W, Xu G. The optimal time of initiation of renal replacement therapy in acute kidney injury: a meta-analysis. Oncotarget. 2017;8:68795–808.
32. Zou H, Hong Q, Xu G. Early versus late initiation of renal replacement therapy impacts mortality in patients with acute kidney injury post cardiac surgery: a meta-analysis. Crit Care. 2017;21:150.
33. Yang XM, Tu GW, Zheng JL, Shen B, Ma GG, Hao GW, et al. A comparison of early versus late initiation of renal replacement therapy for acute kidney injury in critically ill patients: an updated systematic review and meta-analysis of randomized controlled trials. BMC Nephrol. 2017;18:264.
34. Mavrakanas TA, Aurian-Blajeni D, Charytan DM. Early versus late initiation of renal replacement therapy in patients with acute kidney injury: a meta-analysis of randomized clinical trials. Swiss Med Wkly. 2017;147:w14507.
35. Xu Y, Gao J, Zheng X, Zhong B, Na Y, Wei J. Timing of initiation of renal replacement therapy for acute kidney injury: a systematic review and meta-analysis of randomized-controlled trials. Clin Exp Nephrol. 2017;21:552–62.
36. Doi K, Nishida O, Shigematsu T, Sadahiro T, Itami N, Iseki K, et al. The Japanese clinical practice guideline for acute kidney injury 2016. Ren Replace Ther. 2018;4:36.
37. Smith OM, Wald R, Adhikari NK, Pope K, Weir MA, Bagshaw SM. Standard versus accelerated initiation of renal replacement therapy in acute kidney injury (STARRT-AKI) study protocol for a randomized controlled trial. Trials. 2013;14:320.
38. Wu VC, Ko WJ, Chang HW, Chen YW, Lin YF, Shiao CC, et al. Risk factors of early redialysis after weaning from postoperative acute renal replacement therapy. Intensive Care Med. 2008;34:101–8.
39. Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M, Tan I, et al. Discontinuation of continuous renal replacement therapy: a post hoc analysis of a prospective multicenter observational study. Crit Care Med. 2009;37:2576–82.
40. Kawarazaki H, Uchino S, Tokuhira N, Ohnuma T, Namba Y, Katayama S, et al. Who may not benefit from continuous renal replacement therapy in acute kidney injury. Hemodial Int. 2013;17:624–32.
41. Katayama S, Uchino S, Uji M, Ohnuma T, Namba Y, Kawarazaki H, et al. Factors predicting successful discontinuation of continuous renal replacement therapy. Anaesth Intensive Care. 2016;44:453–7.

42. Raurich JM, Llompart-Pou JA, Novo MA, Talavera C, Ferreruela M, Ayestarán I. Successful weaning from continuous renal replacement therapy. Associated risk factors. J Crit Care. 2018;45:144–8.
43. Schiffl H. Discontinuation of renal replacement therapy in critically ill patients with severe acute kidney injury: predictive factors of renal function recovery. Int Urol Nephrol. 2018;50:1845–51.
44. Ronco C, Bellomo R, Homel P, et al. Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial. Lancet. 2000;356:26–30.
45. Bouman CSC, Oudemans-Van Straaten HM, Tijssen JGP, Zandstra DF, Kesecioglu J. Effects of early high-volume continuous venovenous hemofiltration on survival and recovery of renal function in intensive care patients with acute renal failure: a prospective, randomized trial. Crit Care Med. 2002;30:2205–11.
46. Saudan P, Niederberger M, Seigneux SD, Romand J, Pugin J, Perneger T, et al. Adding a dialysis dose to continuous hemofiltration increases survival in patients with acute renal failure. Kidney Int. 2006;70:1312–7.
47. Tolwani AJ, Campbell RC, Stofan BS, Lai KB, Oster RA, Wille KM. Standard versus high-dose CVVHDF for ICU-related acute kidney injury. J Am Soc Nephrol. 2008;19:1233–8.
48. The VA/NIH Acute Renal Failure Trial Network, Palevsky PM, Zhang JH, O'Connor TZ, Chertow GM, Crowley ST, Choudhury D, et al. Intensity of renal support in critically ill patients with acute kidney injury. N Engl J Med. 2008;359:7–20.
49. The RENAL Replacement Therapy Study Investigators, Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, Lo S, et al. Intensity of continuous renal-replacement therapy in critically ill patients. N Engl J Med. 2009;361:1627–38.
50. The Kidney Disease Improving Global Outcomes (KDIGO) Working Group: dialysis interventions for treatment of AKI. Kidney Int. 2012 (Supplements 2):89–115.
51. Jun M, Lambers Heerspink HJ, Ninomiya T, Gallagher M, Bellomo R, Myburgh J, et al. Intensities of renal replacement therapy in acute kidney injury. Clin J Am Soc Nephrol. 2010;5:956–63.
52. Van Wert R, Friedrich JO, Scales DC, Wald R, Adhikari NK, University of Toronto Acute Kidney Injury Research Group. High-dose renal replacement therapy for acute kidney injury: systematic review and meta-analysis. Crit Care Med. 2010;38:1360–9.
53. Negash DT, Dhingra VK, Copland M, Griesdale D, Henderson W. Intensity of continuous renal replacement therapy in acute kidney injury in the intensive care unit: a systematic review and meta-analysis. Vasc Endovascular Surg. 2011;45:504–10.
54. Fayad A, Buamscha DG, Ciapponi A. Intensity of continuous renal replacement therapy for acute kidney injury. Cochrane Database Syst Rev. 2016;10:CD010613.
55. Wang Y, Gallagher M, Li Q, Lo S, Cass A, Finfer S, et al. Renal replacement therapy intensity for acute kidney injury and recovery to dialysis independence: a systematic review and individual patient data meta-analysis. Nephrol Dial Transplant. 2018;33:1017–24.
56. Joannes-Boyau O, Honoré PM, Perez P, Bagshaw SM, Grand H, Canivet JL, et al. High-volume versus standard-volume haemofiltration for septic shock patients with acute kidney injury (IVOIRE study): a multicentre randomized controlled trial. Intensive Care Med. 2013;39:1535–46.
57. Park JT, Lee H, Kee YK, Park S, Jung H, Han SH, et al. High-dose versus conventional-dose continuous venovenous hemodialiftration and patient and kidney survival and cytokine removal in sepsis-associated acute kidney injury: a randomized controlled trial. Am J Kidney Dis. 2016;68:599–608.
58. Fujii T, Namba Y, Fujitani S, Sasaki J, Narihara K, Shibagaki Y, et al. Low-dose continuous renal replacement therapy for acute kidney injury. Int J Artif Organs. 2012;35:525–30.
59. Uchino S, Toki N, Takeda K, Ohnuma T, Namba Y, Katayama S, et al. Validity of low-intensity continuous renal replacement therapy. Crit Care Med. 2013;41:2584–91.

60. Vesconi S, Cruz DN, Fumagalli R, Kindgen-Milles D, Monti G, Mariho A, et al. Delivered dose renal replacement therapy and mortality in critically ill patients with acute kidney injury. Crit Care. 2009;13:R57.
61. Claure-Del Granado R, Macedo E, Chertow GM, Soroko S, Himmelfarb J, Ikizler TA, et al. Effluent volume in continuous renal replacement therapy overestimates the delivered dose of dialysis. Clin J Am Soc Nephrol. 2011;6:467–75.
62. Davenport A, Will EJ, Davison AM, Swindells S, Cohen AT, Miloszewski KJA, et al. Changes in intracranial pressure during haemofiltration in oliguric patients with grade IV hepatic failure. Nephron. 1989;53:142–6.
63. Mehta RL, McDonald B, Gabbai FB, Pahl M, Pascual MT, Farkas A, et al. A randomized clinical trial of continuous versus intermittent dialysis for acute renal failure. Kidney Int. 2001;60:1154–63.
64. John S, Griesbach D, Baumgärtel M, Weihprecht H, Schmieder RE, Geiger H. Effects of continuous haemofiltration vs intermittent haemodialysis on systemic haemodynamics and splanchnic regional perfusion in septic shock patients: a prospective, randomized clinical trial. Nephrol Dial Transplant. 2001;16:320–7.
65. Gašparović V, Filipović-Grćić I, Merkler M, Pišl Z. Continuous renal replacement therapy (CRRT) or intermittent hemodialysis (IHD)—what is the procedure of choice in critically ill patients? Ren Fail. 2003;25:855–62.
66. Augustine JJ, Sandy D, Seifert TH, Paganini EP. A randomized controlled trial comparing intermittent with continuous dialysis in patients with ARF. Am J Kidney Dis. 2004;44:1000–7.
67. Kielstein JT, Kretschmer U, Ernst T, Hafer C, Bahr MJ, Haller H, et al. Efficacy and cardiovascular tolerability of extended dialysis in critically ill patients: a randomized controlled study. Am J Kidney Dis. 2004;43:342–9.
68. Kumar VA, Yeun JY, Depner TA, Don BR. Extended daily dialysis vs. continuous hemodialysis for ICU patients with acute renal failure: a two-year single center report. Int J Artif Organs. 2004;27:371–9.
69. Uehlinger DE, Jakob SM, Ferrari P, Eichelberger M, Huynh-Do U, Marti HP, et al. Comparison of continuous and intermittent renal replacement therapy for acute renal failure. Nephrol Dial Transplant. 2005;20:1630–7.
70. Vinsonneau C, Camus C, Combes A, Costa de Beauregard MA, Klouche K, Boulain T, et al. Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: a multicentre randomised trial. Lancet. 2006;368:379–85.
71. Noble JSC, Simpson K, Allison ME. Long-term quality of life and hospital mortality in patients treated with intermittent or continuous hemodialysis for acute renal failure. Ren Fail. 2006;28:323–30.
72. Abe M, Okada K, Suzuki M, Nagura C, Ishihara Y, Fujii Y, et al. Comparison of sustained hemodiafiltration with continuous venovenous hemodiafiltration for the treatment of critically ill patients with acute kidney injury. Artif Organs. 2010;34:331–8.
73. Lins RL, Elseviers MM, Van der Niepen P, Hoste E, Malbrain ML, Damas P, et al. Intermittent versus continuous renal replacement therapy for acute kidney injury patients admitted to the intensive care unit: results of a randomized clinical trial. Nephrol Dial Transplant. 2009;24:512–8.
74. Abe M, Maruyama N, Matsumoto S, Okada K, Fujita T, Matsumoto K, et al. Comparison of sustained hemodiafiltration with acetate-free dialysate and continuous venovenous hemodiafiltration for the treatment of critically ill patients with acute kidney injury. Int J Nephrol. 2011;2011:432094.
75. Schwenger V, Weigand MA, Hoffmann O, Dikow R, Kihm LP, Seckinger J, et al. Sustained low efficiency dialysis using a single-pass batch system in acute kidney injury—a randomized interventional trial: the REnal Replacement Therapy Study in Intensive Care Unit PatiEnts. Crit Care. 2012;16:R140.

76. Schefold JC, von Haehling S, Pschowski R, Bender T, Berkmann C, Briegel S, et al. The effect of continuous versus intermittent renal replacement therapy on the outcome of critically ill patients with acute renal failure (CONVINT): a prospective randomized controlled trial. Crit Care. 2014;18:R11.
77. Bell M, SWING, Granath F, Schön S, Erkbom A, Martling CR. Continuous renal replacement therapy is associated with less chronic renal failure than intermittent haemodialysis after acute renal failure. Intensive Care Med. 2007;33:773–80.
78. Wald R, Schariff SZ, Adhikari NKJ, Bagshaw SM, Burns KEA, Friedrich JO, et al. The association between renal replacement therapy modality and long-term outcomes among critically ill adults with acute kidney injury: a retrospective cohort study. Crit Care Med. 2014;42:868.
79. Bonnassieux MB, Duclos A, Schneider AG, Schmidt A, Pharm DSB, Cacalotte C, et al. Renal replacement therapy modality in the ICU and renal recovery at hospital discharge. Crit Care Med. 2018;46:e102–10.
80. Tonelli M, Manns B, Feller-Kopman D. Acute renal failure in the intensive care unit: a systematic review of the impact of dialytic modality on mortality and renal recover. Am J Kidney Dis. 2002;40:875–85.
81. Kellum JA, Angus DC, Johnson JP, Leblanc M, Griffin M, Ramakrishnan N, et al. Continuous versus intermittent renal replacement therapy: a meta-analysis. Intensive Care Med. 2002;28:29–37.
82. Rabindranath K, Adams J, MacLeod AM, Muirhead N. Intermittent versus continuous renal replacement therapy for acute renal failure in adults. Cochrane Database Syst Rev. 2007;3:CD003773.
83. Ghahramani N, Shadrou S, Hollenbeak C. A systematic review of continuous renal replacement therapy and intermittent haemodialysis in management of patients with acute renal failure. Nephrology. 2008;13:570–8.
84. Bagshaw SM, Berthiaume LR, Delaney A, Bellomo R. Continuous versus intermittent renal replacement therapy for critically ill patients with acute kidney injury: a meta-analysis. Crit Care Med. 2008;36:610–7.
85. Pannu N, Klarenbach S, Wiebe N, Manns B, Tonelli M, Alberta Kidney Disease Network. Renal replacement therapy in patients with acute renal failure: a systematic review. JAMA. 2008;299:29–37.
86. Schneider AG, Bellomo R, Bagshaw SM, et al. Choice of renal replacement therapy modality and dialysis dependence after acute kidney injury: a systematic review and meta-analysis. Intensive Care Med. 2013;39:987–97.
87. Zhang L, Yang J, Eastwood GM, Zhu G, Tanaka A, Bellomo R. Extended daily dialysis versus continuous renal replacement therapy for acute kidney injury: a meta-analysis. Am J Kidney Dis. 2015;66:322–30.
88. Nash DM, Przech S, Wald R, O'Reilly D. Systematic review and meta-analysis of renal replacement therapy modalities for acute kidney injury in the intensive care unit. J Crit Care. 2017;41:138–44.
89. Kellum JA, Johnson JP, Kramer D, Palevsky P, Brady JJ, Pinsky MR. Diffusive vs. convective therapy: effects on mediators of inflammation in patients with severe systemic inflammatory response syndrome. Crit Care Med. 1998;26:1995–2000.
90. Morgera S, Slowinski T, Melzer C, Sobottke V, Vargas-Hein O, Volk T, et al. Renal replacement therapy with high-cutoff hemofilters: impact of convection and diffusion on cytokine clearances and protein status. Am J Kidney Dis. 2004;43:444–53.
91. Daud KM, Leong GB, Visvanathan R. Acute dialytic support for the critically ill: continuous venovenous haemodialysis versus continuous venovenous haemofiltration. Int Med J. 2006;13:37–42.
92. Wald R, Friedrich JO, Bagshaw SM, Burns KE, Garg AX, Hladunewich MA, et al. Optimal mode of clearance in critically ill patients with acute kidney injury (OMAKI)-a pilot randomized

controlled trial of hemofiltration versus hemodialysis: a Canadian Critical Care Trials Group project. Crit Care. 2012;16:R205.
93. Friedrich JO, Wald R, Bagshaw SM, Burns KE, Adhikari NK. Hemofiltration compared to hemodialysis for acute kidney injury: systematic review and meta-analysis. Crit Care. 2012;16:R146.
94. Uchino S, Bellomo R, Morimatu H, Morgera S, Schetz M, Tan I, et al. Continuous renal replacement therapy: a worldwide practice survey. Intensive Care Med. 2007;33:1563–70.
95. Gabriel DP, Caramori JT, Martim LC, Barretti P, Balbi AL. High volume peritoneal dialysis vs daily hemodialysis: a randomized, controlled trial in patients with acute kidney injury. Kidney Int. 2008;73:S87–93.
96. Chionh CY, Soni SS, Finkelstein FO, Ronco C, Cruz DN. Use of peritoneal in AKI: a systematic review. Clin J Am Soc Nephrol. 2013;8:1649–60.
97. Schiffl H, Lang SM, König A, Strasser T, Haider MC, Held E. Biocompatible membranes in acute renal failure: prospective case-controlled study. Lancet. 1994;344:570–2.
98. Jones CH, Goutcher E, Newstead CG, Will EJ, Dean SG, Davison AM. Hemodynamics and survival of patients with acute renal failure treated by continuous dialysis with two synthetic membranes. Artif Organs. 1998;22:638–43.
99. Jörres A, Gahl GM, Dobis C, Polenakovic MH, Cakalaroski K, Rutkowski B, et al. Haemodialysis-membrane biocompatibility and mortality of patients with dialysis-dependent acute renal failure: a prospective randomised multicentre trial. Lancet. 1999;354:1337–41.
100. Gastaldello K, Melot C, Kahn RJ, Vanherweghem JL, Vincent JL, Tielemans C. Comparison of cellulose diacetate and polysulfone membranes in the outcome of acute renal failure. A prospective randomized study. Nephrol Dial Transplant. 2000;15:224–30.
101. Albright RC Jr, Smelser JM, McCarthy JT, Homburger HA, Bergstralh EJ, Larson TS. Patient survival and renal recovery in acute renal failure: randomized comparison of cellulose acetate and polysulfone membrane dialyzers. Mayo Clin Proc. 2000;75:1141–7.
102. Ponikvar JB, Rus RR, Kenda RB, Bren AF, Ponikvar RR. Low-flux versus high-flux synthetic dialysis membrane in acute renal failure: prospective randomized study. Artif Organs. 2001;25:946–50.
103. Alonso A, Lau J, Jaber BL. Biocompatible hemodialysis membranes for acute renal failure. Cochrane Database Syst Rev. 2008;23:CD005283.
104. Hirasawa H, Oda S, Nakamura M, Watanabe E, Shiga H, Matsuda K. Continuous hemodiafiltration with a cytokine-adsorbing hemofilter for sepsis. Blood Purif. 2012;34:164–70.
105. Nakada T, Oda S, Matsuda K, Sadahiro T, Nakamura M, Abe R, et al. Continuous hemodiafiltration with PMMA hemofilter in the treatment of patients with septic shock. Mol Med. 2008;14:257–63.
106. Matsuda K, Moriguchi T, Harii N, Goto J. Comparison of efficacy between continuous hemodiafiltration with PMMA membrane hemofilter and a PAN membrane hemofilter in the treatment of a patient with septic acute renal failure. Transfus Apher Sci. 2009;40:49–53.
107. Shiga H, Hirasawa H, Nishida O, Oda S, Nakamura M, Mashiko K, et al. Continuous hemodiafiltration with a cytokine-adsorbing hemofilter in patients with septic shock: a preliminary study. Blood Purif. 2014;38:211–8.
108. Doi K, Iwagami M, Yoshida E, Marshall MR. Association of polyethylenimine-coated AN69ST membrane in continuous renal replacement therapy with the intensive care outcomes: observations from a claims database from Japan. Blood Purif. 2017;44:184–92.

Chapter 18
Short-Term and Long-Term Outcomes of AKI Patients

Kengo Furuichi, Yuta Yamamura, and Takashi Wada

Abstract This section focuses primarily on long-term outcomes after an episode of acute kidney injury, particularly chronic kidney disease, end-stage renal disease, cardiovascular disease, and death. It goes on to assess a number of prognostic factors that may predict poor outcomes. Some of these are patient-specific factors such as age or preexisting chronic kidney disease. Others relate to the course of the acute kidney injury, including severity of the renal dysfunction, duration of the dysfunction before recovery, and whether dialysis was temporarily required. The section concludes with recommendations on follow-up after an episode of acute kidney injury, including the importance of ongoing monitoring by a nephrologist.

Keywords Prognostic factors · Recovery from AKI · Follow-up after AKI
Cardiovascular events · Long-term outcome

18.1 Introduction

In recent years, the incidence of AKI has been increasing annually because of factors such as aging of the population, lifestyle diseases, and complications of medical treatment [1]. A number of epidemiologic studies of AKI have been carried out since international diagnostic criteria have been available. Data indicate various clinical situations that have a high incidence of AKI. Regardless of the underlying illness, when AKI intervenes, there is a significantly poorer prognosis than when renal

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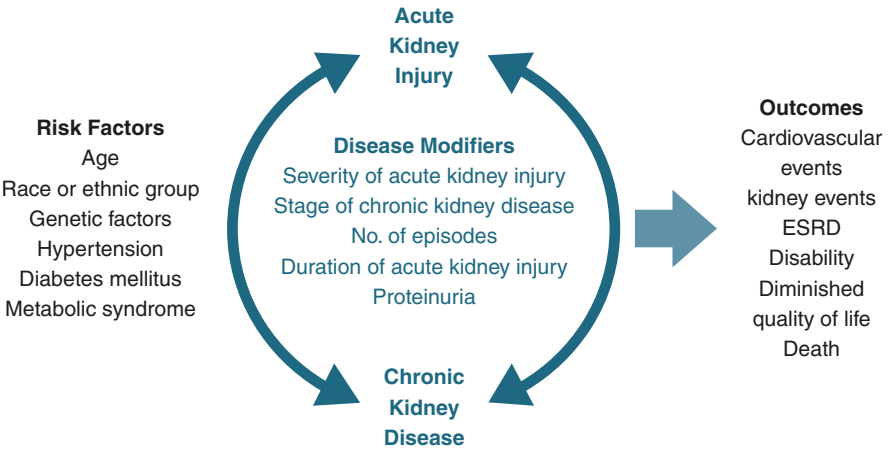

Fig. 18.1 Acute kidney injury and chronic kidney disease share common risk factors and outcomes [7]

function remains normal [2–5]. AKI clearly has an impact on long-term as well as short-term outcomes; the latter often measured by in-hospital mortality and length of intensive care unit (ICU) stay [6]. CKD is a risk factor for AKI and, in turn, AKI is a risk factor for CKD, both of which share common risk factors and outcomes (Fig. 18.1) [7]. As AKI increases hospital length of stay and medical costs, it is an important issue not only for clinical reasons but also because of its effect on medical economics [8]. In this section, we review the impact of AKI on long-term health outcomes.

18.2 Epidemiology

18.2.1 AKI, CKD, and ESRD

In recent years, numerous cohort studies have reported that AKI is closely related not only to acute clinical outcomes, but also to long-term outcomes and CKD [9–17]. CKD is not unusual as a sequela to AKI requiring renal replacement therapy [18, 19], but even relatively minor AKI that does not require dialysis is also a risk factor for CKD [10, 20]. There have been no randomized controlled trials for AKI, but there are some systematic reviews and meta-analyses [6, 21, 22].

Coca and colleagues carried out a systematic review and meta-analysis of 13 studies comparing patients with and without AKI, with CKD, and ESRD as outcomes [21]. The incidence of CKD in the AKI group was 25.8/100 person-years, the incidence of ESRD was 8.6/100 person-years, and the adjusted relative risk (AKI vs. no AKI) was 8.8 (95% CI 3.1–25.5) for ESRD and 3.1 (95% CI 1.9–5.0) for ESRD.

In 2015, Sawhney et al. reported a systematic review of the relationship between AKI and death, the onset or progression of CKD, and the onset of ESRD, according

to the kidney function before and after AKI [6]. The data indicated that non-recovery of kidney function after AKI is a prognostic indicator of poor kidney function 1 year after AKI. Moreover, pre-AKI CKD was associated with doubling of deaths and a fourfold to fivefold increase in poor renal outcomes.

In 2018, See et al. reviewed 82 studies, comparing the incidence of CKD and ESRD among groups with or without an episode of AKI. Those with AKI were at high risk for progression to CKD (HR 2.67, 95% CI 1.99–3.58; 17.76 versus 7.59 cases per 100 person-years), and ESRD (HR 4.81, 95% CI 3.04–7.62; 0.47 versus 0.08 cases per 100 person-years). Furthermore, the relative risk of CKD and ESRD increased as the severity of the AKI increased [22].

18.2.2 AKI and Cardiovascular Events

The relationship between AKI and cardiovascular and cerebrovascular diseases is widely recognized [23–25]. In addition, AKI is a strong risk factor for CKD, and CKD is highly correlated with higher rates of cardiovascular events and death [26]. In 2017, Odutayo et al. reported a systematic review and meta-analysis comparing outcomes of cardiovascular disease between patients with and without AKI. Among 25 studies, the adjusted relative risk (95% CI) was 1.86 (1.72–2.01) for cardiovascular death, 1.38 (1.23–1.55) for cardiovascular events, 1.40 for acute myocardial infarction (1.23–1.59), and 1.15 for stroke (1.03–1.28) (Fig. 18.2) [27].

18.3 Prognostic Factors for Long-Term Outcomes After AKI

Factors influencing the outcome after an episode of AKI include the type of renal replacement therapy [28–31]; age [32–36]; CKD before AKI onset [37–39]; comorbidities such as hypertension, diabetes, and heart disease [33, 36, 37], AKI severity [12, 22, 40–42]; the pattern of recovery from AKI [10, 34, 43]; and the general condition during the acute phase [34, 44, 45].

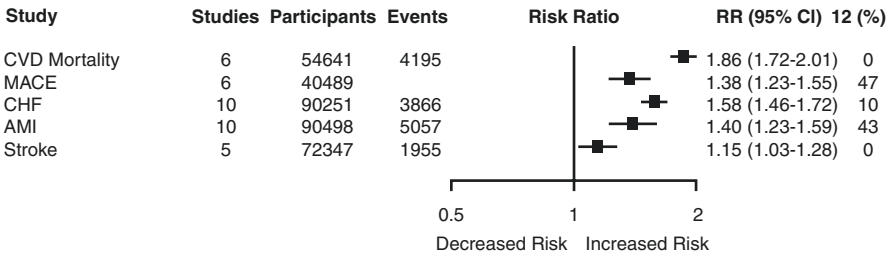

Fig. 18.2 Association between AKI and cardiovascular disease [27]

18.3.1 Type of Renal Replacement Therapy

Several retrospective cohort studies have investigated the effect of the type of renal replacement therapy on long-term outcome after AKI. Continuous rather than intermittent dialysis in critically ill adults with AKI is associated with a lower incidence of chronic dialysis [28]. Another study found that continuous dialysis conveyed a benefit in terms of renal recovery, although mortality did not differ between those on continuous or intermittent therapy [29]. In addition to these retrospective cohort studies, pooled analyses of observational studies suggested a higher rate of dialysis dependence among survivors after AKI who initially received intermittent as compared with continuous dialysis (relative risk 1.99). However, pooled analyses of randomized controlled trials showed no difference in the type of renal replacement therapy among survivors after AKI [30]. Moreover, a recent prospective observational multicenter cohort database study indicates that continuous dialysis did not appear to improve 30-day and 6-month patient outcomes [31]. Furthermore, high-quality studies are necessary to provide definite conclusions on this issue.

18.3.2 Age

Older patients with CKD who develop AKI are at increased risk of failure of recovery of kidney function, needing chronic dialysis, and higher long-term mortality [33]. A systematic review noted similar findings, with 31.3% of surviving elderly patients over age 65 not recovering kidney function compared with only 26% of younger patients [34]. These data indicate that the elderly have a high risk after AKI of long-term kidney dysfunction and death.

18.3.3 CKD Before AKI Onset

In elderly individuals, preexisting CKD confers a significantly higher risk of ESRD [37]. A multicenter observational study of 9425 patients who survived to hospital discharge after major surgery found that patients with AKI who had preexisting CKD were at higher risk for death and for dialysis after hospital discharge than those without CKD [38]. In a large cohort study of 920,985 adults, the adjusted rates of admission with AKI and kidney injury requiring dialysis were higher in participants with heavy dipstick proteinuria for all values of eGFR 38). Comorbidities such as hypertension, diabetes, and heart disease are also risk factors for a poor long-term outcome after AKI [33, 36, 37].

18.3.4 AKI Severity

The severity of renal dysfunction during AKI also affects the long-term outcome after AKI. In patients with AKI after cardiac surgery, increases in the percent change from baseline to peak creatinine levels were found to be associated with an increased incidence of CKD, progression of CKD, and 5-year mortality after AKI [41]. In patients who underwent coronary angiography, the fully adjusted risk of death increased twofold in those with AKI stage 1 and threefold in those with AKI stage 2 or 3 [42]. In the review by See et al. of 82 studies with follow-up for at least 1 year, the incidence of CKD and ESRD was higher in those with versus those without AKI, and the relative risk of these outcomes increased as the severity of AKI increased [22].

18.3.5 Duration of AKI

Of 18 studies included in systematic review, the effect of the duration of AKI on long-term survival was reported in 8 [43]. The pooled risk ratio (RR) for poor long-term survival was generally higher the longer the duration of AKI. The RRs for short, medium, and long duration of AKI were 1.42 (95% CI 1.21–1.66, $n = 8$ studies), 1.92 (95% CI 1.34–2.75, $n = 4$ studies), and 2.28 (95% CI 1.77–2.94, $n = 8$ studies), respectively. The duration of AKI was independently associated with a higher risk of cardiovascular outcomes and incident stage 3 CKD when stratified within each stage of AKI.

18.3.6 Need for Dialysis

In general, patients with AKI who require dialysis have a poor prognosis for recovery of kidney function and survival. Results of studies have varied as to whether undergoing renal replacement therapy is itself an independent risk factor for subsequent poor kidney function. A meta-analysis indicates that the type of dialysis does not significantly affect ICU mortality rate, in-hospital mortality rate, or the need for dialysis [46].

18.3.7 Limitation on Assessment of Risk Factors

Depending on where the study was done, the findings of studies of risk factors for poor outcome after AKI differ to some extent. Independent risk factors associated with in-hospital mortality include older age, residence in an emerging country,

use of vasopressors (emerging countries only), dialysis and mechanical ventilation, and higher APACHE scores and cumulative fluid balance (developed countries only). A lower probability of renal recovery was associated with residence in an emerging country, higher APACHE score (emerging countries only) and dialysis, while mechanical ventilation was associated with better renal recovery (developed countries only) [45].

18.4 Recovery from AKI

From the viewpoint of recovery from AKI, the length of time from peak serum creatinine to recovery is important. The US Centers for Disease Control and Prevention CKD Surveillance Team compared 104,764 patients without preexisting CKD who survived for more than 1 year after hospital discharge, including 17,049 with and 87,715 without AKI. They investigated the subsequent new onset of CKD stratified by length of time for recovery from AKI: early (within 2 days), intermediate (3–10 days), late (10 days or more), or no recovery [6]. The early recovery group comprised over 70% of the total study population. Among those with AKI stage 1 (91% of all patients with AKI), the adjusted risk ratio for CKD in the early recovery group was 1.43 (1.39–1.48) compared with 2.00 (1.88–2.12) for the intermediate group and 2.65 (2.51–2.80) for the late and no recovery groups. Those with AKI stage 2 or 3 had similar results [10]. Kellum and colleagues reported on the rate of recovery in 16,968 patients with stage 2 or 3 AKI, finding five different patterns of recovery, for example, early recovery that was maintained, early recovery with relapse, or even no recovery at all. The later or more complicated the recovery from AKI, the higher is the death rate at 1 year; for example, it was only 9.8% for those with an early recovery pattern but 59.8% for those whose renal function did not recover after AKI [34].

A systematic review and meta-analysis by Mehta and colleagues also indicated that the time for recovery from AKI is an important factor for estimating long-term prognosis. The duration of AKI was independently associated with long-term mortality, cardiovascular events, and development of incident CKD stage 3 [43]. Their data suggest the importance of trying to prevent recurrence after an initial episode of AKI during hospitalization.

18.5 AKI and Quality of Life

In patients who have had an episode of AKI, better quality of life (QOL) was associated with patient factors such as younger age and no CKD; the severity of the acute illness, such as no sepsis, short ICU, and/or hospital stay; and conditions after discharge [47]. Prior to the hospital admission during which an episode of AKI occurred, the preadmission QOL of patients who survived AKI was reported to be

significantly lower in two dimensions compared with age-matched controls from the general population. However, 6 months after ICU discharge, QOL did not differ significantly between patients who had or did not have AKI. However, compared with age-matched controls in the general population, QOL was poorer in both groups [48].

18.6 Follow-Up After AKI

Given the risk that an episode of AKI poses for ESRD, CKD, or death, careful follow-up is important. According to KDIGO's AKI clinical practice guidelines, patients should be reassessed within 3 months after discharge [49].

For those who had severe AKI, closer monitoring is advisable. For patients with severe AKI requiring dialysis, the mortality rate was lower among those followed after discharge by a nephrologist compared with those not seeing a nephrologist (Fig. 18.3) [50]. On the other hand, it is reported that only about 30% of patients who survived AKI were specifically followed to monitor their renal function [51]. A US Veterans Hospital study found that only about 20% of patients with AKI stages

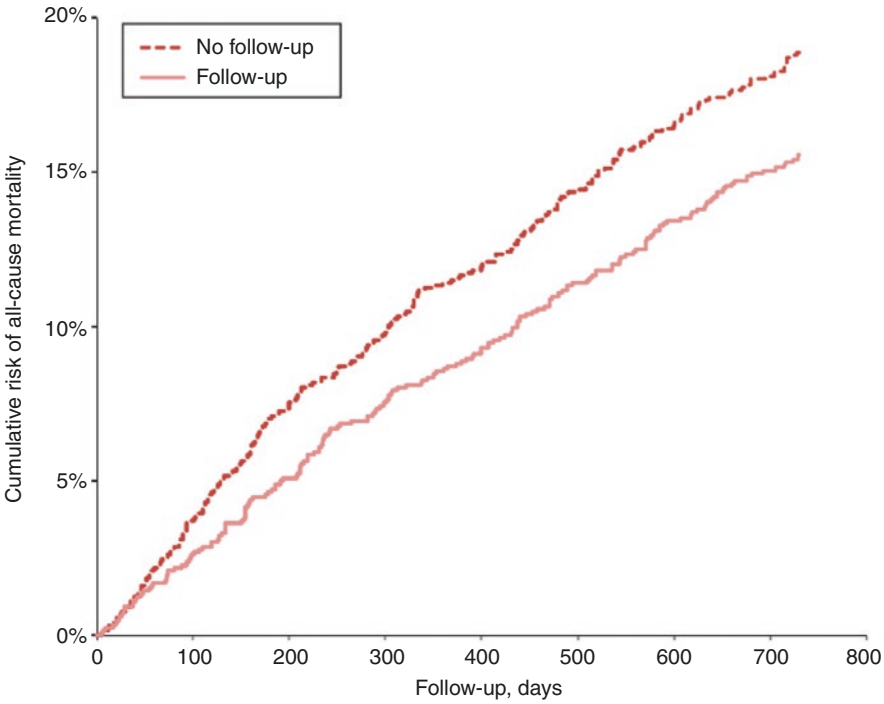

Fig. 18.3 All-cause mortality in survivors of severe AKI. Long-term outcomes of acute kidney injury [50]

2 and 3 were followed after discharge by nephrologists [52]. These data indicate that there is an opportunity to improve long-term follow-up after AKI with a view to improving outcomes.

References

1. Hsu RK, McCulloch CE, Dudley RA, Lo LJ, Hsu CY. Temporal changes in incidence of dialysis-requiring AKI. J Am Soc Nephrol. 2013;24:37–42.
2. Susantitaphong P, Cruz DN, Cerda J, Abulfaraj M, Alqahtani F, Koulouridis I, Jaber BL, Acute Kidney Injury Advisory Group of the American Society of Nephrology. World incidence of AKI: a meta-analysis. Clin J Am Soc Nephrol. 2013;8:1482–93.
3. Uchino S, Bellomo R, Goldsmith D, Bates S, Ronco C. An assessment of the RIFLE criteria for acute renal failure in hospitalized patients. Crit Care Med. 2006;34:1913–7.
4. Ricci Z, Cruz D, Ronco C. The RIFLE criteria and mortality in acute kidney injury: a systematic review. Kidney Int. 2008;73:538–46.
5. Joannidis M, Metnitz B, Bauer P, Schusterschitz N, Moreno R, Druml W, Metnitz PG. Acute kidney injury in critically ill patients classified by AKIN versus RIFLE using the SAPS 3 database. Intensive Care Med. 2009;35:1692–702.
6. Sawhney S, Mitchell M, Marks A, Fluck N, Black C. Long-term prognosis after acute kidney injury (AKI): what is the role of baseline kidney function and recovery? A systematic review. BMJ Open. 2015;5:e006497.
7. Chawla LS, Eggers PW, Star RA, Kimmel PL. Acute kidney injury and chronic kidney disease as interconnected syndromes. N Engl J Med. 2014;371:58–66.
8. Collister D, Pannu N, Ye F, James M, Hemmelgarn B, Chui B, Manns B, Klarenbach S, Alberta Kidney Disease Network. Health care costs associated with AKI. Clin J Am Soc Nephrol. 2017;12:1733–43.
9. Pannu N, James M, Hemmelgarn B, Klarenbach S, Alberta Kidney Disease Network. Association between AKI, recovery of renal function, and long-term outcomes after hospital discharge. Clin J Am Soc Nephrol. 2013;8:194–202.
10. Heung M, Steffick DE, Zivin K, Gillespie BW, Banerjee T, Hsu CY, Powe NR, Pavkov ME, Williams DE, Saran R, Shahinian VB, Centers for Disease Control and Prevention CKD Surveillance Team. Acute kidney injury recovery pattern and subsequent risk of CKD: an analysis of veterans health administration data. Am J Kidney Dis. 2016;67:742–52.
11. Bagshaw SM, Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A, Oudemans-van Straaten HM, Ronco C, Kellum JA, Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) Investigators. Septic acute kidney injury in critically ill patients: clinical characteristics and outcomes. Clin J Am Soc Nephrol. 2007;2:431–9.
12. Chawla LS, Amdur RL, Amodeo S, Kimmel PL, Palant CE. The severity of acute kidney injury predicts progression to chronic kidney disease. Kidney Int. 2011;79:1361–9.
13. Lai CF, Wu VC, Huang TM, Yeh YC, Wang KC, Han YY, Lin YF, Jhuang YJ, Chao CT, Shiao CC, Tsai PR, Hu FC, Chou NK, Ko WJ, Wu KD, National Taiwan University Hospital Study Group on Acute Renal Failure (NSARF). Kidney function decline after a non-dialysis-requiring acute kidney injury is associated with higher long-term mortality in critically ill survivors. Crit Care. 2012;16:R123.
14. Rimes-Stigare C, Frumento P, Bottai M, Martensson J, Martling CR, Walther SM, Karlstrom G, Bell M. Evolution of chronic renal impairment and long-term mortality after de novo acute kidney injury in the critically ill; a Swedish multi-centre cohort study. Crit Care. 2015;19:221.

15. Bucaloiu ID, Kirchner HL, Norfolk ER, Hartle JE 2nd, Perkins RM. Increased risk of death and de novo chronic kidney disease following reversible acute kidney injury. Kidney Int. 2012;81:477–85.
16. van Kuijk JP, Flu WJ, Chonchol M, Hoeks SE, Winkel TA, Verhagen HJ, Bax JJ, Poldermans D. Temporary perioperative decline of renal function is an independent predictor for chronic kidney disease. Clin J Am Soc Nephrol. 2010;5:1198–204.
17. Jones J, Holmen J, De Graauw J, Jovanovich A, Thornton S, Chonchol M. Association of complete recovery from acute kidney injury with incident CKD stage 3 and all-cause mortality. Am J Kidney Dis. 2012;60:402–8.
18. Lo LJ, Go AS, Chertow GM, McCulloch CE, Fan D, Ordonez JD, Hsu CY. Dialysis-requiring acute renal failure increases the risk of progressive chronic kidney disease. Kidney Int. 2009;76:893–9.
19. Wald R, Quinn RR, Luo J, Li P, Scales DC, Mamdani MM, Ray JG, University of Toronto Acute Kidney Injury Research Group. Chronic dialysis and death among survivors of acute kidney injury requiring dialysis. JAMA. 2009;302:1179–85.
20. Wald R, Quinn RR, Adhikari NK, Burns KE, Friedrich JO, Garg AX, Harel Z, Hladunewich MA, Luo J, Mamdani M, Perl J, Ray JG, University of Toronto Acute Kidney Injury Research Group. Risk of chronic dialysis and death following acute kidney injury. Am J Med. 2012;125:585–93.
21. Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. Kidney Int. 2012;81:442–8.
22. See EJ, Jayasinghe K, Glassford N, Bailey M, Johnson DW, Polkinghorne KR, Toussaint ND, Bellomo R. Long-term risk of adverse outcomes after acute kidney injury: a systematic review and meta-analysis of cohort studies using consensus definitions of exposure. Kidney Int. 2019;95:160–72.
23. Wu VC, Wu PC, Wu CH, Huang TM, Chang CH, Tsai PR, Ko WJ, Chen L, Wang CY, Chu TS, Wu KD, National Taiwan University Study Group on Acute Renal Failure Group. The impact of acute kidney injury on the long-term risk of stroke. J Am Heart Assoc. 2014;3.
24. Go AS, Hsu CY, Yang J, Tan TC, Zheng S, Ordonez JD, Liu KD. Acute kidney injury and risk of heart failure and atherosclerotic events. Clin J Am Soc Nephrol. 2018;13:833–41.
25. Wu VC, Wu CH, Huang TM, Wang CY, Lai CF, Shiao CC, Chang CH, Lin SL, Chen YY, Chen YM, Chu TS, Chiang WC, Wu KD, Tsai PR, Chen L, Ko WJ, NSARF Group. Long-term risk of coronary events after AKI. J Am Soc Nephrol. 2014;25:595–605.
26. Matsushita K, Coresh J, Sang Y, Chalmers J, Fox C, Guallar E, Jafar T, Jassal SK, Landman GW, Muntner P, Roderick P, Sairenchi T, Schottker B, Shankar A, Shlipak M, Tonelli M, Townend J, van Zuilen A, Yamagishi K, Yamashita K, Gansevoort R, Sarnak M, Warnock DG, Woodward M, Arnlov J, CKD Prognosis Consortium. Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data. Lancet Diabetes Endocrinol. 2015;3:514–25.
27. Odutayo A, Wong CX, Farkouh M, Altman DG, Hopewell S, Emdin CA, Hunn BH. AKI and long-term risk for cardiovascular events and mortality. J Am Soc Nephrol. 2017;28:377–87.
28. Wald R, Shariff SZ, Adhikari NK, Bagshaw SM, Burns KE, Friedrich JO, Garg AX, Harel Z, Kitchlu A, Ray JG. The association between renal replacement therapy modality and long-term outcomes among critically ill adults with acute kidney injury: a retrospective cohort study∗. Crit Care Med. 2014;42:868–77.
29. Bell M, SWING, Granath F, Schon S, Ekbom A, Martling CR. Continuous renal replacement therapy is associated with less chronic renal failure than intermittent haemodialysis after acute renal failure. Intensive Care Med. 2007;33:773–80.
30. Schneider AG, Bellomo R, Bagshaw SM, Glassford NJ, Lo S, Jun M, Cass A, Gallagher M. Choice of renal replacement therapy modality and dialysis dependence after acute kidney injury: a systematic review and meta-analysis. Intensive Care Med. 2013;39:987–97.

31. Truche AS, Darmon M, Bailly S, Clec'h C, Dupuis C, Misset B, Azoulay E, Schwebel C, Bouadma L, Kallel H, Adrie C, Dumenil AS, Argaud L, Marcotte G, Jamali S, Zaoui P, Laurent V, Goldgran-Toledano D, Sonneville R, Souweine B, Timsit JF, OUTCOMEREA Study Group. Continuous renal replacement therapy versus intermittent hemodialysis in intensive care patients: impact on mortality and renal recovery. Intensive Care Med. 2016;42:1408–17.
32. Macedo E, Zanetta DM, Abdulkader RC. Long-term follow-up of patients after acute kidney injury: patterns of renal functional recovery. PLoS One. 2012;7:e36388.
33. Schmitt R, Coca S, Kanbay M, Tinetti ME, Cantley LG, Parikh CR. Recovery of kidney function after acute kidney injury in the elderly: a systematic review and meta-analysis. Am J Kidney Dis. 2008;52:262–71.
34. Kellum JA, Sileanu FE, Bihorac A, Hoste EA, Chawla LS. Recovery after acute kidney injury. Am J Respir Crit Care Med. 2017;195:784–91.
35. Ali T, Khan I, Simpson W, Prescott G, Townend J, Smith W, Macleod A. Incidence and outcomes in acute kidney injury: a comprehensive population-based study. J Am Soc Nephrol. 2007;18:1292–8.
36. Srisawat N, Wen X, Lee M, Kong L, Elder M, Carter M, Unruh M, Finkel K, Vijayan A, Ramkumar M, Paganini E, Singbartl K, Palevsky PM, Kellum JA. Urinary biomarkers and renal recovery in critically ill patients with renal support. Clin J Am Soc Nephrol. 2011;6:1815–23.
37. Ishani A, Xue JL, Himmelfarb J, Eggers PW, Kimmel PL, Molitoris BA, Collins AJ. Acute kidney injury increases risk of ESRD among elderly. J Am Soc Nephrol. 2009;20:223–8.
38. Wu VC, Huang TM, Lai CF, Shiao CC, Lin YF, Chu TS, Wu PC, Chao CT, Wang JY, Kao TW, Young GH, Tsai PR, Tsai HB, Wang CL, Wu MS, Chiang WC, Tsai IJ, Hu FC, Lin SL, Chen YM, Tsai TJ, Ko WJ, Wu KD. Acute-on-chronic kidney injury at hospital discharge is associated with long-term dialysis and mortality. Kidney Int. 2011;80:1222–30.
39. James MT, Hemmelgarn BR, Wiebe N, Pannu N, Manns BJ, Klarenbach SW, Tonelli M, Alberta Kidney Disease Network. Glomerular filtration rate, proteinuria, and the incidence and consequences of acute kidney injury: a cohort study. Lancet. 2010;376:2096–103.
40. Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A, Straaten HO, Ronco C, Kellum JA. Discontinuation of continuous renal replacement therapy: a post hoc analysis of a prospective multicenter observational study. Crit Care Med. 2009;37:2576–82.
41. Ishani A, Nelson D, Clothier B, Schult T, Nugent S, Greer N, Slinin Y, Ensrud KE. The magnitude of acute serum creatinine increase after cardiac surgery and the risk of chronic kidney disease, progression of kidney disease, and death. Arch Intern Med. 2011;171:226–33.
42. James MT, Ghali WA, Knudtson ML, Ravani P, Tonelli M, Faris P, Pannu N, Manns BJ, Klarenbach SW, Hemmelgarn BR, Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) Investigators. Associations between acute kidney injury and cardiovascular and renal outcomes after coronary angiography. Circulation. 2011;123:409–16.
43. Mehta S, Chauhan K, Patel A, Patel S, Pinotti R, Nadkarni GN, Parikh CR, Coca SG. The prognostic importance of duration of AKI: a systematic review and meta-analysis. BMC Nephrol. 2018;19:91.
44. Harel Z, Bell CM, Dixon SN, McArthur E, James MT, Garg AX, Harel S, Silver S, Wald R. Predictors of progression to chronic dialysis in survivors of severe acute kidney injury: a competing risk study. BMC Nephrol. 2014;15:114.
45. Bouchard J, Acharya A, Cerda J, Maccariello ER, Madarasu RC, Tolwani AJ, Liang X, Fu P, Liu ZH, Mehta RL. A prospective international multicenter study of AKI in the intensive care unit. Clin J Am Soc Nephrol. 2015;10:1324–31.
46. Nash DM, Przech S, Wald R, O'Reilly D. Systematic review and meta-analysis of renal replacement therapy modalities for acute kidney injury in the intensive care unit. J Crit Care. 2017;41:138–44.

47. Morsch C, Thome FS, Balbinotto A, Guimaraes JF, Barros EG. Health-related quality of life and dialysis dependence in critically ill patient survivors of acute kidney injury. Ren Fail. 2011;33:949–56.
48. Hofhuis JG, van Stel HF, Schrijvers AJ, Rommes JH, Spronk PE. The effect of acute kidney injury on long-term health-related quality of life: a prospective follow-up study. Crit Care. 2013;17:R17.
49. Palevsky PM, Liu KD, Brophy PD, Chawla LS, Parikh CR, Thakar CV, Tolwani AJ, Waikar SS, Weisbord SD. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for acute kidney injury. Am J Kidney Dis. 2013;61:649–72.
50. Harel Z, Wald R, Bargman JM, Mamdani M, Etchells E, Garg AX, Ray JG, Luo J, Li P, Quinn RR, Forster A, Perl J, Bell CM. Nephrologist follow-up improves all-cause mortality of severe acute kidney injury survivors. Kidney Int. 2013;83:901–8.
51. Karsanji DJ, Pannu N, Manns BJ, Hemmelgarn BR, Tan Z, Jindal K, Scott-Douglas N, James MT. Disparity between nephrologists' opinions and contemporary practices for community follow-up after AKI hospitalization. Clin J Am Soc Nephrol. 2017;12:1753–61.
52. Siew ED, Peterson JF, Eden SK, Hung AM, Speroff T, Ikizler TA, Matheny ME. Outpatient nephrology referral rates after acute kidney injury. J Am Soc Nephrol. 2012;23:305–12.

Chapter 19
Management of Pediatric AKI

Koichi Kamei

Abstract The Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines are used to diagnose acute kidney injury (AKI) in children, similar to in adults. However, while there are age-specific reference levels of serum creatinine used as a standard for diagnosing AKI, the criteria have yet to be defined for infants younger than 3 months of age. Preterm and low-birth-weight children have high risks of developing AKI, and those who do indeed present with AKI have a worse survival than their non-AKI patients. Extrarenal disease is a common cause; according to a Japanese nationwide survey, kidney disease was the underlying disease in 33.6% of the pediatric patients who underwent blood purification therapy indicated for AKI. Evaluation of fluid overload is especially important in pediatric AKI, and survival is poor with percent fluid overload (%FO) ≥20%. There are treatments specific to pediatric patients for blood purification therapy; for example, the catheter, column, and conditions are set according to the patient's body weight. When AKI occurs in children who are expected to develop serious disorders or have a poor life expectancy, it is necessary to provide a thorough explanation to the parents after a detailed and open discussion among the medical staff and to subsequently determine the indications for the initiation and continuation of blood purification therapy. In the Japanese nationwide survey, the survival of pediatric patients who underwent blood purification therapy was 54.1%. Although patients with nephrogenic AKI have a good life expectancy and a poor renal prognosis, patients with secondary AKI have a good renal prognosis and a poor life expectancy.

Keywords Acute kidney injury · KDIGO · Serum creatinine · Biomarker · Fluid overload · Percent fluid overload (%FO) · Blood purification therapy · Low-birth-weight children · Serious disorder · Long-term prognosis

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19.1 Introduction

Some of the key points in the clinical care of pediatric acute kidney injury (AKI) include: detecting even mild presentations of renal disorders; ensuring the absence of errors in the timing of introducing dialysis; and following the patients long term, since proteinuria and hypertension may develop later after recovery. This article describes the cause, diagnosis, indications and management of blood purification therapy, and the long-term prognosis of pediatric AKI.

19.2 Diagnosis of Pediatric AKI

The diagnosis and treatment of acute kidney injury (AKI) is crucial to the improvement of the outcomes not only in adults, but also in children. Several diagnostic criteria have been suggested for children. These have included the pediatric RIFLE (pRIFLE), AKIN, and Kidney Disease: Improving Global Outcomes (KDIGO) criteria. It is known that the normal serum creatinine (sCr) values change with the age (Table 19.1) [1]. As urine collection is difficult in children, the pRIFLE classification

Table 19.1 Pediatric reference ranges of serum creatinine (mg/dL)

Age	2.5%	50%	97.5%
3~5 months	0.14	0.20	0.26
6~8 months	0.14	0.22	0.31
9~11 months	0.14	0.22	0.34
1 year	0.16	0.23	0.32
2 years	0.17	0.24	0.37
3 years	0.21	0.27	0.37
4 years	0.20	0.30	0.40
5 years	0.25	0.34	0.45
6 years	0.25	0.34	0.48
7 years	0.28	0.37	0.49
8 years	0.29	0.40	0.53
9 years	0.34	0.41	0.51
10 years	0.30	0.41	0.57
11 years	0.35	0.45	0.58

	2.5%		50%		97.5%	
Age	Boy	Girl	Boy	Girl	Boy	Girl
12 years	0.40	0.40	0.53	0.52	0.61	0.66
13 years	0.42	0.41	0.59	0.53	0.80	0.69
14 years	0.54	0.46	0.65	0.58	0.96	0.71
15 years	0.48	0.47	0.68	0.56	0.93	0.72
16 years	0.62	0.51	0.73	0.59	0.96	0.74

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uses a Schwartz formula-based [2] calculation of the estimated glomerular filtration rate (eGFR) [3].

Sutherland et al. compared the pRIFLE, AKIN, and KDIGO diagnostic criteria in 14,795 children aged under 18 who were hospitalized for AKI [4]. The AKIN and KDIGO classifications, which both use the sCr criteria, were almost in agreement; however, as the eGFR-based pRIFLE classification has a higher incidence of stage 1 than the AKIN or KDIGO classifications; a larger number of patients were diagnosed with mild AKI. In all three classifications, the mortality was higher in patients with AKI than in those without AKI; particularly in the intensive care unit (ICU), the increasing severity of AKI (according to all three classifications) was associated with increased mortality. Selewski et al. used the KDIGO classification to examine the AKI outcomes in 2415 patients in pediatric ICUs [5]. In comparison with patients who did not develop AKI, pediatric AKI patients demonstrated a significantly increased length of mechanical ventilation, a longer ICU stay, a longer duration of hospitalization, and a higher mortality rate. In addition, the length of the ICU stay was proportional to the worsening of the KDIGO AKI stages. These two single-center retrospective observational studies involved sufficient numbers of patients to demonstrate that the KDIGO classification is useful for the diagnosis of pediatric AKI. Moreover, as the KDIGO classification does not involve an estimation of the GFR but instead allows staging AKI based on the sCr, it can be considered superior to the pRIFLE classification. Therefore, we suggest the use of the KDIGO diagnostic criteria for pediatric AKI patients aged ≥3 months. However, it must be noted that the use of the AKI diagnostic criteria has not yet been specifically evaluated in Japanese children.

Neonates and children aged <3 months must be considered separately from those aged ≥3 months due to its unique background and immaturity. Although there have been investigations of the AKI diagnosis, treatment, and outcomes in neonates, there used to be no definitive diagnostic criteria for neonatal AKI [6, 7]. In 2014, Jetton et al. and Askenazi et al. introduced the neonatal modified KDIGO criteria, which are based on the KDIGO diagnostic criteria [6, 7]. Similar to the adult and pediatric KDIGO criteria, the neonatal modified KDIGO criteria define stages 1, 2, and 3 AKI according to sCr values 1.5–1.9, 2.0–2.9, and ≥3 times higher than baseline, respectively. The normal value of sCr is only established at age ≥3 months in Japan [1] and not in children under 3 months. The level of sCr in neonates immediately after birth is extremely close to the level of maternal sCr (generally ≤1 mg/dL) [8]. It peaks at day 0–3 and declines to a minimum value (0.2–0.5 mg/dL) over the following 1 week to 20 months [8–10]. Going forward, it is necessary to collect data on Japanese neonates to establish their baseline sCr levels. It should be taken into consideration that the current absence of established baseline levels requires multiple measurements.

Koralkar et al. used the neonatal modified KDIGO criteria to examine AKI and mortality in 229 very low-birth-weight infants both at 36 weeks of gestational age and with a birth weight of 500–1500 kg [11]; the very low-birth-weight infants with AKI had a significantly higher mortality than those not diagnosed with AKI. In

an examination of 455 very low-birth-weight infants using the neonatal modified KDIGO criteria, Carmody et al. found AKI to be associated with mortality and prolonged hospitalization [12]. In addition, a gestational age <28 weeks was strongly associated with the onset of AKI. Rhone et al. used the neonatal modified KDIGO criteria to examine the association between the AKI onset and nephrotoxic medications in 107 very low-birth-weight infants; consequently, these drugs were shown to be associated with the onset of AKI [13]. In an examination of 96 neonates with moderate to severe asphyxia, Sarkar et al. demonstrated that abnormal brain MRIs at 7–10 days of age were significantly more frequent in infants diagnosed with AKI according to the neonatal modified KDIGO criteria [14]. As detailed above, many recent studies have employed the neonatal modified KDIGO criteria for the diagnosis of neonatal AKI.

19.3 Biomarkers of Pediatric AKI

Neutrophil gelatinase-associated lipocalin (NGAL) is a secretory protein of a molecular weight of 25,000 Da and is secreted from activated neutrophils and tubular epithelial cells. The levels of NGAL in the blood and urine are known to be elevated in the hyperacute phase of kidney injury. In an examination of 71 children undergoing a cardiopulmonary bypass (CPB) [15], the children who developed AKI showed significantly elevated levels of serum and urinary NGAL 2 h after the CPB, with areas under the receiver operating characteristic curve (AUC) of 0.998 and 0.906, respectively; this study was the first to indicate the utility of biomarkers for the early diagnosis of AKI. An examination of 311 children undergoing cardiac surgery for congenital heart disease registered at three institutions [16] also indicated that the urinary NGAL is useful for the early diagnosis of AKI. The urinary NGAL was also reported to be useful for the early diagnosis of AKI in a heterogeneous pediatric intensive care unit (PICU) patient cohort which had undergone mechanical ventilation and bladder catheterization [17]. With regard to the survival outcomes, two studies have reported that NGAL is significantly associated with mortality [18, 19].

Cystatin C is a low-weight molecular protein (molecular weight: approximately 13,000 Da) produced by nucleated cells all over the body, and it has been indicated to be useful for early, accurate diagnoses of AKI [20, 21]. Interleukin-18 (IL-18) [22, 23], L-type fatty acid-binding protein (L-FABP) [24], and kidney injury molecule-1 (KIM-1) [25] are also known to show a marked increase in urine as a result of kidney injury; these biomarkers have been studied for their potential utility in the early diagnosis of AKI. However, many of these studies involved relatively homogeneous populations, e.g., children undergoing CPB; the utility of these biomarkers has not been sufficiently assessed in populations of patients with diverse pathologies. Furthermore, the interventions based on these indicators have not yet been reported to improve the renal outcomes or survival outcomes of AKI; therefore, their utility is limited.

19.4 Causes of Pediatric AKI

An extrarenal disease is often the cause of AKI in pediatric patients who undergo renal replacement therapy. In a report by Symons et al. of 344 patients who underwent prospective pediatric continuous renal replacement therapy (ppCRRT) in the United States, kidney disease was the cause for a mere 9% of the patients. The most common cause was sepsis, followed by post-bone marrow transplantation, heart disease, and kidney disease [26].

A nationwide survey was also conducted in Japan during the 2 years from 2007 to 2008 in <15-year-old pediatric patients who underwent renal replacement therapy [27]. The survey included 699 patients from 121 institutions. The median age was 2.1 years, with the majority of the patients being infants or toddlers (<1 year old, 41.5%; ≥1 year old but <3 years old, 17.0%). The median body weight was 10.9 kg, with 45.6% weighing less than 10 kg. Of these patients, 283 (42.3%) underwent renal replacement therapy indicated for the treatment of AKI. Although kidney disease was the most common primary disease ($n = 95$, 33.6%), all other (extrarenal) diseases accounted for two-thirds of all primary diseases (Table 19.2). Similar to the previous reports, hemolytic uremic syndrome was the most common in those with kidney disease as the primary disease.

19.5 Indication of Blood Purification for Pediatric AKI

In pediatric acute kidney injury (AKI), life-threatening conditions resistant to conservative therapy, such as hyperkalemia, severe fluid overload (pulmonary edema, heart failure, etc.) metabolic acidosis, and uremia symptoms (pericarditis, impaired

Table 19.2 Causes of AKI and survival in children who received blood purification (2007–2008, registry in Japan, $n = 283$)

Causes of AKI	Total patients	Survivors	Non-survivors	Unknown	Mortality rate (%)
Renal disease	95	81	5	9	5.8
Cardiac disease	54	14	39	1	73.6
Hematologic disease/ malignancy	40	11	28	1	71.8
Sepsis	21	4	15	2	78.9
Neuromuscular disease	19	10	6	3	37.5
Digestive system disease	13	5	8	0	61.5
Pulmonary disease	6	5	1	0	16.7
Inborn error of metabolism	5	2	3	0	60.0
Liver disease	4	0	4	0	100.0
Collagen disease	3	1	1	1	50.0
Other	23	11	12	0	52.2
Total	283	144	122	17	45.9

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consciousness, convulsions, etc.), are absolute indications for blood purification just like in adult AKI. In these cases, blood purification must be initiated immediately. Although they were only observational studies, many recent papers have reported that fluid overload at the initiation of blood purification affects the survival outcomes. The percent fluid overload (%FO) is considered to be useful for the assessment of fluid overload.

$$\%\text{Fluid overload}\left(\%\text{FO}\right) = \left(\text{fluid in} - \text{fluid out}\right) / \text{PICU admission body weight} \times 100\left(\%\right)$$

Fluid in – fluid out : in – out balance before and after PICU admission

In 2001, Goldstein et al. conducted a single-center study [28], followed by a large-scale multicenter study of continuous renal replacement therapy (CRRT) for pediatric AKI [29]. This study examined the predictors of survival in 116 children registered in the prospective pediatric continuous renal replacement therapy (ppCRRT) registry who underwent CRRT for multiple organ failure. The %FO at CRRT initiation was an independent predictor of survival; the %FO was significantly lower in survivors than in non-survivors (survivors: 14.2 ± 15.9 versus non-survivors: 25.4 ± 32.9, $p < 0.05$), while the mortality was significantly higher when the %FO was >20% (<20:40 versus >20:58%) at CRRT initiation. The same group later demonstrated that the %FO at the initiation of blood purification was correlated with mortality (<10:29.4%, 10–20:43.1%, >20:65.6%) [30]. Modem et al. reported that FO is a factor of poor survival outcomes [31]. Many studies of AKI in multiple organ failure [32–34], stem cell transplantation [35], and extracorporeal membrane oxygenation (ECMO) following cardiac surgery [36, 37] have also reported that a lower %FO at CRRT initiation is associated with more favorable outcomes. Similar results have also been reported in assessments of FO based on the body weight at hospital admission, at intensive care unit (ICU) admission, and at the initiation of blood purification [38]. Therefore, the early initiation of blood purification to prevent severe fluid overload may improve the survival outcomes; when determining whether blood purification is indicated in pediatric AKI, we suggest that the fluid overload assessment be taken into consideration in addition to absolute indications.

However, these results all were obtained from observational studies; there is no high-quality evidence from prospective studies. In addition, a study of blood purification in children undergoing cardiac surgery failed to find an effective timing for initiation [39], while fluid overload was reported not to be an absolute predictor of the survival outcomes [40]. Unnecessary blood purification should be avoided in cases of mild AKI, in which the renal function recovers quickly. Blood purification carries serious complications, including catheter-related infection, an increased risk of bleeding, and hemodynamic fluctuations unique to children of small constitution; therefore, the timing of initiation of blood purification must be considered comprehensively.

In neonatal AKI, renal replacement therapy (RRT) is also considered when prolonged oliguria/anuria prevents the appropriate adjustment of the body fluid, electrolytes, and blood nitrogen level. The overall mortality in neonatal AKI is reported to range between 11.3 and 48.3% [41–51]; while the mortality is reported to be 4.1–71.7% in premature neonates [52–55], 13.9–70.0% in asphyxiated neonates [56, 57], 2.9–11.6% in neonates undergoing a cardiopulmonary bypass/cardiac surgery [58–60], 71.2% in sepsis [61], and 50–100% in neonates with AKI who undergo blood purification [42, 46–48]. The risk factors for death in neonatal AKI include mechanical ventilation, hypervolemia (%FO ≥ 7%), chronic heart failure, a low birth weight, hypoxia, oliguria/anuria, dialysis, and metabolic acidosis [41]. The risk of death is particularly high in neonates with oliguria [41–45, 52, 56, 57]. However, no studies have discussed FO in neonatal AKI. Low-birth-weight infants present technical problems such as vascular access; however, the indication for acute blood purification in neonates must be determined comprehensively on a case-by-case basis.

19.6 Management of Blood Purification for Pediatric AKI

19.6.1 Vascular Access

Due to the small body weight, it is often difficult to obtain vascular access in children. The approximate size of the inserted catheter is 6–7Fr for ≤10 kg, 8Fr for 10–15 kg, and 9Fr for 15–20 kg [62]. The internal jugular vein or external jugular vein is usually selected as the insertion site, and the internal jugular vein is often the first choice. For patients with a high chance of transitioning to chronic dialysis, it is desirable to avoid the subclavian vein or femoral vein whenever possible. When the subclavian vein becomes stenosed or occluded, venous hypertension due to venous stenosis may occur if an internal shunt is created in the future. When the femoral vein becomes occluded, there may be difficulties in the eventual procedure of renal transplantation. Moreover, in low-birth-weight children, it is extremely likely for the catheter to hit the vascular wall of the femoral vein, resulting in poor blood removal.

19.6.2 Blood Purification Device

A blood purification device with a size that is appropriate for body weight is used, and the membrane area of the blood purification device is selected such that it is the same as or about 75% of the body surface area. Currently, the smallest membrane on the market is 0.09 m^2, with a priming volume of 9 mL. Additionally, while it is desirable to use a small circuit for pediatric patients, this can be problematic from the perspective of the likely reduction in the liquid surface of the chamber.

19.6.3 Sedation

Since vascular access is likely to be problematic due to body movement, sedation is often necessary. In infants and toddlers, the management of dialysis under general anesthesia is often inevitable. However, because long-term artificial ventilation management can lead to respiratory infection or extubation difficulties, it should be aimed, whenever possible, to continue blood purification after extubation. Although the catheter is inserted under general anesthesia in most pediatric patients, it is ideal to extubate after improving the fluid overflow/pulmonary edema through several days of water removal and manages the patient under awake conditions.

19.6.4 Prevention of Initial Hypotension

In infants, an initial drop of blood pressure, or hypotension, at the start of therapy, is likely to occur, and this risk is especially high when the priming volume exceeds 10% of circulating blood volume [63]. Typically, when the body weight is <8 kg, even when a small circuit and filtration membrane are selected in accordance with the body frame, the priming volume often exceeds 10% of the blood volume. In this situation, it is better to perform blood priming [64]. When performing blood priming, it is important to note the risk of hypocalcemia from the citric acid in the red blood cell concentrate entering the body all at once and to neutralize the citric acid using calcium formulations in the circuit immediately prior to connecting to the device.

19.7 Indication of Blood Purification for Children with Serious Impairments and Poor Survival Prognoses

There are no definitive criteria upon which to determine the indication for RRT in children with severe impairments; thus, it must be considered on a case-by-case basis. The health care team should decide on a therapeutic strategy after considering the patient's present status and long-term survival prognosis among themselves, explaining the nature of the treatments to the patient's family, and presenting the respective advantages and disadvantages of treatment versus no treatment. This concept is called shared decision-making; essentially, health care professionals must share information with the patient's family and decide on a therapeutic strategy together.

Before providing information to the patient's family, the health care staff must gather information and share it in order to determine the patient's present

status. Discussions should not only include the attending physician's department, but also intensive care specialists, neonatal intensive care specialists, and nurses; when necessary, clinical psychologists, a palliative care team, medical social workers, and other departments and disciplines should also be included. Based on these discussions, conceivable treatments should be identified as options, and the problems and invasiveness of each option should be abstracted (for example, for acute blood purification, these include complications associated with catheter insertion, the risk of hypotension associated with dialysis initiation, blood transfusion, etc.). Suitable strategies are then examined based on a prediction of the patient's prognosis (survival prognosis and sequelae) and on the consideration of the advantages and disadvantages of the potential treatments. When considering withholding or discontinuing treatment, the relevant facility's institutional review board may be convened, or a conference may be held to discuss ethical issues.

When explaining therapeutic strategies to the patient's family, the parents must always be present; other individuals may attend the explanation if requested by the parents (grandparents, etc.). The name of the child's illness, its disease condition, the respective advantages and disadvantages of treatments such as blood purification (including their complications) versus no treatment, and the prognosis (sequelae and survival prognosis) should be explained comprehensively in a way that is easy to understand. Important information should be provided in writing. In addition, the family must be informed that even after a strategy is decided, it can be reconsidered if they change their minds. The content of this explanation, the way it is explained, and the course by which a strategy is chosen must be written in the patient's medical record. In particular, when treatment is withheld, it is important to record the course and content of the discussion that led to the treatment withdrawal. When the patient's family and the health care team cannot agree on a strategy, advice should be sought from a committee comprising the institutional review board and many other experts.

Even after a strategy is decided, the patient's family will require continuous mental support. After blood purification is initiated, the patient's impairment may progress irreversibly, thereby requiring discontinuation of the treatment. On the other hand, even if the patient's family initially decides not to perform treatment, treatment may later be performed if they change their minds (or for other reasons). These reconsiderations of the therapeutic strategies require a new round of discussion. Moreover, when changing the therapeutic strategy, a consensus must be obtained among the health care team as appropriate. If the patient's family wishes to discontinue dialysis, it is necessary to confirm that this is not based on temporary emotion, but on a careful consideration and sufficient understanding of the child's status. The patient may also die shortly after discontinuing treatment; therefore, when deciding to do so, the timing of the discontinuation must also be discussed.

19.8 Prognosis of Pediatric AKI

According to the ppCRRT registry in the United States, overall mortality was 58% [26]. While life expectancy was good among those with drug toxicity or kidney disease, it was poor in sepsis, post-bone marrow transplantation, heart disease, liver disease, and lung disease. On the other hand, a report on the 3 to 5 years long-term prognosis of 174 pediatric patients with AKI who underwent renal replacement therapy showed that survival was 56.8%, and a transition to end-stage renal failure was observed in 16 patients (9%). The percentage of patients who transitioned to end-stage renal failure was greater in those with renal/urinary disease (11/35 patients, 31.4%) than in those with other diseases (5/139 patients, 3.6%) [65].

A Japanese nationwide survey in 283 pediatric patients who underwent renal replacement therapy indicated for treating AKI showed that survival was 73.6% at 28 days after treatment start, 58.3% of discharge, and 54.1% at last verification [27]. An analysis by disease type showed that mortality due to kidney disease was extremely low (5.8%), but the prognosis of secondary AKI was extremely poor (Table 19.2). Mortality risk factors determined by multivariate analysis demonstrated that sepsis presented the greatest risk, with an odds ratio of 3.67 ($p = 0.007$). Comorbid respiratory failure had a risk at 2.47 ($p = 0.048$), and that of body weight ≤8 kg was 1.93 ($p = 0.035$). The greatest mortality risk factor was indeed sepsis. The renal prognoses of 146 long-term survivors included the following: 25 were undergoing peritoneal dialysis; 17 had non-end stage chronic renal disorder; and two had received renal transplantation. However, of these patients with chronic renal disorders, 15 were nephrogenic in origin. Based on these findings, patients with nephrogenic AKI have a good life expectancy, but a poor renal prognosis, while, in contrast, patients with secondary AKI have a good renal prognosis, but a poor life expectancy.

Conflict of Interest The author declares no conflict of interest.

References

1. Uemura O, Honda M, Matsuyama T, Ishikura K, Hataya H, Yata N, et al. Age, gender, and body length effects on reference serum creatinine levels determined by an enzymatic method in Japanese children: a multicenter study. Clin Exp Nephrol. 2011;15:694–9.
2. Schwartz GJ, Brion LP, Spitzer A. The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children, and adolescents. Pediatr Clin North Am. 1987;34:571–90.
3. Akcan-Arikan A, Zappitelli M, Loftis LL, Washburn KK, Jefferson LS, Goldstein SL. Modified RIFLE criteria in critically ill children with acute kidney injury. Kidney Int. 2007;71:1028–35.
4. Sutherland SM, Byrnes JJ, Kothari M, Longhurst CA, Dutta S, Garcia P, et al. AKI in hospitalized children: comparing the pRIFLE, AKIN, and KDIGO definitions. Clin J Am Soc Nephrol. 2015;10:554–61.

5. Selewski DT, Cornell TT, Heung M, Troost JP, Ehrmann BJ, Lombel RM, et al. Validation of the KDIGO acute kidney injury criteria in a pediatric critical care population. Intensive Care Med. 2014;40:1481–8.
6. Jetton JG, Askenazi DJ. Acute kidney injury in the neonate. Clin Perinatol. 2014;41:487–502.
7. Selewski DT, Charlton JR, Jetton JG, Guillet R, Mhanna MJ, Askenazi DJ, et al. Neonatal acute kidney injury. Pediatrics. 2015;136:e463–73.
8. Guignard JP, Drukker A. Why do newborn infants have a high plasma creatinine? Pediatrics. 1999;103:e49.
9. Boer DP, de Rijke YB, Hop WC, Cransberg K, Dorresteijn EM. Reference values for serum creatinine in children younger than 1 year of age. Pediatr Nephrol. 2010;25:2107–13.
10. Bateman DA, Thomas W, Parravicini E, Polesana E, Locatelli C, Lorenz JM. Serum creatinine concentration in very-low-birthweight infants from birth to 34–36 wk postmenstrual age. Pediatr Res. 2015;77:696–702.
11. Koralkar R, Ambalavanan N, Levitan EB, McGwin G, Goldstein S, Askenazi D. Acute kidney injury reduces survival in very low birth weight infants. Pediatr Res. 2011;69:354–8.
12. Carmody JB, Swanson JR, Rhone ET, Charlton JR. Recognition and reporting of AKI in very low birth weight infants. Clin J Am Soc Nephrol. 2014;9:2036–43.
13. Rhone ET, Carmody JB, Swanson JR, Charlton JR. Nephrotoxic medication exposure in very low birth weight infants. J Matern Fetal Neonatal Med. 2014;27:1485–90.
14. Sarkar S, Askenazi DJ, Jordan BK, Bhagat I, Bapuraj JR, Dechert RE, et al. Relationship between acute kidney injury and brain MRI findings in asphyxiated newborns after therapeutic hypothermia. Pediatr Res. 2014;75:431–5.
15. Mishra J, Dent C, Tarabishi R, Mitsnefes MM, Ma Q, Kelly C, et al. Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. Lancet. 2005;365:1231–8.
16. Parikh CR, Devarajan P, Zappitelli M, Sint K, Thiessen-Philbrook H, Li S, et al. Postoperative biomarkers predict acute kidney injury and poor outcomes after pediatric cardiac surgery. J Am Soc Nephrol. 2011;22:1737–47.
17. Zappitelli M, Washburn KK, Arikan AA, Loftis L, Ma Q, Devarajan P, et al. Urine neutrophil gelatinase-associated lipocalin is an early marker of acute kidney injury in critically ill children: a prospective cohort study. Crit Care. 2007;11:R84.
18. Bennett M, Dent CL, Ma Q, Dastrala S, Grenier F, Workman R, et al. Urine NGAL predicts severity of acute kidney injury after cardiac surgery: a prospective study. Clin J Am Soc Nephrol. 2008;3:665–73.
19. Dent CL, Ma Q, Dastrala S, Bennett M, Mitsnefes MM, Barasch J, et al. Plasma neutrophil gelatinase-associated lipocalin predicts acute kidney injury, morbidity and mortality after pediatric cardiac surgery: a prospective uncontrolled cohort study. Crit Care. 2007;11:R127.
20. Krawczeski CD, Vandevoorde RG, Kathman T, Bennett MR, Woo JG, Wang Y, et al. Serum cystatin C is an early predictive biomarker of acute kidney injury after pediatric cardiopulmonary bypass. Clin J Am Soc Nephrol. 2010;5:1552–7.
21. Zappitelli M, Krawczeski CD, Devarajan P, Wang Z, Sint K, Thiessen-Philbrook H, et al. Early postoperative serum cystatin C predicts severe acute kidney injury following pediatric cardiac surgery. Kidney Int. 2011;80:655–62.
22. Parikh CR, Mishra J, Thiessen-Philbrook H, Dursun B, Ma Q, Kelly C, et al. Urinary IL-18 is an early predictive biomarker of acute kidney injury after cardiac surgery. Kidney Int. 2006;70:199–203.
23. Liu Y, Guo W, Zhang J, Xu C, Yu S, Mao Z, et al. Urinary interleukin 18 for detection of acute kidney injury: a meta-analysis. Am J Kidney Dis. 2013;62:1058–67.
24. Portilla D, Dent C, Sugaya T, Nagothu KK, Kundi I, Moore P, et al. Liver fatty acid-binding protein as a biomarker of acute kidney injury after cardiac surgery. Kidney Int. 2008;73:465–72.
25. Han WK, Waikar SS, Johnson A, Betensky RA, Dent CL, Devarajan P, et al. Urinary biomarkers in the early diagnosis of acute kidney injury. Kidney Int. 2008;73:863–9.

26. Symons JM, Chua AN, Somers MJ, et al. Demographic characteristics of pediatric continuous renal replacement therapy: a report of the prospective pediatric continuous renal replacement therapy registry. Clin J Am Soc Nephrol. 2007;2:732–8.
27. Ito S. Pediatric AKI and acute blood purification. J Jpn Pediatr Soc. 2012;116:666–78.
28. Goldstein SL, Currier H, Graf C, Cosio CC, Brewer ED, Sachdeva R. Outcome in children receiving continuous venovenous hemofiltration. Pediatrics. 2001;107:1309–12.
29. Goldstein SL, Somers MJ, Baum MA, Symons JM, Brophy PD, Blowey D, et al. Pediatric patients with multi-organ dysfunction syndrome receiving continuous renal replacement therapy. Kidney Int. 2005;67:653–8.
30. Sutherland SM, Zappitelli M, Alexander SR, Chua AN, Brophy PD, Bunchman TE, et al. Fluid overload and mortality in children receiving continuous renal replacement therapy: the prospective pediatric continuous renal replacement therapy registry. Am J Kidney Dis. 2010;55:316–25.
31. Modem V, Thompson M, Gollhofer D, Dhar AV, Quigley R. Timing of continuous renal replacement therapy and mortality in critically ill children∗. Crit Care Med. 2014;42:943–53.
32. Foland JA, Fortenberry JD, Warshaw BL, Pettignano R, Merritt RK, Heard ML, et al. Fluid overload before continuous hemofiltration and survival in critically ill children: a retrospective analysis. Crit Care Med. 2004;32:1771–6.
33. Gillespie RS, Seidel K, Symons JM. Effect of fluid overload and dose of replacement fluid on survival in hemofiltration. Pediatr Nephrol. 2004;19:1394–9.
34. Hayes LW, Oster RA, Tofil NM, Tolwani AJ. Outcomes of critically ill children requiring continuous renal replacement therapy. J Crit Care. 2009;24:394–400.
35. Michael M, Kuehnle I, Goldstein SL. Fluid overload and acute renal failure in pediatric stem cell transplant patients. Pediatr Nephrol. 2004;19:91–5.
36. Selewski DT, Cornell TT, Blatt NB, Han YY, Mottes T, Kommareddi M, et al. Fluid overload and fluid removal in pediatric patients on extracorporeal membrane oxygenation requiring continuous renal replacement therapy. Crit Care Med. 2012;40:2694–9.
37. Sanchez-de-Toledo J, Perez-Ortiz A, Gil L, Baust T, Lines-Palazon M, Perez-Hoyos S, et al. Early initiation of renal replacement therapy in pediatric heart surgery is associated with lower mortality. Pediatr Cardiol. 2015;37:623–8.
38. Selewski DT, Cornell TT, Lombel RM, Blatt NB, Han YY, Mottes T, et al. Weight-based determination of fluid overload status and mortality in pediatric intensive care unit patients requiring continuous renal replacement therapy. Intensive Care Med. 2011;37:1166–73.
39. Kara OD, Dincel N, Kaplan Bulut I, Yilmaz E, Ozdemir K, Gozuoglu G, et al. Success of continuous veno-venous hemodiafiltration treatment in children monitored in the intensive care units. Ren Fail. 2014;36:1411–5.
40. de Galasso L, Emma F, Picca S, Di Nardo M, Rossetti E, Guzzo I. Continuous renal replacement therapy in children: fluid overload does not always predict mortality. Pediatr Nephrol. 2016;31:651–9.
41. Duzova A, Bakkaloglu A, Kalyoncu M, Poyrazoglu H, Delibas A, Ozkaya O, et al. Etiology and outcome of acute kidney injury in children. Pediatr Nephrol. 2010;25:1453–61.
42. Agras PI, Tarcan A, Baskin E, Cengiz N, Gurakan B, Saatci U. Acute renal failure in the neonatal period. Ren Fail. 2004;26:305–9.
43. Bolat F, Comert S, Bolat G, Kucuk O, Can E, Bulbul A, et al. Acute kidney injury in a single neonatal intensive care unit in Turkey. World J Pediatr. 2013;9:323–9.
44. Bezerra CT, Vaz Cunha LC, Liborio AB. Defining reduced urine output in neonatal ICU: importance for mortality and acute kidney injury classification. Nephrol Dial Transplant. 2013;28:901–9.
45. Hui-Stickle S, Brewer ED, Goldstein SL. Pediatric ARF epidemiology at a tertiary care center from 1999 to 2001. Am J Kidney Dis. 2005;45:96–101.
46. Askenazi DJ, Ambalavanan N, Hamilton K, Cutter G, Laney D, Kaslow R, et al. Acute kidney injury and renal replacement therapy independently predict mortality in neonatal and pediatric noncardiac patients on extracorporeal membrane oxygenation. Pediatr Crit Care Med. 2011;12:e1–6.

47. Alabbas A, Campbell A, Skippen P, Human D, Matsell D, Mammen C. Epidemiology of cardiac surgery-associated acute kidney injury in neonates: a retrospective study. Pediatr Nephrol. 2013;28:1127–34.
48. Selewski DT, Jordan BK, Askenazi DJ, Dechert RE, Sarkar S. Acute kidney injury in asphyxiated newborns treated with therapeutic hypothermia. J Pediatr. 2013;162:725–9.
49. Sutherland SM, Ji J, Sheikhi FH, Widen E, Tian L, Alexander SR, et al. AKI in hospitalized children: epidemiology and clinical associations in a national cohort. Clin J Am Soc Nephrol. 2013;8:1661–9.
50. Cataldi L, Leone R, Moretti U, De Mitri B, Fanos V, Ruggeri L, et al. Potential risk factors for the development of acute renal failure in preterm newborn infants: a case-control study. Arch Dis Child Fetal Neonatal Ed. 2005;90:F514–9.
51. Mortazavi F, Hosseinpour Sakha S, Nejati N. Acute kidney failure in neonatal period. Iran J Kidney Dis. 2009;3:136–40.
52. Viswanathan S, Manyam B, Azhibekov T, Mhanna MJ. Risk factors associated with acute kidney injury in extremely low birth weight (ELBW) infants. Pediatr Nephrol. 2012;27:303–11.
53. Askenazi DJ, Griffin R, McGwin G, Carlo W, Ambalavanan N. Acute kidney injury is independently associated with mortality in very low birthweight infants: a matched case-control analysis. Pediatr Nephrol. 2009;24:991–7.
54. Walker MW, Clark RH, Spitzer AR. Elevation in plasma creatinine and renal failure in premature neonates without major anomalies: terminology, occurrence and factors associated with increased risk. J Perinatol. 2011;31:199–205.
55. Morgan CJ, Zappitelli M, Robertson CM, Alton GY, Sauve RS, Joffe AR, et al. Risk factors for and outcomes of acute kidney injury in neonates undergoing complex cardiac surgery. J Pediatr. 2013;162:120–7.
56. Gupta BD, Sharma P, Bagla J, Parakh M, Soni JP. Renal failure in asphyxiated neonates. Indian Pediatr. 2005;42:928–34.
57. Perlman JM, Tack ED. Renal injury in the asphyxiated newborn infant: relationship to neurologic outcome. J Pediatr. 1988;113:875–9.
58. Morelli S, Ricci Z, Di Chiara L, Stazi GV, Polito A, Vitale V, et al. Renal replacement therapy in neonates with congenital heart disease. Contrib Nephrol. 2007;156:428–33.
59. Blinder JJ, Goldstein SL, Lee VV, Baycroft A, Fraser CD, Nelson D, et al. Congenital heart surgery in infants: effects of acute kidney injury on outcomes. J Thorac Cardiovasc Surg. 2012;143:368–74.
60. Zappitelli M, Bernier PL, Saczkowski RS, Tchervenkov CI, Gottesman R, Dancea A, et al. A small post-operative rise in serum creatinine predicts acute kidney injury in children undergoing cardiac surgery. Kidney Int. 2009;76:885–92.
61. Mathur NB, Agarwal HS, Maria A. Acute renal failure in neonatal sepsis. Indian J Pediatr. 2006;73:499–502.
62. Goldstein SL. Overview of pediatric renal replacement therapy in acute kidney injury. Semin Dial. 2009;22:180–4.
63. Strazdins V, Watson AR, Harvey B, European Pediatric Peritoneal Sialysis Working Group. Renal replacement therapy for acute renal failure in children: European guidelines. Pediatr Nephrol. 2004;19:199–207.
64. Hackbarth RM, Eding D, Gianoli Smith C, et al. Zero balance ultrafiltration (Z-BUF) in blood-primed CRRT circuits achieves electrolyte and acid-base homeostasis prior to patient connection. Pediatr Nephrol. 2005;20:1328–33.
65. Askenazi DJ, Feig DI, Graham NM, et al. 3-5 year longitudinal follow-up of pediatric patients after acute renal failure. Kidney Int. 2006;69:184–9.

Part IV
Experimental Novel Findings

Chapter 20
AKI-to-CKD Transition

Jun-Ya Kaimori

Abstract Previously conceived to be a benign syndrome, AKI has now proven to be one important cause of CKD. So far, eight kinds of rodent models have been introduced to the basic research model for the AKI-to-CKD transition. Among these, the unilateral ischemia-reperfusion injury (uIRI) and repeated low-dose cisplatin (RLDC) models were proposed as consistent rodent models for the AKI-to-CKD transition. However, these two rodent models demonstrate divergent data on kidney injury, and an easy and accurate way of monitoring renal function will be needed. In the proposed mechanism, renal hypoxia plays a pivotal role in the AKI-to-CKD transition with capillary rarefaction, abnormally differentiated tubular cells, epigenetic changes in fibroblasts, and persisting inflammation.

Keywords Animal models for the AKI-to-CKD transition · Hypoxia Microvasculature rarefaction · Incomplete recovery of tubular cells · Epigenetic modification in fibroblasts · Chronic inflammation

20.1 Clinical Importance of the AKI-to-CKD Transition

Acute kidney injury (AKI) was previously conceived to be a benign syndrome. Once the temporal decrement in kidney function after AKI is reversed, patients become totally safe thereafter. But this benign notion of AKI has proven to be incorrect in recent times [1, 2]. Three papers have been published with systematic reviews and meta-analyses of the AKI-to-CKD transition [3–5]. From these analyses, AKI patients make the transition to CKD, ESRD, and even death at significantly higher rates relative to patients without AKI (Table 20.1). It is therefore important to carry out further research into the AKI-to-CKD transition using experimental kidney injury models.

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Table 20.1 Pooled estimated hazard ratio of CKD, ESRD, and mortality in patients with AKI

	CKD	ESRD	Mortality
Coca et al. (2009)	NA	NA	2.59 (95%CI: 1.97–3.42)
Coca et al. (2012)	8.8 (95%CI: 3.1–25.5)	3.1 (95%CI: 1.9–5.0)	2.0(95%CI: 1.3–3.1)
See et al. (2018)	2.67 (95%CI: 1.99–3.58)	4.81 (95%CI: 3.04–7.62)	1.80 (95%CI: 1.61–2.02)

NA not available

Table 20.2 Animal models of the AKI-to-CKD transition

	Merits	Weakness
bIRI	Mimicking human pathophysiology/easy to monitor GFR	Lots of death/variation and inconsistency in renal injury
uIRI	Longer observation time with less animal loss/consistent	Difficult GFR monitor
uIRIx	Easy GFR monitor	Lots of animal loss/variability
Multi IRI	Simulate human patient	Slighter injury than expected
RLDC	Longer observation time with less animal loss/consistent/fewer animal loss	Fibrosis very slight
Repeated DT	Consistent	Need to make transgenic mice/complex
Repeated AA	Easy GFR monitor	Few reports
FA	Easy GFR monitor	Variation and inconsistency in renal injury

20.2 Animal Models of the AKI-to-CKD Transition

To gain mechanistic insight into the AKI-to-CKD transition, it is vital to select appropriate animal models for the research. Here, I will describe eight rodent models of the AKI-to-CKD transition(Table 20.2) [6].

20.2.1 Bilateral Ischemia-Reperfusion Injury (bIRI) Model of the AKI-to-CKD Transition

This model is induced by blocking the blood supply to both kidneys. Previously, SD rats [1], FVB/NJ background mice [7], BALB/c mice [8], and C57BL/6 mice [9] have been proposed as models of the AKI-to-CKD transition. Researchers have set the ischemic time for moderate and severe injury models and several observation times at up to 2 months. The bIRI model agrees well with real human AKI-to-CKD transition pathophysiology, and the monitoring of renal function in the serum or urine is relatively easy. The problems with this model are in variation,

inconsistency, and high mortality. The severity of the injury decides further outcomes of AKI. If the injury is too severe, many animals will be lost before they reach the observation period. If too mild, the injury does not progress to CKD. In the case of bIRI, the severity of AKI is easily influenced by body temperature, ischemic period, anesthetic drugs, different strains, and sometimes even different animal colonies [10]. Notably, animal body temperature and ischemic duration cause significant differences in the severity of AKI. One researcher used an egg-breeding device to maintain body temperature during the ischemic procedure and an infrared lamp during wake-up [11]. Researchers have highly recommended setting experimental conditions for each specific purpose and animal models to minimize the variations in AKI injury, keeping in mind that even a small difference in injury in the acute phase can result in large variations in outcome in the chronic phase.

20.2.2 Unilateral Ischemia-Reperfusion Injury (uIRI) Model of the AKI-to-CKD Transition

This model is induced by blocking the blood supply to one kidney with the contralateral kidney intact. Previous reports include different rodent strains (CD-1 mice [12], C57BL/6 background mice [13], RMB mice [14], and BALB/c mice [8]). The lower mortality of this model due to the functional contralateral kidney provides researchers with a much longer observation time compared with the bIRI model. Additionally, in this model, the same ischemic time can cause more tissue damage than in bIRI or uIRI with contralateral nephrectomy. Because of these features, uIRI is used as a reliable model of the AKI-to-CKD transition. The only weakness in this model is the difficulty in monitoring renal function. Researchers are recommended to consider using the sophisticated methods described later in this paper.

20.2.3 Unilateral Ischemia-Reperfusion Injury (uIRI) with Contralateral Nephrectomy (uIRIx) Model of AKI-to-CKD Transition

This model is induced by blocking the blood supply to one kidney with contralateral nephrectomy. The researchers made the contralateral nephrectomy several days after uIRI. Previous reports of uIRIx contained different rodent strains (SD rats [15], BALB/c [16] and BALB/c background [8]). Counterintuitively, the same ischemic time resulted in slighter tissue damage after a long observation time in uIRIx than in uIRI only, suggesting that the contralateral nephrectomy confers immunity to AKI-induced tissue damage [8]. Multiple causes may contribute to the lower fibrotic damage in uIRIx than in uIRI, but the major factor is the renal hemodynamic change caused by the presence of the contralateral kidney.

20.2.4 Repeated IRI Model of the AKI-to-CKD Transition

This model is induced by blocking the blood supply to one or both kidneys twice. Previous reports of repeated IRI included different rodent strains (BALB/c mice [17] and female SD rats [12]). The second IRI results in protective effects on the previously injured kidney but not on the contralateral kidney [18]. Taking these effects, which are known as "preconditioning," into account, it is unlikely that repeated IRI results in the progression from kidney injury to CKD, and this model may not be appropriate for the AKI-to-CKD transition.

20.2.5 Repeated Low-dose Cisplatin Model of the AKI-to-CKD Transition

Cisplatin (CDDP) is usually used as an anti-cancer drug which sometimes affects renal function. Compromised renal function caused by CDDP limits its effective use for future cancer treatment. So far, researchers have focused on the renal toxicity of CDDP, particularly in the acute phase, using single- and high-dose CDDP administration. However, in real clinical settings, CDDP tends to be given to cancer patients repeatedly. As a result, the focus has moved to the chronic effects of repeated CDDP administration. Repeated low-dose cisplatin model included different rodent models (FVB/n mice [19, 20], C57BL/6 mice [21, 22], and C57BL/6 background mice [23]). These rodent models were given CDDP once a week for up to 4 weeks and were observed for up to 25 weeks. Their kidneys revealed features suggestive of CKD (increased level of fibrotic markers, interstitial fibrosis, atrophic kidney, and increased creatinine) [19, 21]. These data indicate that the repeated low-dose cisplatin model is appropriate for AKD-CKD transition research. Researchers note that the CDDP dosage and administration methods should be carefully titrated for each study and that a fresh preparation will be needed for each administration [6].

20.2.6 Repeated Diphtheria Toxin (DT) Model of the AKI-to-CKD Transition

In the animal models introduced so far, any renal cells were affected by stimuli or toxins at the same time. Using Cre-RoxP technology, researchers can induce injuries in only the interested cells as many times as they want by DT administration. So far, two research groups have utilized this system to induce AKI-to-CKD transition models (SIX2-Cre-LoxP [17] and ERT2-Cre-LoxP [24]). They both found that repeated DT stimuli resulted in the development of characteristic features of CKD 3–4 weeks later, indicating that this model is one feasible option for research into the AKI-to-CKD transition.

20.2.7 Aristolochic Acid Nephropathy (AAN) Model of the AKI-to-CKD Transition

Aristolochic acid nephropathy, also called Chinese Herb nephropathy, is characterized by progressive proximal tubular atrophy and interstitial fibrosis [25, 26]. Repeated intraperitoneal administration of AA was reported to result in AKI which progressed to CKD. However, because of the scarce reports of this model being adopted for the AKI-to-CKD transition, researchers should find the appropriate conditions for each study.

20.2.8 Folic Acid (FA) Model of the AKI-to-CKD Transition

FA is a normally used nephrotoxic agent used to cause AKI in experimental settings [27–29]. Researchers administered single doses of FA to induce AKI, and after an observation time of up to 28 days, they discovered the characteristic features of CKD, suggesting that this model can be used for the AKI-to-CKD transition. However, in our experience, this model demonstrated significant variations in the severity of the AKI injury.

20.3 Reliable Methods of Monitoring Rodent Renal Function

The repeated monitoring of renal function in the same animals is important for basic AKI-to-CKD transition research. However, in the acute phase of IRI, it is impossible to monitor the real renal function by conventional measurement of the serum creatinine concentration [30]. Therefore, new technology is required for monitoring the renal function of rodents with AKI. Here, we present two reliable noninvasive techniques for monitoring kidney function in rodents. The first is the use of dynamic renal scintigraphy with ^{99m}Tc-mercaptoacetyltriglycine (MAG3) [30]. ^{99m}Tc-MAG3 is efficiently extracted from the kidney following disposition by the renal tubular system, and it has already been approved for human use. ^{99m}Tc-MAG3 images captured by a mobile gamma camera provide a powerful tool for evaluating different renal perfusions, tubular functions, and kidney injury in each kidney. It is particularly useful in unilateral IRI. The other technique is GFR monitoring using a transcutaneous fluorescent sensing device to measure the FITC-sinistrin disappearance curves (Fig. 20.1) [31]. The gold standard for GFR measurement is accurate clearance determination of an exogenous renal marker, like inulin, in the urine or plasma. However, this procedure has not been utilized in real clinical settings because of the necessity for frequent and punctual blood samplings. These unmet needs produced transcutaneous detection techniques for the clearance of radioactive [32], fluorescent [33–38], and gadolinium-conjugated [39] renal markers. The major advantage

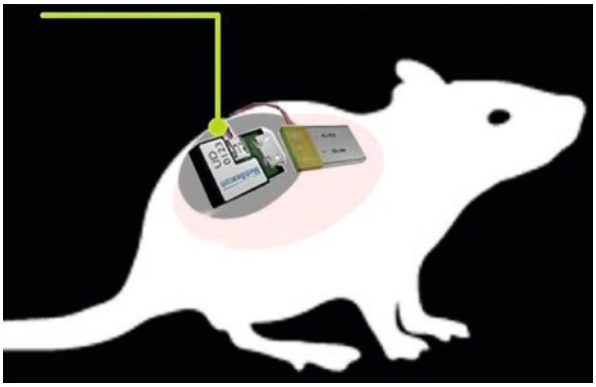

Fig. 20.1 Photograph of a transcutaneous fluorescent sensing device for measuring FITC-sinistrin disappearance curves

of these procedures is freedom from the necessity to take frequent blood samples from animals. The weakness is the fact that the animals must be anesthetized during the measurement. It is possible that anesthetizing agents could affect GFR in animals. The sensing device assessed the FITC-sinistrin elimination kinetics transcutaneously. GFR was calculated from the measured half-lives, using the formula [36].

20.4 Comparison of Two Representative Rodent Models of the AKI-to-CKD Transition

When basic researchers plan studies for the AKI-to-CKD transition, they should select an appropriate animal model to provide answers to their scientific questions. As described so far and judging from the abundance of previous reports, reliable and consistent rodent models of the AKI-to-CKD transition are uIRI and the repeated low-dose cisplatin model (RLDC). Interestingly, according to Black et al. [40], these two mouse models of the AKI-to-CKD transition demonstrate divergent features of renal injury leading to the same CKD phenotypes (Table 20.3). The author induced the AKI-to-CKD transition in a male C57BL/6 mouse model (10 weeks of age) by uIRI for 30 min at 37 °C and weekly administration (9 mg) of CDDP for 4 weeks. From the renal function point of view, GFR monitoring by transcutaneous FITC-sinistrin clearance identified a dramatic reduction in GFR in 7 days after uIRI, with only a gradual and progressive GFR reduction in RLDC. ^{99m}Tc-MAG3 imaging of the IR kidney identified decreased perfusion, excretion, and/or basolateral epithelial organic anion uptake at days 7, 14, and 21 after uIRI compared with the IR-contralateral kidney. In the RLDC cases, perfusion, uptake, and excretion were virtually maintained relative to the vehicle-administrated mice. From the viewpoint of leukocytic infiltration, absolute counting of intrarenal inflammatory

Table 20.3 The highlighted differences between uIRI and RLDC models of AKI-to-CKD transition

	uIRI	RLDC
Methods	IR 30 min at 37 °C	Weekly 9 mg CDDP for 4 weeks
GFR change	Acute at the beginning	Gradual decrease
Split hemodynamics	+	–
$CD45^{+}$infiltration	↑ day7, ↑ day14, →day21	↓day10, ↓day24
PMN infiltration	↑ day7, ↑ day14, →day21	↓day10, →day24
$F4/80^{HI}$infiltration	↑ day7, → day14, →day21	↓day10, ↓day24
$F4/80^{Low}$infiltration	↑ day7, → day14, →day21	↓day10, ↓day24
CD4 infiltration	→day7, ↑ day14, ↑ day21	→day10, ↓day24
CD8 infiltration	→day7, ↑ day14, ↑ day21	→day10, →day24
B cell infiltration	→ day7, →day14, →day21	→day10, ↓day24
NK cell infiltration	↑ day7, ↑ day14, →day21	→day10, ↓day24
IL-6	↑	→
CSF-1	↑	↑
IL-1β	↑	→
TNF-α	↑	→
MCP-1	↑	→
NGAL	↑	→
HMGB-1	↑	↑
NOS2	↑	→
KIM-1	→	↑
Fibrosis	↑	→
Fn	↑	→
TGF-β	↑	→
COL I	↑	→
α-SMA	↑	→

cells by flow cytometry identified a remarkable increase in $CD45^{+}$ cells relative to sham control at days 7 and 14, resolving at day 12, with a significant decrease in $CD45^{+}$ cells relative to the vehicle-administrated models at days 10 and 24. Further analyses of $CD45^{+}$ cells infiltrating the uIRI kidney identified that myeloid lineage cells including PMN, $F4/80^{Hi}$, and $F4/80^{Low}$ Mϕ, B cells and NK cells followed almost the same trend as the $CD45^{+}$ cells. However, CD4 and CD8 cells demonstrated a progressive increase up to day 21. In the CDDP-treated kidney, almost none of the $CD45^{+}$ myeloid lineage cells increased, suggesting that CDDP administration suppressed leukocytic infiltration. These dramatic differences in inflammation between the two models were also identified in the pro-inflammatory cytokines gene expression profile. The gene expressions of IL-6, IL-1β, MCP-1, and TNF-α in uIRI increased significantly relative to sham control, whereas there was no increase in RLDC. The only exception was CSF-1, which showed a significant increase in both models. From the histopathologic point of view, massive interstitial fibrosis was demonstrated in uIRI, with almost the same in RLDC relative to the

vehicle-administered mice. The gene expressions of fibronectin and collagen I consisted of interstitial fibrosis data in both models. The divergent data manifested by these two representative AKI-to-CKD transition models indicate that two kinds of AKI stimuli confer different and injury-specific pathophysiologic mechanisms leading to CKD. Researchers should note these differences between the two models before they start their studies.

20.5 Proposed Mechanisms of the AKI-to-CKD Transition

The importance of the AKI-to-CKD transition in real clinical settings has compelled investigators to identify the key mechanisms in the AKI-to-CKD transition [41–43]. So far several important insights have been identified (Fig. 20.2). However, the difficulty in AKI-to-CKD transition research lies in finding real answers to the interesting question, "Why does the inflammatory or healing process instigated by AKI not stop?" One characteristic feature of CKD is that interstitial fibrosis is essentially a self-limiting repair process, although fibrosis is sometimes taken as a part of the noxious and self-destructive events. After tissue damage as a response to various stimuli, fibroblasts proliferate and secrete extracellular matrix but then regress without over-proliferating or invading normal tissue. Thus, these insights into the pathologic events teach us that "progressive" fibrosis needs to be investigated through repeated and severe damage to the nephrons, beyond the threshold of starting the noxious cycle of the healing process.

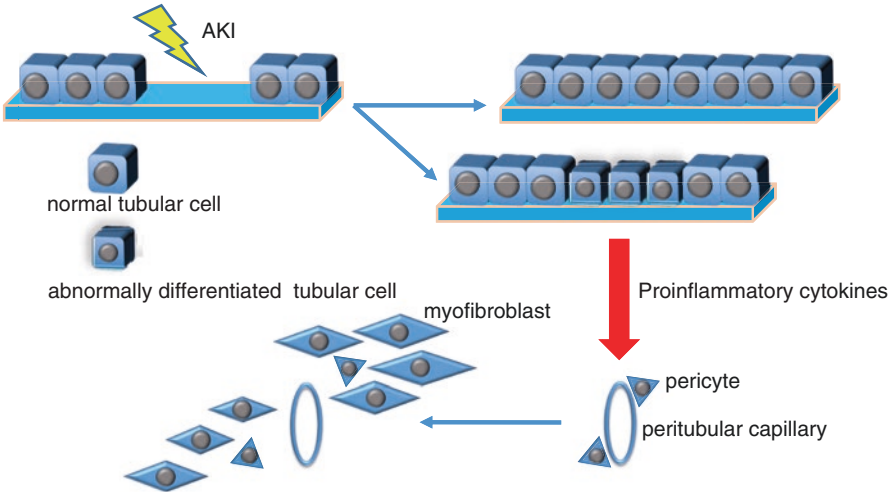

Fig. 20.2 One proposed mechanism for the AKI-to-CKD transition. The survived tubular cells regenerate. But the regenerated cells sometimes assume abnormal differentiation, resulting in secreting centers of pro-inflammatory cytokines. Such proinflammatory factors transform the pericytes into myofibroblasts and then cause a proliferation of myofibroblasts

20.5.1 Hypoxia as a Key Player in the AKI-to-CKD Transition

One of the driving forces that keep this cycle running may be hypoxia [41, 44]. In spite of the kidneys receiving as much as 20% of the blood ejected by the heart, each kidney has a physiologically hypoxic region, particularly in the cortex and medulla, where pO_2 can be normally as low as 20–60 mmHg and 10–30 mmHg, respectively [44–47]. An investigation of oxygen-sensing transgenic mice revealed that the kidneys have lower oxygen levels relative to other body parts and that the oxygen supply to the kidneys is subject to the status of renal perfusion [48]. The kidney parenchymal cells can extract only 10% of the oxygen supplied by the renal artery, because almost all the oxygen delivered by the renal artery makes a shortcut to the renal vein, which acts as an arteriovenous diffusional oxygen shunt [49–52]. These constructive defects and inefficiency of oxygen extraction predispose the kidneys to hypoxic damage. Moreover, capillary rarefaction caused by AKI amplifies hypoxic damage in these vulnerable renal tissues. The accelerated hypoxia then causes profound damage to the tubular epithelial cells, fibroblasts, and inflammatory cells, resulting in tubulointerstitial fibrosis and progression to CKD.

20.5.2 Microvasculature Rarefaction

Small vessel dysfunction characterized by compromised autoregulation of the blood flow and nitric production loss in the endothelial cells continues for several days after AKI [53, 54]. Here there is a system defect in the regeneration of microvasculature. Vascular endothelial growth factor (VEGF), which is definitely needed for angiogenesis, is not produced in sufficient quantities during the kidney recovery process. Instead, incompetent VEGF-188 dominates and replaces VEGF, then inducing fibrosis [55]. MMP-9 has been reported to be involved in VEGF reduction after AKI. In MMP-9 null mice, microvasculature was well maintained after AKI relative to the control mice [56].

Kidney pericytes make a significant contribution to maintaining the stability of the microvascular structure by producing the tissue inhibitor metalloproteinase 3 (TIMP-3) [57–61]. After AKI, pericytes are transformed into myofibroblasts and gain release from their perivascular location. This time, myofibroblasts destabilize the microvascular structure by activating a disintegrin and metalloprotease with thrombospondin motifs-1 (ADAMTS1) [60].

20.5.3 Incomplete Recovery of Tubular Cells

Previously, people believed that mesenchymal stem cells contribute to tubular recovery after AKI [62, 63]. But now, a lineage tracing technique based on the Cre-RoxP system has clearly proven that the surviving tubular cells play a central role in

regeneration of the tubular structure [64]. After AKI, they are induced to de-differentiate and start proliferating, theoretically until all the injured and lost cells are replaced by avatars which start to differentiate again. But in reality, this does not proceed smoothly. The tubular regeneration process sometimes ends up shortening the proximal tubules, atubular glomeruli, and remaining fibrosis, indicating that the tubular regeneration ability is limited [65]. One possible cause underlying the incomplete recovery of the tubular structure is the failed differentiation of the regenerating epithelium. Although these abnormally differentiated cells demonstrate growth arrest and atrophic appearance, they exhibit intensive signaling activity, leading to the secretion of profibrotic factors contributing to interstitial fibrosis [66–68]. Yang et al. added detailed mechanistic insights into these interesting phenomena [8]. They noticed that the abnormally differentiated tubular cells showed cell cycle arrest in G2/M. These G2/M arrested cells can increase the production of profibrotic factors like TGF-β1 and CTGF although c-jun NH2-terminal kinase signaling activation. Instead of making these cells apoptosis, the autocrine TGF-β1 prevents the arrested cells from proceeding with the cell cycle and enhances the production of profibrotic cytokines, leading to the progression of interstitial fibrosis through induction of pericytes to the myofibroblast transition followed by a proliferation of myofibroblasts [69]. Interestingly enough, G2/M arrest in tubular cells after AKI is induced by the activation of the ATM-ATR pathway [8].

20.5.4 Epigenetic Modification in Fibroblasts

Epigenetic modification includes DNA methylation and covalent post-translational modifications to histone. Bechtel et al. discovered that the gene encoding an inhibitor of Ras protein, *RASAL1,* was hypermethylated and silenced after folic acid-induced AKI [70]. The continually activated Ras protein makes it possible for fibroblasts to proliferate endlessly, leading to CKD transition. This *RASAL1* gene hypermethylation was mediated by the methyltransferase Dnmt1. DNA demethylation by 5′-azacytidine ameliorates kidney fibrosis [70]. Chang et al. also identified that DNA hypermethylation contributed to the reduction in EPO gene expression and the pericyte to myofibroblast transition in AKI-to-CKD transition models [71].

20.5.5 Chronic Inflammation

As previously described in Sect. 20.4, in AKI-to-CKD transition models, inflammatory infiltrating cells remain in the renal tissue in the chronic phase with persistently elevated pro-inflammatory cytokines and tissue injury markers [40, 72]. Consistent with the data, mounting references demonstrated persistent inflammation in the kidney after AKI in spite of a fully functional recovery [73]. Aged people have been identified as showing an easy transition from AKI to CKD [74]. Sato et al. identified

the increased development of tertiary lymphoid tissues (TLT) after IRI in aged mice [75]. TLT scale is positively associated with the severity of the renal injury and pro-inflammatory cytokine expression, suggesting that TLT can contribute to the remaining chronic inflammation in the AKI-to-CKD transition. IF TLT is diminished by the late administration of dexamethasone, the AKI-to-CKD transition is improved [75].

References

1. Basile DP, Donohoe D, Roethe K, Osborn JL. Renal ischemic injury results in permanent damage to peritubular capillaries and influences long-term function. Am J Physiol Renal Physiol. 2001;281(5):F887–99.
2. Basile DP. Rarefaction of peritubular capillaries following ischemic acute renal failure: a potential factor predisposing to progressive nephropathy. Curr Opin Nephrol Hypertens. 2004;13(1):1–7.
3. Coca SG, Yusuf B, Shlipak MG, Garg AX, Parikh CR. Long-term risk of mortality and other adverse outcomes after acute kidney injury: a systematic review and meta-analysis. Am J Kidney Dis. 2009;53(6):961–73.
4. Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. Kidney Int. 2012;81(5):442–8.
5. See EJ, Jayasinghe K, Glassford N, Bailey M, Johnson DW, Polkinghorne KR, et al. Long-term risk of adverse outcomes after acute kidney injury: a systematic review and meta-analysis of cohort studies using consensus definitions of exposure. Kidney Int. 2019;95(1):160–72.
6. Fu Y, Tang C, Cai J, Chen G, Zhang D, Dong Z. Rodent models of AKI-CKD transition. Am J Physiol Renal Physiol. 2018;315(4):F1098–106.
7. Horbelt M, Lee SY, Mang HE, Knipe NL, Sado Y, Kribben A, et al. Acute and chronic microvascular alterations in a mouse model of ischemic acute kidney injury. Am J Physiol Renal Physiol. 2007;293(3):F688–95.
8. Yang L, Besschetnova TY, Brooks CR, Shah JV, Bonventre JV. Epithelial cell cycle arrest in G2/M mediates kidney fibrosis after injury. Nat Med. 2010;16(5):535–43, 1p following 143.
9. Xiao L, Zhou D, Tan RJ, Fu H, Zhou L, Hou FF, et al. Sustained activation of Wnt/beta-catenin signaling drives AKI to CKD progression. J Am Soc Nephrol. 2016;27(6):1727–40.
10. Wei Q, Dong Z. Mouse model of ischemic acute kidney injury: technical notes and tricks. Am J Physiol Renal Physiol. 2012;303(11):F1487–94.
11. Marschner JA, Schafer H, Holderied A, Anders HJ. Optimizing mouse surgery with online rectal temperature monitoring and preoperative heat supply. Effects on post-ischemic acute kidney injury. PLoS One. 2016;11(2):e0149489.
12. Zager RA, Johnson AC, Becker K. Acute unilateral ischemic renal injury induces progressive renal inflammation, lipid accumulation, histone modification, and "end-stage" kidney disease. Am J Physiol Renal Physiol. 2011;301(6):F1334–45.
13. Lech M, Rommele C, Grobmayr R, Eka Susanti H, Kulkarni OP, Wang S, et al. Endogenous and exogenous pentraxin-3 limits postischemic acute and chronic kidney injury. Kidney Int. 2013;83(4):647–61.
14. Danelli L, Madjene LC, Madera-Salcedo I, Gautier G, Pacreau E, Ben Mkaddem S, et al. Early phase mast cell activation determines the chronic outcome of renal ischemia-reperfusion injury. J Immunol. 2017;198(6):2374–82.

15. Finn WF, Fernandez-Repollet E, Goldfarb D, Iaina A, Eliahou HE. Attenuation of injury due to unilateral renal ischemia: delayed effects of contralateral nephrectomy. J Lab Clin Med. 1984;103(2):193–203.
16. Skrypnyk NI, Voziyan P, Yang H, de Caestecker CR, Theberge MC, Drouin M, et al. Pyridoxamine reduces postinjury fibrosis and improves functional recovery after acute kidney injury. Am J Physiol Renal Physiol. 2016;311(2):F268–77.
17. Grgic I, Campanholle G, Bijol V, Wang C, Sabbisetti VS, Ichimura T, et al. Targeted proximal tubule injury triggers interstitial fibrosis and glomerulosclerosis. Kidney Int. 2012;82(2):172–83.
18. Park KM, Chen A, Bonventre JV. Prevention of kidney ischemia/reperfusion-induced functional injury and JNK, p. 38, and MAPK kinase activation by remote ischemic pretreatment. J Biol Chem. 2001;276(15):11870–6.
19. Sharp CN, Doll MA, Dupre TV, Shah PP, Subathra M, Siow D, et al. Repeated administration of low-dose cisplatin in mice induces fibrosis. Am J Physiol Renal Physiol. 2016;310(6):F560–8.
20. Sharp CN, Doll MA, Megyesi J, Oropilla GB, Beverly LJ, Siskind LJ. Subclinical kidney injury induced by repeated cisplatin administration results in progressive chronic kidney disease. Am J Physiol Renal Physiol. 2018;315(1):F161–72.
21. Torres R, Velazquez H, Chang JJ, Levene MJ, Moeckel G, Desir GV, et al. Three-dimensional morphology by multiphoton microscopy with clearing in a model of cisplatin-induced CKD. J Am Soc Nephrol. 2016;27(4):1102–12.
22. Ravichandran K, Wang Q, Ozkok A, Jani A, Li H, He Z, et al. CD4 T cell knockout does not protect against kidney injury and worsens cancer. J Mol Med (Berl). 2016;94(4):443–55.
23. Katagiri D, Hamasaki Y, Doi K, Negishi K, Sugaya T, Nangaku M, et al. Interstitial renal fibrosis due to multiple cisplatin treatments is ameliorated by semicarbazide-sensitive amine oxidase inhibition. Kidney Int. 2016;89(2):374–85.
24. Takaori K, Nakamura J, Yamamoto S, Nakata H, Sato Y, Takase M, et al. Severity and frequency of proximal tubule injury determines renal prognosis. J Am Soc Nephrol. 2016;27(8):2393–406.
25. Debelle FD, Vanherweghem JL, Nortier JL. Aristolochic acid nephropathy: a worldwide problem. Kidney Int. 2008;74(2):158–69.
26. Depierreux M, Van Damme B, Vanden Houte K, Vanherweghem JL. Pathologic aspects of a newly described nephropathy related to the prolonged use of Chinese herbs. Am J Kidney Dis. 1994;24(2):172–80.
27. Fan Y, Xiao W, Lee K, Salem F, Wen J, He L, et al. Inhibition of reticulon-1A-mediated endoplasmic reticulum stress in early AKI attenuates renal fibrosis development. J Am Soc Nephrol. 2017;28(7):2007–21.
28. Jiang C, Shao Q, Jin B, Gong R, Zhang M, Xu B. Tanshinone IIA attenuates renal fibrosis after acute kidney injury in a mouse model through inhibition of fibrocytes recruitment. Biomed Res Int. 2015;2015:867140.
29. Stallons LJ, Whitaker RM, Schnellmann RG. Suppressed mitochondrial biogenesis in folic acid-induced acute kidney injury and early fibrosis. Toxicol Lett. 2014;224(3):326–32.
30. Roberts J, Chen B, Curtis LM, Agarwal A, Sanders PW, Zinn KR. Detection of early changes in renal function using 99mTc-MAG3 imaging in a murine model of ischemia-reperfusion injury. Am J Physiol Renal Physiol. 2007;293(4):F1408–12.
31. Schock-Kusch D, Xie Q, Shulhevich Y, Hesser J, Stsepankou D, Sadick M, et al. Transcutaneous assessment of renal function in conscious rats with a device for measuring FITC-sinistrin disappearance curves. Kidney Int. 2011;79(11):1254–8.
32. Rabito CA, Moore RH, Bougas C, Dragotakes SC. Noninvasive, real-time monitoring of renal function: the ambulatory renal monitor. J Nucl Med. 1993;34(2):199–207.
33. Chinen LK, Galen KP, Kuan KT, Dyszlewski ME, Ozaki H, Sawai H, et al. Fluorescence-enhanced europium-diethylenetriaminepentaacetic (DTPA)-monoamide complexes for the assessment of renal function. J Med Chem. 2008;51(4):957–62.
34. Dorshow RB, Bugaj JE, Burleigh BD, Duncan JR, Johnson MA, Jones WB. Noninvasive fluorescence detection of hepatic and renal function. J Biomed Opt. 1998;3(3):340–5.

35. Rabito CA, Chen Y, Schomacker KT, Modell MD. Optical, real-time monitoring of the glomerular filtration rate. Appl Opt. 2005;44(28):5956–65.
36. Schock-Kusch D, Sadick M, Henninger N, Kraenzlin B, Claus G, Kloetzer HM, et al. Transcutaneous measurement of glomerular filtration rate using FITC-sinistrin in rats. Nephrol Dial Transplant. 2009;24(10):2997–3001.
37. Yu W, Sandoval RM, Molitoris BA. Rapid determination of renal filtration function using an optical ratiometric imaging approach. Am J Physiol Renal Physiol. 2007;292(6):F1873–80.
38. Wang E, Sandoval RM, Campos SB, Molitoris BA. Rapid diagnosis and quantification of acute kidney injury using fluorescent ratio-metric determination of glomerular filtration rate in the rat. Am J Physiol Renal Physiol. 2010;299(5):F1048–55.
39. Boss A, Martirosian P, Gehrmann M, Artunc F, Risler T, Oesingmann N, et al. Quantitative assessment of glomerular filtration rate with MR gadolinium slope clearance measurements: a phase I trial. Radiology. 2007;242(3):783–90.
40. Black LM, Lever JM, Traylor AM, Chen B, Yang Z, Esman SK, et al. Divergent effects of AKI to CKD models on inflammation and fibrosis. Am J Physiol Renal Physiol. 2018;315(4):F1107–18.
41. Venkatachalam MA, Weinberg JM, Kriz W, Bidani AK. Failed tubule recovery, AKI-CKD transition, and kidney disease progression. J Am Soc Nephrol. 2015;26(8):1765–76.
42. Chou YH, Huang TM, Chu TS. Novel insights into acute kidney injury-chronic kidney disease continuum and the role of renin-angiotensin system. J Formos Med Assoc. 2017;116(9):652–9.
43. Strausser SA, Nakano D, Souma T. Acute kidney injury to chronic kidney disease transition: insufficient cellular stress response. Curr Opin Nephrol Hypertens. 2018;27(4):314–22.
44. Tanaka S, Tanaka T, Nangaku M. Hypoxia as a key player in the AKI-to-CKD transition. Am J Physiol Renal Physiol. 2014;307(11):F1187–95.
45. Brezis M, Rosen S. Hypoxia of the renal medulla—its implications for disease. N Engl J Med. 1995;332(10):647–55.
46. Haase VH. Mechanisms of hypoxia responses in renal tissue. J Am Soc Nephrol. 2013;24(4):537–41.
47. Whitehouse T, Stotz M, Taylor V, Stidwill R, Singer M. Tissue oxygen and hemodynamics in renal medulla, cortex, and corticomedullary junction during hemorrhage-reperfusion. Am J Physiol Renal Physiol. 2006;291(3):F647–53.
48. Safran M, Kim WY, O'Connell F, Flippin L, Gunzler V, Horner JW, et al. Mouse model for noninvasive imaging of HIF prolyl hydroxylase activity: assessment of an oral agent that stimulates erythropoietin production. Proc Natl Acad Sci U S A. 2006;103(1):105–10.
49. Levy MN, Sauceda G. Diffusion of oxygen from arterial to venous segments of renal capillaries. Am J Phys. 1959;196(6):1336–9.
50. Ngo JP, Kar S, Kett MM, Gardiner BS, Pearson JT, Smith DW, et al. Vascular geometry and oxygen diffusion in the vicinity of artery-vein pairs in the kidney. Am J Physiol Renal Physiol. 2014;307(10):F1111–22.
51. Schurek HJ, Jost U, Baumgartl H, Bertram H, Heckmann U. Evidence for a preglomerular oxygen diffusion shunt in rat renal cortex. Am J Phys. 1990;259(6 Pt 2):F910–5.
52. Welch WJ, Baumgartl H, Lubbers D, Wilcox CS. Nephron pO2 and renal oxygen usage in the hypertensive rat kidney. Kidney Int. 2001;59(1):230–7.
53. Conger JD, Robinette JB, Hammond WS. Differences in vascular reactivity in models of ischemic acute renal failure. Kidney Int. 1991;39(6):1087–97.
54. Chen X, Wang CC, Song SM, Wei SY, Li JS, Zhao SL, et al. The administration of erythropoietin attenuates kidney injury induced by ischemia/reperfusion with increased activation of Wnt/beta-catenin signaling. J Formos Med Assoc. 2015;114(5):430–7.
55. Schrimpf C, Duffield JS. Mechanisms of fibrosis: the role of the pericyte. Curr Opin Nephrol Hypertens. 2011;20(3):297–305.
56. Lee SY, Horbelt M, Mang HE, Knipe NL, Bacallao RL, Sado Y, et al. MMP-9 gene deletion mitigates microvascular loss in a model of ischemic acute kidney injury. Am J Physiol Renal Physiol. 2011;301(1):F101–9.

57. Lin SL, Chang FC, Schrimpf C, Chen YT, Wu CF, Wu VC, et al. Targeting endothelium-pericyte cross talk by inhibiting VEGF receptor signaling attenuates kidney microvascular rarefaction and fibrosis. Am J Pathol. 2011;178(2):911–23.
58. Chang FC, Chou YH, Chen YT, Lin SL. Novel insights into pericyte-myofibroblast transition and therapeutic targets in renal fibrosis. J Formos Med Assoc. 2012;111(11):589–98.
59. Kramann R, Wongboonsin J, Chang-Panesso M, Machado FG, Humphreys BD. Gli1(+) pericyte loss induces capillary rarefaction and proximal tubular injury. J Am Soc Nephrol. 2017;28(3):776–84.
60. Schrimpf C, Xin C, Campanholle G, Gill SE, Stallcup W, Lin SL, et al. Pericyte TIMP3 and ADAMTS1 modulate vascular stability after kidney injury. J Am Soc Nephrol. 2012;23(5):868–83.
61. Lin SL, Kisseleva T, Brenner DA, Duffield JS. Pericytes and perivascular fibroblasts are the primary source of collagen-producing cells in obstructive fibrosis of the kidney. Am J Pathol. 2008;173(6):1617–27.
62. Morigi M, Imberti B, Zoja C, Corna D, Tomasoni S, Abbate M, et al. Mesenchymal stem cells are renotropic, helping to repair the kidney and improve function in acute renal failure. J Am Soc Nephrol. 2004;15(7):1794–804.
63. Herrera MB, Bussolati B, Bruno S, Fonsato V, Romanazzi GM, Camussi G. Mesenchymal stem cells contribute to the renal repair of acute tubular epithelial injury. Int J Mol Med. 2004;14(6):1035–41.
64. Humphreys BD, Czerniak S, DiRocco DP, Hasnain W, Cheema R, Bonventre JV. Repair of injured proximal tubule does not involve specialized progenitors. Proc Natl Acad Sci U S A. 2011;108(22):9226–31.
65. Endo T, Nakamura J, Sato Y, Asada M, Yamada R, Takase M, et al. Exploring the origin and limitations of kidney regeneration. J Pathol. 2015;236(2):251–63.
66. Lan R, Geng H, Polichnowski AJ, Singha PK, Saikumar P, McEwen DG, et al. PTEN loss defines a TGF-beta-induced tubule phenotype of failed differentiation and JNK signaling during renal fibrosis. Am J Physiol Renal Physiol. 2012;302(9):F1210–23.
67. Geng H, Lan R, Wang G, Siddiqi AR, Naski MC, Brooks AI, et al. Inhibition of autoregulated TGFbeta signaling simultaneously enhances proliferation and differentiation of kidney epithelium and promotes repair following renal ischemia. Am J Pathol. 2009;174(4):1291–308.
68. Geng H, Lan R, Singha PK, Gilchrist A, Weinreb PH, Violette SM, et al. Lysophosphatidic acid increases proximal tubule cell secretion of profibrotic cytokines PDGF-B and CTGF through LPA2- and Galphaq-mediated rho and alphavbeta6 integrin-dependent activation of TGF-beta. Am J Pathol. 2012;181(4):1236–49.
69. Wu CF, Chiang WC, Lai CF, Chang FC, Chen YT, Chou YH, et al. Transforming growth factor beta-1 stimulates profibrotic epithelial signaling to activate pericyte-myofibroblast transition in obstructive kidney fibrosis. Am J Pathol. 2013;182(1):118–31.
70. Bechtel W, McGoohan S, Zeisberg EM, Muller GA, Kalbacher H, Salant DJ, et al. Methylation determines fibroblast activation and fibrogenesis in the kidney. Nat Med. 2010;16(5):544–50.
71. Chang YT, Yang CC, Pan SY, Chou YH, Chang FC, Lai CF, et al. DNA methyltransferase inhibition restores erythropoietin production in fibrotic murine kidneys. J Clin Invest. 2016;126(2):721–31.
72. Ko GJ, Grigoryev DN, Linfert D, Jang HR, Watkins T, Cheadle C, et al. Transcriptional analysis of kidneys during repair from AKI reveals possible roles for NGAL and KIM-1 as biomarkers of AKI-to-CKD transition. Am J Physiol Renal Physiol. 2010;298(6):F1472–83.
73. Cheng SY, Chou YH, Liao FL, Lin CC, Chang FC, Liu CH, et al. Losartan reduces ensuing chronic kidney disease and mortality after acute kidney injury. Sci Rep. 2016;6:34265.
74. Newsome BB, Warnock DG, McClellan WM, Herzog CA, Kiefe CI, Eggers PW, et al. Long-term risk of mortality and end-stage renal disease among the elderly after small increases in serum creatinine level during hospitalization for acute myocardial infarction. Arch Intern Med. 2008;168(6):609–16.
75. Sato Y, Mii A, Hamazaki Y, Fujita H, Nakata H, Masuda K, et al. Heterogeneous fibroblasts underlie age-dependent tertiary lymphoid tissues in the kidney. JCI Insight. 2016;1(11):e87680.

Chapter 21
Role of the Nervous System in Acute Kidney Injury

Rie Uni, Chikara Abe, Reiko Inagi, and Tsuyoshi Inoue

Abstract Although its parasympathetic innervation has not been elucidated, the sympathetic innervation of the kidney is well studied. Renal sympathetic overactivity has been observed in essential hypertension and chronic kidney disease. Renal sympathetic nerve activation decreases glomerular filtration rate and increases sodium absorption, which further deteriorates renal function. Sympathetic overactivity presents without uremia, suggesting that the cause is intrinsic to the diseased kidney itself. By disrupting signaling from the injured kidney, renal nerve denervation is expected to be beneficial in patients with kidney disease. Additionally, the immune system mediates an indirect association between the kidney and nervous system via the cholinergic anti-inflammatory pathway (CAP), whose main players include the vagus nerve, spleen, α7 acetylcholine receptor-positive macrophages, $CD4^+$ T cells, and β2-adrenergic receptors. In animal models, AKI attenuation was achieved via CAP activation induced by vagus nerve stimulation or ultrasound treatment, although the exact mechanism remains unclear. Novel techniques, such as optogenetics, may help elucidate the CAP mechanisms and promote the clinical use of CAP-targeted immunomodulating therapy for prevention and treatment of kidney disease. Here, we provide an overview of kidney innervation and discuss the relationship between the kidney and the nervous system, including the CAP, in the context of acute kidney injury.

Keywords Cholinergic anti-inflammatory pathway (CAP) · Vagus nerve · Acute kidney injury

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21.1 Introduction

There are several interactions between the kidney and other important organs. Interactions with the heart and liver are referred to as the cardio-renal syndrome and hepato-renal syndrome, respectively. An interaction between the nervous system and the kidney has also been recognized. Acute kidney injury (AKI) is estimated to affect approximately 15% of hospitalized patients and 60% of critically ill patients [1]. Despite substantial advancements in healthcare technology and availability, the incidence of AKI is increasing, and its morbidity and mortality remain high [2, 3]. In addition, AKI is a risk factor of chronic kidney disease (CKD) and end-stage renal disease (ESRD) [4]. Therefore, it is very important to prevent AKI development and progression to CKD. In this review, we first focus on the direct link between the nervous system and the kidney, discussing the relevant neurological anatomy and innervation, as well as strategies such as renal nerve denervation, which aims to disrupt the sympathetic innervation of the kidney and has been effective in lowering blood pressure. Afterwards, given the increasing evidence of neuronal control of the inflammatory system [5] and considering the major role of inflammation in AKI pathogenesis, we will focus on the relationship between the nervous system and AKI from the perspective of immunity. The nervous system processes the input from peripheral inflammation and issues output for effector cells in a circuit referred to as the inflammatory reflex, with the vagus nerve as an essential component. Novel therapies including ultrasound treatment and vagus nerve stimulation (VNS) aim to modulate this pathway and have been helpful in attenuating inflammatory diseases such as inflammatory bowel disease and rheumatoid arthritis. Animal studies have suggested that these methods may also be effective for kidney protection, but the exact mechanism underlying this effect remains unclear. The newly developed technique of optogenetics, whereby light is used to modulate the activity of living cells, is expected to help reveal the role and function of the nervous system in the inflammatory pathway.

21.2 Innervation of the Kidney

The relationship between the nervous system and kidney function was first demonstrated using animal renal denervation models as early as the mid-nineteenth century [6]. Since the 1960s, when the neural control of renin secretion from the kidney came into focus, it has been revealed that changes in the renal sympathetic nerve activity were accompanied by corresponding changes in renin secretion from the kidney. As the activation of the renal sympathetic nerve is so intense that it causes a decrease in renal blood flow, which itself stimulates renin release, it was originally thought that renal blood flow changes were the main cause of renin secretion. In order to demonstrate the direct effect of sympathetic nerve activation on the renal tubule or the

juxtaglomerular apparatus, later studies focused on renal sympathetic nerve stimulation that did not affect renal blood flow or glomerular filtration rate, concluding that sympathetic nerve stimulation caused an increase in renin secretion and a decrease in urinary salt excretion, which suggested a direct renal sympathetic nervous system effect on renal tubular cells [7]. Renal innervation had not been clarified at the time, but a direct synaptic contact between the intra-renal nerve fiber and renal tubular epithelial cell membranes was discovered in 1972–1973 [8]. Since then, there has been growing interest in elucidating the neural control of renal function. Later studies in rat revealed that the extrinsic innervation of the kidney included nerve fibers derived from the celiac plexus, lumbar splanchnic nerves, and intermesenteric plexus [9].

21.2.1 Sympathetic Nervous System

The kidneys receive more abundant nerve supply than any other abdominal organs, except for the adrenal glands. The kidney is innervated with sympathetic efferent fibers that run along the vasculature [10, 11]. The renal plexus is composed of nerve fibers derived from the celiac ganglion, inferior and posterior renal ganglia, superior mesenteric ganglion, and thoracic splanchnic nerves. The bulk of the plexus is located around the intermediate and distal thirds of the renal artery [11]. Most components of the renal plexus are adrenergic, with noradrenaline as the main neurotransmitter. While adrenergic renal innervation seems to be limited to vascular smooth muscle cells, nerve endings unrelated to the renal arteries were also found, suggesting a direct sympathetic innervation of renal tubular cells. Although the presence of neuroeffector junctions on renal tubules [12] and direct sympathetic functional modulation of renal tubular cells [13] have been confirmed in rodents, a direct neural control of renal tubular cell function has not been clearly established in humans. Renal sensory afferent nerves are mainly located in the renal pelvic area, with the greatest density at the renal pelvic wall [14, 15]. Because they contain neuropeptides such as substance P and calcitonin gene-related peptide, renal sensory afferent nerves serve as mechanosensitive and chemosensitive neurons [16], which are activated by an increase in renal pelvic pressure and changes in the chemical composition of the urine, respectively [15]. The cell bodies of these sensory nerves are located in the dorsal root ganglia and synapse with interneurons in the dorsal horn, transmitting information to the central nervous system (Fig. 21.1).

21.2.2 Parasympathetic Nervous System

The parasympathetic innervation of the kidney remains a topic of controversy [17]. In 2016, Amsterdam et al. reported the presence of parasympathetic fibers near the human renal artery [18]. However, Amsterdam et al. only examined the levels of

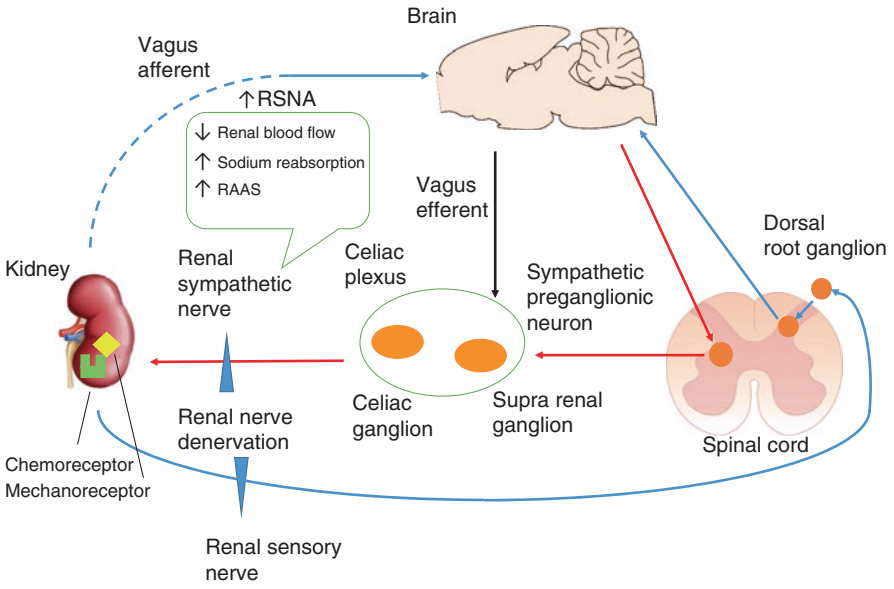

Fig. 21.1 Extrinsic innervation of the kidney. Sympathetic preganglionic neurons residing in the intermediolateral cell column of the spinal cord synapse with the renal sympathetic nerve. Sensory afferent nerves having the cell body in the dorsal root ganglia synapse with neurons in the dorsal horn of the spinal cord and transduce information to the brain. There seems to be no direct vagus innervation of the kidney. *RSNA* renal sympathetic nerve activity, *RAAS* renin-angiotensin-aldosterone system

nitric oxide synthase, a parasympathetic nerve marker that might not be sufficiently specific. Therefore, further research using additional parasympathetic markers is needed to confirm the presence of a parasympathetic nerve supply to the kidney. Animal studies employing acetylcholinesterase staining have provided information about the extrinsic parasympathetic innervation of the kidney. Specifically, the kidney receives branches from the celiac ganglion, which gains input from the vagus nerve, suggesting that the kidney is parasympathetically innervated via the vagus nerve (Fig. 21.1) [9]. As for intrinsic innervation, while the sympathetic nervous system of the kidney is relatively well understood, little is known about the kidney parasympathetic nervous control. Because acetylcholine is the main neurotransmitter of parasympathetic postganglionic nerve terminals, it was speculated that the presence of acetylcholinesterase in the kidney reflected the presence of parasympathetic nerve fibers. However, histofluorescence evidence indicates that acetylcholinesterase is also present in adrenergic nerve fibers [19], which suggests that the presence of acetylcholinesterase in the kidney does not necessarily reflect the direct parasympathetic innervation of the kidney. Therefore, kidney parasympathetic innervation requires further confirmation, based on other markers or techniques.

21.2.3 Renal Denervation for Hypertension

The first surgical denervation of the kidney in a human was conducted in 1924 and aimed to relieve intractable back pain originating from the kidney [20]. Since sympathetic overflow was observed in essential hypertension [21], renal denervation has been investigated as a potential treatment for refractory hypertension. The first bilateral sympathetic nerve denervation of the kidneys was performed in 1934 and aimed to treat resistant essential hypertension [22]. Although the procedure was safe, it did not achieve satisfactory blood pressure control and has since evolved into a more radical form of surgical denervation referred to as splanchnicectomy, which was proven to be more effective in patients with malignant hypertension [23]. For the following two decades, surgical thoracolumbar splanchnicectomy was the treatment of choice in patients with resistant hypertension, until the first oral antihypertensive drug became available in the 1950s. However, these procedures were associated not only with severe postural hypotension but also with perioperative morbidity and mortality, as well as with long-term complications such as erectile, bladder, and bowel dysfunction. Therefore, safer and less invasive strategies were needed.

The introduction of catheter-based selective renal denervation was facilitated by the development of catheter ablation for cardiology applications, as well as by the fact that, from an anatomic perspective, the renal sympathetic nerve fibers are easily approachable. To achieve renal denervation, the ablation catheter is inserted percutaneously through the ipsilateral femoral artery to reach the renal artery, where it delivers thermal energy produced by a radiofrequency generator to disrupt both the afferent and efferent sympathetic nerve fibers without interfering with other abdominal or pelvic innervation. In 2009, sympathetic renal nerve denervation was proven to be effective and safe for treating patients with resistant hypertension [24]. A sustained blood pressure-lowering effect was reported in a study with a follow-up of 3 years [25]. These successful results prompted the initiation of a prospective randomized controlled trial (SYMPLICITY HTN-3), which enrolled 535 patients with resistant hypertension [26]. However, SYMPLICITY HTN-3 failed to prove the superiority of renal nerve denervation over a sham procedure with respect to lowering blood pressure, which prompted two further trials (also randomized and sham-controlled) in 2017 and 2018, with refinement of the study design and renal denervation procedure [27, 28]. Although these trials are relatively small and the observation period is short (3 months in both trials), they found a favorable effect of renal denervation on hypertension [27, 28]. A method for evaluating denervation activity in real time is currently under development and might help establish a suitable strategy for renal denervation.

21.2.4 Denervation for Kidney Disease

Increased sympathetic tone is commonly noted not only in hypertension but also in various diseases such as cardiac arrhythmias, left ventricular hypertrophy, obesity, diabetes, polycystic ovary syndrome, obstructive sleep apnea, cirrhosis, and chronic

kidney disease [20]. The relationship between sympathetic nervous system tone and chronic renal failure was first demonstrated in 1992 [29], when a study reported increased muscle sympathetic nerve activity in ESRD patients on hemodialysis; this was also the first study to reveal the importance of the diseased kidney in sympathetic activation, as bilateral nephrectomy reduced sympathetic drive and lowered blood pressure, in contrast to the initial notion that uremia was the cause of sympathetic activation. This idea is supported by the fact that increased sympathetic tone is observed even in acute renal failure or autosomal dominant polycystic kidney disease with normal kidney function [30].

In the healthy kidney, stimulation of the renal efferent sympathetic nerve leads to renal vasoconstriction, reduced renal blood flow and glomerular filtration rate, and increased sodium absorption and angiotensin II synthesis (Fig. 21.1). On the other hand, activation of the afferent renal nerves has an inhibitory effect on the efferent nerves, a phenomenon known as the renorenal reflex [15]. This inhibitory reflex is suppressed in the presence of renal injury, as shown in an animal model of ischemia reperfusion injury (IRI), leading to overactivity of the renal sympathetic system. Activation of the sympathetic nerve leads to an increase in angiotensin II production by stimulating the release of renin from the juxtaglomerular cells [31]. Increased angiotensin II levels further weaken the inhibitory renorenal reflex, creating a vicious cycle [32]. In addition, increased sympathetic nerve activity decreases nitric oxide synthesis and increases the levels of reactive oxygen species. The combination of these physiological conditions leads to endothelial dysfunction, vasoconstriction, decreased glomerular filtration rate, and renal fibrosis.

Because hypoxia and subsequent renal fibrosis eventually lead to ESRD [33], preventing renal fibrogenesis is a useful strategy to hinder the progression of CKD. Renal denervation was effective in preventing renal fibrosis in animal models of unilateral ureteral obstruction [34] and IRI [35]. Local infusion of efferent nerve-derived noradrenaline or afferent nerve-derived calcitonin gene-related peptide induced fibrosis in the denervated kidney, whereas the antagonists of these receptors inhibited fibrosis, suggesting that both the afferent and efferent pathways are involved in the progression of kidney fibrosis. Selective renal denervation [36] may help elucidate the role each pathway plays in fibrogenesis. Renal nerve denervation also retarded the progression of renal failure in five of six nephrectomized rats [37] and prevented glomerular hyperfiltration in diabetic rats [38]. In 2015, Ott et al. demonstrated that renal denervation slowed the progression of renal function decrease in patients with CKD stage 3 and 4 [39]. Although there are other factors contributing to CKD progression, renal nerve denervation represents a promising treatment option.

Renal denervation is a therapeutic option in AKI because increased sympathetic nerve activity and catecholamine levels may be related to progressive renal damage after ischemic injury [40], which is considered a cause of AKI. Fujii et al. found that, in a rat model of IRI, the increase in noradrenaline overflow was suppressed by renal denervation or pharmacological ganglionic blockade with pentolinium, suggesting a pathogenetic role of sympathetic nerve activity [41]. Pharmacological denervation of noradrenaline-containing nerves inhibited IRI-induced kidney injury in a mouse model of AKI [42].

While the above-described outcomes of renal nerve denervation have a beneficial effect on AKI prognosis, a negative effect has also been reported. Ischemic preconditioning, such as myocardial preconditioning, was shown to have a protective effect in a rat model of kidney ischemia/reperfusion [43]. However, renal denervation abolished this protective effect, suggesting that sympathetic nerve activity plays a role in ischemic preconditioning, although the exact mechanism underlying this effect remains unclear [44]. Further studies are needed to clarify the effect of denervation on inhibiting the progression of AKI.

21.3 Nervous System–Immune System Interaction

Within the framework of humorism, the initial theory of disease as systemized in ancient Greece by Galen, disease was caused by an imbalance of body fluids. The germ theory, which recognizes that many diseases are caused by microorganisms, was advanced by Louis Pasteur in the nineteenth century. Since the 1980s, the prevalent framework has been the cytokine theory of disease, wherein cytokines produced by the immune system are responsible for the signs, symptoms, and aftereffects of the disease [45]. The relationship between the nervous system and immune system was discovered as early as the 1950s [46, 47]. Subsequently, Besedovsky et al. demonstrated that peripheral inflammation altered anti-inflammatory signaling in the hypothalamus [47], whereas Watkins et al. described the sensory role of the afferent vagus nerves in an animal model of interleukin-1 (IL-1)-induced hyperthermia, which was blocked by vagotomy [48, 49].

21.3.1 Inflammatory Reflex

The body secretes a variety of endogenous anti-inflammatory cytokines and glucocorticoids to prevent cytokine-mediated disease. The hypothalamic-pituitary-adrenal (HPA) axis is one of these humoral anti-inflammatory responses [50, 51], which functions as follows. The blood–brain barrier, which serves to protect the brain from water-soluble substances, is not present around the preoptic nucleus of the hypothalamus. Certain neurons in this area have receptors for cytokines released by immune cells; by this mechanism, cytokines such as IL-1, tumor necrosis factor-α (TNF-α), and IL-6 can cross into the brain. Preoptic neurons communicate with neurons in the paraventricular nucleus of the hypothalamus. The HPA axis is activated upon stimulation of the paraventricular nucleus and release of corticotropin-releasing hormone from the hypothalamus, which in turn stimulates the secretion of the adrenocorticotropic hormone and subsequent release of glucocorticoids from the adrenal gland [52, 53]. An alternative mechanism of controlling cytokine release was proposed to rely on the vagal afferent and efferent nerves [54]. Cytokines produced by damaged cells activate afferent sensory fibers. Vagal afferent nerves

express several kinds of receptors to bind inflammatory molecules such as TNF, IL, and the immunoglobulin Fc region [55–57]. On detection of peripheral inflammation, these nerve fibers transmit inflammatory signals from the peripheral tissues to the tractus solitarius in the brainstem [58, 59]. This, in turn, activates the efferent vagus nerve and modulates peripheral immunological reactions, though it is unknown how the afferent vagus nerves activate efferent nerves. These afferent vagus nerve fibers not only convey peripheral inflammatory signals to the central nervous system, but also affect the HPA axis [60]. Stimulation of the afferent vagal nerve is a very crucial part of modulating adrenocorticotropin and fever response in exdotoxemia and cytokinemia [61–63]. Thus, the humoral pathway and vagal pathway work together to make up the inflammatory reflex.

21.4 Cholinergic Anti-inflammatory Pathway (CAP)

Compared to afferent vagal signaling in anti-inflammatory response, little was known about the role of efferent vagal nerve signaling until 2000, when Borovikova et al. first described the role of the efferent vagal nerve in controlling immune response [64]. Efferent VNS induced leukocyte release from the rat thymus, an action mediated by nicotinic receptors [65]. Furthermore, nicotine administration was effective in some patients with inflammatory bowel disease [66, 67]. These findings highlighted the role of nicotinic acetylcholine receptors and shifted the focus towards the inflammatory pathway based on acetylcholine signaling. Borovikova et al. showed that direct stimulation of the efferent vagal nerve in rats inhibited TNF synthesis and prevented the development of shock. The same study indicated that acetylcholine inhibits the release of TNF and other cytokines through a post-transcriptional mechanism that is dependent on α-bungarotoxin-sensitive nicotinic receptors on primary human macrophages. Borovikova et al. referred to this nervous-immune relationship as the cholinergic anti-inflammatory pathway (CAP).

Wang et al. then demonstrated that the α7 subunit of the acetylcholine receptor was essential for inhibiting CAP-mediated cytokine synthesis in α7-knockout (α7KO) mice [68]. Subsequently, a splenectomy study revealed the importance of the spleen in the CAP [69, 70]. The reticuloendothelial system, which consists of phagocytic cells such as macrophages and monocytes in the spleen, lungs, liver, and other organs, is the body's defense mechanism against bacteria or bacterial products that have penetrated into the blood, with the spleen serving as a major component of the reticuloendothelial system [71]. This study demonstrated that the spleen is a major site of cytokine production in an experimental model of sepsis, as splenectomy abolished the suppression of cytokine release by VNS, suggesting that the spleen contributes to the CAP. The authors also revealed that modulation of TNF synthesis in the spleen requires the expression of the α7 acetylcholine receptor on the surface of macrophages. Signaling mediated by the α7 acetylcholine receptor inhibits STAT3 phosphorylation and the NF-κB pathway, leading to suppression of inflammatory cytokine synthesis [72, 73].

CD4⁺ T cells are also key players in the CAP [74]. Vida et al. demonstrated that VNS inhibits TNF production in endotoxemia, an effect mediated by the β2-adrenoreceptor located on CD4⁺CD25⁻ T cells [75]. The authors showed that VNS-mediated TNF-α suppression induced by lipopolysaccharides was abolished by administration of a β2 antagonist and was completely absent in β2-adrenergic receptor-deficient mice. Reconstitution of β2-adrenergic receptor-deficient mice with CD4⁺CD25⁻ T cells (non-regulatory T cells), but not with CD4⁺CD25⁺ cells (regulatory T cells), from wild-type mice rescued the VNS-mediated TNF-α suppressive effect.

Although the importance of the spleen in the CAP was implied, there was no distinct evidence of direct cholinergic innervation of the spleen at that time. Recently, immunohistochemistry investigations revealed limited cholinergic innervation in the spleen [76]. In the disynaptic model (Fig. 21.2) [77], preganglionic

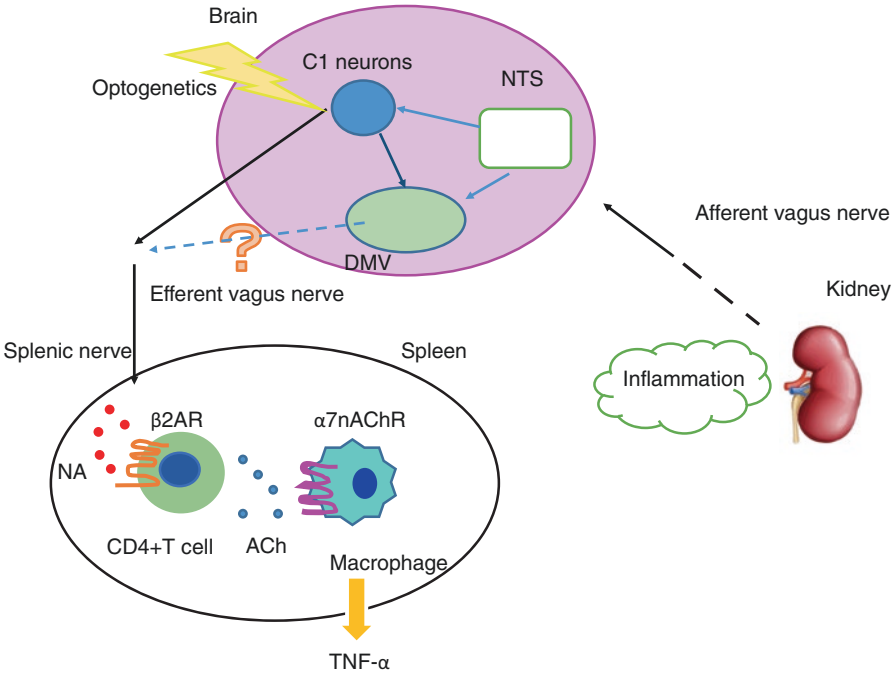

Fig. 21.2 Cholinergic anti-inflammatory pathway. Inflammatory signals from the kidney are transmitted to the central nervous system via the afferent vagus nerve. This, in turn, activates the vagus efferent nerve through the DMV. Efferent vagus nerves possibly stimulate the splenic nerve and the subsequent anti-inflammatory pathway. C1 neurons also activate the CAP via efferent sympathetic nerve activation. In the spleen, NA released from the terminal of the activated splenic nerve activates ChAT⁺ T cells expressing β2AR. These stimulated ChAT⁺ T cells release ACh, which binds to α7nAChR on macrophages, resulting in suppression of inflammatory cytokines and subsequent anti-inflammatory action. *NTS* nucleus tractus solitaries, *DMV* dorsal motor nucleus of the vagus, *β2AR* β2-adrenergic receptor, *α7nAChR* α7 nicotinic acetylcholine receptor, *ACh* acetylcholine, *TNF-α* tumor necrosis factor-α, *NA* noradrenaline

neurons in the vagus nerves presumably synapse with postganglionic sympathetic neurons in the celiac ganglion, and vagus nerve fibers travel together with the splenic nerve to innervate the spleen. However, Bratton et al. casted doubt on the disynaptic model paradigm, and several new models were proposed to reconcile this argument [78, 79]. Bratton et al. denied the existence of a synaptic connection between preganglionic vagal efferent neurons and postganglionic splenic neurons, insisting that the sympathetic nervous system of the spleen is composed of the efferent arm of the inflammatory reflex. In the new models, T lymphocytes capable of acetylcholine synthesis play an important role in linking the vagus nerve and macrophages. Rosas-Ballina et al. showed that $CD4^{+}CD44^{high}CD62L^{low}$ memory T cells in the spleen possess the acetylcholine biosynthetic enzyme choline acetyltransferase (ChAT) and can produce acetylcholine [80]. Although the TNF-α suppressive effect of VNS is lost in mice without functional T cells, reconstitution of such mice with $ChAT^{+}CD4^{+}$ T cells partially restores the VNS-induced anti-inflammatory effect. The presence of these acetylcholine synthesizing T cells, which are located in the vicinity of the catecholaminergic terminals of the splenic nerve in the white pulp of the spleen, could support the non-neuronal connection between the vagus nerve and the splenic nerve. However, it remains unclear how the splenic nerve is activated after VNS.

Although the exact anatomical relationship between the nervous system and immune cells remains to be clarified, methods for CAP modulation (such as VNS) have already been developed. Clinical trials have confirmed the efficacy of VNS for the treatment of rheumatoid arthritis [81] and Crohn's disease [82], both of which are characterized by chronic inflammation and increased cytokine levels.

21.4.1 CAP in the Kidney

Inflammation plays an important role in AKI pathogenesis [83]. Much of the current knowledge of the inflammatory response during AKI comes from studies on animal models of IRI, as ischemia is a major cause of AKI. Both the adaptive and innate immune system contribute to inflammatory response in AKI. In the IRI model, inflammatory response occurs in the initial ischemic insult and further deterioration occurs upon reperfusion. In the ischemic kidney, the synthesis of cytokines such as IL-1, IL-6, and TNF-α is promoted by transcription factors such as NF-κB, heat shock factor-1, and hypoxia-inducible factor-1, which are induced by hypoxia [84, 85].

In the post-ischemic kidney, immune cells are recruited through pro-inflammatory damage-associated molecular patterns, hypoxia-inducible factors, and adhesion molecules. These molecules increase the permeability of the renal vascular endothelium and are associated with the release of pro-inflammatory chemokines and cytokines, as well as with the activation of toll-like-receptors [86], which play an important role in recruiting immune cells. In the mouse kidney, neutrophil infiltration is observed within a few hours following ischemia [87]. Although it is recognized that the effector cells of the innate immune system serve an important function

in pathogen phagocytosis and generation of reactive oxygen species, the precise role of these cells and the kinetics of processes induced by such cells remain unclear. Macrophages are also key players in the kidney immune response. Activated macrophages exert phagocytic activity and release cytokines such as IL-1, IL-6, IL-8, IL-12, and TNF [86]. Importantly, although the number of macrophages residing in the normal kidney is low, macrophage influx occurs upon reperfusion after kidney ischemia [88]. In the initial injury phase, macrophages have the polarized pro-inflammatory M1 phenotype, which is characterized by the expression of inducible nitric oxide synthase and facilitates the inflammatory cascade causing damage to the kidney. In the recovery phase, however, macrophages switch into the anti-inflammatory M2 phenotype, which is characterized by the expression of arginase-1 and of the mannose receptor [89]. Taking these inflammatory responses into consideration, AKI is a good candidate for immunomodulating therapy.

21.4.2 Ultrasound Stimulation

Ultrasound treatment can activate the CAP [90]. Gigliotti et al. were the first to investigate the effectiveness of contrast-enhanced ultrasound for vasculature regeneration in the post-ischemic kidney, reporting that a modified contrast-enhanced ultrasound protocol could improve blood flow to the skeletal muscle [91]. However, the authors found that ultrasound exposure alone (i.e., without contrast) was effective for attenuating kidney damage by reducing leukocyte infiltration and suppressing inflammation. This protective effect was completely abolished by splenectomy, suggesting that the beneficial action of ultrasound treatment is mediated by the spleen. The authors next investigated the relationship between immune cells and the protective effect of ultrasound against IRI in $Rag1^{-/-}$ mice, which lack functional B cells and T cells. Ultrasound treatment did not confer protection against IRI in $Rag1^{-/-}$ mice, but reconstitution with wild-type $CD4^+$ T cells 10 days before IRI restored the protective effect, suggesting that both the spleen and $CD4^+$ T cells are required for the beneficial effect of ultrasound treatment. The contribution of the α7 nicotinic acetylcholine receptor (α7nAChR) to ultrasound-mediated renoprotection was confirmed in α7KO mice, who were not protected against IRI despite ultrasound pretreatment. These findings suggest that ultrasound treatment attenuates IRI in an α7nAChR-dependent manner. Additionally, bone marrow chimera experiments in mice confirmed the essential role of hematopoietic α7nAChR in the CAP [92]. Therefore, ultrasound treatment confers protection from AKI via CAP activation. While several possible mechanisms underlying ultrasound-mediated activation of the CAP have been proposed, as described below, the actual mechanism remains unknown. Ultrasound treatment can modulate nerve activity in mice [93], suggesting that ultrasound-induced nerve activation might activate the CAP. Alternatively, ultrasound treatment might activate immune cells in the abdomen directly, and these cells would then contribute to the CAP. Elucidating the mechanism underlying ultrasound-induced activation of the CAP may help clarify the molecular mechanisms of the CAP itself.

21.4.3 Vagus Nerve Stimulation (VNS)

VNS, which represents a very effective strategy for CAP activation, was approved by the Food and Drug Administration in 1997 for the treatment of refractory partial-onset epilepsy [94]. In 2005, VNS was also approved for the treatment of chronic or recurring depression [95]. Given its anti-inflammatory effect, VNS is a potent tool for treating inflammatory disorders such as sepsis, lung injury, rheumatoid arthritis, inflammatory bowel disease, and diabetes [96]. Clinical trials to clarify the effectiveness of VNS for such disorders are ongoing. By August 2014, more than 100,000 VNS devices had been implanted in over 75,000 patients worldwide [97]. The VNS device is a battery-powered apparatus similar to a cardiac pacemaker. In most models, stimulating leads are surgically implanted in the carotid sheath around the left vagus nerve. Noninvasive transcutaneous VNS devices have also been developed [98, 99], wherein the vagus nerve is stimulated via the auricular branch of the nerve by small, earphone-like electrodes. Although no randomized clinical trial for transcutaneous VNS has been conducted to date, this strategy was effective in attenuating cerebral ischemic injury in rats [100] and pediatric epilepsy [98]. In addition, a pilot study demonstrated that noninvasive VNS downregulated inflammatory cytokine release in healthy subjects [99]. These results suggest that noninvasive VNS is safe enough to be used in hospital settings, promoting further research and the widespread adoption of noninvasive VNS as a promising therapy for AKI and other inflammatory diseases.

In 2016, Inoue and Abe et al. evaluated the effectiveness of VNS applied 24 h prior to IRI in the mouse kidney [101], reporting that VNS protected the kidney against ischemic injury, as reflected by the attenuated elevation of plasma creatinine levels and mitigated acute tubular necrosis. VNS also suppressed the secretion of pro-inflammatory cytokines such as IL-6, IL-10, IL-15, and TNF. Splenectomy experiments confirmed the involvement of the spleen in the VNS-induced protection against IRI. Specifically, splenectomy abolished the favorable effect of VNS without affecting kidney function. Furthermore, adoptive transfer of splenocytes from VNS-pretreated donor mice 1 day prior to IRI protected the recipient mice from IRI. These results reinforce the importance of the spleen in the CAP. On the other hand, VNS-treated α7KO mice were not protected against kidney IRI. Transfer of splenocytes from α7KO VNS-treated mice to wild-type mice abolished the protective effect as well, highlighting the importance of α7nAChR-positive splenocytes. As macrophages are also important in the CAP [68], their post-IRI dynamics were examined using flow cytometry. After IRI, the number of macrophages in the kidney increased in both wild-type and α7KO mice, but there was no difference between wild-type and α7KO mice regarding the number of macrophages. On the contrary, assessment of macrophage phenotype markers revealed that VNS affected the polarization of macrophages. IRI alone increased the expression of all M1 markers and most M2 markers, but suppressed arginase-1 (an M2 marker) expression in wild-type mice. Pre-IRI VNS rescued arginase-1 expression in wild-type mice but not in α7KO mice, suggesting that VNS exerts its renoprotective effect by

enhancing the macrophage switch to M2 phenotype, which is thought to have an important role in the recovery phase [89]. Very recently, Inoue et al. showed that adoptive transfer of α7nAChR-positive macrophages protected against kidney IRI under nicotine stimulation [102]. Using RNA sequencing, the authors further identified the hairy and enhancer of split-1 (Hes1) as a new signaling component downstream of α7nAChR in macrophages. Hes1-overexpressing macrophages mainly induced M2 markers (including arginase-1) and suppressed TNF production after lipopolysaccharide stimulation. VNS-mediated induction of Hes1 was also confirmed in macrophages in vivo. Moreover, the authors showed that the kidney was protected by adoptive transfer of Hes1-overexpressing macrophages. Taken together, these recent results reveal Hes1 as a new key molecule in the CAP [102].

Another interesting finding is that afferent and efferent VNS had a similar effect in terms of protection against kidney IRI [101]. Afferent VNS achieved by stimulating the central end of the cut nerve may activate the contralateral efferent vagus nerve. Since the experimental animals could not survive after bilateral vagotomy, blockade of the right vagus nerve was achieved using local anesthesia. Surprisingly, left afferent vagal stimulation protected the kidney from IRI even in the absence of right efferent vagal nerve activation, suggesting that afferent and efferent VNS might protect the kidney from IRI to the same extent but via a different mechanism. Further research employing optogenetic techniques to examine the afferent and efferent pathways separately (as described below) is warranted to clarify this aspect. Another interesting finding of the same study is that, although VNS applied 10 min prior to IRI did not confer kidney protection, VNS at 24–48 h before IRI provided a significant and long-lasting renoprotective effect that was maintained for at least 48 h. These findings suggest that there is a delay between VNS and the establishment of VNS-induced renoprotection, but that, once established, the protective effect is maintained without continuous stimulation. Given the rather instantaneous property of neural conduction, there seems to be a complex immunological mechanism underlying the relationship between VNS and renoprotection.

21.4.4 Optogenetics

Optogenetic techniques involve expressing light-activated microbial opsin proteins in neuronal or non-neuronal cells [103, 104]. The history of optogenetics dates back to 1971, to the discovery of bacteriorhodopsin, an ion pump that can be activated by visible light [105]. Later, other members of this rhodopsin family were discovered, including halorhodopsin in 1997 and channelrhodopsin in 2002. Channelrhodopsin 2 (ChR2) is a light-gated cation channel found in the unicellular green algae *Chlamydomonas reinhardtii* [106]. In 2005, ChR2 was safely introduced in mammalian neurons, which depolarized immediately upon illumination with blue light. Based on these results, optogenetics became a topic of enthusiastic research for an entire decade. In 2007, the selective silencing of neurons expressing halorhodopsin was achieved under yellow light [107]. This method enabled selective activation or

silencing of the target neurons without affecting other neurons. In addition, by using the Cre-Lox system, these light-sensitive proteins could be expressed in specific cell types. Optogenetics is currently widely investigated as a promising therapeutic tool not only in the field of neurology but also in other areas including diabetes, cardiovascular system dysfunction, cancer, and skeletal muscle disorders [103].

Optogenetics may also help clarify the complex mechanisms underlying the CAP. Recent studies based on this technique have reported that vagus afferent neurons can be of several subtypes, each with a different function in controlling internal systems [108, 109]. Using optogenetics, Abe and Inoue et al. reported the contribution of C1 neurons in activating the CAP [110]. C1 neurons are glutamatergic, catecholaminergic, and peptidergic neurons residing in the medullary reticular formation [111, 112] and mainly serve to synapse with sympathetic preganglionic neurons in the spinal cord, dorsal vagal complex, hypothalamic paraventricular nucleus, and other lower brain stem noradrenergic neurons [111, 113]. C1 cells are activated in response to physical stresses such as infection, inflammation, pain, hypoxia, hemorrhage, hypotension, and hypoglycemia, playing an important role in the central regulation of autonomic function [114]. In addition, the fact that some populations of C1 neurons are activated by circulating IL-1 and lipopolysaccharides suggests they may play a role in immune system regulation. Abe and Inoue et al. investigated whether C1 stimulation could protect the kidney from IRI via modulating the inflammatory reflex pathway [110]. They selectively stimulated C1 neurons optogenetically by injecting ChR2 into the rostral ventrolateral medulla oblongata, which is a brainstem region thought to be rich in C1 neurons, of transgenic mice. Optogenetic stimulation of C1 neurons attenuated the elevation of plasma creatinine levels and the degree of acute tubular necrosis induced by renal IRI. Restraint stress also protected the kidney from IRI, and the effect was dependent on C1 neuron activation. This C1 neuron-mediated organ protective effect required the presence of β2-adrenergic receptors, α7nAChRs, and spleen, suggesting a potential involvement of the CAP. Surprisingly, neither subdiaphragmatic vagotomy nor corticosterone blockade could abolish this protection, suggesting that CAP activation by C1 neurons is achieved via the sympathetic pathway, independently of efferent VNS and the HPA axis. These results challenge the prevalent disynaptic model of the CAP, which postulates that preganglionic vagal efferent neurons synapse with the postganglionic splenic nerve. Optogenetics might help clarify this apparent discrepancy. Further studies are needed to elucidate the exact mechanism of the CAP.

21.5 Conclusion

Here, we focused on the link between the nervous system and the kidney. While the sympathetic innervation of the kidney is relatively well understood, there is persistent uncertainty regarding the parasympathetic innervation. Increased sympathetic tone is related to hypertension and CKD. Renal denervation, which was mainly investigated as an invasive therapy for refractory hypertension, is a potential

treatment tool for direct modulation of renal autonomic control. On the other hand, growing evidence suggests that stimulation of the parasympathetic nerve can induce immune-mediated renoprotection via the CAP, as inflammation is a major component of the AKI pathogenesis. Given the wide prevalence and high morbidity and mortality of AKI, it is desirable to develop AKI therapies based on noninvasive CAP stimulation.

Although the major components of the CAP have been identified (spleen, macrophages, $CD4^+$ T cells, vagus nerve, and splenic nerve), the interplay of these components has not been fully characterized. All CAP components may represent therapeutic targets for AKI. Advancements in the field of optogenetics are expected to help clarify such aspects and promote research to develop safer treatment strategies for AKI. In the future, such techniques might become useful not only for AKI treatment but also for AKI prevention in critically ill patients.

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References

1. Wonnacott A, Meran S, Amphlett B, Talabani B, Phillips A. Epidemiology and outcomes in community-acquired versus hospital-acquired AKI. Clin J Am Soc Nephrol. 2014;9(6):1007–14.
2. Lafrance JP, Miller DR. Acute kidney injury associates with increased long-term mortality. J Am Soc Nephrol. 2010;21(2):345–52.
3. Mehta RL, Burdmann EA, Cerda J, Feehally J, Finkelstein F, Garcia-Garcia G, et al. Recognition and management of acute kidney injury in the International Society of Nephrology 0by25 Global Snapshot: a multinational cross-sectional study. Lancet. 2016;387(10032):2017–25.
4. Okusa MD, Molitoris BA, Palevsky PM, Chinchilli VM, Liu KD, Cheung AK, et al. Design of clinical trials in acute kidney injury: a report from an NIDDK workshop—prevention trials. Clin J Am Soc Nephrol. 2012;7(5):851–5.
5. Pavlov VA, Tracey KJ. Neural circuitry and immunity. Immunol Res. 2015;63(1–3):38–57.
6. DiBona GF. Neural control of renal function. Physiol Rev. 1997;77(1):75–197.
7. La Grange RG, Sloop CH, Schmid HE. Selective stimulation of renal nerves in the anesthetized dog. Effect on renin release during controlled changes in renal hemodynamics. Circ Res. 1973;33(6):704–12.
8. Barajas L, Müller J. The innervation of the juxtaglomerular apparatus and surrounding tubules: a quantitative analysis by serial section electron microscopy. J Ultrastruct Res. 1973;43(1):107–32.
9. Drukker J, Groen GJ, Boekelaar AB, Baljet B. The extrinsic innervation of the rat kidney. Clin Exp Hypertens A. 1987;9(Suppl 1):15–31.
10. Barajas L, Liu L, Powers K. Anatomy of the renal innervation: intrarenal aspects and ganglia of origin. Can J Physiol Pharmacol. 1992;70(5):735–49.
11. Mompeo B, Maranillo E, Garcia-Touchard A, Larkin T, Sanudo J. The gross anatomy of the renal sympathetic nerves revisited. Clin Anat. 2016;29(5):660–4.

12. Barajas L, Powers K. Innervation of the renal proximal convoluted tubule of the rat. Am J Anat. 1989;186(4):378–88.
13. Kowalski R, Kreft E, Kasztan M, Jankowski M, Szczepanska-Konkel M. Chronic renal denervation increases renal tubular response to P2X receptor agonists in rats: implication for renal sympathetic nerve ablation. Nephrol Dial Transplant. 2012;27(9):3443–8.
14. Marfurt CF, Echtenkamp SF. Sensory innervation of the rat kidney and ureter as revealed by the anterograde transport of wheat germ agglutinin-horseradish peroxidase (WGA-HRP) from dorsal root ganglia. J Comp Neurol. 1991;311(3):389–404.
15. Kopp UC. Role of renal sensory nerves in physiological and pathophysiological conditions. Am J Physiol Regul Integr Comp Physiol. 2015;308(2):R79–95.
16. Okusa MD, Rosin DL, Tracey KJ. Targeting neural reflex circuits in immunity to treat kidney disease. Nat Rev Nephrol. 2017;13(11):669–80.
17. Hering D, Winklewski PJ. Autonomic nervous system in acute kidney injury. Clin Exp Pharmacol Physiol. 2017;44(2):162–71.
18. van Amsterdam WA, Blankestijn PJ, Goldschmeding R, Bleys RL. The morphological substrate for renal denervation: nerve distribution patterns and parasympathetic nerves. A post-mortem histological study. Ann Anat. 2016;204:71–9.
19. Barajas L, Wang P. Simultaneous ultrastructural visualization of acetylcholinesterase activity and tritiated norepinephrine uptake in renal nerves. Anat Rec. 1983;205(2):185–95.
20. Papademetriou V, Rashidi AA, Tsioufis C, Doumas M. Renal nerve ablation for resistant hypertension: how did we get here, present status, and future directions. Circulation. 2014;129(13):1440–51.
21. Esler M, Jennings G, Lambert G, Meredith I, Horne M, Eisenhofer G. Overflow of catecholamine neurotransmitters to the circulation: source, fate, and functions. Physiol Rev. 1990;70(4):963–85.
22. Page IH, Heuer GJ. The effect of renal denervation on the level of arterial blood pressure and renal function in essential hypertension. J Clin Invest. 1935;14(1):27–30.
23. PEET MM. Hypertension and its surgical treatment by bilateral supradiaphragmatic splanchnicectomy. Am J Surg. 1948;75(1):48–68.
24. Krum H, Schlaich M, Whitbourn R, Sobotka PA, Sadowski J, Bartus K, et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. Lancet. 2009;373(9671):1275–81.
25. Esler MD, Böhm M, Sievert H, Rump CL, Schmieder RE, Krum H, et al. Catheter-based renal denervation for treatment of patients with treatment-resistant hypertension: 36 month results from the SYMPLICITY HTN-2 randomized clinical trial. Eur Heart J. 2014;35(26):1752–9.
26. Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, et al. A controlled trial of renal denervation for resistant hypertension. N Engl J Med. 2014;370(15):1393–401.
27. Townsend RR, Mahfoud F, Kandzari DE, Kario K, Pocock S, Weber MA, et al. Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): a randomised, sham-controlled, proof-of-concept trial. Lancet. 2017;390(10108):2160–70.
28. Kandzari DE, Bohm M, Mahfoud F, Townsend RR, Weber MA, Pocock S, et al. Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial. Lancet. 2018;391(10137):2346–55.
29. Converse RL. Sympathetic overactivity in patients with chronic renal failure. N Engl J Med. 1992;327(27):1912–8.
30. Klein IH, Ligtenberg G, Oey PL, Koomans HA, Blankestijn PJ. Sympathetic activity is increased in polycystic kidney disease and is associated with hypertension. J Am Soc Nephrol. 2001;12(11):2427–33.
31. Petras D, Koutroutsos K, Kordalis A, Tsioufis C, Stefanadis C. The role of sympathetic nervous system in the progression of chronic kidney disease in the era of catheter based sympathetic renal denervation. Curr Clin Pharmacol. 2013;8(3):197–205.

32. Lambert E. The role of renal sympathetic nerves in ischemia reperfusion injury. Auton Neurosci. 2017;204(1872–7484 (electronic)):105–11.
33. Nangaku M. Chronic hypoxia and tubulointerstitial injury: a final common pathway to end-stage renal failure. J Am Soc Nephrol. 2006;17(1):17–25.
34. Kim J, Padanilam BJ. Renal nerves drive interstitial fibrogenesis in obstructive nephropathy. J Am Soc Nephrol. 2013;24(2):229–42.
35. Kim J, Padanilam BJ. Renal denervation prevents long-term sequelae of ischemic renal injury. Kidney Int. 2015;87(2):350–8.
36. Foss JD, Wainford RD, Engeland WC, Fink GD, Osborn JW. A novel method of selective ablation of afferent renal nerves by periaxonal application of capsaicin. Am J Physiol Regul Integr Comp Physiol. 2015;308(2):R112–22.
37. Campese VM, Kogosov E, Koss M. Renal afferent denervation prevents the progression of renal disease in the renal ablation model of chronic renal failure in the rat. Am J Kidney Dis. 1995;26(5):861–5.
38. Abramowicz D. European renal best practice guideline on kidney donor and recipient evaluation and perioperative care. Nephrol Dial Transplant. 2015;30(11):1790–7.
39. Ott C. Renal denervation preserves renal function in patients with chronic kidney disease and resistant hypertension. J Hypertens. 2015;33(6):1261–6.
40. Baines AD. Nervous disorders of renal function. Clin Biochem. 1983;16(2):134–40.
41. Fujii T. The role of renal sympathetic nervous system in the pathogenesis of ischemic acute renal failure. Eur J Pharmacol. 2003;481(2–3):241–8.
42. Mutoh J, Ohsawa M, Hisa H. Involvement of renal sympathetic nerve activation on the progression of ischemic acute kidney injury in the mouse. J Pharmacol Sci. 2014;125(4):415–21.
43. Ogawa T. Ischaemic preconditioning ameliorates functional disturbance and impaired renal perfusion in rat ischaemia-reperfused kidneys. Clin Exp Pharmacol. 2000;27(12):997–1001.
44. Ogawa T. Renal denervation abolishes the protective effects of ischaemic preconditioning on function and haemodynamics in ischaemia-reperfused rat kidneys. Acta Physiol Scand. 2002;174(3):291–7.
45. Tracey KJ. Physiology and immunology of the cholinergic antiinflammatory pathway. J Clin Invest. 2007;117(2):289–96.
46. Wexler BC, Dolgin AE, Tryczynski EW. Effects of a bacterial polysaccharide (Piromen®) on the pituitary-adrenal axis: adrenal ascorbic acid, cholesterol and histologic alterations. Endocrinology. 1957;61(3):300–8.
47. Besedovsky H, Besedovsky HFS. Hypothalamic changes during the immune response. Eur J Immunol. 1977;7(5):323–5.
48. Watkins LR, Maier SF. Implications of immune-to-brain communication for sickness and pain. Proc Natl Acad Sci U S A. 1999;96(14):7710–3.
49. Watkins LR, Goehler LE, Relton JK, Tartaglia N, Silbert L, Martin D, et al. Blockade of interleukin-1 induced hyperthermia by subdiaphragmatic vagotomy: evidence for vagal mediation of immune-brain communication. Neurosci Lett. 1995;183(1–2):27–31.
50. Black PH. Immune system-central nervous system interactions: effect and immunomodulatory consequences of immune system mediators on the brain. Antimicrob Agents Chemother. 1994;38(1):7–12.
51. Inoue T, Okusa MD. Neuroimmune control of acute kidney injury and inflammation. Nephron. 2015;131(2):97–101.
52. Bellavance MA, Rivest S. The HPA—immune axis and the immunomodulatory actions of glucocorticoids in the brain. Front Immunol. 2014;5:136.
53. Sternberg EM. Neural-immune interactions in health and disease. J Clin Invest. 1997;100(11):2641–7.
54. Tracey KJ. The inflammatory reflex. Nature (London). 2002;420(6917):853–9.
55. Page AJ, O'Donnell TA, Blackshaw LA. P2X purinoceptor-induced sensitization of ferret vagal mechanoreceptors in oesophageal inflammation. J Physiol. 2000;523(Pt 2):403–11.

56. Hermann GE, Rogers RC. TNFalpha: a trigger of autonomic dysfunction. Neuroscientist. 2008;14(1):53–67.
57. van der Kleij H, Charles N, Karimi K, Mao YK, Foster J, Janssen L, et al. Evidence for neuronal expression of functional Fc (epsilon and gamma) receptors. J Allergy Clin Immunol. 2010;125(3):757–60.
58. Mascarucci P, Perego C, Terrazzino S, De Simoni MG. Glutamate release in the nucleus tractus solitarius induced by peripheral lipopolysaccharide and interleukin-1 beta. Neuroscience. 1998;86(4):1285–90.
59. Kalia M, Sullivan JM. Brainstem projections of sensory and motor components of the vagus nerve in the rat. J Comp Neurol. 1982;211(3):248–65.
60. Tracey KJ. Reflex control of immunity. Nat Rev Immunol. 2009;9(6):418–28.
61. Romanovsky AA, Simons CT, Székely M, Kulchitsky VA. The vagus nerve in the thermoregulatory response to systemic inflammation. Am J Phys. 1997;273(1 Pt 2):R407–13.
62. Gaykema RP, Dijkstra I, Tilders FJ. Subdiaphragmatic vagotomy suppresses endotoxin-induced activation of hypothalamic corticotropin-releasing hormone neurons and ACTH secretion. Endocrinology. 1995;136(10):4717–20.
63. Fleshner M, Goehler LE, Schwartz BA, McGorry M, Martin D, Maier SF, et al. Thermogenic and corticosterone responses to intravenous cytokines (IL-1beta and TNF-alpha) are attenuated by subdiaphragmatic vagotomy. J Neuroimmunol. 1998;86(2):134–41.
64. Borovikova LV, Ivanova S, Zhang M, Yang H, Botchkina GI, Watkins LR, et al. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. Nature. 2000;405(6785):458–62.
65. Antonica A, Magni F, Mearini L, Paolocci N. Vagal control of lymphocyte release from rat thymus. J Auton Nerv Syst. 1994;48(3):187–97.
66. Sandborn WJ, Tremaine WJ, Offord KP, Lawson GM, Petersen BT, Batts KP, et al. Transdermal nicotine for mildly to moderately active ulcerative colitis. A randomized, double-blind, placebo-controlled trial. Ann Intern Med. 1997;126(5):364–71.
67. Guslandi M. Nicotine treatment for ulcerative colitis. Br J Clin Pharmacol. 1999;48(4):481–4.
68. Wang H, Yu M, Ochani M, Amella CA, Tanovic M, Susarla S, et al. Nicotinic acetylcholine receptor alpha7 subunit is an essential regulator of inflammation. Nature. 2003;421(6921):384–8.
69. Huston JM, Ochani M, Rosas-Ballina M, Liao H, Ochani K, Pavlov VA, et al. Splenectomy inactivates the cholinergic antiinflammatory pathway during lethal endotoxemia and polymicrobial sepsis. J Exp Med. 2006;203(7):1623–8.
70. Huston JM, Wang H, Ochani M, Ochani K, Rosas-Ballina M, Gallowitsch-Puerta M, et al. Splenectomy protects against sepsis lethality and reduces serum HMGB1 levels. J Immunol. 2008;181(5):3535–9.
71. Mebius RE, Kraal G. Structure and function of the spleen. Nat Rev Immunol. 2005;5(8):606–16.
72. Wang H, Liao H, Ochani M, Justiniani M, Lin X, Yang L, et al. Cholinergic agonists inhibit HMGB1 release and improve survival in experimental sepsis. Nat Med. 2004;10(11):1216–21.
73. Peña G, Cai B, Liu J, van der Zanden EP, Deitch EA, de Jonge WJ, et al. Unphosphorylated STAT3 modulates alpha 7 nicotinic receptor signaling and cytokine production in sepsis. Eur J Immunol. 2010;40(9):2580–9.
74. Inoue T, Tanaka S, Okusa MD. Neuroimmune interactions in inflammation and acute kidney injury. Front Immunol. 2017;8:945.
75. Vida G, Peña G, Kanashiro A, Thompson-Bonilla Mdel R, Palange D, Deitch EA, et al. β2-adrenoreceptors of regulatory lymphocytes are essential for vagal neuromodulation of the innate immune system. FASEB J. 2011;25(12):4476–85.
76. Gautron L, Rutkowski JM, Burton MD, Wei W, Wan Y, Elmquist JK. Neuronal and nonneuronal cholinergic structures in the mouse gastrointestinal tract and spleen. J Comp Neurol. 2013;521(16):3741–67.
77. Rosas-Ballina M, Ochani M, Parrish WR, Ochani K, Harris YT, Huston JM, et al. Splenic nerve is required for cholinergic antiinflammatory pathway control of TNF in endotoxemia. Proc Natl Acad Sci U S A. 2008;105(31):11008–13.

78. Martelli D, McKinley MJ, McAllen RM. The cholinergic anti-inflammatory pathway: a critical review. Auton Neurosci. 2014;182:65–9.
79. Bratton BO, Martelli D, McKinley MJ, Trevaks D, Anderson CR, McAllen RM. Neural regulation of inflammation: no neural connection from the vagus to splenic sympathetic neurons. Exp Physiol. 2012;97(11):1180–5.
80. Rosas-Ballina M, Olofsson PS, Ochani M, Valdés-Ferrer SI, Levine YA, Reardon C, et al. Acetylcholine-synthesizing T cells relay neural signals in a vagus nerve circuit. Science. 2011;334(6052):98–101.
81. Koopman FA, Chavan SS, Miljko S, Grazio S, Sokolovic S, Schuurman PR, et al. Vagus nerve stimulation inhibits cytokine production and attenuates disease severity in rheumatoid arthritis. Proc Natl Acad Sci U S A. 2016;113(29):8284–9.
82. Bonaz B, Sinniger V, Hoffmann D, Clarencon D, Mathieu N, Dantzer C, et al. Chronic vagus nerve stimulation in Crohn's disease: a 6-month follow-up pilot study. Neurogastroenterol Motil. 2016;28(6):948–53.
83. Rabb H, Griffin MD, McKay DB, Swaminathan S, Pickkers P, Rosner MH, et al. Inflammation in AKI: current understanding, key questions, and knowledge gaps. J Am Soc Nephrol. 2016;27(2):371–9.
84. Cao CC, Ding XQ, Ou ZL, Liu CF, Li P, Wang L, et al. In vivo transfection of NF-kappaB decoy oligodeoxynucleotides attenuate renal ischemia/reperfusion injury in rats. Kidney Int. 2004;65(3):834–45.
85. Eickelberg O, Seebach F, Riordan M, Thulin G, Mann A, Reidy KH, et al. Functional activation of heat shock factor and hypoxia-inducible factor in the kidney. J Am Soc Nephrol. 2002;13(8):2094–101.
86. Jang HR, Rabb H. Immune cells in experimental acute kidney injury. Nat Rev Nephrol. 2015;11(2):88–101.
87. Nemoto T, Burne MJ, Daniels F, O'Donnell MP, Crosson J, Berens K, et al. Small molecule selectin ligand inhibition improves outcome in ischemic acute renal failure. Kidney Int. 2001;60(6):2205–14.
88. Ysebaert DK, De Greef KE, Vercauteren SR, Ghielli M, Verpooten GA, Eyskens EJ, et al. Identification and kinetics of leukocytes after severe ischaemia/reperfusion renal injury. Nephrol Dial Transplant. 2000;15(10):1562–74.
89. Lee S, Huen S, Nishio H, Nishio S, Lee HK, Choi BS, et al. Distinct macrophage phenotypes contribute to kidney injury and repair. J Am Soc Nephrol. 2011;22(2):317–26.
90. Inoue T, Tanaka S, Rosin DL, Okusa MD. Bioelectronic approaches to control neuroimmune interactions in acute kidney injury. Cold Spring Harb Perspect Med. 2019;9(6).
91. Gigliotti JC, Huang L, Ye H, Bajwa A, Chattrabhuti K, Lee S, et al. Ultrasound prevents renal ischemia-reperfusion injury by stimulating the splenic cholinergic anti-inflammatory pathway. J Am Soc Nephrol. 2013;24(9):1451–60.
92. Gigliotti JC, Huang L, Bajwa A, Ye H, Mace EH, Hossack JA, et al. Ultrasound modulates the splenic neuroimmune axis in attenuating AKI. J Am Soc Nephrol. 2015;26(10):2470–81.
93. Tufail Y, Yoshihiro A, Pati S, Li MM, Tyler WJ. Ultrasonic neuromodulation by brain stimulation with transcranial ultrasound. Nat Protoc. 2011;6(9):1453–70.
94. Stacey WC, Litt B. Technology insight: neuroengineering and epilepsy-designing devices for seizure control. Nat Clin Pract Neurol. 2008;4(4):190–201.
95. Cai PY, Bodhit A, Derequito R, Ansari S, Abukhalil F, Thenkabail S, et al. Vagus nerve stimulation in ischemic stroke: old wine in a new bottle. Front Neurol. 2014;5:107.
96. Johnson RL, Wilson CG. A review of vagus nerve stimulation as a therapeutic intervention. J Inflamm Res. 2018;11:203–13.
97. Chakravarthy K, Chaudhry H, Williams K, Christo PJ. Review of the uses of vagal nerve stimulation in chronic pain management. Curr Pain Headache Rep. 2015;19(12):54.
98. Stefan H, Kreiselmeyer G, Kerling F, Kurzbuch K, Rauch C, Heers M, et al. Transcutaneous vagus nerve stimulation (t-VNS) in pharmacoresistant epilepsies: a proof of concept trial. Epilepsia. 2012;53(7):e115–8.

99. Lerman I, Hauger R, Sorkin L, Proudfoot J, Davis B, Huang A, et al. Noninvasive transcutaneous Vagus nerve stimulation decreases whole blood culture-derived cytokines and chemokines: a randomized, blinded, healthy control pilot trial. Neuromodulation. 2016;19(3):283–90.
100. Ay I, Nasser R, Simon B, Ay H. Transcutaneous cervical vagus nerve stimulation ameliorates acute ischemic injury in rats. Brain Stimul. 2016;9(2):166–73.
101. Inoue T, Abe C, Sung SS, Moscalu S, Jankowski J, Huang L, et al. Vagus nerve stimulation mediates protection from kidney ischemia-reperfusion injury through alpha7nAChR+ splenocytes. J Clin Invest. 2016;126(5):1939–52.
102. Inoue T, Abe C, Kohro T, Tanaka S, Huang L, Yao J, et al. Non-canonical cholinergic anti-inflammatory pathway-mediated activation of peritoneal macrophages induces Hes1 and blocks ischemia/reperfusion injury in the kidney. Kidney Int. 2019;95:563.
103. Montgomery KL, Iyer SM, Christensen AJ, Deisseroth K, Delp SL. Beyond the brain: Optogenetic control in the spinal cord and peripheral nervous system. Sci Transl Med. 2016;8(337):337rv5.
104. Tanaka S, Okusa MD. Optogenetics in understanding mechanisms of acute kidney injury. Nephron. 2018;140(2):152–5.
105. Deisseroth K. Optogenetics. Nat Methods. 2011;8(1):26–9.
106. Boyden ES, Zhang F, Bamberg E, Nagel G, Deisseroth K. Millisecond-timescale, genetically targeted optical control of neural activity. Nat Neurosci. 2005;8(9):1263–8.
107. Han X, Boyden ES. Multiple-color optical activation, silencing, and desynchronization of neural activity, with single-spike temporal resolution. PLoS One. 2007;2(3):e299.
108. Williams EK, Chang RB, Strochlic DE, Umans BD, Lowell BB, Liberles SD. Sensory neurons that detect stretch and nutrients in the digestive system. Cell. 2016;166(1):209–21.
109. Chang RB, Strochlic DE, Williams EK, Umans BD, Liberles SD. Vagal sensory neuron subtypes that differentially control breathing. Cell. 2015;161(3):622–33.
110. Abe C, Inoue T, Inglis MA, Viar KE, Huang L, Ye H, et al. C1 neurons mediate a stress-induced anti-inflammatory reflex in mice. Nat Neurosci. 2017;20(5):700–7.
111. Guyenet PG, Stornetta RL, Bochorishvili G, Depuy SD, Burke PG, Abbott SB. C1 neurons: the body's EMTs. Am J Physiol Regul Integr Comp Physiol. 2013;305(3):R187–204.
112. Abe C, Inoue T. Role of C1 neurons in anti-inflammatory reflex: mediation between afferents and efferents. Neurosci Res. 2018;136:6–12.
113. DePuy SD, Stornetta RL, Bochorishvili G, Deisseroth K, Witten I, Coates M, et al. Glutamatergic neurotransmission between the C1 neurons and the parasympathetic preganglionic neurons of the dorsal motor nucleus of the vagus. J Neurosci. 2013;33(4):1486–97.
114. Li HY, Ericsson A, Sawchenko PE. Distinct mechanisms underlie activation of hypothalamic neurosecretory neurons and their medullary catecholaminergic afferents in categorically different stress paradigms. Proc Natl Acad Sci U S A. 1996;93(6):2359–64.

Chapter 22
AKI and Immune System

Sang Kyung Jo and Won Yong Cho

Abstract Acute kidney injury (AKI) substantially contributes to high morbidity and mortality in hospitalized patients. Ischemic, nephrotoxic injury and infection are the leading causes of AKI. Evidence from the last several decades shows that AKI provokes intrarenal, systemic inflammation and both innate and adaptive immune system play important roles in the pathogenesis of kidney injury. Infiltrating neutrophils, T lymphocytes, monocytes, natural killer (NK) cells, natural killer T (NKT) cells as well as kidney resident macrophages/dendritic cells (DCs) have been shown to contribute to kidney injury in orchestration with endothelial and epithelial cell injury. Recent evidence also reveals that certain type of immune cells such as macrophages or regulatory T cells (Tregs) participate in the repair process. However, despite substantial progress in understanding of inflammation as critical player in AKI, translation from preclinical model into clinical therapeutics remains primitive. The purpose of this review is to understand the recent advances in the role of immune system in injury and repair processes of AKI especially in ischemia/reperfusion injury (IRI), the most extensively studied model.

Keywords Ischemia/reperfusion injury · Inflammation · Leukocytes
Endothelium · Epithelium

22.1 Introduction

Acute kidney injury (AKI) is clinical syndrome representing rapid deterioration of kidney function from diverse etiologies. The incidence rate is known to be more than 5% in hospitalized patients and mortality of dialysis requiring AKI still exceeds 30% [1]. Increasing number of aged populations with comorbidities, invasive

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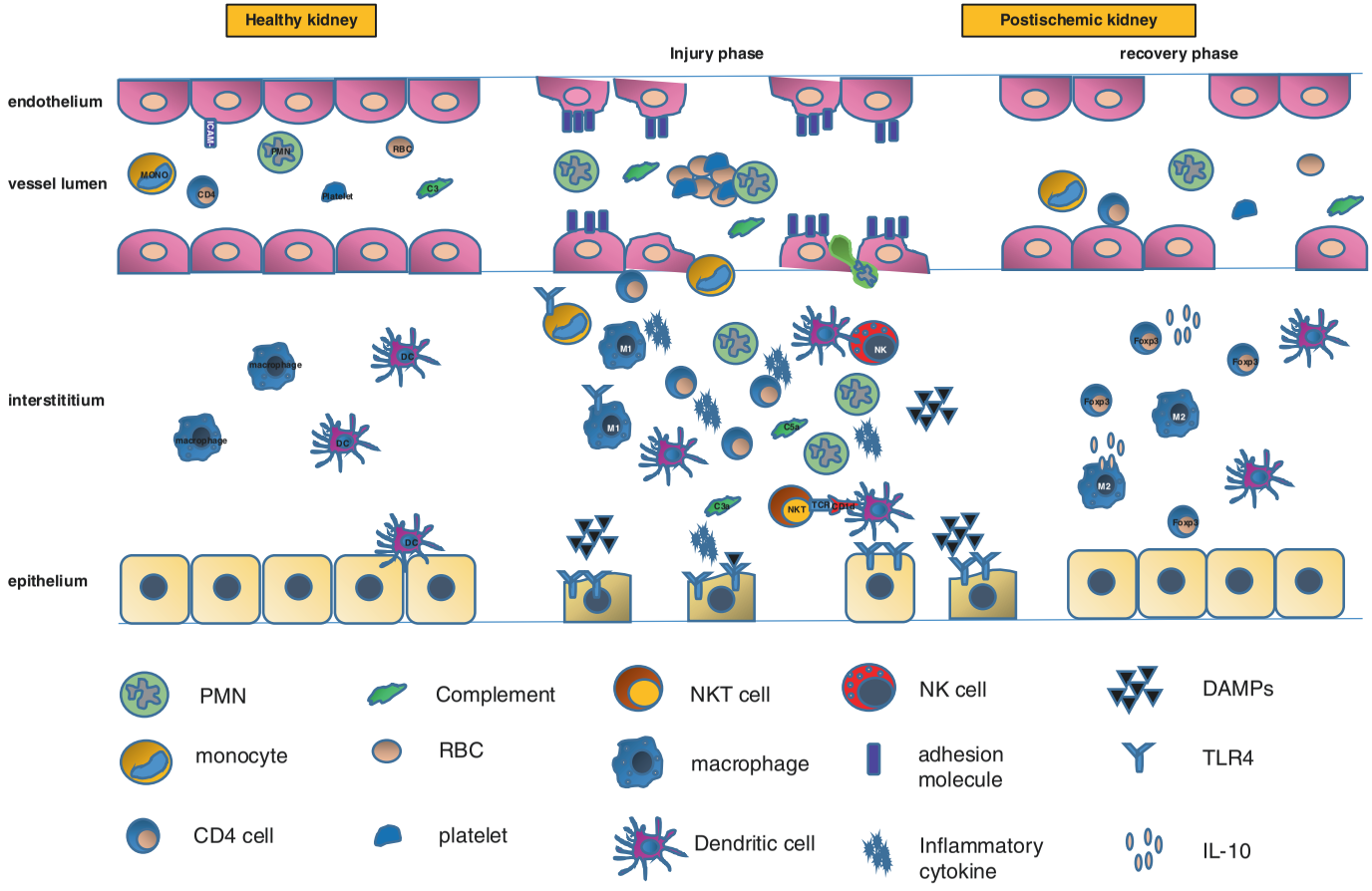
procedures with possible exposure to potential nephrotoxicants or with compromising renal blood flow might be the mechanisms underlying this high incidence as well as mortality rate [2]. Moreover, AKI has been shown to be the most important factor in the progressive CKD leading to end stage kidney disease (ESKD) [3]. However, diagnosis and treatment of AKI have not been changed substantially for the last several decades necessitating the development of novel diagnostic and therapeutic strategies based on better understanding of its pathogenesis.

The pathogenesis of IRI involves a complex interplay between endothelial and epithelial compartments and also the activation of immune system [4, 5]. Early phase of IRI is characterized by endothelial cell injury and increased expression of various adhesion molecules in damaged endothelial cells facilitates transmigration of different kinds of inflammatory cells into kidneys [6]. Innate immune cells such as neutrophils, M1 proinflammatory macrophages, natural killer (NK) cells, natural killer T (NKT) cells as well CD4 T cells and resident dendritic cells contribute to kidney injury by releasing various proinflammatory mediators. Epithelial cells, in addition to dying by apoptosis or necrosis, actively participate in inflammation by releasing molecules called danger or damage associated molecular patterns (DAMPs) that subsequently bind to pattern recognition receptors (PRRs) expressed in innate immune cells [7]. Complement system, another important component in innate immunity also plays an important role in AKI [8]. The series of events involving endothelium, epithelium, and immune system provoke vicious cycle of necroinflammation leading to functional, histological deterioration of kidneys.

Meanwhile, immune system also operates to expedite the repair process. Infiltrated or resident macrophages/dendritic cells convert their phenotype from proinflammatory M1 to proresolving M2 macrophages and Tregs facilitate damaged kidney to regenerate or repair [9–11]. Additional insults that potentially inhibit these normal repair processes might result in impaired recovery of kidney function. However, despite substantial progress in the understanding of pathogenesis or numerous positive results from animal studies, strategies targeting the immune activation have not been translated successfully indicating that more multifaceted approach based on extensive understanding of complex pathophysiology is needed. In this review, we summarize the latest understanding of role of immune activation in the injury and repair process of AKI (Fig. 22.1).

Fig. 22.1 Immune response in IRI. Resident macrophage and dendritic cells participate in patrolling in healthy kidneys. Following IRI, these cells are rapidly activated to produce a variety of inflammatory mediators. Endothelial cells upregulate adhesion molecules and mediate transmigration of circulating polymorphonuclear neutrophil (PMN), monocytes, CD4 T cells as well as NK cells, NKT cells and these migrating leukocytes provoke intense inflammatory response in the kidneys. Circulating red blood cells (RBCs) plugged with platelets and leukocytes further compromise microvascular blood flow. Damaged tubular epithelium also participates in inflammation by releasing DAMPs molecules and also upregulating PRRs such as TLR4. Macrophages, monocytes show M1 classically activated macrophage phenotype and NKT cells, activated by dendritic cells further recruit PMN cells. CD4 T cells also participate in inflammation by producing IFN-γ. During the recovery phase, macrophages shift phenotype into IL-10 producing, proresolving M2 macrophages and infiltrated Tregs also participate in repair process


Healthy kidney
Injury phase
Postischemic kidney
recovery phase
endothelium
vessel lumen
interstitium
epithelium
ICAM-1
PMN
RBC
MONO
CD4
platelet
C3
macrophage
DC
M1
NK
C5a
NKT
TCR
Foxp3
M2
PMN
monocyte
CD4 cell
Complement
RBC
platelet
NKT cell
macrophage
Dendritic cell
NK cell
adhesion molecule
Inflammatory cytokine
DAMPs
TLR4
IL-10

22.2 Immune System in Healthy Kidneys

Dendritic cells (DCs), macrophages, and a small number of lymphocytes constitute a vast majority of resident immune cells in healthy kidneys [12–15]. DCs are cells of immune surveillance, mediator of innate and adaptive immunity while macrophages are cells of innate immunity with phagocytosis. However, clear distinction between these cells is sometimes difficult due to substantial overlapping surface markers and functions. Macrophages can also present antigens to lymphocytes or immature DCs can show phagocytic capacity. Therefore, the term "mononuclear phagocytic cells" that encompass monocytes/macrophages/DCs is increasingly used [16]. Recently, the notion that these cells are originated exclusively from bone marrow has been challenged by several studies showing some tissue resident macrophages derive from embryonic tissues such as fetal liver or yolk sac and coexist with those from adult bone marrow derived macrophages [17, 18]. However, despite different origins, their function in homeostasis or injury does not seem to differ.

Kidney resident DCs are $CD11b^+/CD11c^+/F4/80^+/CX_3CR1^+$ cells. Studies using $CX_3CR1^{GFP/+}$ mice showed that contiguous network of these cells in the interstitial compartment with dendrites protruding into tubular lumen, suggesting the important patrolling role in the healthy kidneys [19]. However, upon injury, DCs rapidly acquire the proinflammatory phenotype and by releasing a variety of tissue destructive mediators, they contribute to early inflammation and injury.

22.3 Role of Endothelial Cells in Inflammation

Normal endothelium not only regulates local blood flow to tissue but also exerts anticoagulatory, anti-inflammatory effect. Injured endothelial cells can die by apoptosis or show breakdown of actin cytoskeleton and adherence junction leading to increased vascular permeability, activation of coagulation pathways, and also inflammation [20]. This phenomenon together with intense renal vasoconstriction induced by an imbalance between vasoconstriction vs vasodilation leads to "no reflow" in outer medullary area, further compromising local tissue perfusion. In addition, enhanced expression of various adhesion molecules expressed on endothelium is playing an important role by facilitating the activation and transmigration of circulating leukocytes to postischemic kidneys. Inhibition or genetic ablation of endothelial or platelet selectin (E, P-selectin) or intercellular adhesion moleculte-1 (ICAM-1) ameliorated IRI with reduced inflammation support the role of endothelial cells in inflammation in IRI-induced AKI [21–23].

22.4 Role of Danger Associated Molecular Patterns (DAMPs)-Pattern Recognition Receptors (PRRs) as Triggers of Inflammation

Innate immune response against invasion of bacteria or virus is highly conserved in different species throughout the evolution. Pattern recognition receptors (PRRs) such as toll-like receptors expressed on immune cells or parenchymal cells immediately bind to bacterial products such as endotoxin or cell wall components, collectively called pathogen associated molecular pattern (PAMPs). This leads to subsequent phagocytosis and eradication of pathogens. Danger or damage associated molecular pattern called DAMPs are endogenous molecules released into extracellular space upon injury and convey danger signal to innate immune system. Ligands of receptor for advanced glycation end products (RAGE) including high mobility group box-1 (HMGB-1), or heat shock proteins (HSPs), nuclear protein histone or chromatin, uric acid or extracellular matrix protein such as hyaluronan and fibrinogen can serve as danger molecules, alarming the immune system [24–28]. DAMPs released after injury can also bind to membrane-bound PRRs such as TLRs and release proinflammatory cytokines and chemokines, causing inflammation and tissue injury. Released histone, a major component of chromatin, was shown to trigger leukocyte recruitment via TLR2- and TLR4-dependent activation of MyD88, NF-κB, and mitogen activated protein kinase (MAPK) signaling in kidney IRI [29]. Several DAMPs can also activate cytoplasmic PRRs, such as NOD-like receptor protein 3 (NLRP-3), forming the inflammasome in immune cells and activate caspase 1 with release of IL-1β and IL-18, provoking inflammation [30].

22.5 Role of Tubular Epithelial Cells in Inflammation

Tubular epithelial cells are also important as triggers of inflammation in IRI. In addition to cell death by apoptosis or necrosis, damaged tubular cells act as both a releaser of a variety of DAMP molecules, and also as PRRs that bind to DAMPs. Allam et al. showed that dying epithelial cells release histones and also that histone induced both apoptosis and necrosis of endothelial/epithelial cells with facilitation of leukocytes recruitment [29]. The observation that blocking histones partially reduce inflammation and kidney injury further supports the important role of extracellular histones from damaged tubular cells in inflammation. Damaged tubule cells have also been shown to serve as a sensor of danger signals. Upon release of DAMPs, tubular epithelial cells upregulate the expression of PRRs such as TLRs with release of proinflammatory mediators. Loss of epithelial TLR4 or TLR2 has been shown to result in marked reduction of leukocyte infiltration and kidney dysfunction [31, 32]. Mice lacking the cytoplasmic PRRs in NLR3 −/− mice also showed marked renoprotective effect [30].

22.6 Neutrophils

Neutrophils are one of the first responders of antigen nonspecific innate immunity after IRI and contribute to kidney injury by producing reactive oxygen species, proteases, myeloperoxidase, and proinflammatory cytokines and chemokines. In mouse models of IRI, neutrophils bind to intercellular adhesion molecule-1 (ICAM-1), selectins, or integrins expressed in endothelium and transmigrate to kidney interstitium. Neutrophil infiltration is seen early after reperfusion in animal models [33, 34] and was also demonstrated in human biopsy samples [35, 36]. The important role of neutrophil-mediated sterile inflammation in the pathogenesis of IRI has been demonstrated by studies using anti-neutrophil serum or those targeting neutrophil-endothelial interaction. Pretreatment with anti-neutrophil serum and blocking Ab to ICAM-1 or genetic ablation of ICAM-1 showed renoprotective effect [23]. Decreased rate of delayed graft function in patients treated with ICAM-1 blocking Ab in phase 1 clinical trial also supports the critical role of neutrophils in sterile inflammation as well as kidney injury [37]. However, there are also inconsistent data that failed to show protective effect of depletion or blockade of neutrophils and thus needs to be further studied.

Recent several studies showed that neutrophil contributes to inflammation and kidney injury by forming neutrophil extracellular traps (NETs). NETs are a structure composed of networks of extracellular fibers of DNA and granular proteins from neutrophils, first described by Brinkmann et al. [38]. NETs are known to result from unique form of cell death called "NETosis" that neutrophils die with degradation of their intracellular granules and decondensation of chromatin followed by release of these intracellular materials [38]. NETs are known to contribute to kidney inflammation and injury by directly inducing tubular cell necrosis or indirectly acting as one of DAMP molecules further aggravating the recruitment of inflammatory cells into postischemic kidneys. Histones released from damaged tubule cells can also prime neutrophils for NET formation making viscous cycles of necroinflammation [29]. NETs adjacent to microvasculature may also trap cells, debris, or platelets that make microthrombi, further compromising medullary oxygenation. Jansen et al. recently demonstrated the increased colocalization of DNA, platelets, and neutrophils in postischemic kidneys and also that NET formation was suppressed by anti-platelet clopidogrel [39].

Despite some conflicting results, neutrophils seem to be critical in early inflammation and injury after IRI. However, fate of neutrophils during the recovery phase has not been shown clearly and recent study by Cho et al. suggested that neutrophils are cleared from the kidney by apoptosis or by returning back into the circulation by a process called reverse endothelial transmigration mediated by junctional adhesion molecule-C (JAM-C) [40]. Persistence of kidney neutrophils seems to delay or impair the normal repair process because chimeric mice whose bone marrow derived cells are resistant to apoptosis due to absence of bax gene showed persistent neutrophil infiltration and impaired recovery [40].

22.7 Macrophages/Dendritic Cells

Macrophages are unique cell types of substantial plasticity according to local milieu. After IRI, circulating monocytes of bone marrow origin adhere to vasa recta and migrate toward chemokine gradient into kidney interstitium. These migrating cells and resident mononuclear phagocytes become proinflammatory "M1 macrophages" by kidney microenvironment and by producing a variety of mediators such as TNF-α, interleukin-1β, inducible nitric oxide synthase (iNOS), and IL-6, they participate in early kidney inflammation and injury [41, 42]. Systemic depletion of mononuclear phagocytes using liposome clodronate significantly attenuated kidney injury in mouse and rat model of IRI [43, 44]. Jo et al. demonstrated that ED-1$^+$ rat macrophages are seen as early as 4 h after reperfusion and systemic depletion of mononuclear phagocytes resulted in decreased number of kidney macrophages as well as proinflammatory cytokines and chemokines [43]. The critical role of macrophages was also shown by adoptive transfer experiment that showed that transferring of mouse macrophage RAW cells partially restored the injury [44].

CD11c$^+$F4/80$^+$ kidney resident DCs also seem to acquire proinflammatory phenotype and depletion of these cells also resulted in renoprotective effect. Dong et al. showed the significantly increased level of TNF-α, IL-6, RANTES, and MCP-1 only in isolated CD11c-enriched kidney leukocytes, suggesting that intrarenal DCs are the major source of inflammatory mediators in postischemic kidneys [45]. However, there are also reports showing the opposite function of DCs in IRI. DCs can confer renoprotection if their phenotype could be changed into regulatory. Li et al. showed that transient treatment of DCs ex vivo with adenosine 2A receptor agonist, ATL313 resulted in an increase of tolerogenic DC phenotype and these DCs with regulatory function reduced NKT cell activation and markedly protected kidneys from IRI [46]. However, given that migrating proinflammatory monocytes/macrophages or resident DCs have substantial overlapping surface markers such as CD11c or F4/80, and also liposome clodronate depletes both cell types, caution should be paid in understanding the role of specific cell types [47].

While transmigrated monocytes and resident mononuclear phagocytes facilitate early kidney inflammation and injury, these cells have also been shown to convert their phenotype from M1 proinflammatory to M2 proresolving macrophages inside the kidneys during the recovery phase [11]. In contrast to classically activated M1 macrophages, M2 macrophages are alternatively activated cells that are mannose receptor positive with production of arginase-1, IL-10, and transforming growth factor-β (TGF-β) [48]. The observation that late depletion of mononuclear phagocytes during the recovery phase of IRI resulted in persistent tissue injury and delayed recovery supports the important role of mononuclear phagocytes in the repair process [9]. Lee et al. showed that the number of F4/80 macrophages further increased during the recovery phase and also that these cells showed predominant secretion of arginase and IL-10 rather than TNF-α [11]. The mechanisms underlying M1-M2 shift have not been fully understood. However, they seem to be dependent on a

variety of factors such as macrophage phagocytosis of apoptotic cells or macrophage colony stimulating factor-1 (CSF-1) signaling. Macrophages in culture have been shown to produce TGF-β or IL-10 upon binding or uptake of apoptotic cells [48–50]. Genetic or pharmacological blockade of CSF-1 resulted in decreased number of M2 macrophages and inhibition of renal recovery [50]. Tubular secretion of granulocyte-macrophage CSF (GM-CSF) has also been demonstrated to stimulate the alternative activation of macrophages through signal transducer and activator of transcription-5 (STAT-5) pathways [51].

Recent study by Lech et al. showed an important role of IL-1 receptor associated kinase-M (IRAK-M), a macrophage-specific inhibitor of toll-like receptor and IL-1 receptor signaling, in macrophage phenotype shift by demonstrating that the genetic deletion of IRAK resulted in persistent M1-mediated inflammation during the recovery phase with ultimate development of tubule atrophy and interstitial fibrosis [52]. Th2 cytokine also seems to be important because double knockout of IL-4/IL-13 also led to persistent M1 dominant inflammation in kidney and fibrosis [53]. Although substantial evidence indicate that M1 to M2 shift is a vital process in achieving the repair or recovery after IRI, and also that failed shift led to kidney fibrosis, there are recent studies showing the persistence of M2 macrophage was also associated with AKI to CKD transition. Kim et al. showed depletion of mononuclear phagocytes using liposome clodronate during the extended period of recovery phase of IRI resulted in marked inhibition of fibrosis [54]. These macrophages are likely to M2 macrophages due to their preferential production of arginase-1, but not iNOS. They also showed that this inhibitory effect of mononuclear phagocytes depletion on fibrosis was partially lost by adoptive transfer of in vitro differentiated M2c macrophages that predominantly secrete TGF-β, but not by M1 macrophages. These data showed a possible important role of TGF-β secreting M2 macrophage in the development of fibrosis after AKI. Another study by Wang et al. that showed a direct transdifferentiation of M2 macrophages into myofibroblast also supports the important role of M2 macrophages in the development of fibrosis [55].

However, the role of TGF-β secreting M2 macrophage in AKI to CKD transition needs to be further studied because others have reported that selective deletion of macrophage TGF-β did not affect fibrosis after AKI [56]. Despite substantial progress in macrophage phenotype and dynamics, further studies of the exact role and regulators of macrophages or macrophage phenotypic change in injury or repair mechanisms of IRI are needed and should be understood in the context of the very complex microenvironment where endothelial, epithelial cell repair mechanisms operate in well-orchestrated manner.

22.8 Lymphocytes

Lymphocytes are key effector cells of adaptive immunity. The fact that 2–3 days are usually needed for expansion of antigen specific T cells that is preceded by recognition and presentation of atigens by presenting cells in the presence of costimulatory

molecules might preclude the role of lymphocytes in early inflammation in IRI. However, the critical role of lymphocytes in the pathogenesis has been clearly demonstrated.

The landmark study showing the important role of CD4 T cells was done in T-cell-deficient athymic nu/nu mice. These T-cell-deficient mice are protected from IRI and reconstitution with CD4 T cell partially restored the postischemic phenotype [57]. The observation from the same study showing only CD4-deficient mice but not CD8-deficient mice were renoprotective indicates that CD4 T lymphocytes are important mediator of IRI.

There are also indirect evidence indicating the importance of T cells. Pretreatment with Cytotoxic T lymphocytes Associated protein-4-immunoglobulin (CTLA-4 Ig) that blocks the antigen-independent costimulatory pathway between T cell and antigen presenting cells also confers marked renoprotective effect [58]. Reconstitution of T-cell-deficient mice with CD4 T cells from IFN-g KO mice which is an important T-cell cytokine, failed to restore the postischemic injury can also be indirect evidence supporting the role of T cells in the pathogenesis of IRI [57].

In addition to antigen-independent early activation, antigen-dependent activation of T cell was also found to mediate kidney injury. Satpute et al. demonstrated the significantly worse renal function in DO11.10 mice immunized with OVA-CFA compared to those immunized with CFA alone showing that TCR repertoire-dependent factors are also important in mediating the early injury in kidney IRI [59].

Other indirect evidence showing the role of T cell came from a study by Day et al. who demonstrated that adenosine 2A (A2A) receptor agonist induced renoprotective effect is mediated by its action on $CD4^+$ cells. They showed that the renoprotection observed in T- and B-cell deficient Rag-1 KO mice was reversed in mice that were adoptively transferred $CD4^+$ T cells. They also showed that A(2A) receptor agonist attenuated injury only when WT $CD4^+$ cell were adoptively transferred to Rag-1 KO mice but not in A(2A) KO $CD4^+$ cells were trasnsferred [60].

Compared to CD4 T cell, studies focusing on the role of B cells are relatively sparse and inconsistent.

While B-cell deficiency conferred protection in one study [61], another study showed sustained worse renal injury [62]. Regarding the role of B cells, more studies are needed.

22.9 Natural Killer Cells

NK cells are rapidly acting cytotoxic lymphoid cells of large granule originated from common lymphoid progenitor generating B and T lymphocytes. NK cells do not express T-cell antigen receptors (TCR) or pan T marker CD3 or B-cell receptors, but they usually express CD16 (FcγRIII) and CD56 in humans, NK1.1 or NK1.2 in C57BL/6 mice. Previous studies showed that NK cells contribute to kidney injury by inducing apoptosis of tubular epithelial cells possibly mediated by tubular cell osteopontin [63, 64]. Osteopontin expression markedly increased after

IRI and could directly activate NK cells and mediate tubular cell apoptosis. Osteopontin-deficient mice were shown to have decreased number of NK cells with reduced kidney injury following IRI [65]. Another recent study showed the involvement of TLR2 signaling in recruitment of NK cells. Endogenous TLR2 ligands from damaged tubular cells induced CCR5 chemokine seem to be important in promoting NK cell recruitment to postischemic kidneys [66].

22.10 Natural Killer T Cells

NKT cells are an unique subset of T cells that coexpress an αβ T-cell receptor, and also molecular marker that are typically represent NK cells, such as NK1.1. NKT cells differ from conventional αβ T cells in that their T-cell receptors are more limited in diversity and instead of recognizing peptide antigens presented by major histocompatibility complexes (MHC)-class I or II molecules, they recognize glycolipid in the context of the class I-like molecule, CD1d. IFN-γ producing NKT cells were shown as early as 3 h after IRI and the important role of NKT cells have been demonstrated by significant renoprotection in mice with blockade of CD1d, depletion of NKT cells or in mice deficient of NKT cells (Jα18(−/−)) [67]. All these mice showed reduced number of IFN-γ producing NKT cells, neutrophils as well as renal dysfunction.

In contrast, Yang et al. demonstrated the opposite, renoprotective role of type II NKT cells. These type II NKT cells are activated by glycolipid 3-sulfated galactosylceramide (sulfatide) and can be identified by sulfatide/CD1d-tetramers. Type II NKT cells induced renoprotection was mediated by inhibition of tubular cell apoptosis via hypoxia-inducible factor (HIF)-1α and IL-10 pathways [68].

22.11 Regulatory T Cells

The regulatory T cells (Tregs) are subpopulation of T cells with immunosuppressive function that is important in maintaining tolerance to self-antigens or downregulating the activation of effector T cells. Mechanisms underlying the immunosuppression are via production of anti-inflammatory cytokine IL-10 or TGF-β, induction of effector cell apoptosis via granzyme, or inhibition of costimulatory pathways. Given that the overwhelmed innate immune response including a variety of inflammatory cell activation is critical player in the pathogenesis of IRI, it is expected that Tregs can counterbalance the early inflammation or participate in repair process. Although small number, Tregs increased in postischemic kidneys [10, 69]. The role of Tregs was demonstrated by a model that used Treg depletion strategy with CD25 depleting Ab. Pretreatment of CD25 depleting Ab resulted in more severe inflammation and kidney injury [70]. Adoptive transfer of lymph node cells from Foxp3-deficient Scurfy mice into RAG-1 KO mice resulted more severe injury compared to mice with cells from WT mice [70]. Another study showing that IL-2/anti-IL-2 complex

(IL-2C), a mediator of Treg expansion, can attenuate renal IRI also supports the important role of Tregs in preventing kidney injury [71].

There are also data portending the role of Tregs in repair process. Treg depletion starting 1 day after IRI led to reduced tubular proliferation on day 3 and 10 with increased number of CD4 T cells while administration of Tregs on day 1 led to improved repair and reduced cytokine generation at 10 days [10].

In addition to direct depletion or addition, there have been many data showing that the protective effect of many different preventive or therapeutic strategies is partially mediated via expansion of Tregs. Expansion of Tregs and induction of systemic immune suppression was found to be one mechanism of ischemic preconditioning, an endogenous adaptive response that provides local protection against subsequent I/R injury [69]. Heat preconditioning was also associated with expansion of Tregs. Kim et al. demonstrated that splenocytes from heat-preconditioned mice had Treg expansion and T cells from heat-preconditioned mice failed to reconstitute postischemic injury when adoptively transferred to T-cell-deficient nu/nu mice in contrast to those from control mice [72]. They also showed that Tregs were also increased in heat-preconditioned ischemic kidneys and depleting Tregs before heat preconditioning abolished the renoprotective effect, while adoptive transfer of these cells back into Treg-depleted mice partially restored the beneficial effect of heat preconditioning. The renoprotective effect of sphingosine-1-phosphate analogue, FTY 720 [73] or paracrine effect of infused mesenchymal stem cell was also demonstrated to be partially mediated via expansion of regulatory DCs and Tregs in the prevention of IRI [74].

Despite theoretical advantages of Tregs in decreasing the intense immune response, clinical trials have been hampered due to challenges with the limited techniques of isolating and ex vivo expansion of cells. However, recently completed phase 1 clinical trial showed different doses of Tregs tested were safe with no adverse effects of infections or rejection events up to 2 years in living donor kidney transplantation [75] that could facilitate to proceed to phase II clinical trials.

22.12 Complement System

Complement system is part of the humoral innate immune system composed of more than 20 plasma proteins and cell surface receptors, and the end result of complement activation is stimulation of phagocytes to clear microbes, inflammation, and the formation of membrane attack complex (MAC). Among the three complement pathways, alternative pathway and recently, lectin pathway are likely to be associated with inflammation and injury [76, 77]. Factor B-deficient mice demonstrated a reduced kidney IRI [76] and mice deficient of mannose binding lectin-A (MBL-a) and mannose binding lectin-B (MBL-B) are also renoprotective [77]. Another study also demonstrated that reconstitution of mutant mice with recombinant MBL partially restore postischemic injury [78].

Among the numerous factors, C3a and C5a, called anaphylatoxin, have been demonstrated to be an important mediators of early inflammation and injury. These potent proinflammatory peptides bind to their receptors (C3aR, C5aR) in resident immune cells and tubular cells in the kidney and provoke neutrophil recruitment and increase vascular permeability [79, 80]. Mice that have C5aR or combined C3aR/C5aR deficiency are protected from IRI and this effect was associated with significantly decreased inflammation. Recent report demonstrated that renoprotective effect of C5aR2 deficiency is mediated by enhanced activation of IL-10, heme-oxygenase, and survival kinase Akt [81].

In normal condition, complement activation is strictly regulated by complement regulatory proteins. Miao et al. demonstrated the important role of this complement regulatory protein, called complement receptor 1-related protein (Crry) normally expressed in basolateral aspects of tubular cells by demonstrating that deletion of Crry led to spontaneous C3 deposition with worse injury against IRI [82].

22.13 Conclusion

Numerous studies for the last several decades have brought a substantial progress in understanding the role of immune system in the pathogenesis of injury and repair process of AKI. Different kinds of leukocytes of innate and adaptive immune system and their mediators actively participate in kidney inflammation, injury, and functional deterioration. Endothelial cells, by enhancing the leukocyte-endothelial interation and thus further compromising medullary hypoxia contribute to the development and progression of inflammation. As an important source of DAMPs, alarming the immune system, tubular epithelial cells also play an important role in the inflammation and kidney injury. In addition to a role in early inflammation and injury, recent studies revealed that certain type of immune cells or phenotypic shift of immune cells are also critical in repair process.

Therefore, instead of targeting inflammation alone that does not likely to be effective in prevention or treatment of AKI, we need to develop multitargeted therapies based on further understanding of complex interaction of inflammation, endothelial and epithelial cell compartments during AKI.

References

1. Thadhani R, Pascual M, Bonventre JV. Acute renal failure—reply. N Engl J Med. 1996;335(17):1321–2.
2. Chawla LS, Eggers PW, Star RA, Kimmel PL. Acute kidney injury and chronic kidney disease as interconnected syndromes. N Engl J Med. 2014;371(1):58–66.
3. Chawla LS. Acute kidney injury leading to chronic kidney disease and long-term outcomes of acute kidney injury: the best opportunity to mitigate acute kidney injury? In: Controversies in acute kidney injury. Basel: Karger Publishers; 2011. p. 182–90.
4. Bonventre JV, Yang L. Cellular pathophysiology of ischemic acute kidney injury. J Clin Invest. 2011;121(11):4210–21.

5. Molitoris BA. Therapeutic translation in acute kidney injury: the epithelial/endothelial axis. J Clin Invest. 2014;124(6):2355–63.
6. Molitoris BA, Sutton TA. Endothelial injury and dysfunction: role in the extension phase of acute renal failure. Kidney Int. 2004;66(2):496–9.
7. Liu B-C, Tang T-T, Lv L-L, Lan H-Y. Renal tubule injury: a driving force toward chronic kidney disease. Kidney Int. 2018;93(3):568–79.
8. Rodríguez E, Barrios C, Soler MJ, Pascual J. Role of complement activation in acute kidney injury. Clin Nephrol Res. 2017;1(1):10–1.
9. Kim M-G, Su Boo C, Sook Ko Y, Young Lee H, Yong Cho W, Kyu Kim H, et al. Depletion of kidney CD11c+ F4/80+ cells impairs the recovery process in ischaemia/reperfusion-induced acute kidney injury. Nephrol Dial Transplant. 2010;25(9):2908–21.
10. Gandolfo MT, Jang HR, Bagnasco SM, Ko G-J, Agreda P, Satpute SR, et al. Foxp3+ regulatory T cells participate in repair of ischemic acute kidney injury. Kidney Int. 2009;76(7):717–29.
11. Lee S, Huen S, Nishio H, Nishio S, Lee HK, Choi B-S, et al. Distinct macrophage phenotypes contribute to kidney injury and repair. J Am Soc Nephrol. 2011;22(2):317–26.
12. Kaissling B, Le Hir M. Characterization and distribution of interstitial cell types in the renal cortex of rats. Kidney Int. 1994;45(3):709–20.
13. Krüger T, Benke D, Eitner F, Lang A, Wirtz M, Hamilton-Williams EE, et al. Identification and functional characterization of dendritic cells in the healthy murine kidney and in experimental glomerulonephritis. J Am Soc Nephrol. 2004;15(3):613–21.
14. Woltman AM, De Fijter JW, Zuidwijk K, Vlug AG, Bajema IM, Van der Kooij SW, et al. Quantification of dendritic cell subsets in human renal tissue under normal and pathological conditions. Kidney Int. 2007;71(10):1001–8.
15. Munro DA, Hughes J. The origins and functions of tissue-resident macrophages in kidney development. Front Physiol. 2017;8:837.
16. Gutknecht MF, Bouton AH. Functional significance of mononuclear phagocyte populations generated through adult hematopoiesis. J Leukoc Biol. 2014;96(6):969–80.
17. Merad M, Manz MG, Karsunky H, Wagers A, Peters W, Charo I, et al. Langerhans cells renew in the skin throughout life under steady-state conditions. Nat Immunol. 2002;3(12):1135.
18. Ajami B, Bennett JL, Krieger C, Tetzlaff W, Rossi FM. Local self-renewal can sustain CNS microglia maintenance and function throughout adult life. Nat Neurosci. 2007;10(12):1538.
19. Soos TJ, Sims TN, Barisoni L, Lin K, Littman DR, Dustin ML, et al. CX3CR1+ interstitial dendritic cells form a contiguous network throughout the entire kidney. Kidney Int. 2006;70(3):591–6.
20. Sutton TA, Mang HE, Campos SB, Sandoval RM, Yoder MC, Molitoris BA. Injury of the renal microvascular endothelium alters barrier function after ischemia. Am J Physiol Renal Physiol. 2003;285(2):F191–8.
21. Singbartl K, Ley K. Leukocyte recruitment and acute renal failure. J Mol Med. 2004;82(2):91–101.
22. Nemoto T, Burne MJ, Daniels F, O'Donnell MP, Crosson J, Berens K, et al. Small molecule selectin ligand inhibition improves outcome in ischemic acute renal failure. Kidney Int. 2001;60(6):2205–14.
23. Kelly KJ, Williams WW, Colvin RB, Meehan SM, Springer TA, Gutierrez-Ramos JC, et al. Intercellular adhesion molecule-1-deficient mice are protected against ischemic renal injury. J Clin Invest. 1996;97(4):1056–63.
24. Scaffidi P, Misteli T, Bianchi ME. Release of chromatin protein HMGB1 by necrotic cells triggers inflammation. Nature. 2002;418:191.
25. Scheibner KA, Lutz MA, Boodoo S, Fenton MJ, Powell JD, Horton MR. Hyaluronan fragments act as an endogenous danger signal by engaging TLR2. J Immunol. 2006;177(2):1272–81.
26. Boeynaems J-M, Communi D. Modulation of inflammation by extracellular nucleotides. J Invest Dermatol. 2006;126(5):943–4.
27. Shi Y, Evans JE, Rock KL. Molecular identification of a danger signal that alerts the immune system to dying cells. Nature. 2003;425:516.
28. Flamion B, Jadot I, Habsch I, Giordano L, Caron N, Voisin V, et al. Inhibition of hyaluronan is protective against renal ischaemia–reperfusion injury. Nephrol Dial Transplant. 2013;28(10):2484–93.

29. Allam R, Scherbaum CR, Darisipudi MN, Mulay SR, Hagele H, Lichtnekert J, et al. Histones from dying renal cells aggravate kidney injury via TLR2 and TLR4. J Am Soc Nephrol. 2012;23(8):1375–88.
30. Kim H-J, Lee DW, Ravichandran K, O Keys D, Akcay A, Nguyen Q, et al. NLRP3 inflammasome knockout mice are protected against ischemic but not cisplatin-induced acute kidney injury. J Pharmacol Exp Ther. 2013;346(3):465–72.
31. Castoldi A, Braga TT, Correa-Costa M, Aguiar CF, Bassi ÊJ, Correa-Silva R, et al. TLR2, TLR4 and the MYD88 signaling pathway are crucial for neutrophil migration in acute kidney injury induced by sepsis. Eltzschig HK, editor. PLoS One. 2012;7(5):e37584.
32. Pulskens WP, Teske GJ, Butter LM, Roelofs JJ, van der Poll T, Florquin S, et al. Toll-like receptor-4 coordinates the innate immune response of the kidney to renal ischemia/reperfusion injury. Zimmer J, editor. PLoS One. 2008;3(10):e3596.
33. Chiao H, Kohda Y, McLeroy P, Craig L, Housini I, Star RA. Alpha-melanocyte-stimulating hormone protects against renal injury after ischemia in mice and rats. J Clin Invest. 1997;99(6):1165–72.
34. Jo SK, Yun JW, Cha DR, Cho WY, Kim HK, Won NH. α-MSH decreases apoptosis in ischaemic acute renal failure in rats: possible mechanism of this beneficial effect. Nephrol Dial Transplant. 2001;16(8):1583–91.
35. Solez K, Morel-Maroger L, Sraer J. The morphology of "acute tubular necrosis" in man: analysis of 57 renal biopsies and a comparison with the glycerol model. Medicine (Baltimore). 1979;58(5):362–76.
36. Friedewald JJ, Rabb H. Inflammatory cells in ischemic acute renal failure. Kidney Int. 2004;66(2):486–91.
37. Haug CE, Colvin RB, Delmonico FL, Auchincloss H Jr, Tolkoff-Rubin N, Preffer FI, Rothlein R, Norris S, Scharschmidt L, Cosimi AB. A phase I trial of immunosuppression with anti-ICAM-1 (CD54) mAb in renal allograft recipients. Transplantation. 1993;55:766.
38. Brinkmann V, Reichard U, Goosmann C, Fauler B, Uhlemann Y, Weiss DS, et al. Neutrophil extracellular traps kill bacteria. Science. 2004;303(5663):1532.
39. Jansen MPB, Emal D, Teske GJD, Dessing MC, Florquin S, Roelofs JJTH. Release of extracellular DNA influences renal ischemia reperfusion injury by platelet activation and formation of neutrophil extracellular traps. Kidney Int. 2017;91(2):352–64.
40. Cho W, Song J-Y, Oh SW, Kim MG, Ko YS, Lee HY, et al. Fate of neutrophils during the recovery phase of ischemia/reperfusion induced acute kidney injury. J Korean Med Sci. 2017;32(10):1616.
41. Weidenbusch M, Anders H-J. Tissue microenvironments define and get reinforced by macrophage phenotypes in homeostasis or during inflammation, repair and fibrosis. J Innate Immun. 2012;4(5–6):463–77.
42. Hesketh M, Sahin KB, West ZE, Murray RZ. Macrophage phenotypes regulate scar formation and chronic wound healing. Int J Mol Sci. 2017;18(7):1545.
43. Jo S-K, Sung S-A, Cho W-Y, Go K-J, Kim H-K. Macrophages contribute to the initiation of ischaemic acute renal failure in rats. Nephrol Dial Transplant. 2006;21(5):1231–9.
44. Day Y-J, Huang L, Ye H, Linden J, Okusa MD. Renal ischemia-reperfusion injury and adenosine 2A receptor-mediated tissue protection: role of macrophages. Am J Physiol Renal Physiol. 2005;288(4):F722–31.
45. Dong X, Swaminathan S, Bachman L-A, Croatt A-J, Nath K-A, Griffin M-D. Resident dendritic cells are the predominant TNF-secreting cell in early renal ischemia–reperfusion injury. Kidney Int. 2007;71(7):619–28.
46. Li L, Huang L, Ye H, Song SP, Bajwa A, Lee SJ, et al. Dendritic cells tolerized with adenosine A2AR agonist attenuate acute kidney injury. J Clin Invest. 2012;122(11):3931–42.
47. Rogers NM, Ferenbach DA, Isenberg JS, Thomson AW, Hughes J. Dendritic cells and macrophages in the kidney: a spectrum of good and evil. Nat Rev Nephrol. 2014;10(11):625–43.
48. Fadok VA, Bratton DL, Konowal A, Freed PW, Westcott JY, Henson PM. Macrophages that have ingested apoptotic cells in vitro inhibit proinflammatory cytokine production

through autocrine/paracrine mechanisms involving TGF-beta, PGE2, and PAF. J Clin Invest. 1998;101(4):890–8.
49. Voll RE, Herrmann M, Roth EA, Stach C, Kalden JR, Girkontaite I. Immunosuppressive effects of apoptotic cells. Nature. 1997;390:350.
50. Zhang M-Z, Yao B, Yang S, Jiang L, Wang S, Fan X, et al. CSF-1 signaling mediates recovery from acute kidney injury. J Clin Invest. 2012;122(12):4519–32.
51. Huen SC, Huynh L, Marlier A, Lee Y, Moeckel GW, Cantley LG. GM-CSF promotes macrophage alternative activation after renal ischemia/reperfusion injury. J Am Soc Nephrol. 2015;26(6):1334–45.
52. Lech M, Grobmayr R, Ryu M, Lorenz G, Hartter I, Mulay SR, et al. Macrophage phenotype controls long-term AKI outcomes—kidney regeneration versus atrophy. J Am Soc Nephrol. 2014;25(2):292–304.
53. Zhang M-Z, Wang X, Wang Y, Niu A, Wang S, Zou C, et al. IL-4/IL-13–mediated polarization of renal macrophages/dendritic cells to an M2a phenotype is essential for recovery from acute kidney injury. Kidney Int. 2017;91(2):375–86.
54. Kim M-G, Kim SC, Ko YS, Lee HY, Jo S-K, Cho W. The role of M2 macrophages in the progression of chronic kidney disease following acute kidney injury. Dussaule J-C, editor. PLoS One. 2015;10(12):e0143961.
55. Wang Y-Y, Jiang H, Pan J, Huang X-R, Wang Y-C, Huang H-F, et al. Macrophage-to-myofibroblast transition contributes to interstitial fibrosis in chronic renal allograft injury. J Am Soc Nephrol. 2017;28(7):2053–67.
56. Huen SC, Moeckel GW, Cantley LG. Macrophage-specific deletion of transforming growth factor-β1 does not prevent renal fibrosis after severe ischemia-reperfusion or obstructive injury. Am J Physiol Renal Physiol. 2013;305(4):F477–84.
57. Burne MJ, Daniels F, Ghandour AE, Mauiyyedi S, Colvin RB, O'Donnell MP, et al. Identification of the CD4+ T cell as a major pathogenic factor in ischemic acute renal failure. J Clin Invest. 2001;108(9):9.
58. Takada M, Chandraker A, Nadeau KC, Sayegh MH, Tilney NL. The role of the B7 costimulatory pathway in experimental cold ischemia/reperfusion injury. J Clin Invest. 1997;100(5):1199–203.
59. Satpute SR, Park JM, Jang HR, Agreda P, Liu M, Gandolfo MT, et al. The role for T cell repertoire/antigen-specific interactions in experimental kidney ischemia reperfusion injury. J Immunol. 2009;183(2):984–92.
60. Day Y-J, Huang L, Ye H, Li L, Linden J, Okusa MD. Renal ischemia-reperfusion injury and adenosine 2A receptor-mediated tissue protection: the role of CD4+ T cells and IFN-gamma. J Immunol. 2006;176(5):3108–14.
61. Burne-Taney MJ, Ascon DB, Daniels F, Racusen L, Baldwin W, Rabb H. B cell deficiency confers protection from renal ischemia reperfusion injury. J Immunol. 2003;171(6):3210–5.
62. Renner B, Strassheim D, Amura CR, Kulik L, Ljubanovic D, Glogowska MJ, et al. B cell subsets contribute to renal injury and renal protection after ischemia/reperfusion. J Immunol. 2010;185(7):4393–400.
63. Zhang Z-X, Wang S, Huang X, Min W-P, Sun H, Liu W, et al. NK cells induce apoptosis in tubular epithelial cells and contribute to renal ischemia-reperfusion injury. J Immunol. 2008;181(11):7489–98.
64. Victorino F, Sojka DK, Brodsky KS, McNamee EN, Masterson JC, Homann D, et al. Tissue-resident NK cells mediate ischemic kidney injury and are not depleted by anti–Asialo-GM1 antibody. J Immunol. 2015;195(10):4973–85.
65. Zhang Z-X, Shek K, Wang S, Huang X, Lau A, Yin Z, et al. Osteopontin expressed in tubular epithelial cells regulates NK cell-mediated kidney ischemia reperfusion injury. J Immunol. 2010;185(2):967–73.
66. Kim HJ, Lee JS, Kim A, Koo S, Cha HJ, Han J-A, et al. TLR2 signaling in tubular epithelial cells regulates NK cell recruitment in kidney ischemia-reperfusion injury. J Immunol. 2013;191(5):2657–64.

67. Li L, Huang L, Sung SS, Lobo PI, Brown MG, Gregg RK, et al. NKT cell activation mediates neutrophil IFN- production and renal ischemia-reperfusion injury. J Immunol. 2007;178(9):5899–911.
68. Yang SH, Lee JP, Jang HR, Cha RH, Han SS, Jeon US, et al. Sulfatide-reactive natural killer T cells abrogate ischemia-reperfusion injury. J Am Soc Nephrol. 2011;22(7):1305–14.
69. Cho WY, Choi HM, Lee SY, Kim MG, Kim H-K, Jo S-K. The role of Tregs and CD11c+ macrophages/dendritic cells in ischemic preconditioning of the kidney. Kidney Int. 2010;78(10):981–92.
70. Kinsey GR, Sharma R, Huang L, Li L, Vergis AL, Ye H, et al. Regulatory T cells suppress innate immunity in kidney ischemia-reperfusion injury. J Am Soc Nephrol. 2009;20(8):1744–53.
71. Kim M-G, Koo TY, Yan J-J, Lee E, Han KH, Jeong JC, et al. IL-2/anti-IL-2 complex attenuates renal ischemia-reperfusion injury through expansion of regulatory T cells. J Am Soc Nephrol. 2013;24(10):1529–36.
72. Kim M-G, Jung Cho E, Won Lee J, Sook Ko Y, Young Lee H, Jo S-K, et al. The heat-shock protein-70–induced renoprotective effect is partially mediated by CD4 + CD25 + Foxp3 + regulatory T cells in ischemia/reperfusion-induced acute kidney injury. Kidney Int. 2014;85(1):62–71.
73. Lee HY, Kim H-K, Jo S-K, Cho WY, Ko YS, Kim M-G, et al. CD4+ CD25+ regulatory T cells partially mediate the beneficial effects of FTY720, a sphingosine-1-phosphate analogue, during ischaemia/reperfusion-induced acute kidney injury. Nephrol Dial Transplant. 2010;26(1):111–24.
74. Kim M-G, Kim SH, Noh H, Ko YS, Lee HY, Jo S-K, et al. CD11c+ cells partially mediate the renoprotective effect induced by bone marrow-derived mesenchymal stem cells. Camussi G, editor. PLoS One. 2013;8(8):e72544.
75. Mathew JM, H-Voss J, LeFever A, Konieczna I, Stratton C, He J, et al. A phase I clinical trial with ex vivo expanded recipient regulatory T cells in living donor kidney transplants. Sci Rep [Internet]. 2018 [cited 2019 Jan 26];8(1). http://www.nature.com/articles/s41598-018-25574-7.
76. Thurman JM, Ljubanovic D, Edelstein CL, Gilkeson GS, Holers VM. Lack of a functional alternative complement pathway ameliorates ischemic acute renal failure in mice. J Immunol. 2003;170(3):1517–23.
77. de Vries B, Walter SJ, Peutz-Kootstra CJ, Wolfs TGAM, van Heurn LWE, Buurman WA. The mannose-binding lectin-pathway is involved in complement activation in the course of renal ischemia-reperfusion injury. Am J Pathol. 2004;165(5):1677–88.
78. Moller-Kristensen M, Wang W, Ruseva M, Thiel S, Nielsen S, Takahashi K, et al. Mannan-binding lectin recognizes structures on ischaemic reperfused mouse kidneys and is implicated in tissue injury. Scand J Immunol. 2005;61(5):426–34.
79. Peng Q, Li K, Smyth LA, Xing G, Wang N, Meader L, et al. C3a and C5a promote renal ischemia-reperfusion injury. J Am Soc Nephrol. 2012;23(9):1474–85.
80. de Vries B, Kohl J, Leclercq WKG, Wolfs TGAM, van Bijnen AAJHM, Heeringa P, et al. Complement factor C5a mediates renal ischemia-reperfusion injury independent from neutrophils. J Immunol. 2003;170(7):3883–9.
81. Thorenz A, Derlin K, Schroder C, Dressler L, Vijith V, Pradhan P, et al. Enhanced activation of interleukin-10, heme oxygenase-1, and AKT in C5aR2-deficient mice is associated with protection from ischemia reperfusion injury-induced inflammation and fibrosis. Kidney Int. 2018;94(4):741–55.
82. Miao J, Lesher AM, Miwa T, Sato S, Gullipalli D, Song W-C. Tissue-specific deletion of Crry from mouse proximal tubular epithelial cells increases susceptibility to renal ischemia–reperfusion injury. Kidney Int. 2014;86(4):726–37.

Chapter 23
Acute Kidney Injury and Cytokines

Kazuhiro Furuhashi, Noritoshi Kato, Tomoki Kosugi, and Shoichi Maruyama

Abstract Cytokines and chemokines are potential signaling molecules that maintain homeostasis by activating intracellular communication. Cytokines orchestrate various processes, ranging from cellular survival, proliferation, and chemotaxis for tissue repair to regulation of inflammation. Extracellular vesicles (EVs), which are cell-derived membrane particles such as exosomes and microvesicles, may also play crucial roles similar to cytokines. The kidneys are highly susceptible to intrinsic oxidative stress resulting from ischemia and to the excessive inflammatory response resulting from systemic autoimmunity. These types of stress may eventually result in the development of acute kidney injury (AKI). In this setting, the skewed cytokine profile produced by macrophages and lymphocytes disrupts the reciprocal relationship for regulating tissue repair and remodeling due to amplification of a physiological vicious loop. We have so far shown that AKI induces the secretion of midkine (MK) and CD147/basigin, which are responsible for skewed cytokine production. MK and CD147/basigin secreted by tubular epithelial cells promote the recruitment of macrophages and neutrophils, respectively, which are accompanied by monocyte chemotactic protein-1, transforming growth factor-β, E cadherin, and extracellular matrix metalloproteinase inducer.

This chapter will present the functions of macrophage-related cytokines and EVs and summarize our findings on how MK and CD147/basigin are involved in the pathogenesis of AKI.

Keywords Inflammation · Renal ischemia · Macrophage · Midkine · CD147/Basigin · Extracellular vesicles

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23.1 Introduction

Ischemia, loss of self-tolerance, and bacterial infection induce white blood cells to enter various organs due to activation of chemotactic cytokines and adhesion molecules, eventually resulting in systemic inflammation [1, 2]. Because the kidneys are highly sensitive to intrinsic oxidative stress caused by systemic ischemia and systemic autoimmunity, various stresses can lead to acute kidney injury (AKI) [3]. Renal tubular epithelial cells (TECs) are the antigen-presenting cells in the kidneys. Following activation of cell adhesion molecules resulting from injury to tubules, TECs interact directly with various immune cells such as neutrophils, monocytes, and T lymphocytes [4]. Maintenance of an anti-inflammatory and anti-thrombotic environment and prevention of renal fibrosis require homeostasis of renal endothelial cells [5]. AKI and the immune system show bidirectional cross-talk [6, 7]. Renal damage can result from both adaptive and innate immune cells and recovery from AKI. The etiology of AKI involves dendritic cells (DCs), monocytes/macrophages, neutrophils, T lymphocytes, and B lymphocytes. In addition, M2 macrophages and regulatory T cells mediate inflammatory processes, tissue remodeling, and repair after AKI. Higher levels of cytokines and immune cell dysfunction, especially dysfunctional neutrophils, may exacerbate immune dysfunction and block removal of bacteria during AKI.

A vicious cycle of injury after acute or subacute kidney injury may spread to distant organs, such as the heart, liver, and lungs. Multiple cytokines and chemokines expressed by circulating inflammatory cells and damaged organs may mediate the cross-talk between distant organs and the kidneys. Ischemia-induced AKI may be followed by impaired function of distant organs [8, 9]. Renal inflammation prophylaxis is necessary for reduced mortality and morbidity after kidney injury. Although mediated by different primary disease processes, long-term injury to the kidney leads to permanent abnormalities such as glomerular obsolescence and interstitial fibrosis; these conditions may eventually develop into chronic kidney disease (CKD). Patients with moderate renal dysfunction usually do not show symptoms. Thus, early identification of susceptible patients and increased understanding of mechanisms that induce inflammation may be important for determining therapeutic strategies for treatment of kidney diseases. Studies of cytokines, chemokines, and extracellular vesicles (EVs), as well as their associated mRNAs and miRNAs, are critical for preventing death and improving the health of patients with AKI. Here, we describe in vivo studies of various promising molecules.

23.2 Macrophage-Related Cytokine and Chemokine Portfolio

When cells are damaged and damage-associated molecular patterns are triggered and released from the damaged cells themselves, an inflammatory response is formed around the damaged cells. Next, chemokines (CXCL1, CXCL8, CCL2,

CCL5) are secreted from epithelial cells and resident DCs/macrophages, which recruits neutrophils and monocytes to the sites of inflammation in AKI [3]. At the same time, inflammatory cytokines (tumor necrosis factor-α, interferon-γ, interleukin (IL)-6, IL-1β, IL-23, IL-17) and anti-inflammatory cytokines (IL-4, IL-10, transforming growth factor (TGF)-β, hepatocyte growth factor, resolvins) are secreted from resident and recruited cells at the sites of inflammation [3]. The balance between inflammatory cytokines and anti-inflammatory cytokines are important determinants of when inflammation leads to injury and injury to regeneration.

Macrophages are present in healthy and diseased kidneys where they perform critical roles in maintenance, the immune response, tissue injury, and tissue repair. Macrophages are highly heterogeneous cells and exhibit distinct functions depending on their local microenvironment, which includes cytokines. This macrophage heterogeneity allows the cells to respond to changes in various cytokines. Macrophages are classified into two broad subsets, pro-inflammatory M1 macrophages and anti-inflammatory M2 macrophages (Fig. 23.1). At the time of initial

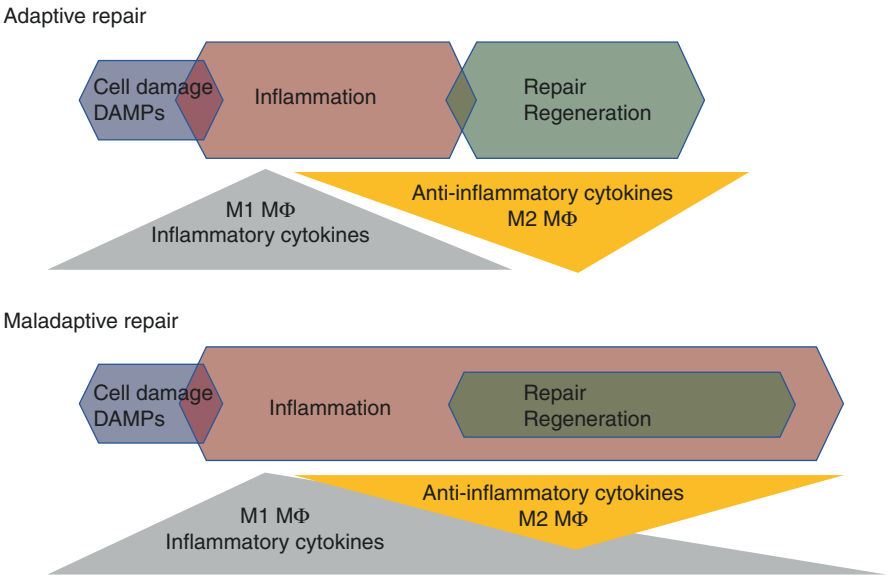

Fig. 23.1 Inflammation and regeneration. Once cells are damaged, they produce damage-associated molecular patterns (DAMPs) and danger signals, leading to activation and recruitment of leukocytes (M1 macrophages). This phase is known as inflammation. The inflammatory signals induce stem cells from dormancy to proliferative state, and the proliferated stem cells differentiate to compensate for the tissue defect. At the peak of inflammation, anti-inflammatory cells (M2 macrophages) begin to appear in the inflamed sites. In the case of adaptive repair, the inflammation is terminated by the increase of anti-inflammatory cells and the concomitant increase of anti-inflammatory cytokines. Anti-inflammatory cytokines restore stem cells from proliferation to dormancy to prevent stem cell exhaustion. In the case of maladaptive repair, the sustained inflammation continues to induce stem cell proliferation and differentiation, and eventually stem cells are exhausted. Tissue repair cannot be achieved due to stem cell exhaustion and persistent attack on differentiated cells by immune cells

injury in AKI, the kidney is protected from ischemic injury by depletion of kidney macrophages [10, 11]. Furthermore, if M1 macrophages induced in vitro are transferred back into mice with ischemic kidney injury, kidney damage is worsened. These observations indicate that M1 macrophages play pathogenic roles in ischemic kidney injury [12]. On the other hand, recovery from ischemic kidney injury is impaired when macrophages are removed after the onset of ischemic AKI [13]. Administration of macrophages during the recovery phase from ischemic AKI induces TEC proliferation and promotes recovery of renal function [14]. These results suggest that M2 macrophages mediate kidney repair and regeneration. M1 macrophages injected during the regeneration phase change their phenotype from M1 to M2 within the kidney [12]. This indicates that macrophages switch from an inflammatory (M1 macrophage) to an anti-inflammatory (M2 macrophage) state as the cytokines change from inflammatory to anti-inflammatory in the inflammatory sites. In other words, macrophages function as effector cells that converge inflammation at the injured site and convert the environment towards a regenerative state by recognizing changes in the surrounding environment. In vitro stimulation or administration of lipopolysaccharide or interferon-γ induces M1 macrophages, whereas M2 macrophages are induced by Th2 cytokines such as IL-4 and IL-10. However, the mechanisms by which in vivo macrophages switch to M2 macrophages in ischemic AKI remains poorly understood.

Apoptotic cells, anti-inflammatory cytokines, and growth factors are important factors in the induction of M2 macrophages. Macrophages take up apoptotic bodies, and sphingosine-1-phosphate from apoptotic cells in mice after ischemic reperfusion promotes induction of M2 macrophages, leading to production of TGF-β and IL-10 [15]. Production of anti-inflammatory cytokines by M2 macrophages enhances M2 polarization at inflamed sites. IL-10 derived from regulatory T cells also plays a partial role in M2 polarization [16]. Steroid treatment increases M2 macrophage numbers in vivo, leading to a reduction in inflammation and injury in the inflamed kidney [17]. Colony stimulating factor-1 derived from TECs in ischemic reperfusion-induced mice polarizes resident macrophages towards M2 macrophages, enhancing regeneration following ischemic renal damage [18]. Once M2 macrophages are induced in inflammatory and damaged lesions, these cells reduce inflammation by removal of cell debris and production of protective mediators such as heme-oxygenase-1 (HO-1) and IL-10. HO-1 is an anti-inflammatory enzyme. HO-1-expressing M2 macrophages promote phagocytosis of apoptotic cells and production of IL-10 [19], which is a strong anti-inflammatory cytokine that blocks inflammatory pathways. Systemic administration of IL-10 protects against ischemic AKI and cisplatin-induced AKI by inhibiting intercellular adhesion molecule-1 and granulocyte activation [20]. Moreover, by secreting angiogenic factors and growth factors, macrophages establish an environment that is necessary for organ regeneration. M2 macrophages locally support vascularization by secreting vascular endothelial growth factor to restore the energy and oxygen that are necessary for organ regeneration. The reparative potentials of M2 macrophages appear to be mediated

by Wnt7b, which leads to cell-cycle progression of renal TECs after ischemic AKI [21]. Further research is needed to investigate the mechanism by which M2 macrophages promote regeneration.

Based on these findings, two therapeutic strategies have been considered for acute renal failure. The first is direct administration of cultured macrophages into the body. Administration of induced pluripotent stem cell-derived M2 macrophages ameliorates nephritis in mice [22]. HO-1-overexpressing macrophages show an anti-inflammatory phenotype with increased IL-10 production [19]. These reports suggest that direct administration of M2 macrophages may be a new treatment strategy for kidney injury.

The second strategy is to induce a change in the inflammatory environment by administering a drug or growth factor that will lead to promotion of regeneration and induction of M2 macrophages. Administration of mesenchymal stem cells (MSCs) can change the inflammatory environment, leading to induction of M2 macrophages and kidney regeneration.

MSCs can differentiate into bone, cartilage, and adipose tissue. Although MSCs are rare populations in bone marrow and adipose tissue, MSCs show excellent growth ability in culture while retaining their growth and multilineage potential. Thus, MSCs may be ideal candidates for cell therapy, and many researchers have examined the therapeutic effects of MSCs in various animal models. MSCs show pleiotropic effects in damaged sites by producing various growth factors and immunoregulatory factors, depending on signals in the inflammatory milieu. In the area of kidney research, administration of cultured MSCs protects against AKI and nephritis via production of hepatocyte growth factor and M2 induction, respectively [23, 24]. Recently, phase 1 and 2 clinical trials using bone marrow- or adipose-derived MSCs have begun to target AKI.

Adenosine may be a therapeutically useful molecule because it alters the inflammatory environment. Adenosine is a purine nucleoside found in many living systems, and it is also a medication. In the clinic, adenosine is used to treat supraventricular tachycardia. Adenosine is constitutively present in physiological conditions at a very low concentration, but its concentration increases in pathological conditions such as hypoxic and inflammatory conditions. CD39 is an extracellular enzyme that catalyzes the conversion of adenosine triphosphate (ATP) and adenosine diphosphate to adenosine monophosphate. CD73 rapidly converts adenosine monophosphate into adenosine. Of the four different types of adenosine receptors (adenosine A_1, A_{2A}, A_{2B}, and A_3 receptors), the A2A adenosine receptor (A2AR) is predominantly expressed in immune cells. Activation of A2AR generally produces immunosuppressive signals, which inhibit activities of T cells, natural killer cells, macrophages, DCs, and neutrophils. An A2AR agonist also induces conversion of macrophages to an M2 phenotype, an activity that is independent of IL-4/IL-4Rα signaling [25]. In A2AR-deficient mice, tissue damage due to inflammation is exacerbated compared to wild-type mice. Some reports show that administration of an A2AR agonist strongly inhibits the induction of inflammatory

diseases. In the area of kidney research, increasing the adenosine concentration reduces the severity of ischemic kidney injuries [26]. Another article indicated that a nonspecific adenosine receptor inhibitor prevents the reduction in renal blood flow following ischemic renal injury [27]. Therefore, whether adenosine in inflamed sites shows protective effects or not in ischemic kidney injuries is still controversial. This discrepancy may be related to expression levels and subtypes of adenosine receptors and may depend on the disease model and injury severity.

By decreasing inflammatory cytokines, decreasing M1 macrophages, and increasing M2 macrophages, dysfunctional organs can shift to a phase of regeneration and repair, eventually leading to adaptive repair. If the transition from inflammation to regeneration is minimal and inflammation remains, chronic inflammation and fibrosis may result. Cellular therapy, cytokine therapy, and growth factor therapy may be new treatment options for patients with acute renal disorders following increased understanding of microenvironmental changes and factors that determine the function and subtype of macrophages in the kidney. Many factors related to inflammation have been identified, and new drugs are being developed as a result. In addition, as the mechanisms of development of inflammation and organ regeneration are elucidated, new therapeutic applications for existing drugs have attracted attention as treatment for acute renal disorder.

23.3 Cytokines and Chemokines Derived from Infiltrating Inflammatory Cells and TECs

23.3.1 Midkine

Midkine (MK; gene, *Mdk*) is a 13-kDa growth factor that contains multiple basic amino acids and cysteines and binds heparin. MK was first identified as a transcript of a retinoic acid-responsive gene. MK plays a role in kidney development, increases cell growth, enhances cell survival, increases cell migration, is anti-apoptotic, and is involved in fibrinolysis and development of cancer [28, 29]. In the normal kidney, MK is expressed in proximal and distal TECs and at lower levels in endothelial cells [5, 30]. MK receptors may form a complex that also includes proteoglycans such as low density lipoprotein receptor-related proteins [28, 31, 32]. MK signaling involves mitogen-activated protein kinase and phosphatidylinositol 3-kinase. The pro-inflammatory role of MK has been shown in various in vivo studies of arterial restenosis [33], rheumatoid arthritis [34], ischemic renal injury [35–37], cisplatin-induced tubulointerstitial injury [38], diabetic nephropathy [39, 40], and endothelial dysfunction [41]. MK has various pathophysiological effects on disorders such as AKI, CKD, high blood pressure, ischemia, and type 2 diabetes.

Renal ischemia is a primary cause of AKI and is related to injury to various organs via organ–organ interactions including the kidney. Renal ischemia also involves several chemokines, with the end result of multiple organ failure [1, 42]. In this setting, TECs become energy deprived, and various beneficial and harmful

systems are activated. This causes direct disruption of the cytoskeleton, aberrant cell polarity, and cell death. Indirect effects that induce chemotaxis are seen including activation of different types of cells such as endothelial cells and leukocytes [5]. Severe depletion of ATP leads to necrosis, whereas GTP depletion tends to promote apoptosis [43]. Necrosis and autophagy are both observed after ischemic reperfusion injury. In this condition, disrupted vascular endothelial cells lead to vascular congestion, edema, decreased blood flow, and migration of neutrophils and macrophages. When these inflammatory cells enter the injured kidney, cytokines are secreted, and the presence of reactive oxygen species (ROS), proteases, myeloperoxidase, and other chemokines can lead to additional injury. These processes have been repeatedly demonstrated in both humans and animal models of renal reperfusion. After ischemic reperfusion in vivo, MK is quickly upregulated in the proximal tubules, which increases macrophage inflammatory protein for neutrophils and monocyte chemotactic protein-1 for macrophages [35, 37]. The inflammatory cells induce severe tubulointerstitial damage. Blocking MK inhibits inflammatory cell movement to the damaged epithelial layer and decreases the severity of kidney injury. Thus, MK increases movement of inflammatory cells into the kidney following ischemic injury and also induces chemokines, thus playing a role in worsening ischemic tissue damage.

Patients with acute or subacute kidney injury should not experience death or complications due to pulmonary dysfunction [44]. Most kidney–lung interactions are accompanied by secretion of cytokines, including TGF-β, IL-1β, IL-6, IL-18, nuclear factor kappa-light-chain enhancer of activated B cells, and tumor necrosis factor-α, as well as MK and induction of renin-angiotensin system (RAS) [44, 45]. Factors that are upstream of the MK-RAS system have been investigated. Our group showed that oxidative stress induces expression of MK [39]. Another group showed that hypoxia increases MK via hypoxia-inducible factor-1α and induces pulmonary vascular remodeling [46]. We hypothesized that NADPH oxidases (Nox), which are enzymes that generate and release superoxide by electron transfer from NADPH to oxygen, are important in *MK induction*. Pulmonary Nox1, 2, and 4 expression in wild-type ($Mdk^{+/+}$) mice is significantly upregulated following kidney ablation, but Nox expression is not affected by ablation in MK-deficient ($Mdk^{-/-}$) mice [47]. Nox-mediated ROS induces pulmonary MK expression. The membrane-permeable radical scavenger, 4-hydroxy-2,2,6,6- tetramethylpiperidine-N-oxyl (Tempol), decreases MK induction and returns plasma Angiotensin (Ang) II to normal levels in the lungs. Tempol also improves blood pressure and decreases kidney damage including glomerular sclerosis and tubular interstitial injury. ROS are unlikely to be transported between the kidney and lung due to their short half-life. Ang II induces Nox expression [48]. Thus, we conclude that the oxidative stress-induced initial increase in MK in the endothelium increases ACE expression in the lung, and the end result is a vicious cycle of Ang II overexpression. The RAS may strongly drive positive feedback induced by oxidative stress.

Segmental breaks in the glomerular basement membrane (GBM) may lead to formation of crescents in the glomerulus, and are often accompanied by fibrinoid necrosis [49]. These phenomena induce deposits of fibrin, infiltration of inflammatory cells, and accumulation of the extracellular matrix. Fibrin deposits disrupt

glomerular blood flow, lead to irreversible ischemia and glomerular obsolescence, and promote entrance of inflammatory cells and cell division by epithelial cells in Bowman's space [50]. Macrophage and neutrophil recruitment is induced by inflammatory mediators such as fibrin, oxidative stress, and different chemokines. The end result is induction of coagulation during crescentic glomerulonephritis (GN), thrombotic microangiopathy, and severe endothelial dysfunction. This vicious cycle must be inhibited to decrease deaths associated with aggressive kidney diseases.

The glycoprotein plasminogen activator inhibitor (PAI)-1, an inhibitor of serine proteases, is the major endogenous inhibitor of plasminogen activators such as tissue-type plasminogen activator and urokinase-type plasminogen activator [51]. Concentrations of PAI-1 in tissues and plasma are extremely low in normal physiological states, but are upregulated in abnormal conditions. PAI-I has multiple effects, including induction of thrombotic disorders and a role in ischemic diseases, fibrotic disorders, metabolic syndrome, type 2 diabetes, and cancer [49, 51, 52]. Increased levels of PAI-1 induced by various factors such as high ambient glucose exposure [53], TGF-β [54], oxidative stress [55], and Ang II [56, 57] lead to recruitment of interstitial macrophages and direct effects of cells following urokinase-type plasminogen activator receptor binding. Reduced PAI-1 decreases the severity of anti-GBM-induced nephritis [58]. Elucidation of signaling induced by PAI-1 may lead to development of novel therapeutic strategies for rapidly progressive GN.

MK is induced by an inflammatory microenvironment, followed by direct and indirect recruitment of macrophages through activation of monocyte chemotactic protein-1. Induction of PAI-1 in both normal and pathological states has been extensively studied. However, the endogenous systems that block induction of PAI-1 are not known. MK increases fibrinolysis by decreasing PAI-1 in vascular endothelial cells [59, 60]. Our group performed in vivo studies and showed that MK has harmful effects on both glomerular damage and tubulointerstitial injury due to its ability to recruit inflammatory cells in mice with accelerated Masugi nephritis [61]. Several studies have shown that MK may protect against crescentic GN, and that the pathological features of this condition may be due to an imbalance in the coagulation-fibrinolysis system.

Capillary endothelial dysfunction and subsequent intravascular fibrin lead to macrophage infiltration, disruption of the GBM, and leakage of its contents, such as fibrin, red blood cells, extracellular matrix, and inflammatory cells. Macrophage recruitment in this condition may be the first step in a critical series of cellular events that lead to crescent formation. Consistent with this idea, deletion of macrophages stops the progression of crescentic GN [62]. PAI-1 both stabilizes the fibrin net and is a chemoattractant for monocytes and leukocytes [50, 63]. Macrophages and PAI-1 increase fibrin formation, and fibrin induces macrophage infiltration and endothelial dysfunction. Consistent with this idea, a study of experimental models of anti-GBM crescentic GN showed that compared to PAI-1-deficient mice, more crescents were formed, more fibrin deposits were seen, and greater macrophage infiltration was present in PAI-1-overexpressing mice [58]. High levels of PAI-1 are observed both in regions with glomerular necrosis and in crescents in progressive GN [64, 65]. Parietal epithelial cells and glomerular endothelial cells preferentially

express PAI-1. Consistent with these in vivo data, our group showed that primary cultured endothelial cells from $Mdk^{-/-}$ mice have higher levels of PAI-1 mRNA after a fibrin challenge, and they also show less fibrinolysis than cells from $Mdk^{+/+}$ mice. PAI-1 is also induced by factors such as high ambient glucose, TGF-β, oxidative stress, and Ang II.

23.3.2 CD147/Basigin

CD147/Basigin, an extracellular matrix metalloproteinase inducer, is a highly glycosylated transmembrane protein that is a member of the immunoglobulin superfamily [66]. CD147 includes a 185-amino acid (aa) extracellular domain with two immunoglobulin domains, a 24-aa transmembrane domain, and a 39-aa cytoplasmic domain [67, 68]. The extracellular domain harbors three N-linked glycosylation sites. Glycosylation is different depending on the organ, and these glycosylation differences may explain the variety of physiological roles of CD147. CD147 is expressed by many cell types including hematopoietic, epithelial, and endothelial cells and leukocytes. This protein is important in oncogenesis and cancer progression due to its ability to induce matrix metalloproteinases and monocarboxylate transporters. CD147 was first discovered in embryonal carcinoma cells where it functions as a receptor for Lotus tetragonolobus agglutinin. This protein has the Lewis X structure: Galβ1→4(Fucα1→3) GlcNAc [69]. CD147 binds to multiple molecules such as caveolin, cyclophilin, monocarboxylate transporter (MCT), and CD147 itself [4, 70]. The extracellular domain of CD147 binds to caveolin-1, β1 integrin, cyclophilin, and CD147 itself, whereas the transmembrane domain is necessary for the association with MCT, CD43, and syndecan [71–74]. Similar to MK, mitogen-activated protein kinase and phosphatidylinositol 3-kinase are involved in CD147 downstream signaling. Normal kidneys, especially the basolateral side of TECs, express high levels of CD147 [75]. In contrast, CD147 expression in glomerular structures and vascular endothelial cells is very low, perhaps explaining the inability of many antibody clones to detect low levels of CD147 with western blotting or immunohistochemistry. Increased CD147 is observed with immunohistochemistry in glomeruli and vessels injured by inflammation, as well as in glomerular adhesions to Bowman's capsule, endocapillary proliferation, and crescent formation. Inflammatory cells that show CD147 induction infiltrate strongly into damaged regions [76]. On the other hand, clearly reduced CD147 expression is observed in the damaged tubulointerstitium in patients with AKI and diabetic nephropathy [77]. CD147 expression does not occur in patients with diabetic nephropathy and nodular glomerulosclerosis.

Short-term harmful events such as ischemia, kidney-specific auto-antigens, and activation of the immune system interact over a period of minutes to days, resulting in AKI. Early in AKI, inflammatory cell infiltration increases disease activity via secretion of chemotactic cytokines and ROS [3]. Increased interactions between leukocytes and endothelial cells due to increased cell–cell adhesion greatly decrease

peritubular capillary blood flow, which leads to oxidative injury to renal tubules and subsequent depletion of ATP [2, 76]. These events lead to cytoskeletal and cell polarity abnormalities, culminating in cell death. A vicious cycle involving multiple cytokines and adhesion molecules ensues. Compared to expression in other organs, CD147 is very highly expressed in the tubules of normal kidneys, suggesting important roles for CD147 in the above events [75]. Insufficient levels of CD147 lead to ATP depletion in ischemia-induced AKI, and hypoxia depletes ATP in primary cultured $Bsg^{-/-}$ TECs. Thus, in normal conditions, CD147 may increase the activity of lactate metabolism via MCT, which induces ATP in renal tubules.

In vivo studies using $Bsg^{-/-}$ mice were performed to confirm in vitro data and increase our understanding of the functions of CD147. $Bsg^{-/-}$ mice with renal ischemic reperfusion show a marked decrease in recruitment of neutrophils and macrophages, resulting in a reduction in tubulointerstitial damage [78]. Thus, CD147 appears to be important for recruitment of inflammatory cells in this type of injury. The CXC chemokines, keratinocyte-derived chemokine and macrophage inflammatory protein-2, attract neutrophils following ischemic injury. However, wild-type and $Bsg^{-/-}$ mice show similar expression levels of these molecules. The role of CD147 in the pathogenesis of ischemia-induced AKI remains unknown. Blocking CD147 pharmacologically inhibits the migration of neutrophils and monocytes/macrophages after myocardial ischemia and reperfusion, and subsequently protects left ventricular function and myocardial tissues [79]. The interaction between CD147 and its ligand cyclophilin A (CyPA) is crucial for regulation of leukocyte recruitment. Results from in vivo studies of conditions such as sepsis-induced AKI, bronchial asthma, lipopolysaccharide-induced lung injury, and collagen-induced arthritis, are consistent with this idea [80–83]. However, wild-type and $Bsg^{-/-}$ mice show similar levels of CyPA expression, and therefore, CD147-CyPA binding may not be involved in the etiology of ischemic AKI. Further studies of this interaction are needed. The infiltration of massive numbers of neutrophils into damaged regions is due to CD147 expression on neutrophils, and not on other cell types such as TECs. In addition, CD147 expressed on neutrophils is a critical physiological ligand for E-selectin; CD147-E-selectin binding mediates adhesion of neutrophils to vascular endothelial cells. Inflammatory stimuli induce selectin specifically in endothelial cells [84, 85]. Consistent with this observation, mice deficient in E-selectin show greatly reduced myeloperoxidase activity, which is an indicator of active neutrophils. CD147 includes a sialyl Lewis X structure, which is necessary for E-selectin recognition [69]. In addition to CD147, other glycoproteins including P-selectin glycoprotein ligand-1 and CD44 bind to E-selectin. The primary interaction between neutrophils and endothelial cells occurs in parallel with P-selectin glycoprotein ligand-1 expression at the tip of neutrophil microvilli. The steady, slow rolling of leukocytes is regulated by CD44, which is expressed on the planar surface of neutrophils [86, 87]. Thus, chemotactic cytokines and adhesion-related molecules may be necessary for leukocyte recruitment. Highly glycosylated CD147 expressed on the planar surfaces and the microvilli of neutrophils binds E-selectin early during formation of leukocyte-endothelial contact, increasing recruitment of neutrophils into the ischemic kidney.

23.4 Extracellular Vesicles (EVs)

EVs are the generic term for cell-derived membrane particles including exosomes, microvesicles, and apoptotic bodies. Exosomes originate from endosomes and are the smallest vesicles (30–100 nm in diameter) among EVs. Microvesicles and apoptotic bodies are derived directly from the plasma membrane and are 0.1–1.0 μm and 1.0–5.0 μm in diameter, respectively. These EVs are sometimes difficult to distinguish from each other. These vesicles do not contain a functional nucleus, but do contain mRNA, microRNA (miRNA), and protein from their parental cells. They transfer their contents to or stimulate cell surface receptors on recipient cells in an autocrine and paracrine manner. In particular, the transfer of mRNA and miRNA can genetically reprogram the phenotypes of recipient cells. EVs have been intensively explored in immunology, oncology, and cardiology research fields. They play roles in intracellular communication such as antigen presentation, distant organ metastasis, and atherosclerosis [88, 89]. Compared with these other research fields, little is known about the contribution of EVs to the pathogenesis of kidney disease. A body of evidence is gradually accumulating that demonstrates the involvement of EVs in disease processes of the kidney, including IgA nephropathy, renal transplantation, thrombotic microangiopathies, nephrotic syndrome, urinary tract infection, cystic kidney disease, CKD, and AKI [90–95]. EVs are not only involved in pathogenesis, but have attracted a great deal of attention as a new class of disease biomarkers. In addition, some basic studies have suggested that exosomes from MSCs or progenitor cells protect against ischemic kidney injury. Below, we discuss the current knowledge regarding the association of EVs with pathogenesis, as a biomarker, and as potential therapy for AKI.

23.4.1 EV-Related Pathogenesis of AKI

Plasma from patients with sepsis-associated AKI induces granulocyte adhesion, apoptosis, and altered polarity in cultured tubular cells [96]. Thus, researchers have speculated that some soluble factors in plasma directly cause AKI. In the lipopolysaccharide-induced AKI mouse model, the amounts of exosomes in urine and kidney are increased and contain higher levels of CCL2 mRNA compared with control mice. An in vitro experiment revealed that BSA-stimulated TECs contain a high level of CCL2 mRNA, and exosomes derived from TECs were directly transferred into macrophages. Combined with these data, intracellular communication between TECs and macrophages through exosomes exists and causes tubulointerstitial inflammation [97].

Necroptosis is a programmed cell death process that is mediated by mixed lineage kinase domain-like protein, and growing evidence has revealed the importance of tubular necroptosis in causing AKI [98]. From that point of view, serum-derived

exosomes from AKI patients increase mixed lineage kinase domain-like protein-mediated necroptosis in cultured HK2 cells via a reduction in miR-500a-3p expression [99]. Further studies are needed to increase the knowledge of the role of exosomes in AKI.

23.4.2 EVs as a Promising Biomarker of AKI

Urinary EVs may be useful as biomarkers of AKI. The level of Na^+/H^+ exchanger isoform 3 is elevated in the urinary membrane fraction of patients with acute tubular necrosis compared with patients with prerenal azotemia and controls [100]. At that time, the contribution of EVs was not mentioned, but the molecules from renal parenchymal cells in urine were proposed to serve as markers of damaged tubules. Studies of animal disease models and human samples have shown that activating transcription factor 3 may serve as a biomarker of tubular injury. On the other hand, Wilms tumor 1 was proposed as an early podocyte injury marker. Both molecules are present in the concentrated exosomal fraction, but not in whole urine [101]. A proteomics study of an animal disease model identified urinary exosomal fetuin A as an AKI biomarker, and the presence of this protein was confirmed in urine samples from ICU patients with AKI [102]. Usually, EVs contain the parental cell's surface proteins. As biomarkers, the strong point of evaluating EVs rather than blood or urine is that the source of the EVs is detectable. Thus, to evaluate tubular damage, tubular EVs should be collected and analyzed intensively.

23.4.3 The Utility of EVs for AKI Therapy

EVs secreted from MSCs or progenitor cells have beneficial effects for many kinds of organ injury by transferring mRNAs, miRNAs, growth factors, and cytokines. Focusing on AKI, single administration of microvesicles secreted from MSCs immediately after rat ischemia/reperfusion injury protects the rats from AKI by inhibiting apoptosis and stimulating TEC proliferation [103]. Another report revealed that MSC-derived exosomes express high levels of C-C motif chemokine receptor 2, and injected MSC-derived exosomes reduce the levels of its ligand, CCL2, in an ischemia/reperfusion injury model. That process attenuates inflammation of the injured kidney [104]. Therapy with a combination of adipose-derived MSCs and exosomes derived from these cells showed a renoprotective effect in the rat ischemia/reperfusion injury model [105]. Exosomes from human cord blood endothelial colony-forming cells are enriched in miR-486-5p, which targets phosphatase and tensin homolog and the Akt pathway. When EVs from endothelial colony-forming cells are given to mice with ischemic kidney injury, renal function was preserved, the kidney miR-486-5p level was increased, phosphatase and tensin homolog expression was decreased, and Akt was activated [106]. Not only EVs derived from MSCs and progenitor cells, but also EVs from renal tubular cells, have

therapeutic potential against established rat ischemia/reperfusion AKI. Furthermore, EVs from hypoxia preconditioned tubular cells show greater improvement of the renal phenotype than EVs from normoxic tubular cells [107].

In addition, several attempts have been made to use EVs as a drug delivery system. A growing concept is that EVs have a preference regarding which organ or cell type will take them up, according to the type of integrins on the EVs. For example, the preference of tumor-derived exosomes explains the pathogenesis of metastatic organotropism due to establishment of a pre-metastatic niche before cancer metastasis [108]. Furthermore, by genetically modifying the expression of membrane proteins on parental cells, secreted EVs can be designed to target specific recipient cells. Surface proteins of the parental cells are usually contained within secreted EVs, and work as ligands for the receptors of EV recipient cells [109]. Thus, EVs can be loaded with therapeutic materials and administered to specific, intended organs. These EV-based medicines are generating a lot of attention and will be used in future clinical trials.

23.5 Conclusion

Following the initiation of AKI, a vicious cycle of injury often spreads to distant organs through activation of various cytokines and chemokines derived from circulating inflammatory cells and damaged organs. Elucidation of the molecular mechanisms underlying AKI from a variety of perspectives is essential for improving mortality and morbidity rates.

References

1. Abuelo JG. Normotensive ischemic acute renal failure. N Engl J Med. 2007;357:797–805.
2. Cantaluppi V, Quercia AD, Dellepiane S, Ferrario S, Camussi G, Biancone L. Interaction between systemic inflammation and renal tubular epithelial cells. Nephrol Dial Transplant. 2014;29(11):2004–11.
3. Kurts C, Panzer U, Anders HJ, Rees AJ. The immune system and kidney disease: basic concepts and clinical implications. Nat Rev Immunol. 2013;13:738–53.
4. Kosugi T, Maeda K, Sato W, Maruyama S, Kadomatsu K. CD147 (EMMPRIN/Basigin) in kidney diseases: from an inflammation and immune system viewpoint. Nephrol Dial Transplant. 2015;30:1097–103.
5. Kosugi T, Sato W. Midkine and the kidney: health and diseases. Nephrol Dial Transplant. 2012;27:16–21.
6. Arango Duque G, Descoteaux A. Macrophage cytokines: involvement in immunity and infectious diseases. Front Immunol. 2014;5:491.
7. Singbartl K, Formeck CL, Kellum JA. Kidney-immune system crosstalk in AKI. Semin Nephrol. 2019;39:96–106.
8. Andres-Hernando A, Altmann C, Ahuja N, Lanaspa MA, Nemenoff R, He Z, Ishimoto T, Simpson PA, Weiser-Evans MC, Bacalja J, Faubel S. Splenectomy exacerbates lung injury after ischemic acute kidney injury in mice. Am J Physiol Renal Physiol. 2011;301:F907–16.
9. Brochner AC, Dagnaes-Hansen F, Hojberg-Holm J, Toft P. The inflammatory response in blood and in remote organs following acute kidney injury. APMIS. 2014;122:399–404.

10. Jo SK, Sung SA, Cho WY, Go KJ, Kim HK. Macrophages contribute to the initiation of ischaemic acute renal failure in rats. Nephrol Dial Transplant. 2006;21:1231–9.
11. Cho WY, Choi HM, Lee SY, Kim MG, Kim HK, Jo SK. The role of Tregs and CD11c(+) macrophages/dendritic cells in ischemic preconditioning of the kidney. Kidney Int. 2010;78:981–92.
12. Lee S, Huen S, Nishio H, Nishio S, Lee HK, Choi BS, Ruhrberg C, Cantley LG. Distinct macrophage phenotypes contribute to kidney injury and repair. J Am Soc Nephrol. 2011;22:317–26.
13. Jang HS, Kim J, Park YK, Park KM. Infiltrated macrophages contribute to recovery after ischemic injury but not to ischemic preconditioning in kidneys. Transplantation. 2008;85:447–55.
14. Vinuesa E, Hotter G, Jung M, Herrero-Fresneda I, Torras J, Sola A. Macrophage involvement in the kidney repair phase after ischaemia/reperfusion injury. J Pathol. 2008;214:104–13.
15. Sola A, Weigert A, Jung M, Vinuesa E, Brecht K, Weis N, Brune B, Borregaard N, Hotter G. Sphingosine-1-phosphate signalling induces the production of Lcn-2 by macrophages to promote kidney regeneration. J Pathol. 2011;225:597–608.
16. Liu G, Ma H, Qiu L, Li L, Cao Y, Ma J, Zhao Y. Phenotypic and functional switch of macrophages induced by regulatory CD4+CD25+ T cells in mice. Immunol Cell Biol. 2011;89:130–42.
17. Ikezumi Y, Suzuki T, Karasawa T, Hasegawa H, Kawachi H, Nikolic-Paterson DJ, Uchiyama M. Contrasting effects of steroids and mizoribine on macrophage activation and glomerular lesions in rat thy-1 mesangial proliferative glomerulonephritis. Am J Nephrol. 2010;31:273–82.
18. Zhang MZ, Yao B, Yang S, Jiang L, Wang S, Fan X, Yin H, Wong K, Miyazawa T, Chen J, Chang I, Singh A, Harris RC. CSF-1 signaling mediates recovery from acute kidney injury. J Clin Invest. 2012;122:4519–32.
19. Ferenbach DA, Ramdas V, Spencer N, Marson L, Anegon I, Hughes J, Kluth DC. Macrophages expressing heme oxygenase-1 improve renal function in ischemia/reperfusion injury. Mol Ther. 2010;18:1706–13.
20. Deng J, Kohda Y, Chiao H, Wang Y, Hu X, Hewitt SM, Miyaji T, McLeroy P, Nibhanupudy B, Li S, Star RA. Interleukin-10 inhibits ischemic and cisplatin-induced acute renal injury. Kidney Int. 2001;60:2118–28.
21. Lin SL, Li B, Rao S, Yeo EJ, Hudson TE, Nowlin BT, Pei H, Chen L, Zheng JJ, Carroll TJ, Pollard JW, McMahon AP, Lang RA, Duffield JS. Macrophage Wnt7b is critical for kidney repair and regeneration. Proc Natl Acad Sci U S A. 2010;107:4194–9.
22. Du Q, Tsuboi N, Shi Y, Ito S, Sugiyama Y, Furuhashi K, Endo N, Kim H, Katsuno T, Akiyama S, Matsuo S, Isobe KI, Maruyama S. Transfusion of CD206(+) M2 macrophages ameliorates antibody-mediated glomerulonephritis in mice. Am J Pathol. 2016;186:3176–88.
23. Katsuno T, Ozaki T, Saka Y, Furuhashi K, Kim H, Yasuda K, Yamamoto T, Sato W, Tsuboi N, Mizuno M, Ito Y, Imai E, Matsuo S, Maruyama S. Low serum cultured adipose tissue-derived stromal cells ameliorate acute kidney injury in rats. Cell Transplant. 2013;22:287–97.
24. Furuhashi K, Tsuboi N, Shimizu A, Katsuno T, Kim H, Saka Y, Ozaki T, Sado Y, Imai E, Matsuo S, Maruyama S. Serum-starved adipose-derived stromal cells ameliorate crescentic GN by promoting immunoregulatory macrophages. J Am Soc Nephrol. 2013;24:587–603.
25. Ferrante CJ, Pinhal-Enfield G, Elson G, Cronstein BN, Hasko G, Outram S, Leibovich SJ. The adenosine-dependent angiogenic switch of macrophages to an M2-like phenotype is independent of interleukin-4 receptor alpha (IL-4Ralpha) signaling. Inflammation. 2013;36:921–31.
26. Bor MV, Durmus O, Bilgihan A, Cevik C, Turkozkan N. The beneficial effect of 2′-deoxycoformycin in renal ischemia-reperfusion is mediated both by preservation of tissue ATP and inhibition of lipid peroxidation. Int J Clin Lab Res. 1999;29:75–9.
27. Lin JJ, Churchill PC, Bidani AK. Theophylline in rats during maintenance phase of post-ischemic acute renal failure. Kidney Int. 1988;33:24–8.
28. Muramatsu T. Midkine and pleiotrophin: two related proteins involved in development, survival, inflammation and tumorigenesis. J Biochem. 2002;132:359–71.

29. Kadomatsu K, Muramatsu T. Midkine and pleiotrophin in neural development and cancer. Cancer Lett. 2004;204:127–43.
30. Hayashi H, Sato W, Kosugi T, Nishimura K, Sugiyama D, Asano N, Ikematsu S, Komori K, Nishiwaki K, Kadomatsu K, Matsuo S, Maruyama S, Yuzawa Y. Efficacy of urinary midkine as a biomarker in patients with acute kidney injury. Clin Exp Nephrol. 2017;21:597–607.
31. Chen S, Bu G, Takei Y, Sakamoto K, Ikematsu S, Muramatsu T, Kadomatsu K. Midkine and LDL-receptor-related protein 1 contribute to the anchorage-independent cell growth of cancer cells. J Cell Sci. 2007;120:4009–15.
32. Sakamoto K, Bu G, Chen S, Takei Y, Hibi K, Kodera Y, McCormick LM, Nakao A, Noda M, Muramatsu T, Kadomatsu K. Premature ligand-receptor interaction during biosynthesis limits the production of growth factor midkine and its receptor LDL receptor-related protein 1. J Biol Chem. 2011;286:8405–13.
33. Horiba M, Kadomatsu K, Nakamura E, Muramatsu H, Ikematsu S, Sakuma S, Hayashi K, Yuzawa Y, Matsuo S, Kuzuya M, Kaname T, Hirai M, Saito H, Muramatsu T. Neointima formation in a restenosis model is suppressed in midkine-deficient mice. J Clin Invest. 2000;105:489–95.
34. Maruyama K, Muramatsu H, Ishiguro N, Muramatsu T. Midkine, a heparin-binding growth factor, is fundamentally involved in the pathogenesis of rheumatoid arthritis. Arthritis Rheum. 2004;50:1420–9.
35. Sato W, Kadomatsu K, Yuzawa Y, Muramatsu H, Hotta N, Matsuo S, Muramatsu T. Midkine is involved in neutrophil infiltration into the tubulointerstitium in ischemic renal injury. J Immunol. 2001;167:3463–9.
36. Sato W, Yuzawa Y, Kadomatsu K, Tayasu T, Muramatsu H, Muramatsu T, Matsuo S. Midkine expression in the course of nephrogenesis and its role in ischaemic reperfusion injury. Nephrol Dial Transplant. 2002;17(Suppl 9):52–4.
37. Sato W, Takei Y, Yuzawa Y, Matsuo S, Kadomatsu K, Muramatsu T. Midkine antisense oligodeoxyribonucleotide inhibits renal damage induced by ischemic reperfusion. Kidney Int. 2005;67:1330–9.
38. Kawai H, Sato W, Yuzawa Y, Kosugi T, Matsuo S, Takei Y, Kadomatsu K, Muramatsu T. Lack of the growth factor midkine enhances survival against cisplatin-induced renal damage. Am J Pathol. 2004;165:1603–12.
39. Kosugi T, Yuzawa Y, Sato W, Kawai H, Matsuo S, Takei Y, Muramatsu T, Kadomatsu K. Growth factor midkine is involved in the pathogenesis of diabetic nephropathy. Am J Pathol. 2006;168:9–19.
40. Kosugi T, Yuzawa Y, Sato W, Arata-Kawai H, Suzuki N, Kato N, Matsuo S, Kadomatsu K. Midkine is involved in tubulointerstitial inflammation associated with diabetic nephropathy. Lab Investig. 2007;87:903–13.
41. Sato Y, Sato W, Maruyama S, Wilcox CS, Falck JR, Masuda T, Kosugi T, Kojima H, Maeda K, Furuhashi K, Ando M, Imai E, Matsuo S, Kadomatsu K. Midkine regulates BP through cytochrome P450-derived eicosanoids. J Am Soc Nephrol. 2015;26:1806–15.
42. Bellomo R, Kellum JA, Ronco C. Acute kidney injury. Lancet. 2012;380:756–66.
43. Padanilam BJ. Cell death induced by acute renal injury: a perspective on the contributions of apoptosis and necrosis. Am J Physiol Renal Physiol. 2003;284:F608–27.
44. Klein CL, Hoke TS, Fang WF, Altmann CJ, Douglas IS, Faubel S. Interleukin-6 mediates lung injury following ischemic acute kidney injury or bilateral nephrectomy. Kidney Int. 2008;74:901–9.
45. Hoke TS, Douglas IS, Klein CL, He Z, Fang W, Thurman JM, Tao Y, Dursun B, Voelkel NF, Edelstein CL, Faubel S. Acute renal failure after bilateral nephrectomy is associated with cytokine-mediated pulmonary injury. J Am Soc Nephrol. 2007;18:155–64.
46. Reynolds PR, Mucenski ML, Le Cras TD, Nichols WC, Whitsett JA. Midkine is regulated by hypoxia and causes pulmonary vascular remodeling. J Biol Chem. 2004;279:37124–32.
47. Hobo A, Yuzawa Y, Kosugi T, Kato N, Asai N, Sato W, Maruyama S, Ito Y, Kobori H, Ikematsu S, Nishiyama A, Matsuo S, Kadomatsu K. The growth factor midkine regulates the renin-angiotensin system in mice. J Clin Invest. 2009;119:1616–25.

48. Mollnau H, Wendt M, Szocs K, Lassegue B, Schulz E, Oelze M, Li H, Bodenschatz M, August M, Kleschyov AL, Tsilimingas N, Walter U, Forstermann U, Meinertz T, Griendling K, Munzel T. Effects of angiotensin II infusion on the expression and function of NAD(P)H oxidase and components of nitric oxide/cGMP signaling. Circ Res. 2002;90:E58–65.
49. Eddy AA, Fogo AB. Plasminogen activator inhibitor-1 in chronic kidney disease: evidence and mechanisms of action. J Am Soc Nephrol. 2006;17:2999–3012.
50. Hertig A, Rondeau E. Role of the coagulation/fibrinolysis system in fibrin-associated glomerular injury. J Am Soc Nephrol. 2004;15:844–53.
51. Ha H, Oh EY, Lee HB. The role of plasminogen activator inhibitor 1 in renal and cardiovascular diseases. Nat Rev Nephrol. 2009;5:203–11.
52. Roelofs JJ, Teske GJ, Bonta PI, de Vries CJ, Meijers JC, Weening JJ, van der Poll T, Florquin S. Plasminogen activator inhibitor-1 regulates neutrophil influx during acute pyelonephritis. Kidney Int. 2009;75:52–9.
53. Lee EA, Seo JY, Jiang Z, Yu MR, Kwon MK, Ha H, Lee HB. Reactive oxygen species mediate high glucose-induced plasminogen activator inhibitor-1 up-regulation in mesangial cells and in diabetic kidney. Kidney Int. 2005;67:1762–71.
54. Jiang Z, Seo JY, Ha H, Lee EA, Kim YS, Han DC, Uh ST, Park CS, Lee HB. Reactive oxygen species mediate TGF-beta1-induced plasminogen activator inhibitor-1 upregulation in mesangial cells. Biochem Biophys Res Commun. 2003;309:961–6.
55. Liao H, Hyman MC, Lawrence DA, Pinsky DJ. Molecular regulation of the PAI-1 gene by hypoxia: contributions of Egr-1, HIF-1alpha, and C/EBPalpha. FASEB J. 2007;21:935–49.
56. Yoshimoto T, Fukai N, Sato R, Sugiyama T, Ozawa N, Shichiri M, Hirata Y. Antioxidant effect of adrenomedullin on angiotensin II-induced reactive oxygen species generation in vascular smooth muscle cells. Endocrinology. 2004;145:3331–7.
57. Yoshimoto T, Gochou N, Fukai N, Sugiyama T, Shichiri M, Hirata Y. Adrenomedullin inhibits angiotensin II-induced oxidative stress and gene expression in rat endothelial cells. Hypertens Res. 2005;28:165–72.
58. Kitching AR, Kong YZ, Huang XR, Davenport P, Edgtton KL, Carmeliet P, Holdsworth SR, Tipping PG. Plasminogen activator inhibitor-1 is a significant determinant of renal injury in experimental crescentic glomerulonephritis. J Am Soc Nephrol. 2003;14:1487–95.
59. Kojima S, Soga W, Hagiwara H, Shimonaka M, Saito Y, Inada Y. Visible fibrinolysis by endothelial cells: effect of vitamins and sterols. Biosci Rep. 1986;6:1029–33.
60. Kojima S, Muramatsu H, Amanuma H, Muramatsu T. Midkine enhances fibrinolytic activity of bovine endothelial cells. J Biol Chem. 1995;270:9590–6.
61. Kojima H, Kosugi T, Sato W, Sato Y, Maeda K, Kato N, Kato K, Inaba S, Ishimoto T, Tsuboi N, Matsuo S, Maruyama S, Yuzawa Y, Kadomatsu K. Deficiency of growth factor midkine exacerbates necrotizing glomerular injuries in progressive glomerulonephritis. Am J Pathol. 2013;182:410–9.
62. Duffield JS, Tipping PG, Kipari T, Cailhier JF, Clay S, Lang R, Bonventre JV, Hughes J. Conditional ablation of macrophages halts progression of crescentic glomerulonephritis. Am J Pathol. 2005;167:1207–19.
63. Oda T, Jung YO, Kim HS, Cai X, Lopez-Guisa JM, Ikeda Y, Eddy AA. PAI-1 deficiency attenuates the fibrogenic response to ureteral obstruction. Kidney Int. 2001;60:587–96.
64. Rondeau E, Mougenot B, Lacave R, Peraldi MN, Kruithof EK, Sraer JD. Plasminogen activator inhibitor 1 in renal fibrin deposits of human nephropathies. Clin Nephrol. 1990;33:55–60.
65. Grandaliano G, Gesualdo L, Ranieri E, Monno R, Schena FP. Tissue factor, plasminogen activator inhibitor-1, and thrombin receptor expression in human crescentic glomerulonephritis. Am J Kidney Dis. 2000;35:726–38.
66. Muramatsu T, Miyauchi T. Basigin (CD147): a multifunctional transmembrane protein involved in reproduction, neural function, inflammation and tumor invasion. Histol Histopathol. 2003;18:981–7.
67. Yoshida S, Shibata M, Yamamoto S, Hagihara M, Asai N, Takahashi M, Mizutani S, Muramatsu T, Kadomatsu K. Homo-oligomer formation by basigin, an immunoglobulin superfamily member, via its N-terminal immunoglobulin domain. Eur J Biochem. 2000;267:4372–80.

68. Nabeshima K, Iwasaki H, Koga K, Hojo H, Suzumiya J, Kikuchi M. Emmprin (basigin/CD147): matrix metalloproteinase modulator and multifunctional cell recognition molecule that plays a critical role in cancer progression. Pathol Int. 2006;56:359–67.
69. Miyauchi T, Kanekura T, Yamaoka A, Ozawa M, Miyazawa S, Muramatsu T. Basigin, a new, broadly distributed member of the immunoglobulin superfamily, has strong homology with both the immunoglobulin V domain and the beta-chain of major histocompatibility complex class II antigen. J Biochem. 1990;107:316–23.
70. Yurchenko V, Constant S, Eisenmesser E, Bukrinsky M. Cyclophilin-CD147 interactions: a new target for anti-inflammatory therapeutics. Clin Exp Immunol. 2010;160:305–17.
71. Cho JY, Fox DA, Horejsi V, Sagawa K, Skubitz KM, Katz DR, Chain B. The functional interactions between CD98, beta1-integrins, and CD147 in the induction of U937 homotypic aggregation. Blood. 2001;98:374–82.
72. Sun J, Hemler ME. Regulation of MMP-1 and MMP-2 production through CD147/extracellular matrix metalloproteinase inducer interactions. Cancer Res. 2001;61:2276–81.
73. Pakula R, Melchior A, Denys A, Vanpouille C, Mazurier J, Allain F. Syndecan-1/CD147 association is essential for cyclophilin B-induced activation of p44/42 mitogen-activated protein kinases and promotion of cell adhesion and chemotaxis. Glycobiology. 2007;17:492–503.
74. Khunkaewla P, Schiller HB, Paster W, Leksa V, Cermak L, Andera L, Horejsi V, Stockinger H. LFA-1-mediated leukocyte adhesion regulated by interaction of CD43 with LFA-1 and CD147. Mol Immunol. 2008;45:1703–11.
75. Maeda-Hori M, Kosugi T, Kojima H, Sato W, Inaba S, Maeda K, Nagaya H, Sato Y, Ishimoto T, Ozaki T, Tsuboi N, Muro Y, Yuzawa Y, Imai E, Johnson R, Matsuo S, Kadomatsu K, Maruyama S. Plasma CD147 reflects histological features in patients with lupus nephritis. Lupus. 2014;23:342.
76. Nagaya H, Kosugi T, Maeda-Hori M, Maeda K, Sato Y, Kojima H, Hayashi H, Kato N, Ishimoto T, Sato W, Yuzawa Y, Matsuo S, Kadomatsu K, Maruyama S. CD147/basigin reflects renal dysfunction in patients with acute kidney injury. Clin Exp Nephrol. 2014;18:746–54.
77. Mori Y, Masuda T, Kosugi T, Yoshioka T, Hori M, Nagaya H, Maeda K, Sato Y, Kojima H, Kato N, Ishimoto T, Katsuno T, Yuzawa Y, Kadomatsu K, Maruyama S. The clinical relevance of plasma CD147/basigin in biopsy-proven kidney diseases. Clin Exp Nephrol. 2018;22(4):815–24.
78. Kato N, Yuzawa Y, Kosugi T, Hobo A, Sato W, Miwa Y, Sakamoto K, Matsuo S, Kadomatsu K. The E-selectin ligand basigin/CD147 is responsible for neutrophil recruitment in renal ischemia/reperfusion. J Am Soc Nephrol. 2009;20:1565–76.
79. Seizer P, Ochmann C, Schonberger T, Zach S, Rose M, Borst O, Klingel K, Kandolf R, MacDonald HR, Nowak RA, Engelhardt S, Lang F, Gawaz M, May AE. Disrupting the EMMPRIN (CD147)-cyclophilin a interaction reduces infarct size and preserves systolic function after myocardial ischemia and reperfusion. Arterioscler Thromb Vasc Biol. 2011;31:1377–86.
80. Gwinn WM, Damsker JM, Falahati R, Okwumabua I, Kelly-Welch A, Keegan AD, Vanpouille C, Lee JJ, Dent LA, Leitenberg D, Bukrinsky MI, Constant SL. Novel approach to inhibit asthma-mediated lung inflammation using anti-CD147 intervention. J Immunol. 2006;177:4870–9.
81. Dear JW, Leelahavanichkul A, Aponte A, Hu X, Constant SL, Hewitt SM, Yuen PS, Star RA. Liver proteomics for therapeutic drug discovery: inhibition of the cyclophilin receptor CD147 attenuates sepsis-induced acute renal failure. Crit Care Med. 2007;35:2319–28.
82. Arora K, Gwinn WM, Bower MA, Watson A, Okwumabua I, MacDonald HR, Bukrinsky MI, Constant SL. Extracellular cyclophilins contribute to the regulation of inflammatory responses. J Immunol. 2005;175:517–22.
83. Damsker JM, Okwumabua I, Pushkarsky T, Arora K, Bukrinsky MI, Constant SL. Targeting the chemotactic function of CD147 reduces collagen-induced arthritis. Immunology. 2009;126:55–62.
84. Ley K, Allietta M, Bullard DC, Morgan S. Importance of E-selectin for firm leukocyte adhesion in vivo. Circ Res. 1998;83:287–94.

85. Zarbock A, Ley K. Mechanisms and consequences of neutrophil interaction with the endothelium. Am J Pathol. 2008;172:1–7.
86. Moore KL, Patel KD, Bruehl RE, Li F, Johnson DA, Lichenstein HS, Cummings RD, Bainton DF, McEver RP. P-selectin glycoprotein ligand-1 mediates rolling of human neutrophils on P-selectin. J Cell Biol. 1995;128:661–71.
87. von Andrian UH, Hasslen SR, Nelson RD, Erlandsen SL, Butcher EC. A central role for microvillous receptor presentation in leukocyte adhesion under flow. Cell. 1995;82:989–99.
88. Witwer KW, Soekmadji C, Hill AF, Wauben MH, Buzas EI, Di Vizio D, Falcon-Perez JM, Gardiner C, Hochberg F, Kurochkin IV, Lotvall J, Mathivanan S, Nieuwland R, Sahoo S, Tahara H, Torrecilhas AC, Weaver AM, Yin H, Zheng L, Gho YS, Quesenberry P, Thery C. Updating the MISEV minimal requirements for extracellular vesicle studies: building bridges to reproducibility. J Extracell Vesicles. 2017;6:1396823.
89. Stahl AL, Johansson K, Mossberg M, Kahn R, Karpman D. Exosomes and microvesicles in normal physiology, pathophysiology, and renal diseases. Pediatr Nephrol. 2019;34:11–30.
90. Lv LL, Cao YH, Ni HF, Xu M, Liu D, Liu H, Chen PS, Liu BC. MicroRNA-29c in urinary exosome/microvesicle as a biomarker of renal fibrosis. Am J Physiol Renal Physiol. 2013;305:F1220–7.
91. Zhou H, Kajiyama H, Tsuji T, Hu X, Leelahavanichkul A, Vento S, Frank R, Kopp JB, Trachtman H, Star RA, Yuen PS. Urinary exosomal Wilms' tumor-1 as a potential biomarker for podocyte injury. Am J Physiol Renal Physiol. 2013;305:F553–9.
92. Dimuccio V, Ranghino A, Pratico Barbato L, Fop F, Biancone L, Camussi G, Bussolati B. Urinary CD133+ extracellular vesicles are decreased in kidney transplanted patients with slow graft function and vascular damage. PLoS One. 2014;9:e104490.
93. Duan ZY, Cai GY, Bu R, Lu Y, Hou K, Chen XM. Selection of urinary sediment miRNAs as specific biomarkers of IgA nephropathy. Sci Rep. 2016;6:23498.
94. Karpman D, Loos S, Tati R, Arvidsson I. Haemolytic uraemic syndrome. J Intern Med. 2017;281:123–48.
95. Karpman D, Stahl AL, Arvidsson I. Extracellular vesicles in renal disease. Nat Rev Nephrol. 2017;13:545–62.
96. Cantaluppi V, Weber V, Lauritano C, Figliolini F, Beltramo S, Biancone L, De Cal M, Cruz D, Ronco C, Segoloni GP, Tetta C, Camussi G. Protective effect of resin adsorption on septic plasma-induced tubular injury. Crit Care. 2010;14:R4.
97. Lv LL, Feng Y, Wen Y, Wu WJ, Ni HF, Li ZL, Zhou LT, Wang B, Zhang JD, Crowley SD, Liu BC. Exosomal CCL2 from tubular epithelial cells is critical for albumin-induced tubulointerstitial inflammation. J Am Soc Nephrol. 2018;29:919–35.
98. Wang S, Zhang C, Hu L, Yang C. Necroptosis in acute kidney injury: a shedding light. Cell Death Dis. 2016;7:e2125.
99. Jiang L, Liu XQ, Ma Q, Yang Q, Gao L, Li HD, Wang JN, Wei B, Wen J, Li J, Wu YG, Meng XM. hsa-miR-500a-3P alleviates kidney injury by targeting MLKL-mediated necroptosis in renal epithelial cells. FASEB J. 2019;33(3):3523–35.
100. du Cheyron D, Daubin C, Poggioli J, Ramakers M, Houillier P, Charbonneau P, Paillard M. Urinary measurement of Na+/H+ exchanger isoform 3 (NHE3) protein as new marker of tubule injury in critically ill patients with ARF. Am J Kidney Dis. 2003;42:497–506.
101. Zhou H, Cheruvanky A, Hu X, Matsumoto T, Hiramatsu N, Cho ME, Berger A, Leelahavanichkul A, Doi K, Chawla LS, Illei GG, Kopp JB, Balow JE, Austin HA 3rd, Yuen PS, Star RA. Urinary exosomal transcription factors, a new class of biomarkers for renal disease. Kidney Int. 2008;74:613–21.
102. Zhou H, Pisitkun T, Aponte A, Yuen PS, Hoffert JD, Yasuda H, Hu X, Chawla L, Shen RF, Knepper MA, Star RA. Exosomal Fetuin-A identified by proteomics: a novel urinary biomarker for detecting acute kidney injury. Kidney Int. 2006;70:1847–57.
103. Gatti S, Bruno S, Deregibus MC, Sordi A, Cantaluppi V, Tetta C, Camussi G. Microvesicles derived from human adult mesenchymal stem cells protect against ischaemia-reperfusion-induced acute and chronic kidney injury. Nephrol Dial Transplant. 2011;26:1474–83.

104. Farzamfar S, Hasanpour A, Nazeri N, Razavi H, Salehi M, Shafei S, Nooshabadi VT, Vaez A, Ehterami A, Sahrapeyma H, Ai J. Extracellular micro/nanovesicles rescue kidney from ischemia-reperfusion injury. J Cell Physiol. 2019;234(8):12290–300.
105. Lin KC, Yip HK, Shao PL, Wu SC, Chen KH, Chen YT, Yang CC, Sun CK, Kao GS, Chen SY, Chai HT, Chang CL, Chen CH, Lee MS. Combination of adipose-derived mesenchymal stem cells (ADMSC) and ADMSC-derived exosomes for protecting kidney from acute ischemia-reperfusion injury. Int J Cardiol. 2016;216:173–85.
106. Vinas JL, Burger D, Zimpelmann J, Haneef R, Knoll W, Campbell P, Gutsol A, Carter A, Allan DS, Burns KD. Transfer of microRNA-486-5p from human endothelial colony forming cell-derived exosomes reduces ischemic kidney injury. Kidney Int. 2016;90:1238–50.
107. Dominguez JH, Liu Y, Gao H, Dominguez JM 2nd, Xie D, Kelly KJ. Renal tubular cell-derived extracellular vesicles accelerate the recovery of established renal ischemia reperfusion injury. J Am Soc Nephrol. 2017;28:3533–44.
108. Hoshino A, Costa-Silva B, Shen TL, Rodrigues G, Hashimoto A, Tesic Mark M, Molina H, Kohsaka S, Di Giannatale A, Ceder S, Singh S, Williams C, Soplop N, Uryu K, Pharmer L, King T, Bojmar L, Davies AE, Ararso Y, Zhang T, Zhang H, Hernandez J, Weiss JM, Dumont-Cole VD, Kramer K, Wexler LH, Narendran A, Schwartz GK, Healey JH, Sandstrom P, Labori KJ, Kure EH, Grandgenett PM, Hollingsworth MA, de Sousa M, Kaur S, Jain M, Mallya K, Batra SK, Jarnagin WR, Brady MS, Fodstad O, Muller V, Pantel K, Minn AJ, Bissell MJ, Garcia BA, Kang Y, Rajasekhar VK, Ghajar CM, Matei I, Peinado H, Bromberg J, Lyden D. Tumour exosome integrins determine organotropic metastasis. Nature. 2015;527:329–35.
109. Alvarez-Erviti L, Seow Y, Yin H, Betts C, Lakhal S, Wood MJ. Delivery of siRNA to the mouse brain by systemic injection of targeted exosomes. Nat Biotechnol. 2011;29:341–5.

Part V
AKI and Regenerative Medicine

Chapter 24
iPS Cell and Renal Regenerative Medicine

Toshikazu Araoka and Kenji Osafune

Abstract Recent progress in kidney regeneration research using induced pluripotent stem (iPS) cells has enabled the induction of nephron progenitor cells (NPCs) and the reconstruction of kidney organoids that include nephron structures in vitro. In this article, we first explain the history of iPS cells and kidney regeneration research. Next, we summarize the current status of cell therapies including the mechanisms of action using human iPS cell-derived NPCs against kidney diseases, such as acute kidney injury (AKI). These therapies would benefit from the development of expansion cultures and purification methods for NPCs. Finally, we discuss the future perspectives of cell therapies and other possible applications using human iPS cell-derived NPCs against kidney diseases.

Keywords iPS cell · nephron progenitor · cell therapy · AKI · regenerative medicine

24.1 Introduction

The kidney is an organ that consists of highly functional and terminally differentiated cells. In particular, it is believed that glomerular podocytes cannot regenerate. Therefore, kidneys in which chronic kidney disease (CKD) has progressed do not recover their function, and blood purification or kidney transplantation therapy is eventually required. The number of CKD patients continues to increase worldwide [1, 2]. Accordingly, the total number of patients with end-stage renal disease (ESRD) undergoing dialysis therapy is increasing year by year [3, 4]. No radical treatments against kidney diseases except for kidney transplantation have been established, and kidney diseases cause major medical and medico-economical problems. Kidney regenerative medicine is expected to reduce the number of

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dialysis patients, improve their quality of life (QOL), and lower bloated medical expenses. In order to realize kidney regenerative medicine, the development of methods to differentiate pluripotent stem cells, such as embryonic stem (ES) cells prepared from fertilized eggs [5, 6] and induced pluripotent stem (iPS) cells derived by introducing reprogramming factors into somatic cells [7–9], into kidney lineage cells is underway. Furthermore, the development of new therapeutic strategies using these stem cells is being vigorously investigated. In this article, we focus on the history of iPS cells and kidney regeneration research including expansion cultures and purification methods for nephron progenitor cells (NPCs). We also outline the current status and future perspectives of cell therapies in kidney regenerative medicine.

24.2 iPS Cells

iPS cells are somatic cells reprogrammed into an ES cell-like state by the introduction of the Yamanaka factors (OCT4, SOX2, KLF4, and c-MYC) [7, 8]. Around the same time, Yu et al. also generated human iPS cells by using a slightly different combination of factors (OCT4, SOX2, NANOG, and LIN28) [9]. iPS cells have advantages over ES cells in that because they can be derived from patient somatic cells, they have fewer ethical problems or immunological rejection after transplantation. In addition, iPS cells can theoretically differentiate into any cell type constituting organs derived from the three embryonic germ layers (ectoderm, mesoderm, and endoderm) and have unlimited proliferative capacity. In recent years, derivation methods to overcome the safety concerns of iPS cell tumorigenicity have been developed using episomal vectors or treatment with only small compounds, which eliminated the integration of reprogramming factors into the genome of donor cells [10–12]. iPS cells are being used in disease modeling and drug screening in addition to cell replacement therapies, because they can be prepared from healthy individuals and patients and be differentiated into diseased cell types that are difficult to access as primary cells. Various differentiation methods to induce iPS cells into the target tissues and cell types have been reported [13]. Notably, clinical trials of cell therapies using human iPS cell-derived retinal pigment epithelial cells and dopamine-producing neuronal cells have begun [14, 15]. In addition, effective drug candidates have been identified by chemical screenings of chondrocyte cells differentiated from patient-derived disease-specific iPS cells of fibrodysplasia ossificans progressiva (FOP), and a clinical trial of an identified candidate compound is currently under way [16].

24.3 Differentiation from Human iPS Cells to Kidney Lineages

In 1992, Moriya et al. reported that treating the multipotent cell mass called animal cap of *Xenopus* embryos with activin A and retinoic acid (RA) forms pronephros [17]. Thomson et al. reported in 1998 that glomerulus- and tubule-like structures

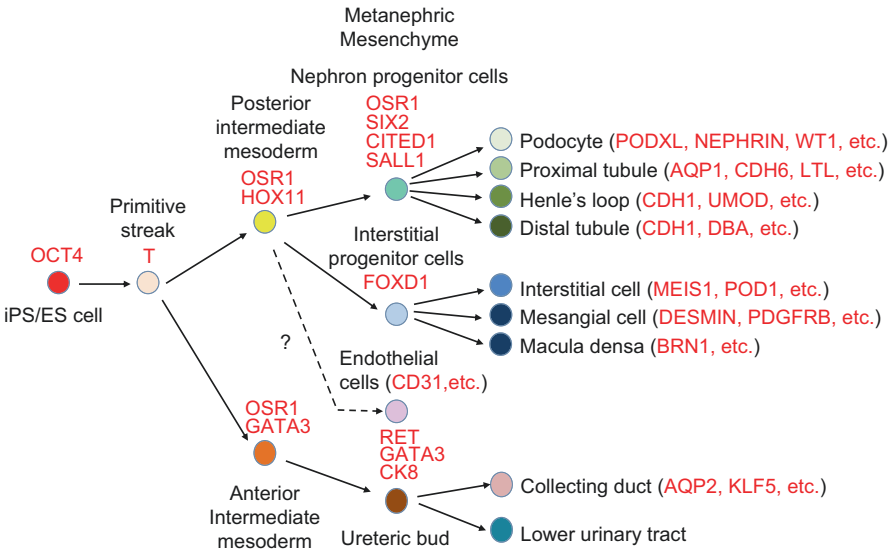

Fig. 24.1 Schema of kidney development and strategy to generate kidney lineage cells from iPS/ES cells. Marker genes in each differentiation step are shown in red

were found in teratomas formed by the transplantation of human ES cells into immunodeficient mice, demonstrating that kidney lineage cells can be generated from human pluripotent stem cells [6]. We reported that NPCs strongly expressing Sall1 in murine metanephric mesenchyme can reconstruct kidney tissues in vitro [18]. Finally, in 2008, lineage-tracing experiments revealed that SIX2(+) cells in the mouse metanephric mesenchyme are NPCs [19]. However, reliable methods to induce the differentiation of human iPS/ES cells into kidney tissues remained to be established.

Because the spatial distribution of NPCs and the developmental process of mouse kidney resemble those of human [20], embryonic mouse kidney is commonly used as a model to study the development of human kidney and differentiate kidney lineage cells from human iPS/ES cells (Fig. 24.1). Early lineage-tracing studies revealed that NPCs, ureteric bud (UB) cells, and stromal progenitor cells derived from an embryonic germ layer, intermediate mesoderm, become all constituent cells of the kidneys except blood vessels. The OSR1 gene was reported as a marker of the earliest intermediate mesoderm [21–23]. Song et al. for the first time succeeded in differentiating podocyte-like cells from human iPS cells by treatment with activin A, bone morphogenetic protein (BMP)7, and RA [24]. This report demonstrated that iPS cells have the potential to differentiate into kidney lineage cells. Focusing on this finding, we generated an OSR1-GFP reporter human iPS cell line, and OSR1(+) intermediate mesoderm cells were generated by treatment with activin A, a glycogen synthase kinase (GSK)3 inhibitor, CHIR99021, and BMP7 [25]. Furthermore, we succeeded in inducing OSR1(+) intermediate mesoderm cells by using only a combination of CHIR99021 and RA analogs, such as TTNPB and

AM580, without any growth factors [26]. Xia et al. succeeded in inducing the UB cells from human iPS cells and showed that the cells were incorporated in the mouse kidney developmental process under coculture with mouse embryonic kidneys [27].

Subsequent research has markedly advanced the generation of NPCs via intermediate mesoderm, and novel differentiation induction methods have been reported [28–34]. In particular, Taguchi et al. analyzed the mouse developmental process in detail and revealed that fertilized mouse egg first forms primitive streak on embryonic day (E)7.5, which then gives rise to two embryonic tissues, anterior intermediate mesoderm on E8.5, and posterior intermediate mesoderm on E9.5. The former forms UB on E11.5 through nephric (Wolffian) duct, while the latter forms metanephric mesenchyme on E11.5 [31]. Thus, the cell fate of intermediate mesoderm depends on the anterior and posterior domains. Takasato et al. reported the generation of kidney organoids including all nephron structures and collecting ducts from human iPS cells [35]. However, since kidney organoids differentiated from human iPS cells using current differentiation protocols are immature [35, 36], further differentiation and maturation is required through vascularization and the addition of physical stimuli, such as urinary flow and shear stress.

24.4 Therapeutic Effects of Human iPS Cell-Derived NPCs on AKI

Very few reports have evaluated the therapeutic effects of human iPS cell-derived NPCs on kidney diseases. In 2015, Imberti et al. reported that the intravenous administration of human iPS cell-derived NPCs to cisplatin-induced mouse acute kidney injury (AKI) models suppressed the elevation of blood urea nitrogen (BUN) and serum creatinine (Cre) levels [33]. In that report, it was suggested that intravenously injected NPCs reached the recipient mouse kidneys through the bloodstream and that the renal function was improved by the integration of the cells into the tubules. However, because the transplanted cells integrated only in part of the recipient's renal tubules, it was assumed that the therapeutic effects were not due to the integration of the transplanted NPCs but to the paracrine effects of humoral factors secreted from the NPCs.

We administered human iPS cell-derived OSR1(+)SIX2(+) NPCs generated from an OSR1-GFP/SIX2-tdTomato knockin human iPS cell line to the renal subcapsule of ischemia/reperfusion (I/R) injury-induced mouse AKI models with unilateral nephrectomy and observed the amelioration of renal function [34]. Moreover, we revealed that cell therapy using human iPS cell-derived NPCs not only improves renal function in the acute phase but also suppresses renal interstitial fibrosis in the subacute phase 12 days after I/R injury (Fig. 24.2 a–c). It has been recently reported that the renal interstitial fibrosis that develops after AKI causes CKD, and the importance of suppressing renal interstitial fibrosis after AKI has been recognized [37, 38]. The therapeutic effects of human iPS cell-derived NPCs on renal interstitial fibrosis after AKI are expected to contribute to the development of novel

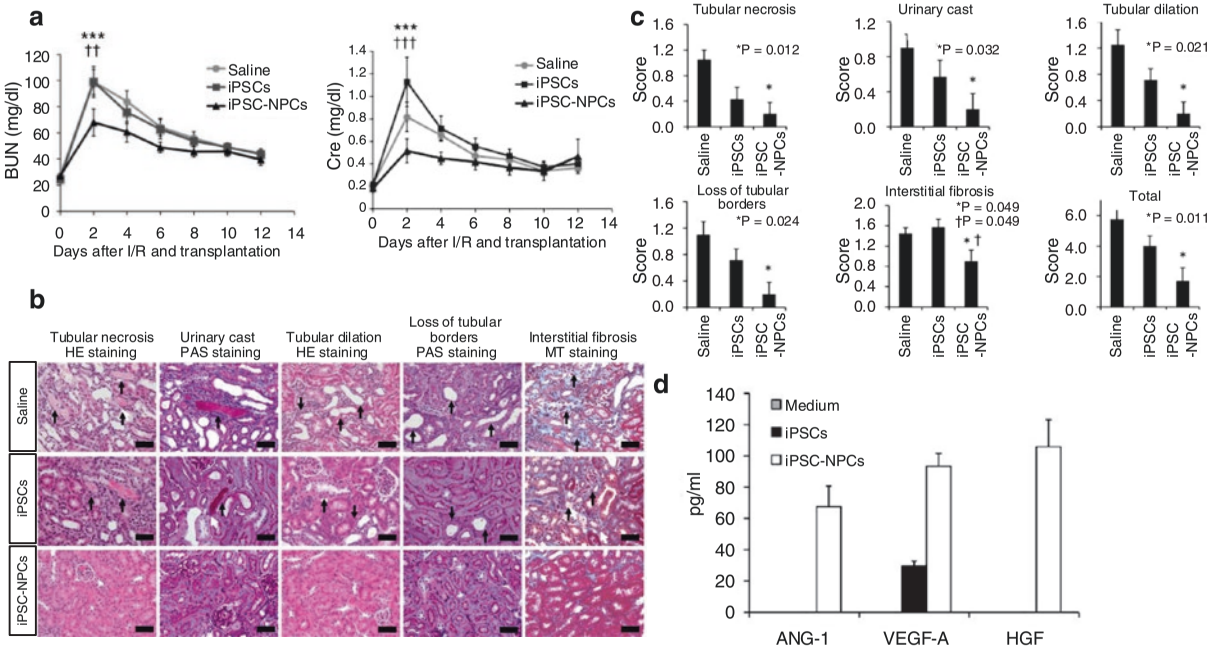

Fig. 24.2 Cell therapy using human iPS cell-derived nephron progenitor cells (NPCs) on acute kidney injury (AKI). (**a**) Serological assessment of the transplantation of human iPS cell-derived NPCs ($n = 6$, iPSC-NPCs, triangle) or undifferentiated hiPSCs ($n = 7$, iPSCs, square) or saline injection ($n = 11$, circle) in ischemia/reperfusion (I/R) injury-induced AKI model mice. *BUN* (blood urea nitrogen), *Cre* (serum creatinine). Statistical significance at the $P < 0.05$ level after multiple testing adjustment: $^{***}P < 0.001$ vs. saline.$^{\dagger\dagger}P < 0.01$ vs. iPSCs. $^{\dagger\dagger\dagger}P < 0.001$ vs. iPSCs. Least square means and 95% confidence intervals were estimated according to the mixed effects model for repeated measures. (**b**) Histological findings at 12 days after I/R injury and transplantation of human iPSCs or iPSC-NPCs or injection of saline in I/R injury-induced AKI mice. The arrows indicate the representative area of each finding. Scale bars: 20 μm. (**c**) Histological scoring of the areas with tubular necrosis, urinary casts, tubular dilatation, loss of tubular borders, interstitial fibrosis, and total scores in the host kidneys 12 days after the I/R injury and transplantation ($n = 5$ for iPSC-NPCs, $n = 7$ for iPSCs, $n = 7$ for saline). $^{*}P < 0.05$ vs. saline. $^{\dagger}P < 0.05$ vs. iPSCs. (**d**) The detection of secreted proteins using human magnetic luminex screening assay in medium only (medium) or cell culture supernatants of iPSCs or iPSC-NPCs. (adapted from [34])

therapeutic strategies to suppress the onset of CKD. In addition, when the therapeutic effects of purified OSR1(+)SIX2(+), OSR1(+)SIX2(−), OSR1(−)SIX2(+), and OSR1(−)SIX2(−) cell populations differentiated from the OSR1-GFP/SIX2-tdTomato reporter human iPS cells were compared, the OSR1(+)SIX2(+) cell population, which has developmental potential to form kidney structures, showed the most potent therapeutic effects on AKI [34]. Again, however, the therapeutic effects were attributed to paracrine effects because the transplanted human iPS cell-derived NPCs did not integrate into the recipient's kidneys, although the OSR1(+)SIX2(+) population did differentiate into renal tubule-like structures in the recipient renal subcapsule.

We then screened monoclonal antibodies for 242 different cell surface antigens in order to purify human iPS cell-derived OSR1(+)SIX2(+) NPCs without using reporter human iPS cell lines [39]. We found that OSR1(+)SIX2(+) NPCs were enriched when using the combination of CD9(−)CD140a(+)CD140b(+)CD271(+). Furthermore, we showed that the transplantation of human iPS cell-derived NPCs purified with this combination of surface markers to the renal subcapsule significantly inhibited the deterioration of renal function and interstitial fibrosis in I/R injury-induced mouse AKI models (Fig. 24.3) [39].

24.5 Expansion Culture of NPCs Derived from Mouse and Human Fetal Kidneys

In an attempt to establish expansion culture methods for NPCs, we focused on Six2-expressing cells because previous lineage-tracing studies showed that Six2 is a specific NPC marker [19, 40]. We used a mouse strain with a GFP cassette knocked-in to the Six2 locus (Six2-GFP mouse) [19] to facilitate the purification of Six2-GFP(+) NPCs from fetal kidneys by flow cytometry. When we cultured isolated Six2-GFP(+) NPCs with BFHY medium, which is a combination of BMP7, fibroblast growth factor (FGF) 9 or FGF2, heparin, and a ROCK inhibitor, Y-27632, based on previous findings that these factors facilitate the proliferation of NPCs [41, 42], we found Six2-GFP(+) NPCs proliferated for 7 days. Next, we screened 36 additional growth factors and chemical inhibitors in BFHY medium conditions using cell viability, growth rate, and the GFP signal as indicators to find the optimal medium conditions that maintain Six2-GFP(+) NPCs for more than 7 days. Through successive examinations, we established the Nephron Progenitor Self-Renewal (NPSR) medium, which includes an optimal combination of BMP7, FGF2, heparin, Y-27632, leukemia inhibitory factor (LIF), CHIR99021, an ALK4, 5, 7 kinase inhibitor, A83-01, and an ALK2, 3 kinase inhibitor, LDN193189. Using NPSR medium, we expanded Six2-GFP(+) NPCs over 150 passages for about 2 years. Furthermore, we succeeded in efficiently producing kidney organoids containing nephron structures by the combination of CHIR99021 and FGF2 (Fig. 24.4). We also observed remarkable therapeutic effects when the expanded mouse NPCs were

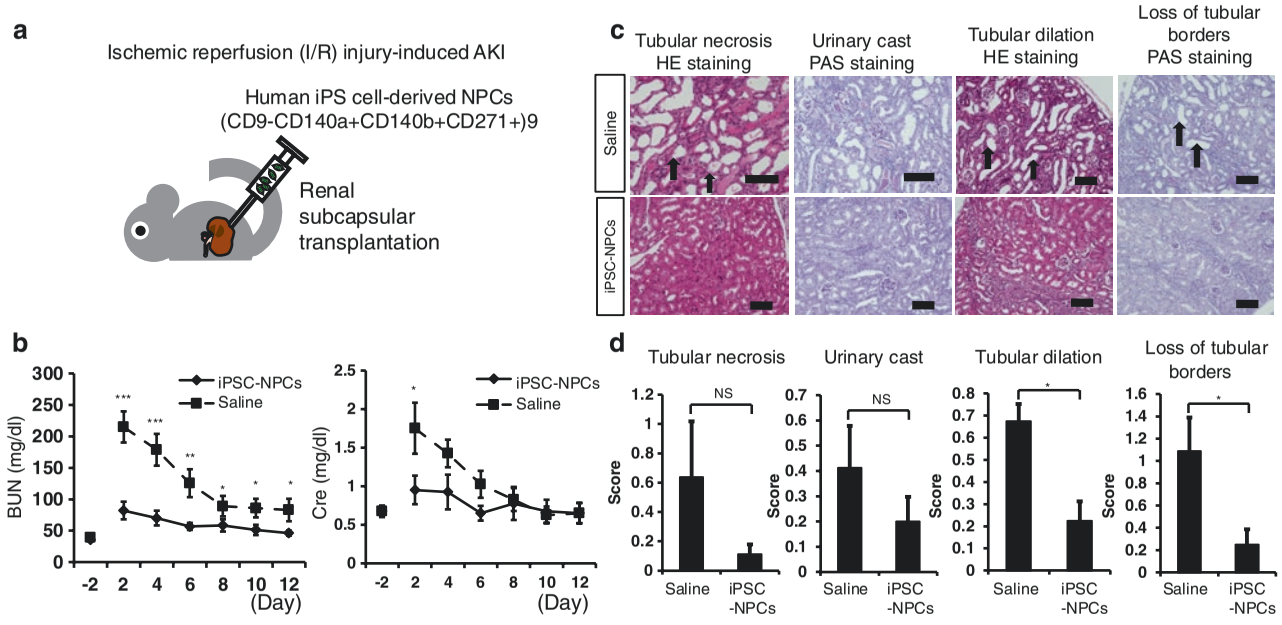

Fig. 24.3 Cell therapy using human iPS cell-derived CD9(−)CD140a(+)CD140b(+)CD271(+) cells on acute kidney injury (AKI). (**a**) Schema of cell therapy using human iPS cell-derived CD9(−)CD140a(+)CD140b(+)CD271(+) cells in ischemia/reperfusion (I/R) injury-induced AKI model mice. (**b**) Serological assessment of the transplantation of human iPS cell-derived CD9(−)CD140a(+)CD140b(+)CD271(+) cells ($n = 4$, iPSC-NPCs, diamond) or saline injection ($n = 4$, square). *BUN* blood urea nitrogen, *Cre* serum creatinine. Statistical significance: $^{***}P < 0.001$ vs. saline, $^{**}P < 0.01$ vs. saline and $^{*}P < 0.05$ vs. saline after multiple testing adjustment. Least square means and 95% confidence intervals were estimated according to the mixed effects model for repeated measures. (**c**) Histological findings at 12 days after I/R injury and injection of saline or transplantation of iPSC-NPCs in I/R injury-induced AKI mice. The arrows indicate representative areas of each finding. (**d**) Histological scoring of the areas with tubular necrosis, urinary casts, tubular dilatation, and loss of tubular borders in the host kidneys 12 days after I/R injury and transplantation ($n = 4$). Statistical significance: $^{*}P < 0.05$ vs. saline after multiple testing adjustment. Scale bars: 100 μm. (adapted from [39])

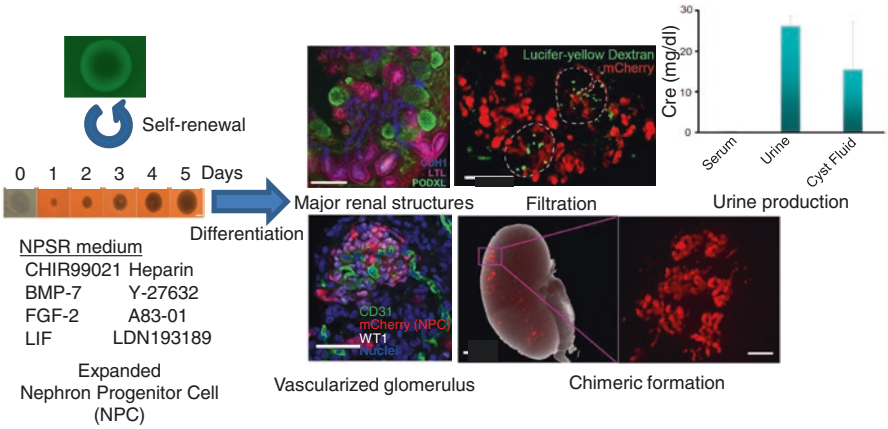

Fig. 24.4 The development of expansion culture conditions for mouse nephron progenitor cells (NPCs). NPCs derived from mouse embryonic kidneys can be maintained with NPSR (Nephron Progenitor Self-Renewal) medium for 2 years (more than 150 passages). The expanded NPCs can differentiate into functional kidney organoids in vivo with urine-producing capability. PODXL (Podocalyxin), WT1: podocyte marker, LTL (*Lotus tetragonolobus* lectin): proximal tubule marker, CDH1 (cadherin 1): Henle's loop or distal tubule marker, CD31: endothelial cell marker, DAPI: nuclei. Scale bars: 100 μm. (adapted from [20])

transplanted to the renal subcapsule of cisplatin-induced mouse AKI models (Fig. 24.5). Moreover, we successfully extracted NGFR(+)EPCAM(−) NPCs from 11-week-old human fetal kidneys and carried out maintenance culture for a long time using the same NPSR medium as in mouse. These human NPCs were also capable of forming kidney organoids [20].

24.6 Expansion Culture of Human iPS Cell-Derived NPCs

Because expanded mouse NPCs isolated from fetal kidneys and unexpanded human iPS cell-derived NPCs have therapeutic effects on AKI [20, 33, 34, 39], it is expected that expanded human iPS cell-derived NPCs will also have therapeutic effects on kidney diseases. However, standard expansion cultures for human iPS cell-derived NPCs have not been established. Brown et al. reported that human iPS cell-derived NPCs induced using Takasato's induction method could only be passaged twice with the combination of BMP7, FGF9, heparin, Y-27632, CHIR99021, LDN193189, BMP4, IGF1, and IGF2 [43]. Tanigawa et al. reported that human iPS cell-derived NPCs induced by their induction method could be expanded for only 8 days with the combination of TGFα, FGF2/9, LIF, Y-27632, CHIR99021, BMP7, and a γ-secretase inhibitor, DAPT [44]. The group also found that the LIF-activated Yap signal maintains NPC-specific genes, such as SIX2, PAX2, and SALL1. On the other hand, we expanded NPCs induced from a SIX2 reporter human iPS cell line by Taguchi's induction method for approximately 6 months with the combination of

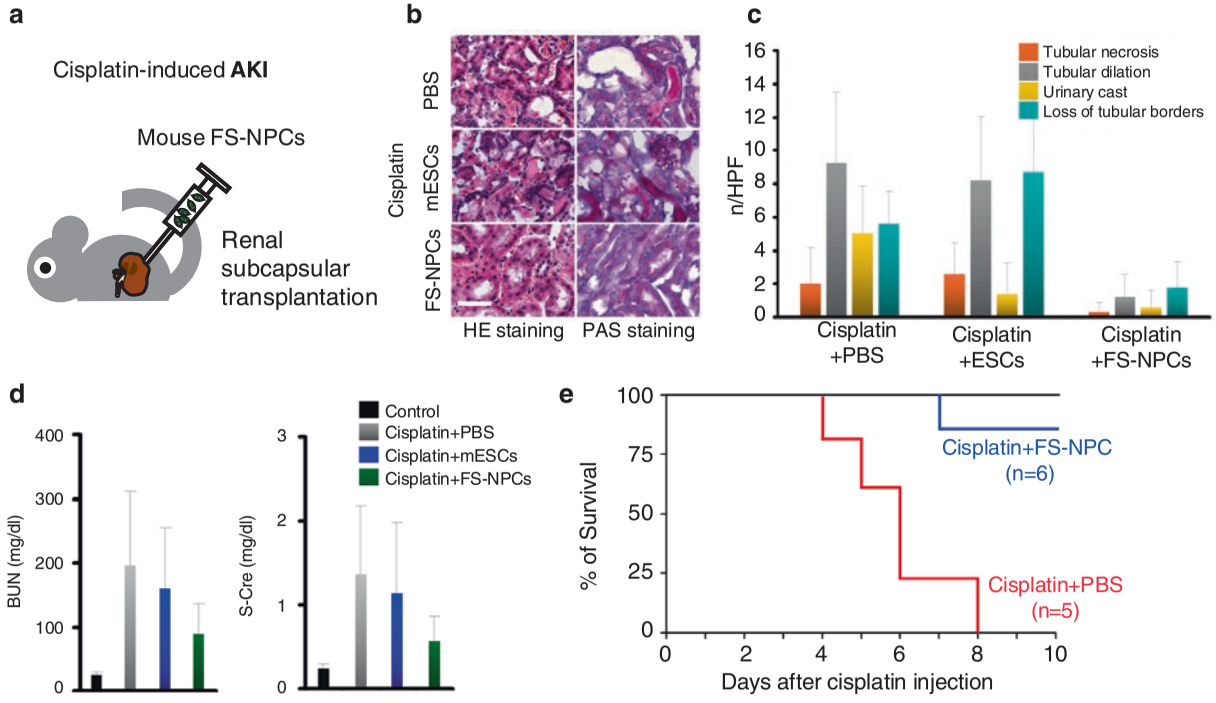

Fig. 24.5 Cell therapy using mouse nephron progenitor cells (mNPCs) on acute kidney injury (AKI). (**a**) Schema of cell therapy using fate specified (FS)-NPCs, which are mNPCs expanded in vitro and then induced with 1 μM CHIR99021 and 200 ng/mL FGF2 for 2 days, in cisplatin-induced AKI model mice. (**b**, **c**) Histological findings at 4 days after cisplatin administration and 3 days after the injection of PBS or transplantation of mESCs or FS-NPCs in cisplatin-induced AKI mice (**b**). Histological scoring of the areas with tubular necrosis, tubular dilatation, urinary casts, and loss of tubular borders in the host kidneys 4 days after cisplatin administration and 3 days after transplantation (**c**). (**d**) Serological assessment of the cell therapy using FS-NPCs at 4 days after cisplatin administration and 3 days after transplantation in cisplatin-induced AKI mice. *BUN* (blood urea nitrogen), *s-Cre* (serum creatinine). (**e**) Survival curve of cisplatin-induced AKI mouse groups that were injected with PBS or transplanted with FS-NPC. Scale bar: 50 μm. (adapted from [20])

BMP7, FGF2, heparin, Y-27632, CHIR99021, LIF, LDN193189, and A83-01. However, our expansion method for human iPS cell-derived NPCs is only applicable to a small number of human iPS cell lines, such as a SIX2 reporter human iPS cell line [20]. Further studies should establish expansion culture methods with broad applications for multiple human iPS/ES cell lines.

24.7 Therapeutic Effects on AKI by Paracrine Factors Secreted from NPCs

Mouse fetal kidney-derived NPCs transplanted into the kidney subcapsule of mouse AKI models show therapeutic effects without integrating into the renal parenchyma of recipient mice, which suggest that the therapeutic benefits result from the paracrine effects of humoral factors secreted from NPCs [20]. Accordingly, we induced expanded primary NPCs into kidney organoids without any exogenous growth factor or chemical compounds, and intraperitoneally administered the culture supernatant after 2 days of the differentiation into cisplatin-induced mouse AKI models. We observed amelioration of the serological and histological findings of AKI and a prolonged survival time [20]. Thus, the therapeutic effects were considered to be paracrine effects of the renal protective factors secreted from the transplanted cells. Future studies should identify the therapeutic factors secreted from NPCs through assays such as mass spectrometry.

In addition, we reported that the transplantation of human iPS cell-derived NPCs into the renal subcapsule resulted in the amelioration of renal injury in acute phase and suppression of renal interstitial fibrosis after AKI in I/R injury-induced mouse AKI models. By screening the proteins secreted from the human iPS cell-derived NPCs, we found previously reported renotrophic factors, such as angiopoietin-1 (ANG-1), vascular endothelial growth factor A (VEGF A), and hepatocyte growth factor (HGF) as candidates (Fig. 24.2d) [34].

24.8 Purification of Human iPS Cell-Derived NPCs

Recent advances in kidney regeneration research have enabled the induction of NPCs and UB cells from human iPS cells to generate kidney organoids [28–35, 45, 46]. However, the research field has not yet reached the levels of clinical application. In particular, since NPC differentiation cultures from human iPS cells contain off-target cell types, it is essential to develop purification methods for NPCs. These off-target cells are evident by the marked differences in the differentiation efficiency among different human iPS/ES cell lines [47, 48]. Searches for cell surface markers specifically expressed in NPCs have been conducted by multiple groups. We examined surface markers by RNA-sequencing of mouse fetal NPCs and found that NGFR(+)EPCAM(−) cells strongly expressed NPC-specific transcription factors,

such as Six2, Sall1, and Cited1 [20]. We also revealed that this combination of surface markers can extract human fetal NPCs. However, human iPS cell-derived NPCs induced by the Taguchi's method could not be extracted by this combination. This result indicates that the NPCs and kidney organoids generated from human iPS cells are different from human fetal NPCs and kidney, at least in terms of marker gene expressions [35, 49, 50]. This difference may limit human iPS cell-derived NPCs in clinical applications. Although Taguchi et al. reported that ITGA(+) PDGFRA(−) cells in mouse metanephric mesenchyme represent NPCs [31], this marker combination does not appear to have sufficient selectivity for human iPS cell-derived NPCs [20]. It was also reported that the marker combination of ROBO2(+)PDGFRB(−)MAFB(−) can extract mouse NPCs [51]. However, it remains unknown whether this combination is applicable to human iPS cell-derived NPCs. On the other hand, we succeeded in enriching OSR1(+)SIX2(+) cells induced from human iPS cells with our differentiation method using the marker combination CD9(−)CD140a(+)CD140b(+)CD271(+) [39]. However, the purity of NPCs is still low, and the method has not been confirmed in multiple human iPS/ES cell lines.

24.9 Discussion

In order to realize regenerative treatments of kidney diseases using human iPS cell-derived NPCs, several hurdles must be overcome, such as the development of purification and expansion culture methods for NPCs, the optimization of NPC delivery systems, and the mechanistic elucidation of therapeutic effects. NPC differentiation cultures from human iPS cells contain heterogenous cell populations [49]. For the transplantation of human iPS cell-derived cell types at clinical levels, it is essential to thoroughly remove undifferentiated iPS cells and other contaminating cells in order to avoid adverse effects such as tumor formation. Furthermore, NPCs and kidney organoids induced from different human iPS/ES cell lines and different experiments show different gene and protein expression levels [34, 35, 49, 50, 52]. Therefore, it is difficult to generate homogeneous NPCs of uniform quality. In addition, there may be differences in both the quality and quantity of the paracrine factors secreted by the human iPS cell-derived NPCs generated from different induction methods. Hence, efficient purification methods are needed. Single-cell analyses of human fetal kidneys could potentially identify new cell surface markers applicable to human iPS cell-derived NPCs [35, 36]. In addition, probes for the transcription factor SIX2 [53] and RNA switches targeting microRNA specifically expressed in human iPS cell-derived NPCs [54] could be used to purify human NPCs.

The establishment of purification methods for NPCs would in turn contribute to the development of expansion culture methods for human iPS cell-derived NPCs, since higher purity should result in NPCs with higher self-renewal capacity like that seen in primary human NPCs [20]. Therefore, both purification and expansion methods depend on technologies that can characterize which cell population has the best self-renewal capacity.

These same methods will also need to consider cost. Transplanting 6.0×10^6 mouse NPCs to the kidney subcapsule of recipient mice has ameliorative effects (Fig. 24.5). When this therapy is translated to human size by weight, approximately 2000 times as many cells (1.2×10^{10} cells) are required for clinical use. When such large amounts of cells are extracted from human iPS cell-derived NPCs with flow cytometry using cell surface markers, the cell therapy cost will increase because of growth factors and chemical compounds used in the NPC differentiation of human iPS cells and antibodies for the flow cytometry. Therefore, purification and expansion culture methods that mainly use small molecules will make these treatments cost-efficient.

At the same time, attempts have already been made to reconstruct large-scale kidney tissues by preparing optimal scaffolds for NPCs. There are several reports describing how NPCs mature and organize into kidney tissues by seeding them inside the scaffolds composed of extracellular matrices remaining after kidney decellularization [55]. In addition, another report described three-dimensional (3D) kidney tissues artificially generated with a 3D printer that might be applicable to NPCs [56]. Finally, organ-on-a-chip technology was used to reproduce mature nephron structures for drug screening by combining the kidney organoids with a vascular network constituted of endothelial cells [57]. By fusing different research fields, it is expected that kidney regeneration research will substantially proceed.

Another hurdle before realizing clinical applications of human iPS cell-derived NPCs is to establish an in vivo delivery system. Candidate approaches include intravascular injection, renal subcapsular transplantation, subcutaneous transplantation, direct administration to the renal parenchyma, and retrograde urinary injection. The intravascular approach may allow a fraction of NPCs to reach the recipient kidneys, as Imberti et al. showed [33]. However, there is the risk of unexpected complications because most cells injected via blood vessels may distribute to other organs. Furthermore, the risk of developing thrombosis should be considered. Direct administration to the renal parenchyma has the risk of massive hemorrhage, which could cause the transplanted cells to flow out of the kidneys. Indeed, we observed that most NPCs directly administered to the renal parenchyma of recipient mice flowed out by bleeding [34]. Retrograde urinary injection may be an excellent method for cell transplantation because it is a closed system that only involves the kidneys and lower urinary tract. However, if the ability of the recipient's kidneys to produce urine is sufficient, the injected cells may be flushed out by the urine flow. Although retrograde urinary injection may be applicable to patients with end-stage renal disease (ESRD) who have lost their ability to produce urine, it is necessary to test whether the human iPS cell-derived NPCs have not only renotrophic effects but also the ability to regenerate the degraded kidneys. Therefore, subcutaneous transplantation or renal subcapsular transplantation may have the best therapeutic benefits of paracrine effects with the fewest complications caused by cell transplantation. Subcutaneous transplantation has already been established clinically, and its safety has been confirmed in parathyroid gland autotransplantation after parathyroidectomy for dialysis patients [58]. Therefore, it may be the most suitable method for

transplantation of human iPS cell-derived NPCs. However, when the paracrine factors secreted by human iPS cell-derived NPCs in subcutaneous tissues pass into the general circulation, the serum concentrations of these factors may decrease, which reduces the therapeutic effects on renal injury. Renal subcapsular transplantation has an advantage in that high concentrations of paracrine factors directly act on the recipient kidneys. However, renal subcapsular transplantation risks more damage to the recipient kidneys than other approaches. Preclinical studies using large-sized animals, such as pigs and monkeys, would help clarify the best delivery technique.

Finally, identification of the paracrine factors responsible for the therapeutic effects on AKI by NPCs for drug development could avoid the complications associated with cell transplantation. However, systemic administration of the identified paracrine factors could significantly increase the cost of treatment and cause adverse effects on other organs. Future works revealing the signaling pathways downstream of the identified paracrine factors might allow us to find innovative and inexpensive therapeutic agents for kidney diseases.

In conclusion, recent advances in kidney regeneration research have enabled the directed differentiation of human iPS cells into NPCs with the developmental capability to reconstruct kidney organoids containing nephron-like tissues. In addition, multiple groups including ours have found that cell therapies using human iPS cell-derived NPCs ameliorate AKI in mice mainly by paracrine effects. Future studies should establish the purification and expansion culture methods for human iPS cell-derived NPCs to advance cell therapies, disease modeling, drug development, and reconstruction of large-scaled functional kidney tissues.

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References

1. Coresh J. Prevalence of chronic kidney disease in the United States. JAMA. 2007;298:2038–47.
2. Japan nephrology society. [Special issue: Clinical practice guidebook for diagnosis and treatment of chronic kidney disease 2012 (CKD guideline 2012)]. Nihon Jinzo Gakkai Shi. 2012;54:1034–191.
3. Lysaght MJ. Maintenance dialysis population dynamics: current trends and long-term implications. J Am Soc Nephrol. 2002;13(suppl 1):S37–40.
4. Nitta K. 2018 Annual Dialysis Data Report, JSDT Renal Data Registry. Nihon Toseki Igakkai Zasshi. 2019;52:679–754.
5. Evans MJ, Kaufman MH. Establishment in culture of pluripotential cells from mouse embryos. Nature. 1981;292:154–6.

6. Thomson JA. Embryonic stem cell lines derived from human blastocysts. Science. 1998;282:1145–7.
7. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell. 2006;126:663–76.
8. Takahashi K. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell. 2007;131:861–71.
9. Yu J. Induced pluripotent stem cell lines derived from human somatic cells. Science. 2007;318:1917–20.
10. Okita K. A more efficient method to generate integration-free human iPS cells. Nat Methods. 2011;8:409–12.
11. Okita K. An efficient nonviral method to generate integration-free human-induced pluripotent stem cells from cord blood and peripheral blood cells. Stem Cells. 2013;31:458–66.
12. Takeda Y. Chemical compound-based direct reprogramming for future clinical applications. Biosci Rep.2018;38.
13. Karagiannis P. Induced pluripotent stem cells and their use in human models of disease and development. Physiol Rev. 2019;99(1):79–114.
14. Mandai M. Autologous induced stem-cell-derived retinal cells for macular degeneration. N Engl J Med. 2017;376:1038–46.
15. Kikuchi T. Human iPS cell-derived dopaminergic neurons function in a primate Parkinson's disease model. Nature. 2017;548:592–6.
16. Hino K. Activin-A enhances mTOR signaling to promote aberrant chondrogenesis in fibrodysplasia ossificans progressiva. J Clin Invest. 2017;127:3339–52.
17. Moriya N. Mesoderm and neural inductions on newt ectoderm by activin A. Dev Growth Differ. 1992;34:589–94.
18. Osafune K. Identification of multipotent progenitors in the embryonic mouse kidney by a novel colony-forming assay. Development. 2006;133:151–61.
19. Kobayashi A. Six2 defines and regulates a multipotent self-renewing nephron progenitor population throughout mammalian kidney development. Cell Stem Cell. 2008;3:169–81.
20. Li Z. 3D culture supports long-term expansion of mouse and human nephrogenic progenitors. Cell Stem Cell. 2016;19:516–29.
21. Mugford JW. Osr1 expression demarcates a multi-potent population of intermediate mesoderm that undergoes progressive restriction to an Osr1-dependent nephron progenitor compartment within the mammalian kidney. Dev Biol. 2008;324:88–98.
22. James RG. Odd-skipped related 1 is required for development of the metanephric kidney and regulates formation and differentiation of kidney precursor cells. Development. 2006;133:2995–3004.
23. Tena JJ. Odd-skipped genes encode repressors that control kidney development. Dev Biol. 2007;301:518–31.
24. Song B. The directed differentiation of human iPS cells into kidney podocytes. PLoS One. 2012;7:e46453.
25. Mae SI. Monitoring and robust induction of nephrogenic intermediate mesoderm from human pluripotent stem cells. Nat Commun. 2013;4:1367.
26. Araoka T. Efficient and rapid induction of human iPSCs/ESCs into nephrogenic intermediate mesoderm using small molecule-based differentiation methods. PLoS One. 2014;9:e84881.
27. Xia Y. Directed differentiation of human pluripotent cells to ureteric bud kidney progenitor-like cells. Nat Cell Biol. 2013;15:1507–15.
28. Takasato M. Directing human embryonic stem cell differentiation towards a renal lineage generates a self-organizing kidney. Nat Cell Biol. 2014;16:118–26.
29. Lam AQ. Rapid and efficient differentiation of human pluripotent stem cells into intermediate mesoderm that forms tubules expressing kidney proximal tubular markers. J Am Soc Nephrol. 2014;25:1211–25.

30. Kang M. Differentiation of human pluripotent stem cells into nephron progenitor cells in a serum and feeder free system. PLoS One. 2014;9:e94888.
31. Taguchi A. Redefining the in vivo origin of metanephric nephron progenitors enables generation of complex kidney structures from pluripotent stem cells. Cell Stem Cell. 2014;14:53–67.
32. Morizane R. Nephron organoids derived from human pluripotent stem cells model kidney development and injury. Nat Biotechnol. 2015;33:1193–200.
33. Imberti B. Renal progenitors derived from human iPSCs engraft and restore function in a mouse model of acute kidney injury. Sci Rep. 2015;5:8826.
34. Toyohara T. Cell therapy using human induced pluripotent stem cell-derived renal progenitors ameliorates acute kidney injury in mice. Stem Cells Transl Med. 2015;4:980–92.
35. Takasato M. Kidney organoids from human iPS cells contain multiple lineages and model human nephrogenesis. Nature. 2015;526:564–8.
36. Lindström NO. Conserved and divergent features of human and mouse kidney organogenesis. J Am Soc Nephrol. 2018;29:785–805.
37. Coca SG. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. Kidney Int. 2012;81:442–8.
38. Takaori K. Severity and frequency of proximal tubule injury determines renal prognosis. J Am Soc Nephrol. 2016;27:2393–406.
39. Hoshina A. Development of new method to enrich human iPSC-derived renal progenitors using cell surface markers. Sci Rep. 2018;8:6375.
40. Self M. Six2 is required for suppression of nephrogenesis and progenitor renewal in the developing kidney. EMBO J. 2006;25:5214–28.
41. Barak H. FGF9 and FGF20 maintain the stemness of nephron progenitors in mice and man. Dev Cell. 2012;22:1191–207.
42. Dudley AT. Interaction between FGF and BMP signaling pathways regulates development of metanephric mesenchyme. Genes Dev. 1999;13:1601–13.
43. Brown AC. A synthetic niche for nephron progenitor cells. Dev Cell. 2015;34:229–41.
44. Tanigawa S. Selective in vitro propagation of nephron progenitors derived from embryos and pluripotent stem cells. Cell Rep. 2016;15:801–13.
45. Mae S, Ryosaka M. Generation of branching ureteric bud tissues from human pluripotent stem cells. Biochem Biophys Res Commun. 2018;495:954–61.
46. Taguchi A. Higher-order kidney organogenesis from pluripotent stem cells. Cell Stem Cell. 2017;21:730–746.e6.
47. Osafune K. Marked differences in differentiation propensity among human embryonic stem cell lines. Nat Biotechnol. 2008;26:313–5.
48. Kajiwara M. Donor-dependent variations in hepatic differentiation from human-induced pluripotent stem cells. Proc Natl Acad Sci U S A. 2012;109:12538–43.
49. Wu H. Comparative analysis and refinement of human PSC-derived kidney organoid differentiation with single-cell transcriptomics. Cell Stem Cell. 2018;23:869–81.
50. Alexander N. Combes, Luke Zappia, Pei Xuan Er, Alicia Oshlack, Melissa H. Little. Single-cell analysis reveals congruence between kidney organoids and human fetal kidney. Genome Medicine. 2019;11:(1).
51. Yoshimura Y. Manipulation of nephron-patterning signals enables selective induction of podocytes from human pluripotent stem cells. J Am Soc Nephrol. 2019;30:304–21.
52. Fukuda T. Isolation and expansion of human pluripotent stem cell-derived hepatic progenitor cells by growth factor defined serum-free culture conditions. Exp Cell Res. 2017;352:333–45.
53. Da Sacco SA. Direct isolation and characterization of human nephron progenitors. Stem Cells Transl Med. 2017;6:419–33.
54. Miki K. Efficient detection and purification of cell populations using synthetic microRNA switches. Cell Stem Cell. 2015;16:699–711.
55. Song JJ. Regeneration and experimental orthotopic transplantation of a bioengineered kidney. Nat Med. 2013;19:646–51.

56. Homan KA. Bioprinting of 3D convoluted renal proximal tubules on perfusable chips. Sci Rep. 2016;6:34845.
57. Musah S. Mature induced-pluripotent-stem-cell-derived human podocytes reconstitute kidney glomerular-capillary-wall function on a chip. Nat Biomed Eng.2017;1.
58. Welk RA. A community hospital experience with total parathyroidectomy and autotransplantation for renal hyperparathyroidism. Am Surg. 1987;53:622–7.

Chapter 25
Kidney Development and Injury: A Road to Regeneration

Shankhajit De and Ryuichi Nishinakamura

Abstract Proximal tubular epithelial cells (PTECs) are the major cellular targets of acute kidney injury (AKI). PTECs, as well as epithelial cells in glomeruli and distal tubules, are derived from nephron progenitors that exist in the embryonic kidney. However, nephron progenitors disappear around birth by terminal differentiation, meaning that mechanisms of repair following AKI will be different from those during development. Although some developmental genes are re-expressed in experimental AKI models, most PTECs are replaced by surviving mature epithelial cells and the functions of genes in these cells can differ from their developmental functions. Recent progresses in stem cell biology have enabled in vitro generation of kidney organoids from human-induced pluripotent stem cells (iPSCs), and the PTECs in the organoids exhibit some functional features. However, kidney organoids are immature and selective PTEC induction has not been established. In this chapter, we discuss the recent findings regarding AKI from the viewpoint of developmental nephrology and the hurdles to overcome in the treatment of AKI and eventual kidney failure.

Keywords iPS cells · Nephron progenitor · Sox9 · Wnt · BMP · Notch

25.1 Introduction: Overview of Kidney Development

Mammalian kidney development involves the formation of three distinct primordia – the pronephros, mesonephros, and metanephros – in an anterior-to-posterior direction along the embryonic body trunk. Most of the pro- and mesonephros structures degenerate during gestation; however, the metanephros differentiates into the adult kidney. At the initial stage of metanephros formation, ureteric buds (UBs)

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invade the metanephric mesenchyme (MM) and a reciprocal inductive interaction leads to further branching of the UB and formation of nephrons from the MM [1]. The MM contains nephron progenitors, which give rise to the epithelia of the glomeruli, proximal tubules, loops of Henle, and distal tubules [2, 3]. The UBs contribute to collecting ducts and the ureter. Meanwhile, some nephron progenitors are maintained during development and continue to contribute to the formation of new nephrons. However, all the nephron progenitors disappear around birth (at approximately 34 weeks of gestation in humans and within a few days after birth in mice) by terminal differentiation [4]. Therefore, the adult kidney does not contain bona fide nephron progenitors, which can explain the poor regenerative capacity of the adult kidney. Although proximal tubular epithelial cells (PTECs) regenerate after acute kidney injury (AKI), nephron progenitors defined by developmental nephrology are unlikely to participate in the recovery processes.

25.2 Nephrogenesis from Nephron Progenitors

In metanephros development, MM secretes glial cell line-derived neurotrophic factor (GDNF), which attracts UBs toward the MM via signaling through RET receptors on UBs [5]. In turn, UBs secrete Wnt9b, which converts mesenchymal nephron progenitors in the MM to epithelial cells (mesenchymal-to-epithelial transition: MET) (Fig. 25.1). The cells undergoing MET secrete Wnt4, which further

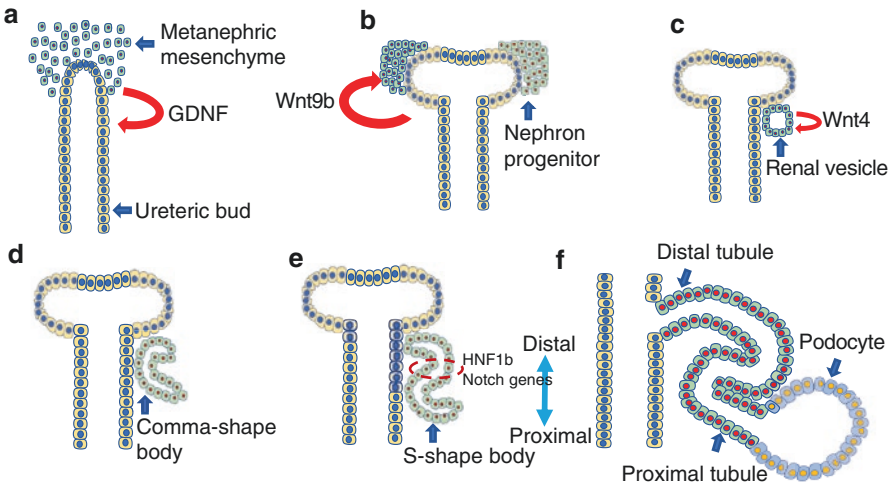

Fig. 25.1 Kidney development from nephron progenitors. Nephron progenitors in the metanephric mesenchyme (**a**, **b**), differentiate into renal vesicles (**c**), comma-shaped bodies (**d**), S-shaped bodies (**e**), and finally form nephron epithelia (**f**). The most proximal end of an S-shaped body forms the glomerulus, the proximal/intermediate domain forms the proximal tubule and the loop of Henle, and the distal domain forms the distal renal tubule (**e, f**). Meanwhile, the ureteric bud branches to form collecting ducts

accelerates the MET process, and form epithelial cysts, also called renal vesicles (RVs). Subsequently, each RV elongates in a cortico-medullary direction to form an S-shaped body; the proximal end becomes the glomerulus, the middle part becomes the proximal renal tubule, while the distal end forms the distal renal tubule. The Wnt signaling gradient plays an important role in this proximal-distal patterning of nephrons [6]. Single-cell RNA sequencing (scRNA-seq) of mouse embryonic kidneys showed that the RVs are already specified into proximal-distal domains in terms of gene expression [7]. Furthermore, scRNA-seq of human embryonic kidneys combined with temporal analyses of nephrogenic lineages revealed that the timing of nephron progenitor recruitment to the vicinity of the Wnt source (UB) directs fate along the proximal-distal axis; the early recruited cells differentiate into distal tubule cells whereas the last cells to be recruited become glomerular podocytes [8].

Along with canonical Wnt signaling, other signaling pathways, such as Notch, play important roles in nephrongenesis [6]. Notch2 deletion in mice leads to impaired S-shape body formation and eventually loss of glomeruli and proximal tubules [9]. It was also proposed that Notch specifies proximal fate in RVs and S-shaped bodies. However, Notch2 activation did not alter cell fate toward proximal nephron structures (glomerulus and proximal tubule) but rather resulted in severe kidney dysgenesis, probably because of a depletion of nephron progenitor cells [10]. More recent studies indicate that Notch signaling primes initial epithelialization of nephron progenitors, rather than specifying the proximal fate [11, 12].

The transcription factor, HNF1b, is expressed in the proximal/intermediate domains of S-shaped bodies and its deletion results in absence of proximal tubules and loops of Henle [13, 14]. Expression of Notch pathway components, including Dll1, Jag1, and Lfng, is reduced after Hnf1b deletion, indicating that Hnf1b lies upstream of the Notch pathway. In contrast, Hnf4a is not required for initial development of proximal tubules but is essential for formation of differentiated PTECs [15]. Thus, deletion of Hnf4a results in the loss of proximal tubule-specific genes and eventually manifests as Fanconi syndrome, which displays excess excretion of water, phosphate, and glucose in the urine. These observations are consistent with the presence of binding sites for HNF4a in a variety of drug-metabolizing enzymes and transporters in proximal tubules [16].

25.3 Proliferation of Resident Tubular Cells Contributes to Recovery from AKI

Among the various segments of nephrons, PTECs are the most vulnerable to AKI. After ischemia-reperfusion injury (IRI) in mice, tubular proliferation occurs within 24–48 h, and the epithelial morphology is restored within 5–7 days, leaving almost no evidence of injury. It is controversial whether this prompt and efficient tissue repair results from compensation by local or exogenous adult-stage progenitors or from proliferation of the residual tubular epithelial cells. Although administration of bone marrow-derived stromal cells in a cisplatin-induced AKI mouse

model showed increased proliferation and decreased death of PTECs, the administered cells did not contribute to PTECs directly and the effects were likely to be mediated by their secreted factors (paracrine effect) [17].

In a study using chimeric mice subjected to IRI, Duffield et al. ruled out a contribution from the bone marrow-derived stem cell population in PTEC repair [18]. When all nephron epithelia in mice were genetically labeled with reporter genes, extensive proliferation of the labeled cells was observed during recovery from IRI [19]. Importantly, there was no dilution of the labeling, indicating that proliferation of the surviving labeled PTECs, and not recruitment of non-labeled stem/progenitor cells outside of the nephron epithelia, is the predominant mechanism for repair from AKI (Fig. 25.2). However, the possibility of the existence of intratubular stem/progenitor cells remained. Thus Kusaba et al. generated mice expressing CreERT2 in mature PTECs under the sodium-dependent inorganic phosphate transporter (Slc34a1) promoter and confirmed that unlabeled intratubular progenitors do not contribute to kidney repair [20]. The labeled mature PTECs proliferated to form clones and expressed putative stem cell markers, such as CD24, CD133, vimentin, and KIM1, indicating that proliferation of terminally differentiated PTECs is the major mechanism for repair and that they simply re-express apparent stem cell markers during the repair process. Another independent study using genetic labeling also supports this conclusion that regeneration of PTECs after injury occurs from any surviving cells and that there are no fixed intratubular progenitors [21].

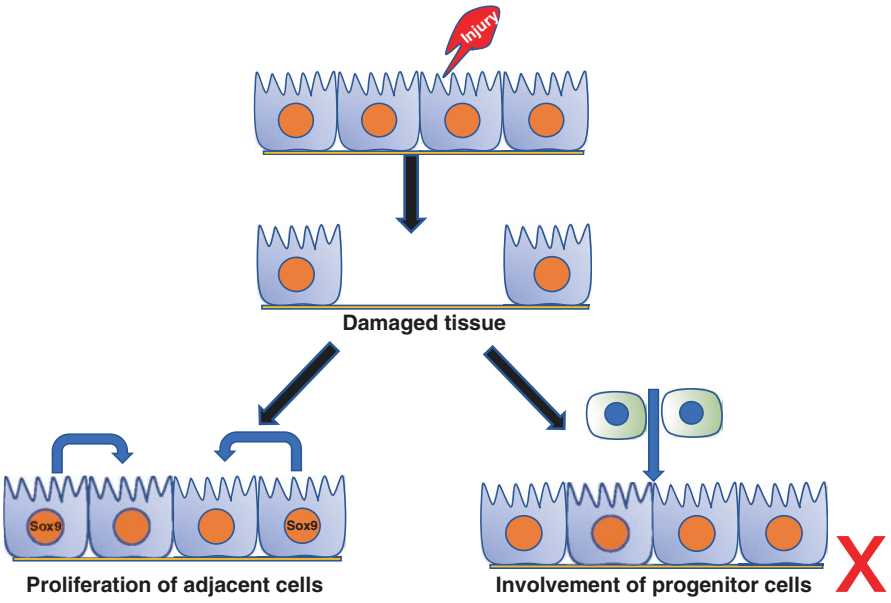

Fig. 25.2 Proliferation of resident tubular cells contributes to recovery from AKI. Mature surviving PTECs, which express Sox9, and not exogenous progenitors, contribute to repair from AKI. BMP signaling supports recovery from AKI, while excessive Wnt and Notch signaling exacerbate AKI

25.4 Excessive Wnt Signaling Exacerbates AKI

Among the many genes induced during injury, some are known to be involved in embryonic kidney development. Wnt4 is involved in MET of nephron progenitors in kidney development but is also expressed in the medullary stroma and controls smooth muscle fate [22]. In a rat AKI model, Wnt4 mRNA levels in the kidney were increased within 6 h after IRI [23]. By using an anti-Wnt4 antibody, the authors concluded that proximal tubules expressed Wnt4. However, this could result from nonspecific staining by the antibody. DiRocco et al. used Wnt4 Cre-dependent reporter mice to show that proliferating medullary interstitial myoblasts, but not PTECs, expressed Wnt4 in two injury models: IRI and unilateral ureter obstruction. Constitutive activation of Wnt/β-catenin signaling in interstitial pericytes and fibroblasts resulted in myofibroblast differentiation without injury, indicating the importance of the Wnt pathway in renal fibrosis [24]. However, conditional deletion of Wnt4 in interstitial cells did not reduce myofibroblast proliferation or gene expression during fibrosis, which may be because of compensation from other Wnt ligands. In a recent study, fibroblast-specific beta-catenin knockout mice subjected to IRI showed milder kidney symptoms with reduced apoptosis and increased cell proliferation. These protective activities may be mediated by hepatocyte growth factor [25], but direct in vivo evidence has not been demonstrated. Taken together, inhibition of excessive Wnt signal from interstitial cells is beneficial for recovery from AKI, while MET of injured PTECs is unlikely to be involved.

25.5 Excessive Notch Signaling Exacerbates AKI

The necessity of Notch signaling in normal kidney development is described above. In a rat IRI model, Notch signaling molecules (Dll1, cleaved Notch2 and Hes1) were upregulated in the injured proximal tubules [26]. Conditional activation of Notch signaling in proximal tubules aggravated tubular damage, while treatment of wild-type mice with the Notch inhibitor reduced the damage [27]. It was reported recently that Notch3-deficient mice were protected against IRI compared with control mice, while Notch3 activation in renal epithelial cells exacerbated infiltration of inflammatory cells. The authors argued that Notch3 in the injured renal epithelia sustained a proinflammatory environment and attracted activated macrophages to the injured sites [28]. While the mechanisms should be examined in more detail, the roles of Notch signaling are apparently different from those in kidney development, and inhibition of excessive Notch activation is beneficial for recovery from AKI.

25.6 BMP Signaling Supports Recovery from AKI

BMP7 is essential for kidney development but also exerts protective effects in AKI or renal fibrosis models [29, 30]. The expression of BMP receptor 1A is elevated after AKI injury and its conditional deletion in PTECs results in enhanced

TGFβ-Smad3 signaling leading to epithelial damage and fibrosis. Administration of a synthetic peptide agonist, THR-123, which functions through BMP receptor 1A, resulted in suppressed inflammation, apoptosis, and EMT [31]. Vigolo et al. found that canonical BMP-Smad1/5/8 signaling is active in adult renal tubules, transiently downregulated upon IRI, and then restored during the recovery phase [32]. Mice with renal tubule-specific deletion of BMP receptor 1A in the recovery phase after injury failed to phosphorylate Smad1/5/8 or induce their target genes (Id1/2/4), resulting in renal fibrosis. Thus canonical BMP signaling in tubular cells is likely to repress the pro-fibrotic response during recovery from AKI. However, the BMP7 agonist, THR-184, was ineffective in preventing postoperative kidney complications, in a randomized, double-blind, placebo-controlled clinical study of 452 patients with cardiac injury, who were at risk of AKI [33]. These data indicate that activation of BMP signaling alone may not be sufficient for preventing complicated AKI cases in humans.

25.7 SOX9 Activation in PTECs Is Required for Recovery from AKI

Conditional knockout of transcription factor genes, Sox8 and Sox9, revealed that they are required for UB branching, and double Sox8/9 knockout mice showed hypoplastic kidneys or renal agenesis [34]. SOX8/9 are required downstream of GDNF for the activation of Ret effector genes in UBs. Sox9 is also expressed in the S-shaped bodies, and conditional Sox8/9 KO mouse mutants showed a marked reduction of proximal and distal nephron segments around birth [35].

Sox9 is highly upregulated within 24 h of AKI model induction in mice and SOX9^{+} cells contribute extensively to the repair of proximal tubules [35]. Surviving mature PTECs undergo de novo activation of Sox9 and proliferate rapidly, contributing majorly to tissue repair (Fig. 25.2). After the recovery of renal functions, some regional SOX9 activity in PTECs is observed, displaying long-term repair responses. Furthermore, PTEC-specific deletion of Sox9 impairs recovery from AKI. Another group also reported that Sox9+ cells contributed to kidney repair and that Sox9 deletion impairs recovery [36]. Thus Sox9 activation is required for kidney repair. Identification of molecular events up and downstream of Sox9 will help elucidate the mechanisms underlying recovery from AKI.

25.8 Directed Reprogramming of Renal Tubules

We have discussed involvement of developmental genes in AKI, but cell therapy is an alternative strategy to treat AKI. Direct reprograming, which converts fibroblasts to nephron epithelial cells, is one option for cell therapy (Fig. 25.3). Forced expression of four transcription factors – Emx2, Hnf1b, Hnf4a and Pax8, all of which play

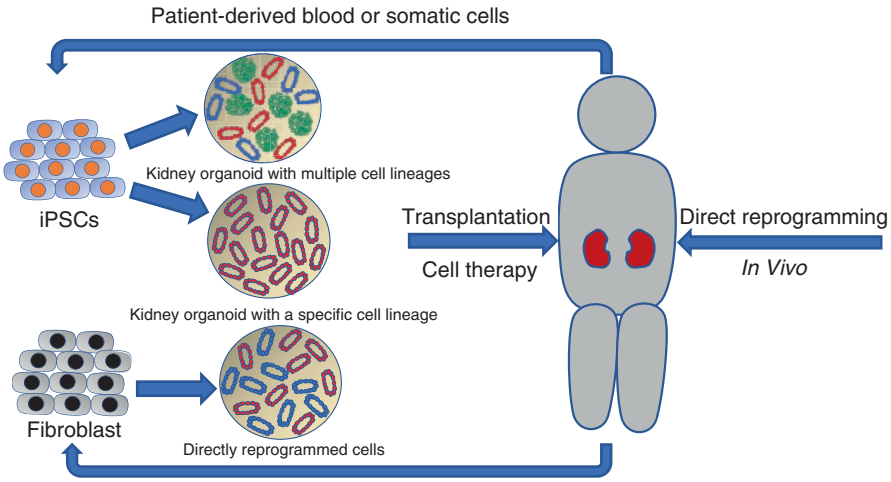

Fig. 25.3 Regenerative medicine strategies for renal failure. iPSCs are induced toward kidney organoids with multiple lineages and transplanted into patients. When a specific cell type is induced, integration into the resident nephrons is necessary. Direct reprogramming of a specific cell type in vitro and in vivo are alternative options, but integration into the residual nephrons is needed

important roles in renal tubule development – converts mouse fibroblasts into renal tubule epithelium-like cells in vitro [37]. These induced cells show similar gene expression to renal tubules and exhibit selective sensitivity to nephrotoxic substances, such as cisplatin. The induced cells participated in tubule formation when aggregated with mouse embryonic kidney cells. The same four transcription factors also converted human fibroblasts to renal tubule-like cells, and their gene expression pattern partially resembled that of the in vivo kidney. Nonetheless, the induced mouse and human cells appeared to be heterogeneous, thus representing multiple renal tubule segments. Different or additional combinations of transcription factors may lead to improved reprogramming to specific tubular subtypes. For example, omission of Hnf4a reduced the expression of proximal tubule genes; therefore, Hnf4a contributes to the induction of PTEC-like cells. Another concern is whether this direct reprogramming works in vivo. If administering four transcription factors into fibrotic tissues in vivo converts them into renal tubule epithelia, it would be a great advance in the field. However, the induced epithelial cells still need to be incorporated and connected to the residual nephrons, which remains a challenge.

25.9 Rebuilding the Kidney for Regenerative Medicine

Knowledge of embryonic kidney development has enabled several groups, including ours, to succeed in inducing human iPSCs toward nephron progenitors, which give rise to glomeruli and renal tubules [38–40] (Fig. 25.3). While these kidney

organoids are likely to represent the first or at best the second trimester of gestation, the proximal tubules in the organoids exhibit some reabsorptive capacity, as well as selective sensitivity to nephrotoxic chemicals [39, 40]. When transplanted into mice, the glomeruli in the organoids were vascularized with host endothelial cells [41–43]. Although some reports claim benefits of human iPSC-derived transplantation in AKI models [44], these improvements are likely to be mediated by released soluble factors (paracrine effects), and not by nephron differentiation or their incorporation into the residual nephrons. In addition, even in transplantation into normal host mice, long-term transplantation resulted in hydronephrosis because of the lack of a collecting duct [41]. We recently reported induction of UBs, the precursor of collecting ducts and ureters, from mouse ESCs and human iPSCs [45]. Reconstitution of nephron progenitors and UBs from mouse ESCs, along with mouse embryo-derived stromal progenitors gives rise to higher order kidney structure in vitro, containing extensively branching UBs with multiple nephrons located at UB tips. Because stromal progenitors are required for this process, induction of this cell lineage from human iPSCs is necessary to generate an authentic kidney structure in humans. Formation of a single ureter, as well as extensive vascularization, is also required to generate fully functional kidney organoids. Furthermore, maturation of these organoids either in vitro or in vivo is necessary to treat patients suffering from kidney failure.

The selective induction of nephron lineages from nephron progenitors is also an important topic of research (Fig. 25.3). We recently reported a selective induction method for podocytes from human iPSCs [46]. This includes transient Wnt stimulation followed by TGFβ inhibition, which at least partially mimics the in vivo podocyte development process. Modulation of this protocol is likely to lead to selective induction of proximal or distal renal tubules. However, further maturation, as well as strategies for incorporation into the surviving nephrons are necessary before this strategy can be applied to the treatment of AKI, similar to the situation with directly reprogrammed PTECs.

25.10 Conclusions

Our knowledge of kidney developmental biology, such as of renal progenitors and signaling, and the techniques used for investigation, such as cell lineage tracing, have contributed significantly to understanding the mechanisms of AKI. It has now become clear that the recovery process from AKI does not recapitulate embryonic kidney development, although some developmental genes are upregulated upon AKI. Application of scRNA-seq will add new findings regarding AKI. The progress of stem cell biology, combined with developmental nephrology, has led to the generation of kidney organoids in vitro. Further development of this organoid technique will accelerate research into kidney diseases, including AKI and AKI-induced chronic kidney diseases.

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References

1. Nishinakamura R. Stem cells in the embryonic kidney. Kidney Int. 2008;73:913–7.
2. Kobayashi A, Valerius MT, Mugford JW, Carroll TJ, Self M, Oliver G, McMahon AP. Six2 defines and regulates a multipotent self-renewing nephron progenitor population throughout mammalian kidney development. Cell Stem Cell. 2008;3:169–81.
3. Osafune K, Takasato M, Kispert A, Asashima M, Nishinakamura R. Identification of multipotent progenitors in the embryonic mouse kidney by a novel colony-forming assay. Development. 2006;133:151–61.
4. Tanigawa S, Taguchi A, Sharma N, Perantoni AO, Nishinakamura R. Selective in vitro propagation of nephron progenitors derived from embryos and pluripotent stem cells. Cell Rep. 2016;15:801–13.
5. Costantini F, Kopan R. Patterning a complex organ: branching morphogenesis and nephron segmentation in kidney development. Dev Cell. 2010;18:698–712.
6. Lindström NO, Lawrence ML, Burn SF, Johansson JA, Bakker ER, Ridgway RA, Chang C-H, Karolak MJ, Oxburgh L, Headon DJ, Sansom OJ, Smits R, Davies JA, Hohenstein P. Integrated β-catenin, BMP, PTEN, and Notch signalling patterns the nephron. Elife. 2015;4:1–29.
7. Brunskill EW, Park J-S, Chung E, Chen F, Magella B, Potter SS. Single cell dissection of early kidney development: multilineage priming. Development. 2014;141:3093–101.
8. Lindström NO, De Sena Brandine G, Tran T, Ransick A, Suh G, Guo J, Kim AD, Parvez RK, Ruffins SW, Rutledge EA, Thornton ME, Grubbs B, McMahon JA, Smith AD, McMahon AP. Progressive recruitment of mesenchymal progenitors reveals a time-dependent process of cell fate acquisition in mouse and human nephrogenesis. Dev Cell. 2018;45:651–660.e4.
9. Cheng H-T, Kim M, Valerius MT, Surendran K, Schuster-Gossler K, Gossler A, McMahon AP, Kopan R. Notch2, but not Notch1, is required for proximal fate acquisition in the mammalian nephron. Development. 2007;134:801–11.
10. Fujimura S, Jiang Q, Kobayashi C, Nishinakamura R. Notch2 activation in the embryonic kidney depletes nephron progenitors. J Am Soc Nephrol. 2010;21:803–10.
11. Marable S, Chung E, Shin J, Park J-S, Deacon P. Notch signaling promotes nephrogenesis by downregulating Six2. Development. 2016;143:3907–13.
12. Chung E, Deacon P, Park J-S. Notch is required for the formation of all nephron segments and primes nephron progenitors for differentiation. Development. 2017;144:4530–9.
13. Heliot C, Desgrange A, Buisson I, Prunskaite-Hyyryläinen R, Shan J, Vainio S, Umbhauer M, Cereghini S. HNF1B controls proximal-intermediate nephron segment identity in vertebrates by regulating Notch signalling components and Irx1/2. Development. 2013;140:873–85.
14. Massa F, Garbay S, Bouvier R, Sugitani Y, Noda T, Gubler M-C, Heidet L, Pontoglio M, Fischer E. Hepatocyte nuclear factor 1β controls nephron tubular development. Development. 2013;140:886–96.
15. Marable SS, Potter SS, Park J-S. Hnf4a deletion in the mouse kidney phenocopies Fanconi renotubular syndrome. JCI Insight. 2018;3:e97497.
16. Martovetsky G, Tee JB, Nigam SK. Hepatocyte nuclear factors 4 and 1 regulate kidney developmental expression of drug-metabolizing enzymes and drug transporters. Mol Pharmacol. 2013;84:808–23.
17. Bi B, Schmitt R, Israilova M, Nishio H, Cantley LG. Stromal cells protect against acute tubular injury via an endocrine effect. J Am Soc Nephrol. 2007;18:2486–96.
18. Duffield JS, Park KM, Hsiao L, Kelley VR, Scadden DT, Ichimura T, Bonventre JV. Restoration of tubular epithelial cells during repair of the postischemic kidney occurs independently of bone marrow-derived stem cells. J Clin Invest. 2005;115:1743–55.
19. Humphreys BD, Valerius MT, Kobayashi A, Mugford JW, Soeung S, Duffield JS, McMahon AP, Bonventre JV. Intrinsic epithelial cells repair the kidney after injury. Cell Stem Cell. 2008;2:284–91.
20. Kusaba T, Lalli M, Kramann R, Kobayashi A, Humphreys BD. Differentiated kidney epithelial cells repair injured proximal tubule. Proc Natl Acad Sci U S A. 2014;111:1527–32.

21. Berger K, Bangen J-M, Hammerich L, Liedtke C, Floege J, Smeets B, Moeller MJ. Origin of regenerating tubular cells after acute kidney injury. Proc Natl Acad Sci U S A. 2014;111:1533–8.
22. Itäranta P, Tuukkanen J, Vainio S, Peltoketo H, Seppänen T, Chi L, Niku M. Wnt-4 signaling is involved in the control of smooth muscle cell fate via Bmp-4 in the medullary stroma of the developing kidney. Dev Biol. 2006;293:473–83.
23. Terada Y, Tanaka H, Okado T, Shimamura H, Inoshita S, Kuwahara M, Sasaki S. Expression and function of the developmental gene Wnt-4 during experimental acute renal failure in rats. J Am Soc Nephrol. 2003;14:1223–33.
24. DiRocco DP, Kobayashi A, Taketo MM, McMahon AP, Humphreys BD. Wnt4/β-catenin signaling in medullary kidney myofibroblasts. J Am Soc Nephrol. 2013;24:1399–412.
25. Zhou D, Fu H, Xiao L, Mo H, Zhuo H, Tian X, Lin L, Xing J, Liu Y. Fibroblast-specific β-catenin signaling dictates the outcome of AKI. J Am Soc Nephrol. 2018;29:1257–71.
26. Kobayashi T, Terada Y, Kuwana H, Tanaka H, Okado T, Kuwahara M, Tohda S, Sakano S, Sasaki S. Expression and function of the Delta-1/Notch-2/Hes-1 pathway during experimental acute kidney injury. Kidney Int. 2008;73:1240–50.
27. Sörensen-Zender I, Rong S, Susnik N, Zender S, Pennekamp P, Melk A, Haller H, Schmitt R. Renal tubular Notch signaling triggers a prosenescent state after acute kidney injury. Am J Physiol Renal Physiol. 2014;306:F907–15.
28. Kavvadas P, Keuylian Z, Prakoura N, Placier S, Dorison A, Chadjichristos CE, Dussaule J-C, Chatziantoniou C. Notch3 orchestrates epithelial and inflammatory responses to promote acute kidney injury. Kidney Int. 2018;94:126–38.
29. Oxburgh L, Brown AC, Muthukrishnan SD, Fetting JL. Bone morphogenetic protein signaling in nephron progenitor cells. Pediatr Nephrol. 2014;29:531–6.
30. Zeisberg M, Hanai J, Sugimoto H, Mammoto T, Charytan D, Strutz F, Kalluri R. BMP-7 counteracts TGF-β1–induced epithelial-to-mesenchymal transition and reverses chronic renal injury. Nat Med. 2003;9:964–8.
31. Sugimoto H, LeBleu VS, Bosukonda D, Keck P, Taduri G, Bechtel W, Okada H, Carlson W, Bey P, Rusckowski M, Tampe B, Tampe D, Kanasaki K, Zeisberg M, Kalluri R. Activin-like kinase 3 is important for kidney regeneration and reversal of fibrosis. Nat Med. 2012;18:396–404.
32. Vigolo E, Markó L, Hinze C, Müller DN, Schmidt-Ullrich R, Schmidt-Ott KM. Canonical BMP signaling in tubular cells mediates recovery after acute kidney injury. Kidney Int. 2019;95:108–22.
33. Himmelfarb J, Chertow GM, McCullough PA, Mesana T, Shaw AD, Sundt TM, Brown C, Cortville D, Dagenais F, de Varennes B, Fontes M, Rossert J, Tardif J-C. Perioperative THR-184 and AKI after cardiac surgery. J Am Soc Nephrol. 2018;29:670–9.
34. Reginensi A, Clarkson M, Neirijnck Y, Lu B, Ohyama T, Groves AK, Sock E, Wegner M, Costantini F, Chaboissier MC, Schedl A. SOX9 controls epithelial branching by activating RET effector genes during kidney development. Hum Mol Genet. 2011;20:1143–53.
35. Kumar S, Liu J, Pang P, Krautzberger AM, Reginensi A, Akiyama H, Schedl A, Humphreys BD, McMahon AP. Sox9 activation highlights a cellular pathway of renal repair in the acutely injured mammalian kidney. Cell Rep. 2015;12:1325–38.
36. Kang HM, Huang S, Reidy K, Han SH, Chinga F, Susztak K. Sox9-positive progenitor cells play a key role in renal tubule epithelial regeneration in mice. Cell Rep. 2016;14:861–71.
37. Kaminski MM, Tosic J, Kresbach C, Engel H, Klockenbusch J, Müller A-L, Pichler R, Grahammer F, Kretz O, Huber TB, Walz G, Arnold SJ, Lienkamp SS. Direct reprogramming of fibroblasts into renal tubular epithelial cells by defined transcription factors. Nat Cell Biol. 2016;18:1269–80.
38. Taguchi A, Kaku Y, Ohmori T, Sharmin S, Ogawa M, Sasaki H, Nishinakamura R. Redefining the in vivo origin of metanephric nephron progenitors enables generation of complex kidney structures from pluripotent stem cells. Cell Stem Cell. 2014;14:53–67.
39. Takasato M, Er PX, Chiu HS, Maier B, Baillie GJ, Ferguson C, Parton RG, Wolvetang EJ, Roost MS, Chuva de Sousa Lopes SM, Little MH. Kidney organoids from human iPS cells contain multiple lineages and model human nephrogenesis. Nature. 2015;526:564–8.

40. Morizane R, Lam AQ, Freedman BS, Kishi S, Valerius MT, Bonventre JV. Nephron organoids derived from human pluripotent stem cells model kidney development and injury. Nat Biotechnol. 2015;33:1193–200.
41. Sharmin S, Taguchi A, Kaku Y, Yoshimura Y, Ohmori T, Sakuma T, Mukoyama M, Yamamoto T, Kurihara H, Nishinakamura R. Human induced pluripotent stem cell-derived podocytes mature into vascularized glomeruli upon experimental transplantation. J Am Soc Nephrol. 2016;27:1778–91.
42. van den Berg CW, Ritsma L, Avramut MC, Wiersma LE, Leuning G, Lievers E, Koning M, Van Den Berg BM, Vanslambrouck JM, Koster AJ, Howden SE, Takasato M, Little MH. Renal subcapsular transplantation of PSC-derived kidney organoids induces neo-vasculogenesis and significant glomerular and tubular maturation in vivo. Stem Cell Reports. 2018;10:751–65.
43. Bantounas I, Ranjzad P, Tengku F, Silajdžić E, Forster D, Asselin M-C, Lewis P, Lennon R, Plagge A, Wang Q, Woolf AS, Kimber SJ. Generation of functioning nephrons by implanting human pluripotent stem cell-derived kidney progenitors. Stem Cell Reports. 2018;10:766–79.
44. Toyohara T, Mae S, Sueta S, Inoue T, Yamagishi Y, Kawamoto T, Kasahara T, Hoshina A, Toyoda T, Tanaka H, Araoka T, Sato-Otsubo A, Takahshi K, Sato Y, Yamaji N, Ogawa S, Yamanaka S, Osafune K. Cell therapy using human induced pluripotent stem cell-derived renal progenitors ameliorates acute kidney injury in mice. Stem Cells Transl Med. 2015;4:980–92.
45. Taguchi A, Nishinakamura R. Higher-order kidney organogenesis from pluripotent stem cells. Cell Stem Cell. 2017;21:730–46.
46. Yoshimura Y, Taguchi A, Tanigawa S, Yatsuda J, Kamba T, Takahashi S, Kurihara H, Mukoyama M, Nishinakamura R. Manipulation of nephron-patterning signals enables selective induction of podocytes from human pluripotent stem cells. J Am Soc Nephrol. 2019;30:304–21.

Chapter 26
Xenotransplanted Embryonic Kidney

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Abstract Acute kidney injury (AKI) is a disease that adversely affects life prognosis and increases the risk of cardiovascular disease. Even if renal function recovers after AKI, this disease tends to contribute to the onset of chronic kidney disease (CKD). Therefore, AKI is one of the reasons for the increase in the number of patients with CKD and end-stage renal disease (ESRD). Dialysis therapy is a common method for treating ESRD but does not replace normal kidney function. Although kidney transplantation is another option, many patients cannot receive a transplant because of the lack of donor organs. Therefore, alternatives to kidney transplantation are needed. In this study, we review recent treatment strategies for replacing kidney function, including heterogeneous kidney transplantation, embryonic kidney transplantation, and the use of a nephrogenic niche for growing xenoembryos (organogenic niche method). Although these strategies require additional refinement prior to clinical application, we believe that these treatment strategies may help us alleviate patient suffering. We are also hopeful that whole-kidney regeneration will be a viable treatment option in the near future.

Keywords Kidney regeneration · Kidney xenotransplantation · Embryonic kidney transplantation · Induced pluripotent stem cell · Chimera · Organogenic niche method

26.1 Introduction

Acute kidney injury (AKI) is frequently encountered in daily clinical practice. Mild acute kidney dysfunction was previously thought to be a transient and reversible disease. However, some patients with AKI remain in failure without complete

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recovery, and other patients eventually require dialysis. The concept of AKI was based on the idea that severe renal dysfunction, such as acute renal failure, and mild renal dysfunction during early-stage disease should be recognized. The long-term prognosis of cardiovascular and renal disorders after AKI is poor [1, 2]. The number of patients suffering from CKD is steadily increasing worldwide, and AKI contributes to the increase in the prevalence of CKD [3]. Although dialysis therapy is the treatment of choice for end-stage renal disease (ESRD), it is not equivalent to full renal function. Furthermore, dialysis therapy is associated with a number of complications, such as an increased risk of cardiovascular disease and death, decreased quality of life, and increased health care costs. Kidney transplantation therapy is the only treatment that replaces the function of a whole kidney. However, because of the severe shortage of human donor organs, many patients are not able to undergo a kidney transplant. Therefore, alternative treatments are urgently needed. To address the shortage of donor organs, there are various strategies, such as the use of the bioartificial kidneys [4]; decellularized cadaveric kidneys as scaffolds for renal regeneration [5]; the xenotransplantation of adult kidneys [6]; embryonic kidney primordia (metanephroi) [7]; the blastocyst complementation method [8]; and new whole kidneys created from stem cells in vitro [9]. Since the development of induced pluripotent stem cells (iPSCs) in recent years, many researchers have attempted to regenerate a whole kidney from iPSCs. However, the kidneys have a complicated anatomy and have numerous delicate functions for maintaining homeostasis and producing urine, renin, erythropoietin, and vitamin D. Therefore, the regeneration of a whole kidney remains challenging.

We used heterogeneous embryonic kidney primordia (metanephroi) as organ factory to generate a functional whole kidney. This approach is based on the concept of borrowing the kidney developing program of a xenoembryo by injecting stem cells into an organ formation niche. After transplanting the metanephros into a patient with renal failure, the metanephros will hopefully become a functional whole kidney inside the patient's body.

26.2 Kidney Xenotransplantation

Kidney xenotransplantation is a potential solution to the shortage of available human donor organs for transplantation. In the 1960s, a successful cadaveric renal transplant was performed in a human under immunosuppressive therapy with azathioprine [10]. During the same period, a chimpanzee kidney was transplanted into a patient with renal failure, and the transplanted kidney functioned for 9 months [11]. Chimpanzees are often used as donor animals for kidney transplantation because of their genetic similarities to humans. However, nonhuman primates are considered unsuitable as a resource for transplantation because of their relative scarcity. Pigs exist almost indefinitely as a transplant source, and they have kidneys that have almost the same size and functions as human kidneys. Therefore, the porcine kidney is considered an ideal source for xenografting [12].

However, the use of porcine kidneys in xenotransplantation presents some problems that need to be addressed. First, there are immunological problems. When a

pig kidney is transplanted into a primate, hyperacute vascular rejection occurs, and this complication is the most problematic complication of xenotransplantation. Natural antibodies in primates bind to the α-galactose-1,3-galactose (Gal) expressed on porcine vascular endothelial cells to activate the human complement. This galactose is added to the cell surface sugar by α-1,3-galactosyltransferase (GalT). Primates, including humans, do not inherit GalT [12].

There are several strategies for preventing rejection. Aphaeresis can remove anti-Gal antibodies from the circulation of the recipient [13]. This therapy reduces the serum levels of anti-Gal antibodies, albeit temporarily. The kidneys of transgenic animals expressing human complement regulatory proteins (human CD55) have been previously transplanted [14]. In this study, the researchers were able to suppress human complement activation. Furthermore, GalT-knockout pigs have been developed [15]. Considering that these transgenic pigs do not express Gal, the anti-Gal antibody will not react with Gal. The GalT-knockout pig kidneys were transplanted into baboons under immunosuppressant agents, and the graft survived for 3 months [16]. The transplantation of the Gal-knockout pigs expressing human CD55 extended xenograft survival by several months [17]. However, it is impossible to completely suppress vascular rejection because of the influence of anti-non-Gal antibodies [18]. Furthermore, the adaptive immune system seems to react to the xenografts as equally or as strongly as it does to the allografts. In both xenografts and allografts, T cells can interact with antigen-presenting cells (APCs) from the donor and host, who posts donor antigens [19]. In 2018, Langin et al. [20] conducted an orthotopic transplantation of the Gal-KO porcine heart expressing a human membrane cofactor protein and thrombomodulin into baboons under safe immunosuppression and the grafts could survive for 195 days. Further development is expected in the transplantation therapy with genetically modified pigs.

There is also the additional problem of infection. Given that pigs can be kept in pathogen-free environments, they have a lower risk of acquiring zoonotic infections than primates. However, there is a porcine endogenous retrovirus (PERV) that cannot be removed by using a pathogen-free environment. Previous studies found that PERV cannot infect human cells in vivo and cause disease; however, it can infect humans in vitro [21, 22]. In 2015, Yang et al. [23] succeeded in knocking out 62 copies of PERV pol gene in porcine cells using the CRISPR/Cas9. Further studies may make it possible to create PERV-free porcine kidneys to be available for use during kidney transplantation.

26.3 Embryonic Kidney Transplantation

The transplantation of embryonic kidney primordia seeks to regenerate a whole kidney. Chan et al. [24] reported the first transplantation of a functional kidney primordia. They induced pronephros-like transplantable structures from animal caps in *Xenopus laevis*, and these structures were transplanted into bilaterally nephrectomized tadpoles. The transplantation of pronephros-like structures reduced swelling and improved the survival of nephrectomized tadpoles. For clinical applications,

the transplantation of metanephros, which is further developed than pronephros (i.e., the metanephros is already committed to becoming a kidney), has been reported. When it is transplanted into a recipient, it differentiates and eventually matures into a kidney. The transplanted metanephros attracts angiogenesis in the recipient animals, thus allowing glomerulus formation, including recipient-derived vasculature [25]. When the ureter of the transplanted metanephros is anastomosed to the ureter of an anephric rat, the developed metanephros could produce urine, and the survival times of the rats were prolonged [26]. Furthermore, the transplanted metanephros also acquires endocrine function, such as erythropoietin and renin production [27, 28]. The location where the metanephros is transplanted also affects endocrine function. Erythropoietin production did not differ, but renin production was better when the transplant was located in the para-aortic region than in other regions. Therefore, embryonic kidney transplantation can reproduce a functional kidney.

One advantage of metanephric transplantation is the lower likelihood of immunologic rejection than adult kidney transplantation. The organ primordia of the earlier stage are avascular; thus, they induce blood vessels from the recipient. By contrast, adult transplanted organs already feature vessels developed by the donor. Therefore, humoral immunity to vascular endothelial cells is less likely to occur following the transplant of organ primordia than the transplant of an adult organ [29]. Furthermore, the embryonic organ grafts obtained during the early developmental stages are less likely to be rejected by cellular immunity. It is possible that human leukocyte antigen (HLA) and APCs are less expressed in the embryonic organ. Foglia et al. [30] transplanted the metanephroi of 15- to 21-day-old rat embryos under the kidney capsule of outbred adult rats. If the pregnancy-dated age of the metanephros was younger, the transplanted metanephros will have a bigger volume and may engraft without immune suppression. Statter et al. [31] transplanted mice metanephros under the kidney capsule of mice. HLA transcripts were progressively lower in the metanephros from younger mice. Furthermore, there was no expression of HLA protein in the kidney primordia graft compared with the adult kidney graft. Velasco et al. [32] transplanted the liver primordia and metanephroi of 15- to 19-day-old rat embryos under the renal capsule of adult rat without immunosuppression. All liver primordia were rejected by posttransplantation day 10. On the contrary, there was a mild degree of rejection in the case of kidney primordia for 15-day-old embryos, and rejection has become strong enough to increase the pregnancy age. Furthermore, when both kidney and liver primordia were simultaneously implanted, severe rejection occurred compared with the implantation of the metanephros alone. According to the authors, fetal liver primordia contained the APCs from the donor, which held donor antigens to host T cells. By contrast, the metanephros did not contain APCs.

When the metanephros of a large animal was transplanted into a small animal recipient, the weight and volume of the grafted metanephros became larger than the recipient [33]. Similar to adult kidney xenotransplantation, the pig is considered suitable for human clinical application as a resource for metanephric transplants. In the case of swine embryonic organ allografts, the metanephros of a 28-day-old porcine embryo was transplanted into an outbred pig, and the graft differentiated without rejection and under no immunosuppression [34]. However, regarding xenotransplantation from pigs to rodents, immunosuppression is necessary [33, 35].

Dekel et al. [35] transplanted the metanephroi of porcine embryos from E20–E21 to E27–E28 under the kidney capsule of an immunodeficient mouse. Metanephroi from 20- to 21-day-old embryos were not fully developed and differentiated into blood vessels, cartilage, and bone and not into glomeruli and tubules. Furthermore, E24–E28 metanephros grafts contained nonrenal cells or tissues. The metanephroi of E27–E28 grew in the renal tubules or glomeruli. Furthermore, for the immunogenicity evaluation of the metanephros, they transplanted an adult porcine kidney and embryonic kidney tissue from E27–E28 donors into immunocompetent mice. Both groups experienced rejection after 2 weeks. Thus, the authors performed short-term immunosuppression with CTLA4-Ig. As a result, all adult grafts were rejected, but the embryonic tissues differentiated up to a mature kidney. In pigs and other animals, embryonic kidney primordia are less immunogenic than adult kidney tissues.

26.4 Stepwise Peristaltic Ureter System

Although the size of the metanephric graft is defined by the species of the donor, the growth of transplanted porcine metanephros into small animals, such as rodents, was clearly limited. Therefore, we used pigs as recipients. To eliminate the effect of rejection, porcine metanephros was transplanted into syngeneic cloned pigs. All porcine metanephroi differentiated into mature kidneys. Three weeks after transplantation, the metanephroi grew to a size of 5–7 mm. After 5 weeks, they grew to 1 cm, and urine began to accumulate in the ureter. After 8 weeks, they were 3 cm. However, the pigs developed hydronephrosis owing to urinary retention [36]. Peristalsis starts in the urinary tract during the embryonic period, and urine needs to be excreted into the bladder. Therefore, to prevent hydronephrosis, the urinary tract of the grafts needs to start peristaltic activity immediately after transplantation. We transplanted metanephroi with bladder (MNB) to recipient animals. When MNB or metanephros alone was transplanted, urine was produced 3 weeks after transplantation in both groups. After 4 weeks, hydronephrosis occurred in the metanephros transplantation group but not in the MNB group. The volume of urine and the levels of UN and Cr were higher in the MNB group than in the metanephros group [36]. Furthermore, we developed a stepwise peristaltic ureter (SWPU) system to promote sustainable urine excretion. After the transplanted MNB sufficiently developed in the recipients, we connected the host ureter to the bladder of the developed MNB. This approach enabled the urine produced from MNB to continuously flow in the host ureter. After the administration of the contrast medium, we observed that urine continuously passed from the bladder of the MNB to the host ureter. Even 8 weeks after transplantation, we did not observe hydronephrosis and instead noted mature glomeruli and tubules. The levels of BUN and Cr from urine in the MNB group were higher than that of the host serum. Furthermore, the SWPU system significantly prolonged survival in the MNB group compared with the control group in nonrenal rats [36]. In a previous research, the ureter of the transplanted metanephros was directly connected to the host ureter (ureteroureterostomy), and the survival period was slightly extended [26]. However, the SWPU system is better at

preventing hydronephrosis than ureteroureterostomy. The anastomosis of the MNB to the host ureter is a simpler procedure than ureteroureterostomy. Considering that the urine is retained in the MNB and the bladder swells, it is easy to anastomose with the host ureter. Furthermore, although it is very difficult to connect two metanephroi to the host urinary tract, they can be transplanted at once by using the SWPU system. In previous studies, larger volumes of metanephroi corresponded with longer survival periods in nonrenal rats [37].

We assume that pluripotent stem cells are transplanted in the metanephros and are used as a niche of kidney regeneration in patients with renal failure. We have examined uremic conditions to determine how human mesenchymal stem cells (hMSCs) and iPSCs influence kidney regeneration [38, 39]. Thus, we investigated whether host uremic conditions affected the structure and function of the MNB [40]. We used a 5/6 renal infarction rat model. Two MNBs from a Lewis rat fetus were transplanted into the para-aorta area of another Lewis rat. After 4 weeks, the left kidney was removed to make a uremic condition, and the branches of the right kidney artery were ligated. One MNB bladder was connected to the left ureter of the host, and the other MNB was not connected. After 8 weeks, the MNBs were harvested. The MNB that was not connected to the host's urinary tract developed hydronephrosis. However, the connected MNB continued to grow. Pathological analysis showed the devastation of the glomeruli and tubules, expansion of the collecting duct, and interstitial fibrosis in the nonconnected group. On the contrary, the connected group showed a mature renal pathological image. PCR was used to analyze gene expression, and the expressions of Na–K–Cl cotransporter 2 and AQP2 were observed in both groups. However, 25-hydroxyvitamin D3 1-α-hydroxylate, which is important for vitamin D metabolism, was expressed only in the anastomosis group. Therefore, in the uremic condition, the SWPU system promoted the maturation of metanephros not only in a pathological aspect but also with regard to endocrine function. Furthermore, we made a diuretic load test to evaluate the tubular function of transplanted MNB under uremia. The group that received furosemide showed increased urine volume from the MNB compared with the control group. We also evaluated the relationship between survival rate and the SWPU system in uremic conditions. The MNB group that developed in uremic conditions had a similar mean survival rate as the MNB group that developed under nonuremic conditions [40]. This suggested that MNB grew functionally in renal failure conditions. In the future, the use of metanephros for kidney regeneration may offer an additional treatment option to patients with renal failure.

26.5 Organogenic Niche Method Using iPSCs and Cell Removal Systems with Drugs

Regenerative medicine using embryonic stem cells and iPSCs is evolving very rapidly. However, the kidney is a complicated organ both structurally and functionally. It is also embryologically complicated. During development, the metanephric

mesenchyme of the kidney is derived from the caudal portion of the nephrogenic cord and produces glial cell line-derived neurotrophic factor (GDNF). GDNF induces the Wolffian duct (WD) to become a germinating ureteric bud (UB). Thereafter, the kidney is generated by the interaction between the metanephric mesenchyme and UB. In recent years, Taguchi et al. [9, 41] succeeded in differentiating human iPSCs into nephron progenitor cells (NPCs) and UB. Takasato et al. [42] successfully and simultaneously induced metanephric mesenchyme and ureteral buds from pluripotent stem cells to produce kidney organoids, including blood vessels and interstitium. However, the ureteral bud of the kidney organoid did not have the same branching ability as the living body. In 2017, the stromal progenitor cells of a mouse embryo were combined with the NPCs and the UB derived from human iPSCs; the higher order structure of the kidney, including the collecting duct and nephron, was then reproduced [41]. However, a method for differentiating human iPSCs into stromal progenitor cells is yet to be established. Therefore, it is currently difficult to differentiate iPSCs into kidneys that can excrete urine.

One solution to this problem is the use of a developmental program from other fertilized eggs to individuals. *Chimera* refers to individual organisms made from cells of two or more different genotypes or different species. It is classified between xenogeneic and allogeneic. Chimera can be classified according to the developmental stage in which the recipient becomes a chimera. For convenience, they are referred to as embryonic, fetal, and postnatal chimera (Table 26.1). The postnatal chimeras are used for organ transplantation, bone marrow transplantation, blood transfusion, etc. The embryonic chimeras include the blastocyst complementation utilizing the blastocyst stage development program. When pluripotent stem cells are

Table 26.1 Summary of chimeras

Classification		Donor		Recipient		Published year	Author
Embryonic chimera	Allo	Mice	ESCs	Mice	Blastocyst	1993	Chen J
		Mice	iPSCs	Mice	Blastocyst	2012	Usui J
		Pig	Blastomere	Pig	Blastomere	2013	Matsunari H
	Xeno	Rat	iPSCs	Mice	Blastocyst	2010	Kobayashi T
		Rat	ESCs	Mice	Blastocyst	2011	Isotani A
		Human	iPSCs	Pig	Blastocyst	2017	Wu J
Fetal chimera	Allo	Sheep	HSCs	Sheep	E55-62	1986	Fake AW
	Xeno	Human	MSCs	Rat	E11	2005	Yokoo T
		Rat	NPCs	Mice	E13	2017	Yamanaka S
Postnatal chimera	Allo	Human	Kidney	Human	Adult	1963	Merrill JP
	Xeno	Pig	Kidney	Baboon	Adult	2005	Yamada K

The table summarizes the typical chimera that has been classified by the developmental period in which the recipient became a chimera. *Allo* allogeneic, *xeno* xenogeneic, *ESCs* embryonic stem cells, *iPSCs* induced pluripotent stem cells, *HSCs* hematopoietic stem cells, *MSCs* mesenchymal stem cells, *NPCs* nephron progenitor cells

transplanted into blastocysts, which are the early embryos of animals, chimeras containing cells of blastocysts and cells of pluripotent stem cells are formed. In 1993, Chen et al. [43] successfully regenerated lymphocytes by transplanting wild-type mouse ES cells into the blastocysts of lymphocyte-deficient mice. Kobayashi et al. [44] successfully reproduced the whole pancreas by transplanting rat iPSCs into blastocysts of pancreas-deficient mice. Furthermore, Isotani et al. [45] successfully regenerated the thymus by implanting rat ES cells into athymic mice embryos. Therefore, the generation mechanism appears compatible between species. By applying the blastocyst complementation method to kidneys, kidneys derived from mouse iPSCs were regenerated into kidney-deficient mice [8]. The size of the regenerated organ was affected by the size of the host. For example, when mouse stem cells are transplanted into rat blastocysts, rat-sized organs are formed instead of mouse-sized organs. To produce human organs in the animal body, the blastocyst complementation method must be performed with large animals. Therefore, pigs are seen as a potential source of organs for transplantation into humans, and the pancreas has been successfully regenerated by performing allogeneic blastocyst complementation in pancreas-deficient pigs [46]. In 2017, a human-to-pig chimera was created by transplanting human iPSCs into porcine blastocysts [47]. Pig kidney is close in size to human kidney; therefore, if a kidney-deficient pig is invented, it may be possible to prepare a kidney composed of human-derived pluripotent stem cells in the porcine body.

Blastocyst complementation has many problems, including the preparation of organ-deficient animals, rejection reactions, and ethical concerns. A method that can produce organs that can function in vivo will be significant.

Another method of utilizing an animal development program is the organogenic niche method (classified as fetal chimera). In the organogenic niche method, foreign organ progenitor cells are transplanted to a site where an animal fetus develops. In 1986, Flake et al. [48] transplanted allogeneic fetal hematopoietic stem cells into sheep fetuses and successfully achieved long-term engraftment. In the renal field, we transplanted hMSCs, which express GDNF, into the site of UB branching. Thereafter, we cultured the recipient embryo in a whole-embryo culture system, and the metanephros removed from the embryo was grown in an organ culture. Transplanted hMSCs were integrated into the metanephros and differentiated to morphologically tubular cells, interstitial cells, and glomerular epithelial cells [49]. When the metanephros was transplanted into the recipient omentum, it integrated with blood vessels from the recipient, and the nephrons derived from hMSCs were regenerated [50]. The neo-kidney produced urine by filtering the host blood, and the level of urea and Cr in the urine was higher than that of the host serum. Furthermore, the neo-kidney derived from hMSCs produced EPO in response to the anemia of the host [51]. Considering that the use of viruses in GDNF gene transfer presents safety concerns, we successfully performed a virus-free introduction of GDNF by using a thermoreversible polymer [52]. However, this system was not able to regenerate the collecting tubules and urinary tract derived from the UB. To determine if hMSCs can differentiate into UB progenitor cells, we injected hMSCs expressing Pax2 into the chicken UB progenitor region. The transplanted cells migrated with the

elongating WD, merged with the WD epithelia, and expressed Lim1 [53]. This demonstrated that hMSC could differentiate into WD by heterologous signals. In the organogenic niche method, it is necessary to inject outside organ progenitor cells into the site where the target organ develops. Furthermore, the differentiation stages of the organ progenitor cells of the host and the external organ progenitor cells must be combined. For the kidney, we need to transplant NPCs into the caudal portion of the nephrogenic cord, which is the main kidney development area. However, it is not enough to transplant NPCs from the outside into animal fetuses. The host embryo also has NPCs, and the host NPC occupies a place. By merely transplanting external NPCs, these external NPCs will form a chimera with host-derived NPCs or fail to grow [54]. Therefore, a system that eliminates only host NPCs is required. This system should also be capable of selectively causing apoptosis by using diphtheria toxin (DT). Rodents such as mice and rats do not have DT receptors (DTRs). If DTRs are specifically expressed by altering the genes of the host mouse, it is possible to induce apoptosis only into target cells by incorporating DT. By combining Six2, which is a transcription factor expressed on NPCs, with the DTR, we can remove host NPCs; that is, it is possible to form a nephron consisting entirely of exogenous NPCs by injecting NPCs into the genetically modified mouse and by using DT (Fig. 26.1) [54]. When the NPCs from a heterologous animal were transplanted, a chimeric kidney can be formed with nephrons derived from the heterologous animal, followed by collecting ducts derived from the host animal. As shown in the hourglass model of vertebrate evolution, the early and late embryonic development stages diverge between species, but the mid-embryonic stage of

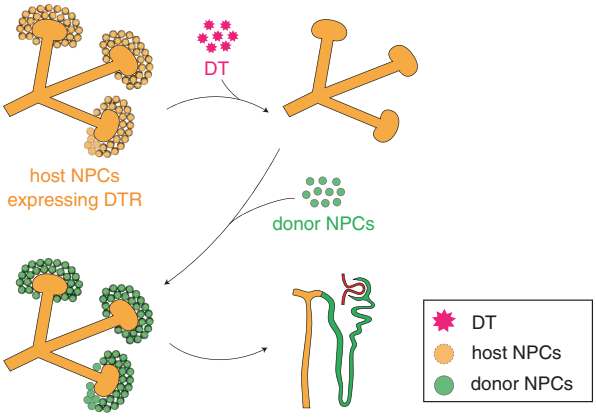

Fig. 26.1 Regeneration of nephrons derived from donor NPCs using drug-induced cell elimination system. DT induces apoptosis in the host NPCs, which are genetically modified to express DTRs. The system allows the replacement of host NPCs with donor NPCs and regeneration of nephrons derived from 100% donor NPCs. *DT* diphtheria toxin, *DTR* diphtheria toxin receptor, *host NPCs* nephron progenitor cells derived from host, *donor NPCs* nephron progenitor cells derived from donor

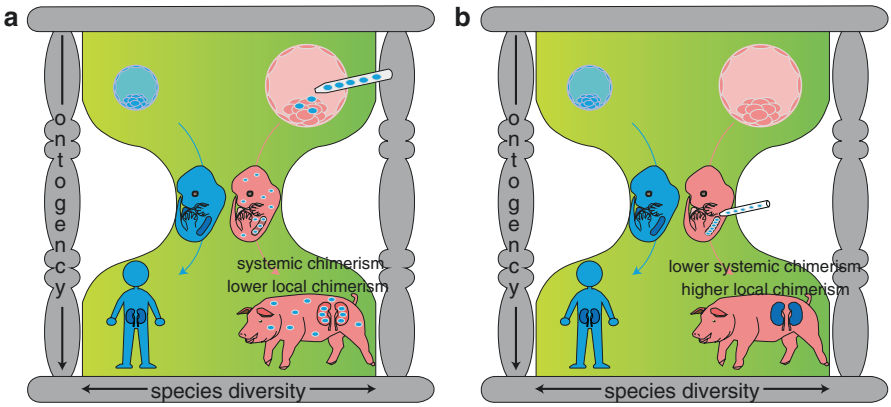

Fig. 26.2 Hourglass model of vertebrate development. The model shows that early and late embryonic development stages diverge between species, while the mid-embryonic stage is conserved [55, 56]. The embryonic chimera in the early embryonic stage might readily result in low chimerism of the target organ and in systemic chimerism leading to fetal death (**a**). The fetal chimera in the mid-embryonic stage can result in locally higher chimerism and lower systemic chimerism (**b**)

organogenesis is comparatively conserved [55, 56]. Accordingly, the embryonic chimera in the early embryonic stage, such as blastocyst complementation, might readily lead to low chimerism or to fetal death from systemic chimerism (Fig. 26.2a). However, a fetal chimera in the mid-embryonic stage, such as this organogenic niche method, can lead to locally higher chimerism and prevent the transition to reproductive and nerve cells because of lower systemic chimerism (Fig. 26.2b) [55, 56]. Given that human cells generally express DTR (human heparin-binding epidermal growth factor)-like growth factor, this system cannot be used when injecting NPCs prepared from human iPSCs; however, we are investigating if we can replace it with a similar system that does not affect human cells with other drugs.

In clinical settings, we may be able to avoid the rejection of neo-kidneys by using NPCs into which patient-derived iPSCs differentiated as resources for transplanted cells. However, the use of stem cells derived from patients in renal failure can be problematic. Uremia may reduce the function of stem cells. We found that uremia reduced the gene expression of p300/CBP-associated factor and angiogenesis in vivo among hMSCs [38]. However, we do not fully understand how uremia affects iPSCs. We reported that iPSCs from patients with ESRD were equivalent to iPSCs from healthy individuals in terms of their ability to differentiate into NPC, the expression levels of nephron progenitor marker, and the angiogenic function of the glomeruli [39]. These findings suggest that iPSCs derived from patients with ESRD are useful for kidney regeneration.

We are working on introducing the NPC removal system into larger animals, such as pigs. We are hopeful that when we transplant NPCs derived from human iPSCs into the nephron progenitor region of transgenic pigs in combination with the SWPU system, we will create a functional neo-kidney that is approximately the same size as a human kidney and with nephrons derived from humans.

26.6 Conclusion

In this chapter, we summarized recent progress toward whole-kidney regeneration by using heterologous embryonic kidney primordia. Despite the rapid technological development of regenerative medicine, we are still not able to reconstruct a whole kidney, and there are several problems that must be overcome. By using a heterologous embryo, we face problems with regard to ethical concerns and the formation of a chimeric structure. On the contrary, when a kidney is reproduced from iPSCs in vitro, we face other problems, such as the induction of stromal progenitor cells and ureter generation. However, we hope that further research can solve these problems and that neo-kidneys will be delivered to patients with renal failure as soon as possible.

References

1. Sawhney S, Mitchell M, Marks A, Fluck N, Black C. Long-term prognosis after acute kidney injury (AKI): what is the role of baseline kidney function and recovery? A systematic review. BMJ Open. 2015;5(1):e006497. https://doi.org/10.1136/bmjopen-2014-006497.
2. Pickering JW, James MT, Palmer SC. Acute kidney injury and prognosis after cardiopulmonary bypass: a meta-analysis of cohort studies. Am J Kidney Dis. 2015;65(2):283–93. https://doi.org/10.1053/j.ajkd.2014.09.008.
3. Chawla LS, Eggers PW, Star RA, Kimmel PL. Acute kidney injury and chronic kidney disease as interconnected syndromes. N Engl J Med. 2014;371(1):58–66. https://doi.org/10.1056/NEJMra1214243.
4. Kim S, Feinberg B, Kant R, Chui B, Goldman K, Park J, Moses W, Blaha C, Iqbal Z, Chow C, Wright N, Fissell WH, Zydney A, Roy S. Diffusive silicon nanopore membranes for hemodialysis applications. PLoS One. 2016;11(7):e0159526. https://doi.org/10.1371/journal.pone.0159526.
5. Song JJ, Guyette JP, Gilpin SE, Gonzalez G, Vacanti JP, Ott HC. Regeneration and experimental orthotopic transplantation of a bioengineered kidney. Nat Med. 2013;19(5):646–51. https://doi.org/10.1038/nm.3154.
6. Cowan PJ, Cooper DK, d'Apice AJ. Kidney xenotransplantation. Kidney Int. 2014;85(2):265–75. https://doi.org/10.1038/ki.2013.381.
7. Hammerman MR. Classic and current opinion in embryonic organ transplantation. Curr Opin Organ Transplant. 2014;19(2):133–9. https://doi.org/10.1097/MOT.0000000000000054.
8. Usui J, Kobayashi T, Yamaguchi T, Knisely AS, Nishinakamura R, Nakauchi H. Generation of kidney from pluripotent stem cells via blastocyst complementation. Am J Pathol. 2012;180(6):2417–26. https://doi.org/10.1016/j.ajpath.2012.03.007.
9. Taguchi A, Kaku Y, Ohmori T, Sharmin S, Ogawa M, Sasaki H, Nishinakamura R. Redefining the in vivo origin of metanephric nephron progenitors enables generation of complex kidney structures from pluripotent stem cells. Cell Stem Cell. 2014;14(1):53–67. https://doi.org/10.1016/j.stem.2013.11.010.
10. Merill JP, Murray JE, Takacs FJ, Hager EB, Wilson RE, Dammin GJ. Successful transplantation of kidney from a human cadaver. JAMA. 1963;185:347–53.
11. Reemtsma K, Mccracken BH, Schlegel JU, Pearl MA, Pearce CW, Dewitt CW, Smith PE, Hewitt RL, Flinner RL, Creech OJ. Renal Heterotransplantation in man. Ann Surg. 1964;160:384–410.
12. Yamada K, Griesemer A, Okumi M. Pigs as xenogeneic donors. Transplant Rev. 2005;19(3):164–77. https://doi.org/10.1016/j.trre.2005.10.004.

13. Watts A, Foley A, Awwad M, Treter S, Oravec G, Buhler L, Alwayn IP, Kozlowski T, Lambrigts D, Gojo S, Basker M, White-Scharf ME, Andrews D, Sachs DH, Cooper DK. Plasma perfusion by apheresis through a Gal immunoaffinity column successfully depletes anti-Gal antibody: experience with 320 aphereses in baboons. Xenotransplantation. 2000;7(3):181–5.
14. Shimizu A, Yamada K, Yamamoto S, Lavelle JM, Barth RN, Robson SC, Sachs DH, Colvin RB. Thrombotic microangiopathic glomerulopathy in human decay accelerating factor-transgenic swine-to-baboon kidney xenografts. J Am Soc Nephrol. 2005;16(9):2732–45. https://doi.org/10.1681/ASN.2004121148.
15. Lai L, Kolber-Simonds D, Park KW, Cheong HT, Greenstein JL, Im GS, Samuel M, Bonk A, Rieke A, Day BN, Murphy CN, Carter DB, Hawley RJ, Prather RS. Production of alpha-1,3-galactosyltransferase knockout pigs by nuclear transfer cloning. Science. 2002;295(5557):1089–92.
16. Yamada K, Yazawa K, Shimizu A, Iwanaga T, Hisashi Y, Nuhn M, O'Malley P, Nobori S, Vagefi PA, Patience C, Fishman J, Cooper DK, Hawley RJ, Greenstein J, Schuurman HJ, Awwad M, Sykes M, Sachs DH. Marked prolongation of porcine renal xenograft survival in baboons through the use of alpha1,3-galactosyltransferase gene-knockout donors and the cotransplantation of vascularized thymic tissue. Nat Med. 2005;11(1):32–4. https://doi.org/10.1038/nm1172.
17. Higginbotham L, Mathews D, Breeden CA, Song M, Farris AB, Larsen CP, Ford ML, Lutz AJ, Tector M, Newell KA, Tector AJ, Adams AB. Pre-transplant antibody screening and anti-CD154 costimulation blockade promote long-term xenograft survival in a pig-to-primate kidney transplant model. Xenotransplantation. 2015;22(3):221–30. https://doi.org/10.1111/xen.12166.
18. Chen G, Qian H, Starzl T, Sun H, Garcia B, Wang X, Wise Y, Liu Y, Xiang Y, Copeman L, Liu W, Jevnikar A, Wall W, Cooper DK, Murase N, Dai Y, Wang W, Xiong Y, White DJ, Zhong R. Acute rejection is associated with antibodies to non-Gal antigens in baboons using Gal-knockout pig kidneys. Nat Med. 2005;11(12):1295–8. https://doi.org/10.1038/nm1330.
19. Yamada K, Sachs DH, DerSimonian H. Human anti-porcine xenogeneic T cell response. Evidence for allelic specificity of mixed leukocyte reaction and for both direct and indirect pathways of recognition. J Immunol. 1995;155(11):5249–56.
20. Langin M, Mayr T, Reichart B, Michel S, Buchholz S, Guethoff S, Dashkevich A, Baehr A, Egerer S, Bauer A, Mihalj M, Panelli A, Issl L, Ying J, Fresch AK, Buttgereit I, Mokelke M, Radan J, Werner F, Lutzmann I, Steen S, Sjoberg T, Paskevicius A, Qiuming L, Sfriso R, Rieben R, Dahlhoff M, Kessler B, Kemter E, Klett K, Hinkel R, Kupatt C, Falkenau A, Reu S, Ellgass R, Herzog R, Binder U, Wich G, Skerra A, Ayares D, Kind A, Schonmann U, Kaup FJ, Hagl C, Wolf E, Klymiuk N, Brenner P, Abicht JM. Consistent success in life-supporting porcine cardiac xenotransplantation. Nature. 2018;564(7736):430–3. https://doi.org/10.1038/s41586-018-0765-z.
21. Fishman JA, Patience C. Xenotransplantation: infectious risk revisited. Am J Transplant. 2004;4(9):1383–90. https://doi.org/10.1111/j.1600-6143.2004.00542.x.
22. Paradis K, Langford G, Long Z, Heneine W, Sandstrom P, Switzer WM, Chapman LE, Lockey C, Onions D, Otto E. Search for cross-species transmission of porcine endogenous retrovirus in patients treated with living pig tissue. The XEN 111 Study Group. Science. 1999;285(5431):1236–41.
23. Yang L, Güell M, Niu D, George H, Lesha E, Grishin D, Aach J, Shrock E, Xu W, Poci J, Cortazio R, Wilkinson RA, Fishman JA, Church G. Genome-wide inactivation of porcine endogenous retroviruses (PERVs). Science. 2015;350(6264):1101–4.
24. Chan TC, Ariizumi T, Asashima M. A model system for organ engineering: transplantation of in vitro induced embryonic kidney. Naturwissenschaften. 1999;86(5):224–7.
25. Rogers SA, Lowell JA, Hammerman NAH, M. R. Transplantation of developing metanephroi into adult rats. Kidney Int. 1998;54(1):27–37. https://doi.org/10.1046/j.1523-1755.1998.00971.x.
26. Rogers SA, Hammerman MR. Prolongation of life in anephric rats following de novo renal organogenesis. Organogenesis. 2004;1(1):22–5.

27. Yokote S, Yokoo T, Matsumoto K, Utsunomiya Y, Kawamura T, Hosoya T. The effect of metanephros transplantation on blood pressure in anephric rats with induced acute hypotension. Nephrol Dial Transplant. 2012;27(9):3449–55. https://doi.org/10.1093/ndt/gfs006.
28. Matsumoto K, Yokoo T, Yokote S, Utsunomiya Y, Ohashi T, Hosoya T. Functional development of a transplanted embryonic kidney: effect of transplantation site. J Nephrol. 2012;25(1):50–5. https://doi.org/10.5301/jn.2011.7426.
29. Hammerman MR. Transplantation of renal primordia: renal organogenesis. Pediatr Nephrol. 2007;22(12):1991–8. https://doi.org/10.1007/s00467-007-0554-7.
30. Foglia RP, DiPreta J, Statter MB, Donahoe PK. Fetal allograft survival in immunocompetent recipients is age dependent and organ specific. Ann Surg. 1986;204(4):402–10.
31. Statter MB, Fahrner KJ, Barksdale EM Jr, Parks DE, Flavell RA, Donahoe PK. Correlation of fetal kidney and testis congenic graft survival with reduced major histocompatibility complex burden. Transplantation. 1989;47(4):651–60.
32. Velasco AL, Hegre OD. Decreased immunogenicity of fetal kidneys: the role of passenger leukocytes. J Pediatr Surg. 1989;24(1):59–63.
33. Rogers SA, Liapis H, Hammerman MR. Normalization of glucose post-transplantation of pig pancreatic anlagen into non-immunosuppressed diabetic rats depends on obtaining anlagen prior to embryonic day 35. Transpl Immunol. 2005;14(2):67–75. https://doi.org/10.1016/j.trim.2005.02.004.
34. Rogers SA, Talcott M, Hammerman MR. Transplantation of pig metanephroi. ASAIO J. 2003;49(1):48–52. https://doi.org/10.1097/01.MAT.0000044737.04648.F5.
35. Dekel B, Burakova T, Arditti FD, Reich-Zeliger S, Milstein O, Aviel-Ronen S, Rechavi G, Friedman N, Kaminski N, Passwell JH, Reisner Y. Human and porcine early kidney precursors as a new source for transplantation. Nat Med. 2003;9(1):53–60. https://doi.org/10.1038/nm812.
36. Yokote S, Matsunari H, Iwai S, Yamanaka S, Uchikura A, Fujimoto E, Matsumoto K, Nagashima H, Kobayashi E, Yokoo T. Urine excretion strategy for stem cell-generated embryonic kidneys. Proc Natl Acad Sci U S A. 2015;112(42):12980–5. https://doi.org/10.1073/pnas.1507803112.
37. Marshall D, Dilworth MR, Clancy M, Bravery CA, Ashton N. Increasing renal mass improves survival in anephric rats following metanephros transplantation. Exp Physiol. 2007;92(1):263–71. https://doi.org/10.1113/expphysiol.2006.036319.
38. Yamanaka S, Yokote S, Yamada A, Katsuoka Y, Izuhara L, Shimada Y, Omura N, Okano HJ, Ohki T, Yokoo T. Adipose tissue-derived mesenchymal stem cells in long-term dialysis patients display downregulation of PCAF expression and poor angiogenesis activation. PLoS One. 2014;9(7):e102311. https://doi.org/10.1371/journal.pone.0102311.
39. Tajiri S, Yamanaka S, Fujimoto T, Matsumoto K, Taguchi A, Nishinakamura R, Okano HJ, Yokoo T. Regenerative potential of induced pluripotent stem cells derived from patients undergoing haemodialysis in kidney regeneration. Sci Rep. 2018;8(1):14919. https://doi.org/10.1038/s41598-018-33256-7.
40. Fujimoto E, Yamanaka S, Kurihara S, Tajiri S, Izuhara L, Katsuoka Y, Yokote S, Matsumoto K, Kobayashi E, Okano HJ, Chikaraishi T, Yokoo T. Embryonic kidney function in a chronic renal failure model in rodents. Clin Exp Nephrol. 2017;21(4):579–88. https://doi.org/10.1007/s10157-016-1337-x.
41. Taguchi A, Nishinakamura R. Higher-order kidney organogenesis from pluripotent stem cells. Cell Stem Cell. 2017;21(6):730–746.e736. https://doi.org/10.1016/j.stem.2017.10.011.
42. Takasato M, Er PX, Chiu HS, Maier B, Baillie GJ, Ferguson C, Parton RG, Wolvetang EJ, Roost MS, Chuva de Sousa Lopes SM, Little MH. Kidney organoids from human iPS cells contain multiple lineages and model human nephrogenesis. Nature. 2015;526(7574):564–8. https://doi.org/10.1038/nature15695.
43. Chen J, Lansford R, Stewart V, Young F, Alt FW. RAG-2-deficient blastocyst complementation: an assay of gene function in lymphocyte development. Proc Natl Acad Sci U S A. 1993;90(10):4528–32.

44. Kobayashi T, Yamaguchi T, Hamanaka S, Kato-Itoh M, Yamazaki Y, Ibata M, Sato H, Lee YS, Usui J, Knisely AS, Hirabayashi M, Nakauchi H. Generation of rat pancreas in mouse by interspecific blastocyst injection of pluripotent stem cells. Cell. 2010;142(5):787–99. https://doi.org/10.1016/j.cell.2010.07.039.
45. Isotani A, Hatayama H, Kaseda K, Ikawa M, Okabe M. Formation of a thymus from rat ES cells in xenogeneic nude mouse↔rat ES chimeras. Genes Cells. 2011;16(4):397–405. https://doi.org/10.1111/j.1365-2443.2011.01495.x.
46. Matsunari H, Nagashima H, Watanabe M, Umeyama K, Nakano K, Nagaya M, Kobayashi T, Yamaguchi T, Sumazaki R, Herzenberg LA, Nakauchi H. Blastocyst complementation generates exogenic pancreas in vivo in apancreatic cloned pigs. Proc Natl Acad Sci U S A. 2013;110(12):4557–62. https://doi.org/10.1073/pnas.1222902110.
47. Wu J, Platero-Luengo A, Sakurai M, Sugawara A, Gil MA, Yamauchi T, Suzuki K, Bogliotti YS, Cuello C, Morales Valencia M, Okumura D, Luo J, Vilarino M, Parrilla I, Soto DA, Martinez CA, Hishida T, Sanchez-Bautista S, Martinez-Martinez ML, Wang H, Nohalez A, Aizawa E, Martinez-Redondo P, Ocampo A, Reddy P, Roca J, Maga EA, Esteban CR, Berggren WT, Nunez Delicado E, Lajara J, Guillen I, Guillen P, Campistol JM, Martinez EA, Ross PJ, Izpisua Belmonte JC. Interspecies chimerism with mammalian pluripotent stem cells. Cell. 2017;168(3):473–486.e415. https://doi.org/10.1016/j.cell.2016.12.036.
48. Flake AW, Harrison MR, Adzick NS, Zanjani ED. Transplantation of fetal hematopoietic stem cells in utero: the creation of hematopoietic chimeras. Science. 1986;233(4765):776–8.
49. Yokoo T, Ohashi T, Shen JS, Sakurai K, Miyazaki Y, Utsunomiya Y, Takahashi M, Terada Y, Eto Y, Kawamura T, Osumi N, Hosoya T. Human mesenchymal stem cells in rodent whole-embryo culture are reprogrammed to contribute to kidney tissues. Proc Natl Acad Sci U S A. 2005;102(9):3296–300. https://doi.org/10.1073/pnas.0406878102.
50. Yokoo T, Fukui A, Ohashi T, Miyazaki Y, Utsunomiya Y, Kawamura T, Hosoya T, Okabe M, Kobayashi E. Xenobiotic kidney organogenesis from human mesenchymal stem cells using a growing rodent embryo. J Am Soc Nephrol. 2006;17(4):1026–34. https://doi.org/10.1681/ASN.2005101043.
51. Yokoo T, Fukui A, Matsumoto K, Ohashi T, Sado Y, Suzuki H, Kawamura T, Okabe M, Hosoya T, Kobayashi E. Generation of a transplantable erythropoietin-producer derived from human mesenchymal stem cells. Transplantation. 2008;85(11):1654–8. https://doi.org/10.1097/TP.0b013e318173a35d.
52. Gheisari Y, Yokoo T, Matsumoto K, Fukui A, Sugimoto N, Ohashi T, Kawamura T, Hosoya T, Kobayashi E. A thermoreversible polymer mediates controlled release of glial cell line-derived neurotrophic factor to enhance kidney regeneration. Artif Organs. 2010;34(8):642–7. https://doi.org/10.1111/j.1525-1594.2009.00928.x.
53. Fukui A, Yokoo T, Matsumoto K, Kawamura T, Hosoya T, Okabe M. Integration of human mesenchymal stem cells into the Wolffian duct in chicken embryos. Biochem Biophys Res Commun. 2009;385(3):330–5. https://doi.org/10.1016/j.bbrc.2009.05.052.
54. Yamanaka S, Tajiri S, Fujimoto T, Matsumoto K, Fukunaga S, Kim BS, Okano HJ, Yokoo T. Generation of interspecies limited chimeric nephrons using a conditional nephron progenitor cell replacement system. Nat Commun. 2017;8(1):1719. https://doi.org/10.1038/s41467-017-01922-5.
55. Irie N. Remaining questions related to the hourglass model in vertebrate evolution. Curr Opin Genet Dev. 2017;45:103–7. https://doi.org/10.1016/j.gde.2017.04.004.
56. Suchy F, Nakauchi H. Interspecies chimeras. Curr Opin Genet Dev. 2018;52:36–41. https://doi.org/10.1016/j.gde.2018.05.007.