Acute Kidney Injury: Transition to Chronic Kidney Disease

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Keywords
AKI · Acute kidney diseases (AKD) · cisplatin-induced AKI · L-FABP, liver fatty acid binding protein · VAP-1, vascular adhesion protein-1

24.1 Case Report

A 49-year-old man was admitted to the dermatology ward to receive chemoradiotherapy for squamous cell carcinoma (SCC) of the left inguinal lymph node. The patient had a "birthmark" at the same lesion, which had gradually formed to become a 2.0 × 4.0 cm tumor mass in the past 2 years. According to the biopsy, computed tomography (CT), and positron emission tomography (PET), this mass was diagnosed as stage 4 SCC. He had hypertension and received 20 mg olmesartan and 20 mg nifedipine. He had no specific family history and allergies. His social history indicated he had smoked 20 cigarettes a day and drunk 500 ml of Japanese vodka a day. He had no history of renal disease, and his estimated glomerular filtration rate (eGFR) was 115.8 ml/min/1.73 m^2 at admission. A 2.3 × 4.8 cm soft, reddish mass was found at the left inguinal lymph node.

The major laboratory findings at admission were as follows:

Blood test: white blood cell 8200/μL, blood hemoglobin 14.3 g/dL, platelet count 203,000/μL, total protein 7.1 g/dL, albumin 3.9 g/dL, lactate dehydrogenase 238 U/L, aspartate transaminase 21 U/L, alanine transaminase 20 U/L, γ-glutamyltransferase 278 U/L, alkaline phosphatase 386 U/L, total bilirubin 0.7 mg/dL, total cholesterol 179 mg/dL, calcium 9.0 mg/dL, blood urea nitrogen 11.6 mg/dL, serum creatinine 0.58 mg/dL, sodium 140 mEq/L, potassium 4.5 mEq/L, chloride 104 mEq/L, C-reactive protein 2.63 mg/dL, fasting blood glucose 166 mg/dL, and glycated hemoglobin (HbA_{1c}) 7.5%

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T. Oohashi et al. (eds.), *Human Pathobiochemistry*, https://doi.org/10.1007/978-981-13-2977-7_24

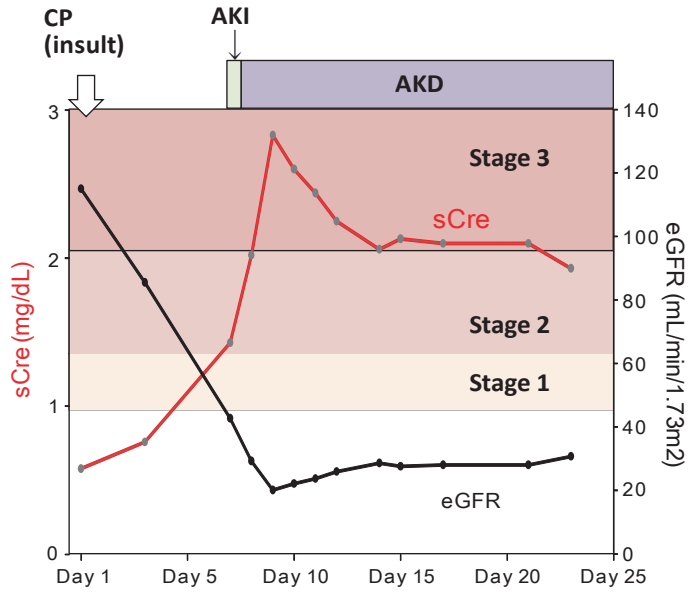

Fig. 24.1 Clinical course of the patient (during admission). CP was given this patient on day 1. On the 8th day, he was diagnosed as stage 2 AKI. Although CP was discontinued and IV fluids therapy was performed, AKI stage increases to stage 3 at day 10 (sCre 2.83 mg/dL). After 7 days duration of AKI, the persistent kidney damage had been recognized as stage 3 AKD but improved to stage 2 AKD, where it was sustained. The patient was discharged on the 26th day. *CP* cisplatin, *IV* intravenous, *AKI* acute kidney injury, *AKD* acute kidney disease. For stage calculation, see Tables 24.1 and 24.4

Urine test: protein (−), glucose (−), and occult blood (−)
Electrocardiography: within normal range and heart rate 83/min
Chest X-ray: cardiothoracic ratio 53% and cardiophrenic angles sharp

He began to receive cisplatin (CP) and 5-fluorourcil (5-FU) chemotherapy. 1000–3000 ml per day of intravenous (IV) fluids was given. Single 20 mg of furosemide was given on day 1 to avoid overhydrating, though his urine flow gradually decreased (3.10 ml/kg/h on day 1 and 0.67 ml/kg/h on day 7). He lost 4 kg in a week. On the 8th day, he was diagnosed with stage 2 acute kidney injury (AKI) due to increased serum creatinine (sCre). Following consultation with nephrology team and considering CP-induced AKI (CP-AKI), CP was discontinued, and he continued receiving an IV fluid replacement therapy. Olmesartan and nifedipine were discontinued as systolic blood pressures were 90 mmHg. Meanwhile he was newly diagnosed with type 2 diabetes. After referral to a diabetologist, he began to receive 50 mg daily vildagliptin. Although sCre began to decrease, it did not return to baseline. The patient was discharged on the 26th day (Fig. 24.1).

One month later after discharge, he received three doses of DTX + 5-FU chemotherapy and was considered in remission from his malignancy. Although he did not show any overt proteinuria during the follow-up period, his sCre did not return to baseline and remained 50–60 ml/min/1.73m^2 of eGFR for 5 years after discharge. This patient was considered to have developed CKD after an episode of CP-AKI (Fig. 24.2).

24.2 Diagnosis

24.2.1 Cisplatin-Induced AKI, Which Led to CKD

AKI is a syndrome characterized by rapid or sudden decrease in kidney function, often accompa-

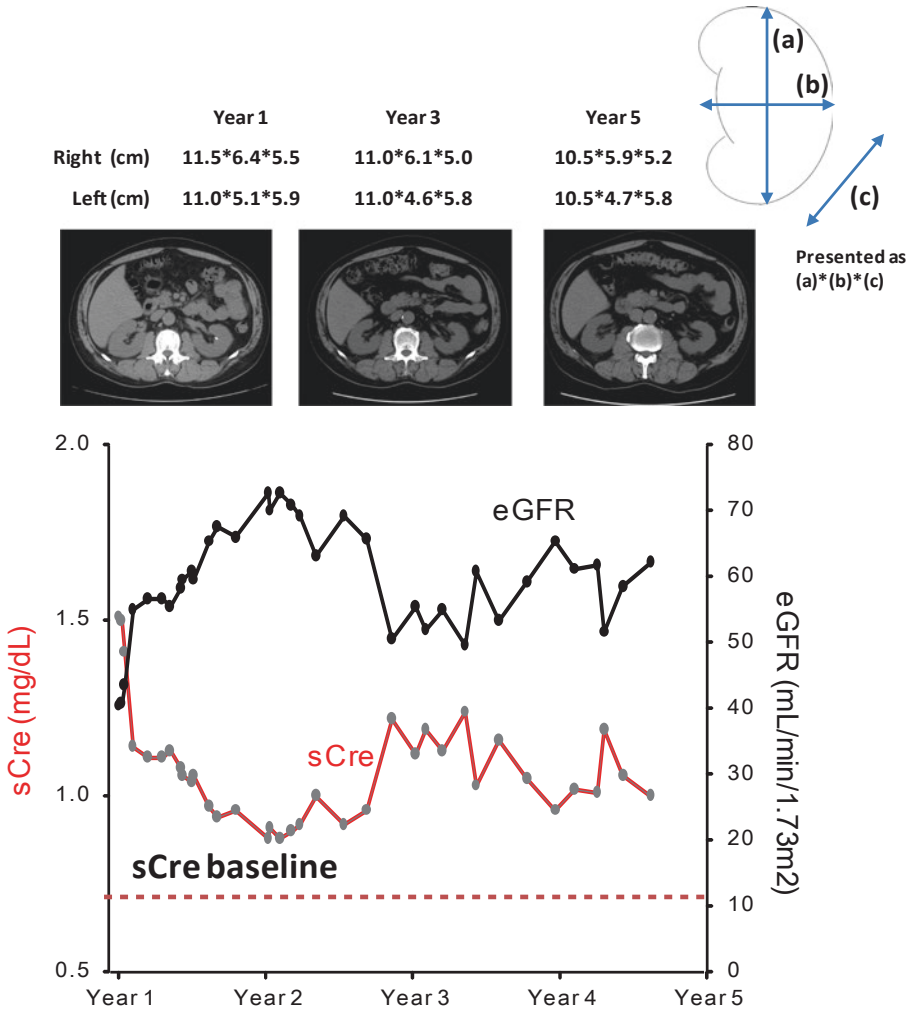

Fig. 24.2 Clinical course of the patient (5 years follow-up). His sCre did not return to baseline (0.58 mg/dL) and remains 50–60 ml/min/1.73 m^2 of eGFR for 5 years after discharge. This patient has been considered to develop CKD after CP-AKI. His follow-up CT presented slightly atrophied kidneys. Note kidneys in each CT presented as (*a*)*(*b*)*(*c*). Year 5 means 4 years later after an admission of the presented case. *eGFR* estimated glomerular filtration rate, *CP-AKI* cisplatin-induced acute kidney injury, *CKD* chronic kidney disease, *CT* computed tomography

nied with oliguria, which happens within a few days. Ischemia-reperfusion injury (IRI), nephrotoxic agents, and sepsis are the major causes of AKI. There are few specific tests to establish the etiology beyond a rising sCre, indicating lack of kidney functioning. AKI has high morbidity/mortality in hospitalized patients, affects >13 million people per year around the world, and causes about 1.7 million deaths/year (Mehta et al. 2015). The risk of AKI among cancer patients has been reported to be 17.5% (1 year) and 27.0% (5 years) (Lam and Humphreys 2012).

It is widely accepted that the eGFR is the most useful kidney function index and that changes in sCre levels are surrogate functional biomarkers for changes in the GFR. Of note eGFR calculations are not valid in the setting of extremes of body mass or under 18-year-old and pregnancy. Two previous criteria for AKI, which were based on sCre levels and urine output, were proposed

and validated: the Risk, Injury, Failure, Loss, End-Stage Renal Disease (RIFLE) criteria (Bellomo et al. 2004) and Acute Kidney Injury Network (AKIN) criteria (Mehta et al. 2007). In 2012, the Kidney Disease: Improving Global Outcomes (KDIGO) AKI Guideline Work Group proposed an integrated definition of AKI, based on sCre elevation and urine output decrease, as below (Kellum and Lameire 2013):

- "Increase in sCre by ≧0.3 mg/dL (26.5 μmol/L) within 48 h"
- "Increase in sCre to ≧1.5 times baseline, which have occurred within 7 days"
- "Urine volume <0.5 ml/kg/h for 6 h"

In this case, the patient sCre was increased from 0.58 (day 1) to 1.43 mg/dL (day 8; 2.4 times) in 7 days. According to the staging of AKI (Table 24.1), the patient was diagnosed as "stage 2 AKI." Nephrotoxicity has been attributed to anywhere from 8 to 60% of hospital-acquired AKI (Schetz et al. 2005). CP is a platinum compound and is known as an effective chemotherapeutic agent for many carcinomas, sarcomas, and lymphomas, though it has adverse effects of nephrotoxicity and ototoxicity (Pabla and Dong 2008). Exposure of tubular epithelial cells to CP activates complex signaling pathways that engender cell injury and death. In the CP-AKI model, the pro-apoptotic family Bax is activated and accumulates in the mitochondria in renal tubular cells (Wei et al. 2007; Katagiri et al. 2013). Generally this nephrotoxicity is reversible, though in some cases, such as in the patient described above, it can be persistent.

The majority of patients will recover their renal function following an episode of AKI, though some AKI survivors have a higher risk of developing chronic kidney disease (CKD) (Cerda et al. 2008). If AKI patients are diagnosed as acute tubular necrosis, or there are multiple causes of the AKI, they have a higher risk of subsequently developing CKD (Humphreys et al. 2016). Also, it is important to evaluate and follow AKI patient's pre-existing risk for CKD, such as advanced age, congestive heart failure, and uncontrolled diabetes. The present patient had newly diagnosed diabetes, though he has not developed overt proteinuria in response to the treatment. CKD is defined as structural/functional abnormalities that persist for >3 months. Patients with eGFR <60 ml/min/1.73 m^2 or with markers of kidney damage such as albuminuria, urine sediment, or electrolyte abnormalities, or a history of kidney transplantation, are defined as CKD (Table 24.2) (KDIGO 2013). To date, the

Table 24.1 Criteria of AKI (KDIGO 2012)

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline or ≧0.3 mg/dL (≧26.5 μmol/L) increase	<0.5 ml/kg/h for 6–12 h
2	2.0–2.9 times baseline	<0.5 ml/kg/h for ≧12 h
3	3.0 times baseline, or increase in serum creatinine to ≧4.0 mg/dL (≧353.6 μmol/L), or initiation of renal replacement therapy	<0.3 ml/kg/h for ≧24 h or anuria for ≧12 h

Anuria is commonly defined in the adult population as a urine passage of less than 50–100 mL per day

Table 24.2 Criteria for CKD (either of the following present for >3 months) (KDIGO 2013)

Markers of kidney damage (one or more)	Albuminuria (AER ≧30 mg/24 h, ACR≧30 mg/g)
	Urine sediment abnormalities
	Electrolyte and other abnormalities due to tubular disorders
	Abnormalities detected by histology
	Structural abnormalities detected by imaging
	History of kidney transplantation
Decreased GFR	GFR <60 ml/min/1.73 m^2

AER albumin excretion rate, *ACR* albumin to creatinine ratio, *GFR* glomerular filtration rate

Table 24.3 Meaning and definition of AKI, AKD, and CKD (Chawla et al. 2017)

	AKI	AKD	CKD
Days post injury	0–7 days	7–90 days	90 days –
Meaning	Sudden decrease of kidney function or structure	Patients with AKD can progress to CKD	Abnormalities of kidney structure/function for >3 months
Definition	See Table 24.1	sCre >1.5 times baseline	See Table 24.2
Follow-up		Patient education, medication, reconciliation, nephrology referral	

AKI acute kidney injury, *AKD* acute kidney disease, *CKD* chronic kidney disease, *sCre* serum creatinine

Table 24.4 Suggested staging of AKD (Chawla et al. 2017)

Stage	Definition
3	sCre ≧3.0 times baseline or increase ≧4.0 mg/dL or renal replacement therapy
2	sCre ≧2.0 times baseline
1	sCre ≧1.5 times baseline
0	B/C: sCre <1.5 times baseline but not back to baseline and continued evidence of ongoing injury, repair, and/or regeneration
	C: sCre <1.5 times baseline but not back to baseline
	B: Continued evidence of ongoing injury, repair and/or regeneration, or indicators of loss of renal glomerular or tubular reserve
	A: Absence of criteria for B or C

AKD acute kidney disease, *sCre* serum creatinine

leading cause of CKD is diabetes in most developed countries, and both CKD and diabetes are well-known risk factors for cardiovascular disease. In a large cohort study, a 30–40% decline in eGFR after AKI can be a surrogate endpoint for end-stage kidney disease (ESKD) (Grams et al. 2016). The continuum of AKI to CKD may cause significant personal and economic strain.

Recently the term acute kidney disease (AKD) has been proposed by KDIGO to define the course after AKI in which the kidney injury is ongoing (Chawla et al. 2017). In this guideline, AKD is defined as a new concept to provide an integrated clinical approach to patients with kidney abnormalities of function and structure, whose kidney damage is more than 7 days but less than 3 months (Table 24.3). (KDIGO 2012).

Regardless of AKI severity, AKI episodes lasting over 72 h after the insult have been reported to be associated with poorer outcome than AKI that is rapidly ameliorated within 72 h (Chawla et al. 2017). AKI resolving within 48 h is often described as transient AKI. This patient was diagnosed as stage 2 AKI at 7 days after first CP treatment, which developed further into AKD stage 3 at day 10 (sCre 2.83 mg/dL). He had persistent kidney damage during AKD, which was sustained as stage 2 (Table 24.4) (Chawla et al. 2017). His sCre did not return to basal level for 30 days, even for 5 years after this AKI episode.

His follow-up CT presented slightly atrophied kidneys with partial renal capsular indentations (Fig. 24.2). Progression of CKD with persistent interstitial fibrosis (IF) is probable with this patient. His clinical course clearly indicates the continuum of AKI to CKD as a result of risk factors and disease modifiers and further predicts clinical outcome (Chawla et al. 2017).

24.3 Molecular Perspectives

Repeated or chronic kidney injury results in extracellular matrix (ECM) accumulation and tubular atrophy that eventually lead to hypoxia and IF in kidney. Proximal tubule injury beyond the potential for adaptive repair will arrest epithelial cells in the G2/M transition of the cell cycle

and will enhance production of pro-fibrotic factors (Bonventre 2014; Yang et al. 2010). Injured epithelial cells produce a number of growth factors, such as epidermal growth factor, hepatocyte growth factor (HGF), and insulin-like growth factor 1. Increased levels of transforming growth factor (TGF)-β lead to upregulation of α-smooth muscle actin (SMA), F-actin, and collagen I by fibroblasts (Borges et al. 2013; Mack and Yanagita 2015). Glomerular injury followed by IF leads to a decrease of glomerular filtration rate. IF typically shows excessive fibrillar collagen accumulation.

CP-AKI is often seen after 8–10 days of CP administration in patients. In rodents, AKI induced by a single high dose of CP is a well-studied as dose dependently. A model of chronic kidney injury induced by a single CP injection presents with glomerular sclerosis, cyst formations, and interstitial fibrosis. We developed multiple, lower CP treatment method in mice as a potential clinically relevant AKD model (Katagiri et al. 2015). Since urinary liver fatty acid-binding protein (L-FABP), one of the novel AKI biomarkers currently reimbursed in Japan and CE marked in EU, shows promise as an AKI biomarker and has also been reported to assist in predicting CKD, we evaluated AKD in L-FABP transgenic (Tg) mice.

Male L-FABP-Tg mice heterozygous for human L-FABP (C57BL/6 background) were administered three CP doses (10 mg/kg; at 0, 1, 3 weeks) for 4 weeks. The mice were sacrificed at 4 weeks after the first CP administration. Increased BUN and elevated sCre were observed at 4 weeks. Urinary L-FABP significantly increased 1 week after every CP injection. L-FABP levels at 3 weeks decreased according to the skip of CP injection at 2 weeks, which did not return to baseline (Fig. 24.3c), suggesting a causal relation of each mild AKI and the development of CKD as a mild but a cumulative CP toxicity. Pathological analysis indicated tubule dilatation with brush border loss and moderate renal IF at 4 weeks (Fig. 24.3). This model is robust and relevant to clinical findings of AKI to CKD in our daily practice. This study also demonstrated urinary L-FABP as a promising early clinical biomarker predictable CP-AKI to CKD and AKD.

24.4 Therapy

Despite recent advances in renal replacement therapy, AKI is still associated with poor outcomes. As per KDIGO guidelines, personalized management and diagnostic steps according to each AKI stages have been suggested (Fig. 24.4) (KDIGO 2012). To predict AKI to CKD development (Fig. 24.5), it is important to distinguish rapid reversal (transient) or persistent AKI. As stated above, rapid reversal AKI, which shows quick recovery within 48 h, has a better renal outcome than persistent AKI that continues beyond 48 h.

Unfortunately, there have been no uniformly reliable biomarkers other than sCre that can evaluate kidney repair. Note that it is hard to distinguish functional recovery and structural reconstitution from decrease of sCre. When we treat patients with persistent AKI, careful monitoring including hemodynamic and volume status is required. Moreover, introduction of adequate renal replacement therapy (RRT) should be considered if complications of AKI such as electrolyte imbalance or fluid overload are severe. On the other hand, the limitations of sCre as a functional biomarker are well known. Delayed intervention with sCre-based diagnosis in intensive care unit (ICU) provides the impetus to searching for novel incisive damage AKI biomarkers. After more than a decade of intensive effort, several novel damage biomarkers have been developed and evaluated to facilitate early detection, differential diagnosis, and prognosis of AKI. These new biomarkers that have been identified and evaluated include neutrophil gelatinase-associated lidocaine (NGAL), kidney injury molecule-1

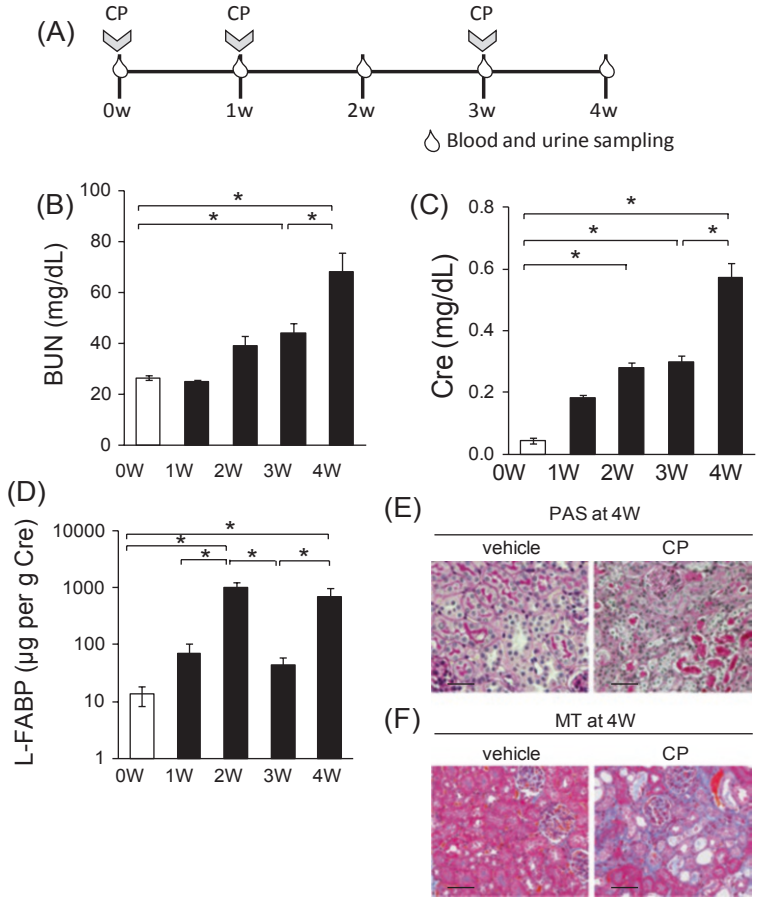

Fig. 24.3 AKD model and interstitial fibrosis by multiple CP treatment (Katagiri et al. 2015). (**a**) Male L-FABP Tg mice were administered three 10 mg/kg CP doses (at 0, 1, 3 weeks) for 4 weeks. *$P < 0.05$ vs. 0 week. CP, cisplatin; L-FABP, L-type fatty acid-binding protein; 4 W, 4 weeks. (**b**–**d**) After exposure to CP, levels of BUN, sCre, and urinary L-FABP were significantly higher at 4 weeks ($n = 7$–8). No further elevation of L-FABP was observed at 3 weeks, following the omission of CP at 2 weeks, but L-FABP also did not revert to baseline levels. (**e**–**f**) Exposure to CP caused brush border loss and interstitial fibrosis at 4 weeks after three CP injections (size bar = 50 μm). *$P < 0.05$. Data are expressed as mean values ± S.E.M. *CP* cisplatin, *sCre* serum creatinine, *BUN* blood urea nitrogen, *L-FABP* L-type fatty acid-binding protein, *W* weeks, *PAS* periodic acid-Schiff, *MT* Masson's trichrome. (http://dx.doi.org/10.1038/ki.2015.327)

(KIM-1), cystatin C, IL-18, urinary L-FABP, urine insulin-like growth factor-binding protein 7 (IGFBP7), and tissue inhibitor of metalloproteinase-2 (TIMP-2).

Duration of this short-term therapeutic window in AKI is highly important to prediction of prognosis for kidney recovery. Limitation of damage during AKI is crucial to tubular cell proliferation and angiogenesis of endothelial cells that lead to kidney repair after insult. As for nephrotoxic-related AKI, it is often difficult to clarify the exact nephrotoxic agents that have induced AKI. Administration of antimicrobials to septic patients, radiocontrast agents to acute coronary syndrome patients, and cisplatin to malignancy patients are examples of agents given to patients who are already have had higher risks for developing AKI. However, it is

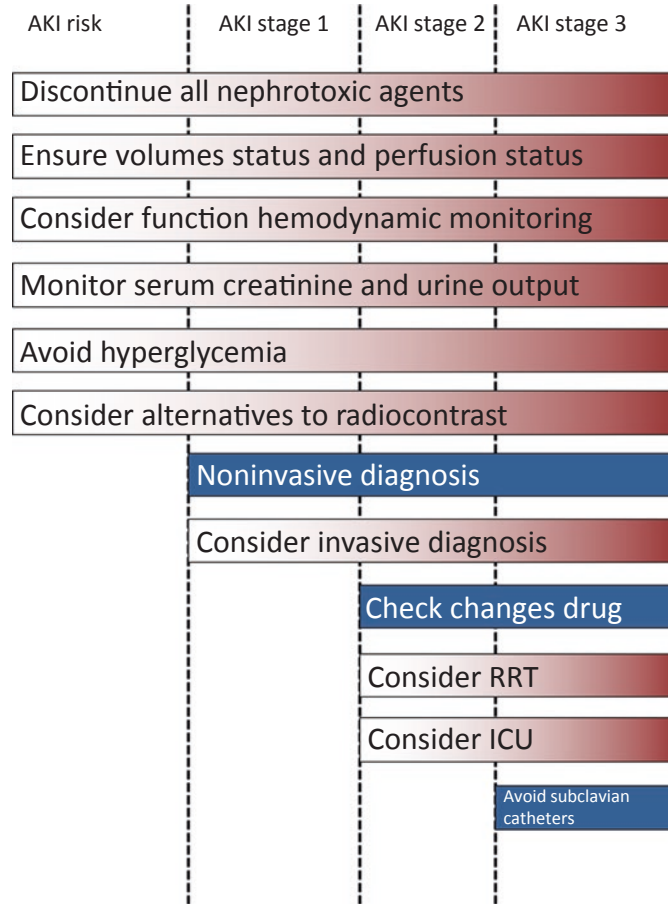

Fig. 24.4 Stage-based AKI management (KDIGO 2012). Personalized management and diagnostic steps according to each AKI stages are suggested by KDIGO guidelines. Blue shading indicates actions that are equally appropriate at all stages, whereas red-graded shading indicates increasing priority as intensity increases. *AKI* acute kidney injury, *RRT* renal replacement therapy, *ICU* intensive care unit, *KDIGO* Kidney Disease: Improving Global Outcomes

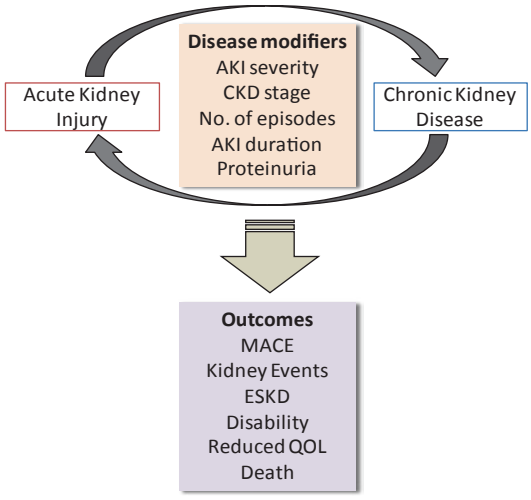

Fig. 24.5 Continuum of AKI and CKD (Chawla et al. 2017). AKI and CKD are not always separate disease states and tend to represent a continuum with patients in the setting of sustained AKI who have an increased risk of developing de novo/existing CKD. The various disease modifiers and risk factors might represent opportunities to intervene. *AKI* acute kidney injury, *CKD* chronic kidney disease, *MACE* major adverse cardiovascular events, *ESKD* end-stage kidney disease, *QOL* quality of life

safe to avoid an additional exposure to a suspected drug if patients develop AKI during treatment.

Vascular adhesion protein-1 (VAP-1) is a circulating and type-1 membrane-bound protein that is expressed predominantly in the endothelium and leukocytes and plays a dual role in mediating inflammation and reactive oxygen species (ROS) production. In our experiment, 1 week of VAP-1 inhibitor treatment during multiple CP injections attenuated biomarker elevation and pathological injury of AKD, with suppression of oxidative stress and IF development (Katagiri et al. 2015). VAP-1 inhibition is focused in nonalcoholic steatohepatitis (NASH) to ameliorate liver fibrosis recently. Above mentioned therapeutic intervention together with sensitive biomarker rather than sCre is necessary for the future pharmaceutical development in this disease entity similarly to pharmaceutical development in the oncology field.

End-of-Chapter Questions

1. Are novel AKI biomarkers useful to monitor the clinical course of AKD? Do AKI biomarkers have a role in indicating further deterioration of AKD as shown in our mice AKD model?
2. How do we evaluate a patient's basal kidney function if he/she already developed AKI without any recent medical records? Could any lab test/imaging/etc. help in evaluating pre-existing CKD?
3. AKI combined with malignancy is expected to be increased in aging countries. What kind of risk factors should we care for AKI among these patients? (ex. anticancer drug, dehydration, infection…)

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