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Acute Kidney Injury (AKI)

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Abstract

Acute kidney injury (AKI) is a serious public health issue, with an increasing incidence and significant associated deleterious effects. Several studies have reported the consequences of AKI, including prolonged hospital stay, increased healthcare costs, morbidity, and mortality. Many factors are known to affect AKI development. Kidney is exposed to a larger proportion and a higher concentration of drugs and toxins than other organs through the secretion of ionic drugs by tubular organic ion transporters across the luminal membranes of renal tubular epithelial cells and through reabsorption of filtered toxins into the lumen of the tubule; these cells are at a greater risk for injury. This section gives an overview of AKI including the definition, causes, and prognosis.

Keywords: acute kidney injury, drug, prognosis

1. Introduction

1.1. AKI definition

Acute kidney injury (AKI) results in an acute and usually transient decrease in renal function. AKI is defined as any of the following (not graded): (1) an increase in serum creatinine (SCr) by ≥ 0.3 mg/dl (≥ 26.5 μ mol/l) within 48 h, or (2) an increase in SCr to ≥ 1.5 times baseline that is known or presumed to have occurred within the prior 7 days, or (3) urine volume < 0.5 ml/kg/h for 6 h.

1.2. Clinical stratification of AKI

The RIFLE (Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function and End-stage kidney disease) classification was proposed as a diagnostic

criterion of acute renal failure (ARF) in order to ameliorate the morbidity and mortality of ARF (**Table 1**) [1–3]. Under this proposal, AKI has instead been proposed to be called ARF. In addition, the AKI Network (AKIN) was formed around the attendees of a critical care and kidney-related conference; the revised version of the RIFLE classification by the AKIN was proposed as the diagnostic criterion of AKI (**Table 2**) [4] and the Kidney Disease Improving Global Outcomes (KDIGO) were used for the diagnosis of AKI, where the clinical conditions are elevated serum creatinine level and a decreased urine output within 48 h (**Table 3**) [5].

SCr, serum creatinine; ESKD, end-stage kidney disease.

An abrupt (within 48 h) reduction in kidney function is currently defined as an absolute increase in serum creatinine of more than or equal to 0.3 mg/dl ($\geq 26.4 \mu\text{mol/l}$), a percentage increase in serum creatinine of more than or equal to 50% (1.5-fold from baseline), or a reduction in urine output (documented oliguria of less than 0.5 ml/kg per hour for more than 6 h). AKI is diagnosed if one of the definitions in 1–3 is met. If a diagnosis is made based solely on urine output, this diagnostic criterion is used under the condition that body fluid volume is properly corrected and urinary tract obstruction or readily reversible oliguria are excluded. SCr, serum creatinine.

	Glomerular filtration rate (GFR)	Urine output
Risk	SCr more than 1.5 times or GFR decrease >25%	Less than 0.5 ml/kg/h for more than 6 h
Injury	SCr more than 2.0 times or GFR decrease >50%	Less than 0.5 ml/kg/h for more than 12 h
Failure	SCr more than 3.0 times, or GFR decrease >75%, or SCr ≥ 0.5 mg/dl with acute elevation SCr ≥ 4 mg/dl	Less than 0.3 ml/kg/h for more than 24 h or anuria for more than 12 h
Loss	Continued ARF (complete loss of kidney function) for more than 4 weeks	Continued ARF (complete loss of kidney function) for more than 4 weeks
ESKD	End-stage kidney disease (dialysis dependency for more than 3 months)	End-stage kidney disease (dialysis dependency for more than 3 months)

Table 1. RIFLE classification.

Stage	SCr	Urine output
Stage 1	Increase in SCr of more than or equal to 0.3 mg/dl or increase to more than or equal to 150–200% (1.5- to 2-fold) from baseline	Less than 0.5 ml/kg/h for more than 6 h
Stage 2	Increase in SCr to more than 200–300% (>2- to 3-fold) from baseline	Less than 0.5 ml/kg/h for more than 12 h
Stage 3	Increase in SCr to more than 300% (>3-fold) from baseline or SCr of more than or equal to 4.0 mg/dl with an acute increase of at least 0.5 mg/dl	Less than 0.3 ml/kg/h for 24 h or anuria for 12 h

Table 2. AKIN classification.

Stage	Classification standard by SCr	Classification standard by urine output
1	SCr more than 27 $\mu\text{mol/l}$ (0.3 mg/dl) or SCr elevated to 1.5–1.9 times normal values	Less than 0.5 ml/kg/h within 6–12 h
2	SCr 2–2.9 times normal values	Less than 0.5 ml/kg/h in more than 12 h
3	SCr elevation to ≥ 3 times normal values or SCr $\geq 354 \mu\text{mol/l}$ (4.0 mg/dl) or start of renal replacement therapy	Anuria for 12 h

Table 3. KDIGO classification.

1.3. Classification of AKI

AKI is classified roughly into prerenal, renal, and postrenal according to the site of onset [6]. Prerenal refers to cases of a decreased blood flow to the kidney as a result of systemic illness. Renal refers to cases with roots in the kidney. Postrenal refers to cases caused by issues in the lower urinary tract (urinary duct, bladder, or urethral tube).

2. Drug-induced AKI

2.1. Definition

Drug-induced kidney injury (DKI) is a general term for newly occurring kidney injury or kidney injury that has been exacerbated by the drugs administered for diagnosis and treatment. Furthermore, DKI can be classified as follows: toxic kidney injury, acute interstitial nephritis by allergy mechanism (hypersensitivity kidney injury), drug-induced indirect toxicity through electrolyte abnormality and blood flow decrease, drug-induced crystal formation, and urinary tract obstruction kidney injury for calculus formation.

2.2. Etiology

Because primary urine, largely filtered by the glomeruli, is reabsorbed in the proximal tubules, drugs and metabolites are easily accumulated in high concentrations in the kidney. For this reason, the kidney is susceptible to drug-induced injury. Because primary urine becomes concentrated in the proximal tubules after primary urine is filtered from the glomeruli, tubular necrosis through direct toxicity occurs with an increased frequency in a dose-related fashion. Drug-induced kidney injury is defined by a new-onset disorder of the kidney or a further exacerbation of the existing dysfunction of the kidney by the administration of drugs. Furthermore, when patients have risk factors, such as older age (elderly), compromised renal function (chronic kidney failure), dehydration, frequent administration of drugs, and baseline disease (diabetes mellitus or myeloma), disorder of the kidney tends to take place. Drugs prone to cause disorder of the kidney may include nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics (aminoglycosides, new quinolones), immunomodulatory agents,

contrasts (iodinated contrast), anticancer drugs (cisplatin), vitamin D and calcium preparations, and drugs for high blood pressure (RAAS blockade in particular) (**Table 4**).

2.3. Pathophysiological

The pathogenic mechanism of drug-induced AKI is poorly understood, but the following are known: the shift of hemodynamic status, the induction of acute interstitial nephritis, the induction of acute renal tubular injury, drug-induced thrombotic microangiopathy, the induction of glomerular nephritis, the induction by crystals in the tubular lumen, and others.

2.4. Kidney hemodynamic change

GFR, which is determined by glomerular pressure and filtration coefficients, is reduced by the inability to maintain glomerular pressure due to renal hemodynamic alterations, which are dependent on the renin-angiotensin aldosterone system (RAAS), endothelin system, prostaglandin system, and nitric oxide (NO). In addition, this condition occurs with minimal change in the vascular smooth muscle of the afferent renal arteriole and the efferent renal arteriole. Non-steroidal anti-inflammatory drugs (NSAIDs) are well-known offending agents and are associated with a high proportion of cases. Compared with internal medications, topical medicines have not been seen as a problem; however, recently, anti-inflammatory

Classification	Prospective drug
Renal hemodynamic alteration	NSAIDs, renin-angiotensin system drugs, active vitamin D, calcineurin inhibitors (cyclosporin and tacrolimus), and diuretics
Thrombotic microangiopathy (TMA)	Angiogenesis inhibitors (VEGF inhibitors), gemcitabine, mitomycin C, interferon, mTOR inhibitors, thienopyridine (antiplatelet drugs), kinin, oxymorphone (opioid), oral contraceptives, and calcineurin inhibitors
Acute renal tubular injury	General chemotherapy (cisplatin, ifosfamide, etc.), antibacterial drugs (aminoglycosides, amphotericin B, vancomycin, etc.), zoledronic acid, BRAF inhibitors, ALK inhibitors, iron chelators, heavy metals, and contrasts
Acute tubulointerstitial nephritis (AIN)	NSAIDs, antibacterial drugs (β-lactam, sulfa drugs, quinolones), diuretics, and PPI
Intratubular obstruction (crystalluria)	Crystal deposition-induced renal disease: antiviral drugs (cisplatin, ifosfamide, etc.), antibacterial drugs (sulfa drugs, ciprofloxacin), methotrexate, triamterene, ascorbic acid, sodium phosphate (laxative), warfarin
Glomerulonephritis	Membranous nephropathy: NSAIDs, platinating agents, bucillamine, and penicillamine
	MCD: NSAIDs, lithium, interferon, pamidronate, vaccines
	FSGS: in addition to the above, hormonal agents and heroin
	lupus nephritis: methyl dopa, hydralazine, procainamide, and quinidine
Others	liquorice root, vitamin D, and antithrombotic agents (Warfarin)

MCD, minimal change disease; FSGS, focal segmental glomerular sclerosis.

Table 4. Causes of drug-induced AKI.

analgesic plasters containing NSAIDs that achieve comparatively higher blood levels have been sold; these forms of administration should also be considered. NSAIDs decrease blood flow in the afferent renal arteriole and GFR by blocking the production of prostaglandins. COX-2-selective inhibitors have turned out to be a cause of AKI development as well as COX-2-nonselective inhibitors, so attention should be paid to these inhibitors regardless of their mechanisms. In addition, RASS inhibitors cause the efferent renal arteriole to dilate and decrease GFR. These drugs have a protective effect for the kidney in CKD patients in the mid- and long term; however, our attention to AKI is required under circumstances where it is easy to reduce renal blood flow.

2.5. Causes of drug-induced thrombotic microangiopathy (drug-induced TMA)

TMA describes a disorder that is thought to be an aftereffect of pathological microvascular endothelial damage and has the three following features: hemolytic anemia, thrombocytopenia, and organ damage. Drugs may induce TMA in some instances, especially angiogenesis inhibitors such as vascular endothelial growth factor (VEGF) and anticancer drugs such as bevacizumab, which carry greater risks. It is thought that VEGF produced by glomerular podocytes is needed to maintain the function of endothelial cells and epidermal cells [7]. A high blood pressure and albuminuria are more problematic in drug-induced TMA; conversely, hemolytic anemia is less problematic. Aside from VEGF inhibitors, it is known that interferon and calcineurin inhibitors could increase drug-induced TMA that shows evidence of thrombocytopenia and schistocytes and signs in glomerular endothelial cells.

2.6. Causes of tubular damage

Drugs taken up by renal tubular epithelial cells mainly cause necrosis in the proximal tubule and apoptosis in the distal tubule and then cast formation in the tubular lumen and blockage by cells that fall behind into the renal tubule lumen, which consequently deteriorate quickly. The following drugs produce renal tubular injury and acute tubular necrosis (ATN) as symptoms progress: antineoplastic drugs such as cisplatin and ifosfamide, antibacterial drugs such as aminoglycosides, and antifungals such as amphotericin B. As a result of renal tubular injury, nephrogenic diabetes insipidus (NDI) and Fanconi syndrome are present. In the case of vancomycin, the pathogenesis of kidney injury is thought to occur as a result of increasing oxidant stress [8] in the proximal kidney tubule, with casts appearing in the kidney tubule [9]. As risk factors, nephrotoxic drugs (aminoglycosides), in combination with high-dose diuretics (4 g/day) and a high level of trough (≥ 20 $\mu\text{g/ml}$), patients in ICU for more than 1 week of treatment period is known. In addition, calcineurin inhibitors are recommended for therapeutic drug monitoring (TDM) for concentration-dependent development in the proximal kidney tubule.

2.7. Causes of acute interstitial nephritis

AIN involves drug-induced delayed hypersensitive reactions such as fever, rash, articular inflammation, or hepatic disorder in combination with declining kidney function, mainly involving neutrophil, T lymphocyte, and monocyte invasion in the renal stroma. However, these extrarenal manifestations are not inevitable and furthermore present with symptoms

of nephrosis with tiny variation at times. Drug-induced AIN occurs with a high frequency. Often, kidney injury occurs a few days to a few weeks after administration of the offending drug, especially antibacterial drugs, such as beta-lactam agents, quinolone agents, and rifampicin, which are all causes of AIN; however, the cases caused by NSAIDs and proton pump inhibitors (PPIs) have tended to increase. Immune checkpoint inhibitors (e.g., PD-1 inhibitor), such as nivolumab, which recently has rapidly been expanded to apply to numerous bacterial species, have been reported to increase kidney injury, including interstitial nephritis.

2.8. Tubule occlusion by crystals (crystal nephropathy)

The drug concentration in the renal tubule lumen increases in order to acidify urine by urinary concentration and excretion of H in the distal convoluted tubule. Under these acidic conditions, crystallization of the drug occurs, inducing a nephropathy called crystal nephropathy. Antiviral drugs such as acyclovir and indinavir and methotrexate are known to cause kidney disorders due to drug-related crystal deposition in the renal tubules. There are many cases where casts are lost into the urine. Psychotropic agents and rhabdomyolysis-inducing drugs, such as statin medications or fibrates, are included in this category because obstruction of the renal tubule by myoglobin is possible. Excessive use of common supplements such as vitamin C carries a danger of promoting oxalic acid crystals.

2.9. Causes of glomerulonephritis-related damage

Glomerulonephritis induces functional disorder by blocking resorption in the renal tubule. The relation between rheumatoid arthritis agents, such as platinating agents or bucillamine and membranous nephropathy and antihypertensive drugs, such as methyldopa or hydralazine and drug-induced lupus kidney inflammation, has been highlighted for some time. Interferon used in clinical application for the treatment of hepatitis, however, has been reported to induce minimal change disease (MCD) or focal segmental glomerular sclerosis (FSGS) [10]. In addition, a relationship between NSAIDs and membranous nephropathy or MCD has been indicated.

2.10. Contrast-induced nephropathy (CIN)

CIN is diagnosed in the case of kidney function declines after the administration of contrast in the absence of other causes (e.g., cholesterol embolus). The mechanism of CIN remains to be completely elucidated; however, the following factors have been considered: (1) a decrease in oxygen supply due to blood vessel spasm in the renal medulla, causing direct toxicity to the renal tubule, (2) a decreased renal perfusion by increased adenosine and endothelin or reduced carbon monoxide [11]; coexisting risk factors such as kidney function disorder, advanced age (more than 75 years old), dehydration, cardiac failure, agents (diuretic agents, NSAIDs, aminoglycoside antibiotics, and vancomycin), diabetes mellitus, and multiple myeloma; in particular, kidney function disorder is the greatest risk factor. In addition, diabetes mellitus, which has become recognized as a risk factor, is considered a factor in itself and promotes a further elevated risk for the development of CIN in CKD patients through its complications. Gadolinium (Gd) contrast agents, including extracellular liquid Gd contrast agents and hepatocyte-specific Gd contrast agents, are classified as linear and macrocyclic or as ionic and

nonionic on the basis of their chelate structure. Gd is a heavy metal element and is highly poisonous in the case of direct administration. Therefore, Gd is administered as a chelate so that it is excreted into the urinary tract (and partly into the biliary tract) without metabolizing inside the body. Adverse events of Gd contrast agents occur in three types: acute adverse effect, occurring within 1 h after intravenous injection; delayed adverse effect, occurring from 1 h to 1 week after intravenous injection; and super-delayed adverse effect, such as nephrogenic systemic fibrosis (NSF), which occurs more than 1 week or even several years after intravenous injection. Moreover, there is a newly recognized problem that Gd remains in the brain without causing kidney disorder [12]. Many subsequent studies have reported that residual Gd in the body is more linear type than macrocyclic type [13, 14] and remains not only in the brain but also throughout the whole body when the residual volume is increased in the presence of kidney disorder [15]. Complications caused by residual Gd have not been reported; however, patients who are frequently exposed to contrast generally have some kind of chronic disease, so the effects of residual Gd may be obscured or misinterpreted as subjective or objective evidence of their disease. Notably, in the case of Gd remaining in the brain, Gd deposits in neuronal nuclei have been observed by electronic microscopy [16]. Gd is not liberated very well; its thermodynamic stability constant and condition stability constant are high, leading to a high chelate stability. Its half-life at pH = 1.0 represents the time required to liberate half of Gd from the chelate under pH = 1.0, but it remains stable much longer under other conditions. In general, linear type chelates have a lower stability than macrocyclic chelates [17].

2.11. Other etiologies

There are cases that result from electrolyte abnormalities; for example, the abnormal use of diuretic drugs or glycyrrhiza causes kidney disorder by hypokalemia and excess administration of vitamin D preparation causes kidney disorder via hypercalcemia. In addition, warfarin, which has been in use as an anticoagulating drug for many years, has been reported to easily cause kidney disorders, particularly when PT-INR exceeds 3; however, the mechanism has yet to be determined [18]. Among the pathological findings of kidney disorder due to warfarin, red blood cell casts have been observed with high frequency.

2.12. Clinical presentation of drug-induced AKI

Symptoms appear within a few hours or a few years after taking or using the offending agents, and in some cases, no symptoms appear. Renal tubular injury sometimes presents with the following symptoms: polyuria, urinary frequency, thirst, fatigue, and anorexia. Skin rash, joint pain, fever, and hematuria are observed as signs of allergy. In the case of thrombotic microangiopathy, purple spots and bleeding tendency with thrombopenia appear in the soft palate and the extremities. In the presence of crystal nephropathy, knock pain is commonly observed dorsally and bilaterally with postrenal acute renal failure. With progression, acute or chronic renal failure develops.

2.13. Diagnosis of drug-induced AKI

The size of the kidney is normal or swollen. The elevation of urinary N-acetyl- β -glucosaminidase (NAG) or L-type fatty acid binding protein (L-FABP) is observed with a urine test. In particular,

the proteinuria is of low grade (less than 1 g/day) and associated with renal tubule dysfunction (mainly β_2 -microglobulin). However, the urinary findings depend on the presence or absence of glomerular lesions. The detection of urinary eosinophils has been used for the diagnosis of drug-induced AKI [19], but is weak evidence for clinical judgment, as it has a lower positive-predictive rate and a higher false-negative rate than other markers. Renal hemodynamic type is rarely examined, but hyperkalemia is presented in patients receiving drugs related to the RAA system. Thrombotic microangiopathy is commonly associated with thrombocytopenia, an appearance of schistocytes, and elevation of lactate dehydrogenase (LDH). In acute tubular necrosis, muddy brown casts are observed in the urinary sediment. The examination of accumulation enhancement in the kidney by gallium scintigraphy is used for the diagnosis of acute interstitial nephritis related to antibacterial drug overdose, but this is not a common diagnostic approach because it is difficult to distinguish between drug accumulation and infection or glomerular disease. Then, there is the problem of the low specificity of the drug-induced lymphocyte stimulation test (DLST), which is used to examine the patient's blood in cases of suspected drug-related AKI. In crystal nephropathies, urinary crystals or high-brightness echo on renal ultrasonography due to crystals may be observed. Renal biopsy is not essential for diagnosing drug-induced AKI, and it is considered to produce a hangover of kidney disorder after drug withdrawal or maintain uric protein in the nephrotic range and glomerular hematuria.

2.14. Treatment of drug-induced AKI

The treatment is essentially discontinuing use of the suspected drugs; treatment also includes proper maintenance of body fluid volume and blood pressure, and sometimes, the use of rehydration or diuretics to maintain adequate perfusion of the kidney. We consider using kidney replacement therapy in cases where the following symptoms are observed: a marked elevation of BUN or hyperkalemia, pulmonary edema that fails to respond to diuretics, or uremic symptoms. In the treatment of drug-induced acute interstitial nephritis, we may consider steroid therapy after early withdrawal of drugs (within 2 weeks), when kidney disorder hangover occurs under the discontinuation of the suspected drug [20]. We use upward of 1 mg/kg/day steroid for a short period, but there are no large-scale studies related to patient characteristics or symptoms that indicate this therapy. In addition, alkalinization of the urine with baking soda or acetazolamide treatment is used to promote the solubility of crystals in the case of kidney disorder caused by the deposition of methotrexate crystals in the renal tubules. Methotrexate has a low molecular weight of 454.44, its protein binding rate is 50%, and it is removed rapidly from plasma; because of these factors, a combination of plasma exchange and hemodialysis with a high-flux membrane is effective. A recombinant enzyme preparation that directly decomposes methotrexate has already been developed in Europe and the United States. Contrast nephropathy rarely needs specific treatment to resolve. With a lower residual renal function or oliguria, treatment is needed for advanced CKD. It is said that the aggressive introduction of blood purification therapy as well as other AKI avoidance is helpful to reduce case fatality rate and complications such as progression of kidney disorder. Treatments such as diuretics, human atrial natriuretic peptide, and low-dose dopamine have been considered by now, but these treatments are not recommended, as their usefulness has not yet been demonstrated. Thus, it is necessary to consider fluid therapy after CIN and important to carefully select the infusion volume after evaluating body fluid volume because an excessive increase in fluid could elevate the case fatality rate.

3. Nondrug-induced AKI

3.1. Heart function and AKI

There are many important factors related to both the heart and the kidney that indicate the following pathway leading to kidney disorder or cardiac arrest (**Figure 1**) [21]. Patients who have suffered acute decompensated heart failure tend to develop AKI during the course of treatment, which is known to worsen renal function despite the correction of heart function [22, 23]. Kidney function disorder results in heart function disorder, and this connection has recently been referred to as cardiorenal syndrome (CRS). Ronco et al. classified clinical conditions into five groups, divided by acute and chronic [24]. In this classification, we give an outline of types CRS1 and CRS3, related to heart function and AKI.

3.2. Hepatorenal syndrome

3.2.1. Pathogenesis of hepatorenal syndrome

The arterial vasodilation theory is universally recognized as underlying hepatorenal syndrome [25]. With progression, hepatic cirrhosis and vascular resistance are reduced, and blood pressure is decreased by vasodepressor factors such as carbon monoxide and cannabinoids [26]. At the early stage of hepatic cirrhosis, compensatory mechanisms such as the elevation of cardiac pumping, the enhancement of renin-angiotensin system, and the expression of sympathetic nervous system or vasopressin work to balance the change, so

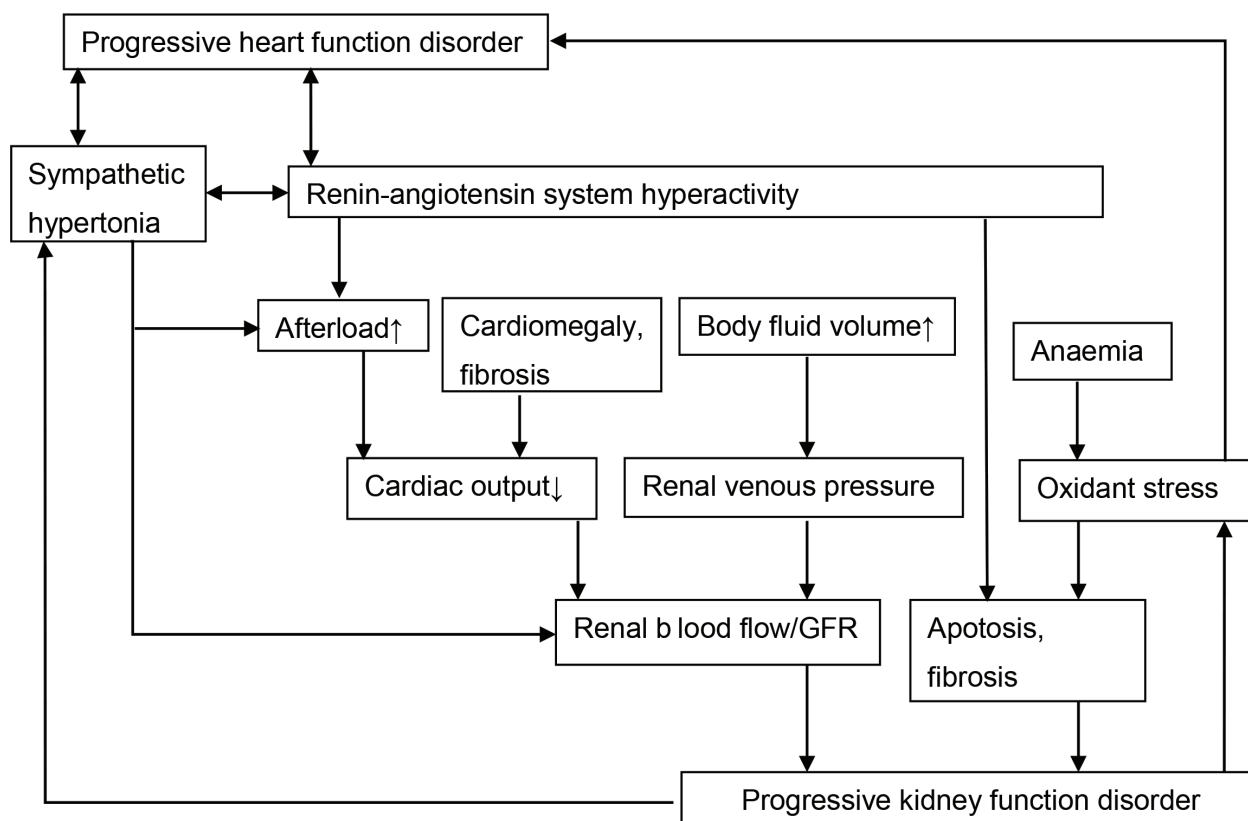


Figure 1. Correlation between heart function disorder and kidney function disorder.

blood pressure increases. However, with further progression of hepatic cirrhosis, the so-called cirrhosis cardiomyopathy occurs, and cardiac output is reduced by the reduction of myocardial extension ability and abnormality in the impulse conducting system [27]. In addition, cirrhosis is often associated with the development of comparative adrenal failure and has the tendency to reduce the blood pressure. To compensate, the renin-angiotensin system and the secretion of vasopressin are further increased [28]. Disorders in which free water cannot be drained from the kidney tubule or sodium retention is elevated cause sympathetic hyperactivity; as a result, circulating plasma volume cannot be reduced, leading to excess fluid accumulation as ascitic fluid or edema and hyponatremia [29]. In addition, sympathetic hyperactivity and vasopressin are vasoconstrictive, and renal blood flow is additionally reduced [25]. In other words, compensation, which was useful to maintain body blood pressure in the early onset of hepatic cirrhosis, reduces renal blood flow and leads to auto-regulation breakdown, inasmuch as it reduces glomerular filtration. Moreover, in cases of hepatic cirrhosis, even where there are no obvious infectious diseases, inflammatory cytokines, such as IL-6 or TNF- α , are elevated, and an impact for portal hypertension and circulation dynamics is considered [30].

3.2.2. Classification of clinical entity in hepatorenal syndrome

In general, hepatorenal syndrome, pathophysiologically, is broadly separated into two categories by the speed of progress of kidney function disorder. Quick progression (type 1) is defined as a serum creatinine level that is elevated more than two times within 2 weeks and elevated to more than 2.5 mg/dl; cases that progress more slowly are type 2. Part of the reason for classifying in this way is that type 1 is associated with singularly poor prognosis. The 3-month mortality rate of type 1 is almost 70%, while that of type 2 is approximately 10%, and it is reported that the median survival time after the onset of type 1 is approximately 2 weeks [31]. Some cases of type 1 involve a natural outbreak that develops into infections, such as spontaneous bacterial peritonitis, pneumonia, and opportunistic urinary tract infections [32, 33]. Therefore, early diagnosis and therapeutic intervention are desirable in type 1.

3.2.3. Diagnosis of hepatorenal syndrome

For diagnosis, the criterion of hepatorenal syndrome that has been traditionally propounded indicates that serum creatinine levels are elevated to more than 1.5 mg/dl [34]. That is, the condition requires that the serum creatinine level was more than 1.5 mg/dl in hepatorenal syndrome, regardless of the baseline level of hepatorenal syndrome or elevation degree and speed. This was viewed with suspicion in distinguishing AKI from CKD [35]. Then, ICA proposed a partial change of the diagnostic criteria for KDIGO, as AKI in hepatorenal syndrome patients, under the guidelines for AKI, which were announced by KDIGO and universally recognized. The difference in diagnostic criteria between ICA and KDIGO is the urinary output cut-off. The reason is that regardless of the relative maintenance of GFR, compared to other AKI, the potential for oliguria in hepatic cirrhosis patients is not negligible [11]. The ICA proposed to set the serum creatinine level within 3 months before admission as baseline, unless serum creatinine had been measured within the previous 7 days [35].

3.3. External injury and AKI

We give an outline of rhabdomyolysis (crush syndrome) in order to understand AKI due to external injury. Crush syndrome is a generalized diagnosis of the symptoms caused by skeletal muscle damage by external or other mechanical injury. First, regional edema occurs in the damaged skeletal muscle of the extremity, so that intravascular volume is reduced. Because the extremity compartment is restricted in space, the inner pressure of the compartment increases exponentially, and this in turn reduces arterial perfusion to the muscle. On the grounds that perfusion pressure is defined by the mean arterial blood pressure and compartment inner pressure, the perfusion pressure is conspicuously reduced under these circumstances, which means arterial blood pressure is low and compartment inner pressure is high. Skeletal muscle cells are destroyed by direct external or ischemic injury, and the intracellular components, including myoglobin, potassium, and urinary acid, are released and circulate at the time of reperfusion [36]. The mechanism of AKI by rhabdomyolysis remains to be explained; however, it is thought that it concerns the constriction of renal blood vessels directly, or ischemic renal tubular injury and tubular obstruction. Many different mechanisms have been related to the renovascular contraction characteristic of AKI by rhabdomyolysis. First, intravascular volume reduces in order to move fluid for the damaged skeletal muscle, and the renin-angiotensin system, vasopressin, or sympathetic nervous system cause hyperactivity, so kidney blood vessels contract. Next, increased levels of vascular mediators such as endothelin-1, thromboxane A₂, TNF- α , and F₂-isoprostane are additionally vasoconstrictive. Conversely, vasoactive nitric oxide (NO) is used to remove myoglobin such that a deficiency develops and renal blood flow becomes further diminished. Finally, a direct disorder caused by inflammation or oxidation with vascular endothelial disorder exacerbates these vascular mediators at the same time [37]. AKI by crush syndrome is also linked to the possibility of the same kidney disorder mechanism that occurs in tumor lysis syndrome, in addition to the mechanism of AKI by rhabdomyolysis described earlier, that is, a large amount of urinary acid being released from the injured skeletal muscle [38]. AKI by crush syndrome is more associated with the development of fluid overload, life-threatening acidosis, and hyperkalemia than AKI of other causes. Notably, an abrupt increase in potassium level, even if it remains within normal range, is an indication for dialysis [39, 40]. The dialysis initiation standards for AKI, especially dialysis initiation in an early period, remain greatly debated even though a large-scale trial has been conducted in recent years [41]. The evidence supporting renal replacement therapy for AKI caused by crush syndrome is limited and thus remains inconclusive. However, given that the high dialysis enforcement rate and clinical indications for fundamental therapy itself do not exist, early introduction may be useful [42]. Nevertheless, we should consider not only renal replacement therapy intended for the removal of myoglobin but also early introduction as for AKI [43].

3.4. Sepsis-associated AKI: SA-AKI

3.4.1. Mechanism of development and pathophysiology in SA-AKI

An “inflammation” mechanism is responsible for a large part of the occurrence of SA-AKI. When excessive inflammation is induced, organ damage is caused by hypercytokinemia, called a

cytokine storm. For example, in endotoxemia caused by Gram-negative bacteria infection, the signal is released via Toll-like receptor (TLR) 4, mediators such as cytokines are released via the MyD88-dependent pathway or TRIF-dependent pathway, and factors promoting adherence to vascular endothelium are produced. Furthermore, in the glomerulus, expanding of the efferent arteriole, changes in tubuloglomerular feedback, and intumescence of the vascular endothelia are induced and result in a reduction of GFR. Furthermore, impaired renal tubular reabsorption of solutes or anaerobic metabolism by mitochondria occurs, and renal tubular dysfunction is caused by hypoxia of the medulla renalis [44]. However, in mice deficient in TLR4, which recognizes the endotoxin, and administered LPS organ-protection, action was not exhibited. In mice deficient in MyD88, which lies downstream of TLR4 [45], or TLR9, which recognizes bacterial DNA, AKI was alleviated [46]. This phenomenon can also be induced by other Gram-positive bacteria or viruses. Furthermore, when Bellomo et al. [47] measured renal blood flow in a sheep model with continuous infusion of bacteria, during hyperdynamic shock, which dilates peripheral blood vessels and increases cardiac output, renal blood flow increased, but glomerular filtration rate decreased. The cause was thought to be that the afferent arteriole dilated but the efferent arteriolar dilated without constriction. Progress of clinical condition additionally induces microvascular injury, which in turn induces afferent arteriole constriction and results in the persistent loss of glomerular filtration.

3.4.2. Risk factors

Risk factors of abnormal balance of tonus in the afferent/efferent, which is recognized in SA-AKI, include older age, preexisting chronic kidney disease (CKD) or cardiovascular condition, severe arteriosclerosis (hypertension, diabetes mellitus), and drug use (especially Ras inhibitors or NSAIDs).

3.4.3. Targeted therapy

Even though life-saving guidelines for sepsis treatment were proposed and practically applied, the incidence and severity of SA-AKI have not been alleviated [48]. The immediate action for patients with AKI is emergency response associated with severe kidney injury represented by severe uremia, hyperkalemia, volume overload (renal failure), or metabolic acidosis. When sepsis occurs, because of the relative lack of volume flow through the circulation, correcting volume flow through the circulation and maintaining perfusion rate of the kidney early are important. On the other hand, because excessive volume administration cannot improve circulatory dynamics and may worsen prognosis, vasoconstricting drugs should be administered after correcting volume flow through the circulation. With regard to the quality of transfusion, because artificial colloid solutions such as HES may cause further kidney injury in patients requiring renal replacement therapy (RRT) compared to extracellular fluids such as saline, their use should be avoided (VISEP study 2008, 6S trial 2012, CHEST study 2012). In the case that hyperdynamic shock occurs, to maintain organ perfusion pressure more than 65 mmHg, a vasoconstrictor drug (noradrenaline: NA) [49] is recommended as the first-line therapy, and vasopressin (VSP) is recommended as the second-line therapy. Furthermore, the focus of infection should be managed by drainage and so on. Antibacterial drugs should be administered as soon as possible, and if possible, injection with broad-spectrum antibiotics should be performed within an hour. At this time, antibiotics should be selected considering renal prognosis.

4. Prognosis of AKI

Studies on the long-term prognosis of AKI have advanced rapidly since approximately 2010 [50–62]. Consequently, advances in the understanding about the association between AKI and cardiovascular disturbance have been seen. The absence of consensus on the definition of recovery from AKI was previously considered problematic [63], and this problem was highlighted again by Sawhney's systematic review [61]. After this systematic review, two large studies, which were likely to be underpinnings of the consensus on the definition of recovery from AKI, were published [64, 65]. Accordingly, the importance of considering the time from the peak of SCr value to recovery and the importance of considering rehospitalization after recovery from AKI were suggested in order to define recovery from AKI. Although AKI or recovery from AKI was defined by SCr in all the above studies, it is impossible to capture changes in the tissues not reflected in kidney function because SCr value is the index of kidney function, and it is possible that changes in the kidney reflected in urine biomarkers have an impact on the long-term prognosis of AKI, even if there is no rise of SCr suggested, according to the article of the TRIBE-AKI study team [66]. It is necessary to think about what we can do for patients with AKI, and in the Japanese guidelines, it is recommended to assess the presence of a transition from AKI to CKD according to KDIGO guidelines. However, giving a referral for follow-up to patients targeted with clinical stratification stage 2 or stage 3, an outpatient department of a facility in Canada suggested, is because doing for patients with AKI includes those at clinical stratification stage 1 (in particular, the rise of SCr 0.3 mg/dl) is not realistic [67]. In actuality, in data from a US veteran's hospital in 2012, the rate of referral, even for patients at clinical stratification stage 2 or 3, to the department of internal nephrology medicine after discharge from a hospital is approximately 20%, and room for improvement was suggested [68]. Among patients with AKI receiving acute renal replacement therapy, there is evidence to suggest that there is a decreased mortality rate for patients who receive follow-up from a kidney physician [69]; it is possible that this outcome is attributable to the careful management by doctors whose reasons have not been considered. There is also an example of outcomes being improved when patients visit a doctor who conducts daily practice, even without a follow-up by a kidney physician [70]. There are data from the US that hospital physicians did not fully inform outpatient doctors during hospitalization for AKI onset [71]. It may be the role of the doctor who diagnosed AKI to inform the outpatient clinician of the risk of CKD onset and progression and avoiding prescription of drugs with renal toxicity after AKI.

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Conflict of interest

None.

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