4
Acute Kidney Injury

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Patients may be admitted to the intensive care unit (ICU) with acute kidney injury (AKI) or it may develop during their stay. This chapter gives an overview of the definition and epidemiology of AKI, along with clinical features and initial investigations.

Definition of AKI

AKI is an abrupt (<7 d) and sustained decrease in kidney function (1). It is accompanied by changes in blood biochemistry (e.g., a rise in serum creatinine), in urine output, or both. There is a spectrum ranging from a mild transient rise in serum creatinine, to overt renal failure needing renal replacement therapy (RRT); hence, the term acute kidney injury (AKI) is more precise than the term "acute renal failure".

Multiple definitions of ARF exist, and the reader is guided to a series of excellent reviews that highlight this problem (1–5). A rise in serum creatinine is often used as a marker of renal dysfunction, but it is affected by extrarenal factors, such as age, sex, race, and muscle bulk. It may lag behind changes in glomerular filtration rate (GFR), either in decline or during recovery, and, therefore, does not always give a true reflection of the GFR. Urine output can be used to define renal failure, but this can be confounded by the use of diuretics, and not all cases of renal failure are associated with oliguria.

Efforts have been made to develop a universal and practical way of defining AKI via either serum creatinine or urine output. One such recent proposal is the RIFLE (5) system; an acronym for three levels of renal dysfunction and two renal outcomes. The levels of renal dysfunction can be defined by changes in serum creatinine, GFR, or urine output.

Risk of Renal Dysfunction
- Serum creatinine increased 1.5 fold *or*
- GFR decreased by more than 25% *or*
- Less than 0.5 mL/kg/h of urine for 6 hours

Injury to the Kidney
- Serum creatinine doubled *or*
- GFR decreased greater than 50% *or*
- Less than 0.5 mL/kg/h of urine for 12 hours

Failure of Kidney Function
- Serum creatinine increased 3 fold *or*
- An acute rise in creatinine of greater than 44 µmol/L so that new creatinine is greater than 350 µmol/L *or*
- GFR decreased more than 75% *or*
- Less than 0.3 mL/kg/h of urine for 24 hours or anuria for 12 hours
- *Note:* This takes into consideration acute-on-chronic renal failure

Loss of Kidney Function
- Complete loss of kidney function for longer than 4 weeks

End-Stage Renal Disease
- The need for dialysis for longer than 3 months

Incidence and Outcome

AKI develops in 5 to 7% of hospitalized patients (6, 7). Six to 25% of patients on the ICU develop AKI (2, 8); overall, 4% of admissions require RRT.

This may underestimate the scale of the problem, however, because when all degrees of kidney dysfunction are considered using the RIFLE criteria, 20% (9) of hospital patients and 67% of ICU patients developed some form of kidney injury (10).

The incidence and progression of AKI varies depending on the patient group studied. For example, up to 20% of cardiac surgery patients will develop some evidence of renal injury (11), but only 1% will need RRT (12).

AKI on the ICU is associated with a hospital mortality of 13 to 80% (2, 8, 10–17) and 57 to 80% if RRT is needed. Renal failure rarely occurs on its own, with up to 80% of patients with renal failure on the ICU having another organ system failure (8). Various factors have been associated with a worse outcome; including comorbidity, increased severity of illness, presence of sepsis, need for mechanical ventilation, oliguria, hospitalization before ICU, and delayed occurrence of AKI (13–15).

The development of AKI dramatically increases mortality across all patient populations studied (8–10, 12, 14). Worsening levels of renal dysfunction, as described by the RIFLE criteria, correlate well with increasing hospital mortality, with up to a 10-fold risk of death with "failure." AKI carries an independent risk of death, but it is unclear whether this is related to the systemic effects of renal failure itself, the effects of its treatment, or is simply a reflection of the severity of the underlying condition.

After AKI needing RRT, 10 to 32% of patients are discharged from hospital still needing RRT (2, 16, 18).

Causes of AKI

Causes of AKI can be divided into prerenal, intrinsic, and obstructive causes. One disease may be associated with different causes of ARF, for example, sepsis is a common cause of renal dysfunction on the ICU, accounting for up to 50% of cases of AKI. AKI occurs in 23% of patients with severe sepsis, and in 51% of patients with septic shock when blood cultures are positive (19). Sepsis is characterized by systemic vasodilation (*prerenal* failure) but intrarenal vasoconstriction, which could progress to tubular damage (*intrinsic* renal failure). Glomerular microthrombi are associated with disseminated intravascular coagulation, and can cause intrinsic AKI (20).

Prerenal Failure

Prerenal failure (Figure 4.1) accounts for 15 to 20% of cases of AKI on the ICU (13, 15). For the kidneys to be perfused and, therefore, function, adequate pressure, flow, volume, and patent vessels are needed.

The kidney autoregulates to maintain a constant renal blood flow (RBF) through a mean arterial pressure range of 65 to 180 mmHg. "Prerenal failure" is an appropriate, albeit exaggerated, physiological response to renal hypoperfusion. Stimulation of the renin-angiotensin-aldosterone system attempts to retain salt and water and, therefore, maintain RBF. Because renal tissue is still preserved, once renal perfusion is restored, function should improve. A profound or prolonged reduction in perfusion can, however, lead to ischemic acute tubular necrosis (ATN) (intrinsic renal failure).

Conditions leading to reduced renal perfusion and, therefore, causing prerenal failure are:

- Hypotension (relative or absolute) secondary to vasodilation (e.g., certain drugs, loss of vascular tone, and sepsis)
- Compromised cardiac function
- Intravascular volume depletion (absolute or effective)
- Increased intra-abdominal pressure (abdominal compartment syndrome)

Intrinsic Renal Failure

The commonest cause of intrinsic renal failure on the ICU is ischemic ATN developing after profound or prolonged prerenal failure (Figure 4.2). Up to 80% of cases of AKI on the ICU are attributed to ATN (2, 13, 15). Although ATN is a histological diagnosis, its development is suggested by the persistence of renal failure following the restoration of adequate renal perfusion. The

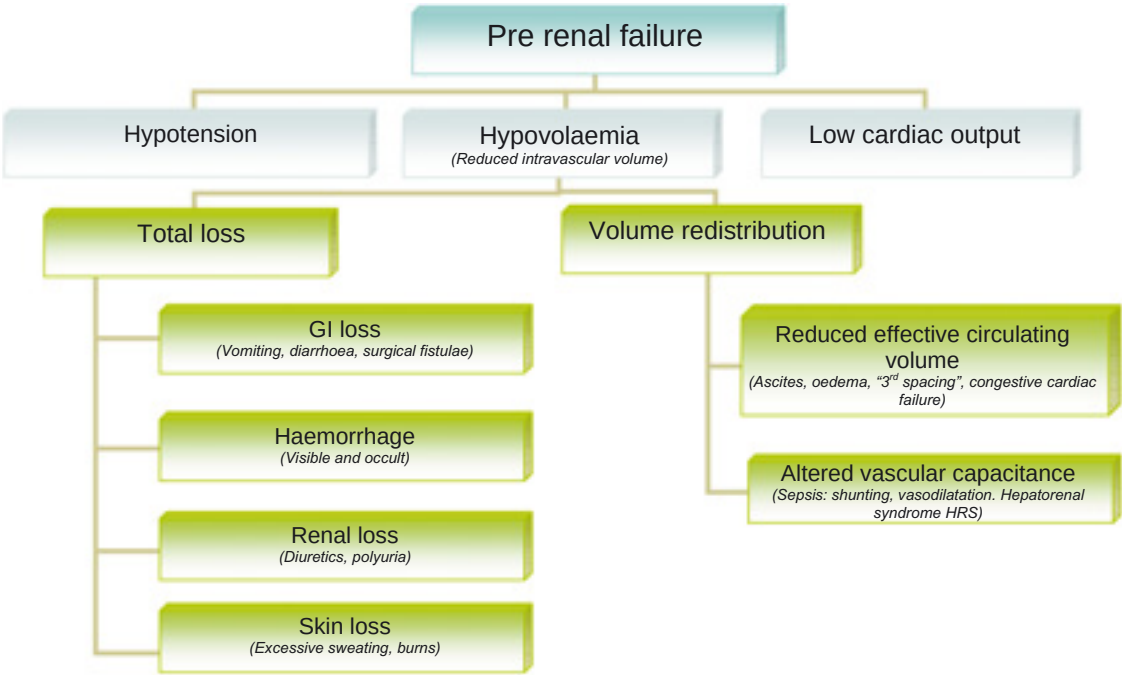

Figure 4.1. Causes of prerenal failure. GI, gastrointestinal.

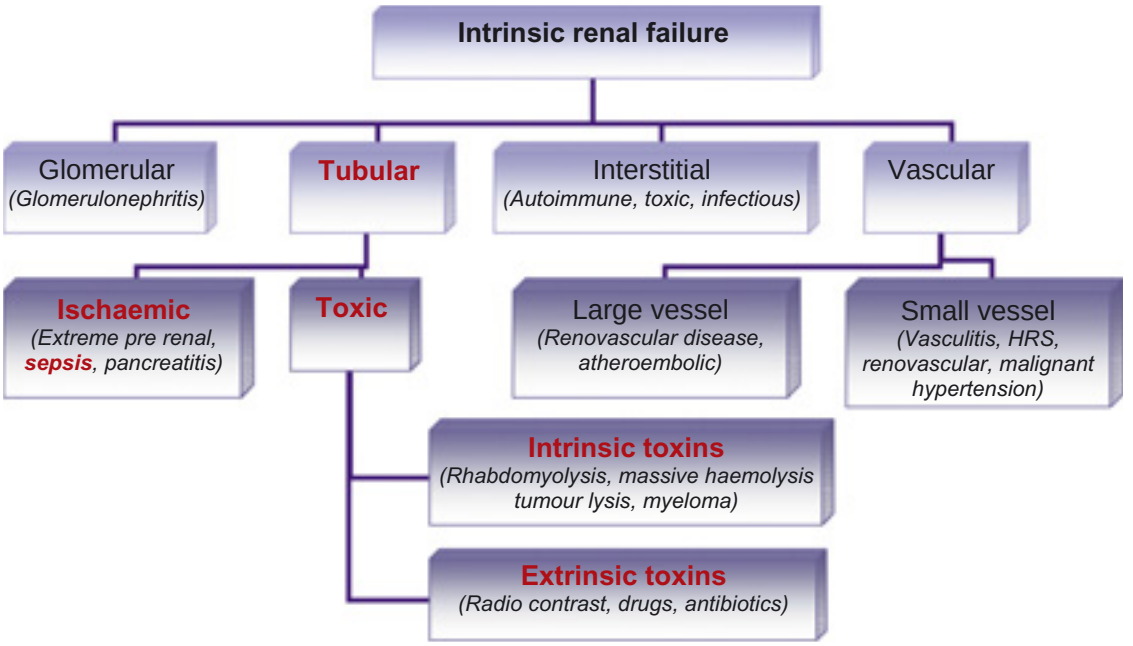

Figure 4.2. Causes of intrinsic renal failure (*red*, commoner causes on the ICU). HRS, hepatorenal syndrome.

pathophysiology of ischemic ATN is reviewed elsewhere (21, 22), but an alteration in glomerular hemodynamics with marked afferent arteriolar renal vasoconstriction causes a fall in glomerular filtration pressure and subsequently causes ischemia. This particularly affects the outer medulla. Tubular damage leads to loss of normal cell-to-cell adhesion and allows back leakage of filtrate into the interstitium. Shed cells precipitate, with protein obstructing the tubules and further compromising tubular function. Local inflammatory mediators respond to cell injury, perpetuating the process.

ATN can also develop secondary to a variety of intrinsic or extrinsic renal toxins. Vascular causes of renal failure may be present at a prerenal or intrarenal level, and should be considered in vasculopaths. The more classic glomerular causes for intrinsic renal failure are seen less frequently on the ICU, but are important to recognize because they require specific treatment.

Postrenal or Obstructive Renal Failure

Obstruction can occur at any level of the urinary collecting system and can be caused by intrinsic (e.g., stones, tumor) or extrinsic causes (e.g., surrounding or infiltrating tumor, large inflammatory abdominal aortic aneurysms). Obstruction is an infrequent cause of AKI on the ICU but is important to be excluded in all cases.

Complications of AKI

AKI is a systemic disease, having effects on practically all organ systems (23). It is becoming increasingly recognized that there is "cross talk" between the injured kidney and other organs through the release of proinflammatory cytokines. Complications related to other failing organs may be seen, but complications specific to the failing kidney are as follows.

Retention of Uremic Toxins

Accumulation of toxins, including urea, can lead to nausea, vomiting, drowsiness, a bleeding tendency, uremic flap, and, rarely, coma (uremic encephalopathy) and a pericardial rub.

Volume Overload

Salt and water retention occurs early, and is a common reason for initiating RRT on the ICU (16). Volume overload may have deleterious effects on cardiac and respiratory function, with the development of peripheral edema affecting wound healing and pressure areas.

Acidosis

There is retention of organic anions (e.g., phosphate) and reduced production of bicarbonate by the failing tubules. In critically ill patients, this may be aggravated by the presence of a non-renal acidosis, for example, lactic acidosis from sepsis and respiratory acidosis from respiratory failure.

Electrolyte and Mineral Disturbances

Hyponatremia, hyperkalemia, and hyperphosphatemia are commonly seen.

Anemia

Anemia can develop because of inappropriate levels of erythropoietin (decreased synthesis) or increased red cell fragility, causing premature red cell destruction. Uremia is also associated with platelet dysfunction and increased risk of gastrointestinal bleeding.

Immunosuppression

Renal failure itself can impair humoral and cellular immunity, putting the patient at risk of infectious complications.

Metabolic Consequences

Hyperglycemia occurs because of peripheral insulin resistance and increased hepatic gluconeogenesis. Protein catabolism is also activated.

Drug Accumulation

Renal failure may be secondary to drugs, but, as GFR falls, renal clearance of drugs and their

metabolites also falls. Renal failure may be exacerbated by drug accumulation, or other side effects can develop, such as morphine metabolites leading to respiratory depression.

Investigation of the Cause of Renal Failure (Table 4.1)

Laboratory Tests (Table 4.2)

Urinalysis

A standard dipstick for blood and protein should be preformed and a fresh sample spun for casts: hyaline casts (nonspecific markers of renal injury), brown/cellular casts (ATN), and red cell casts (acute glomerulonephritis). An estimation of protein excretion may be needed, either a 24-hour urine collection or a spot urine protein-creatinine ratio, depending on local resources.

Urine osmolality and urinary electrolytes can be used to help distinguish prerenal failure from intrinsic kidney disease (Table 4.3). They should be interpreted in light of the clinical setting, but can act as another tool in the assessment of intravascular volume status.

Radiological Investigations

A chest x-ray will help assess volume status, but patchy infiltrates may also represent pulmonary hemorrhage, as seen in certain forms of vasculitis. A renal ultrasound scan should be performed; the timing will depend on the likely cause of renal failure and the patient's clinical state. Further imaging should be guided by the clinical scenario.

Conclusion

AKI is a significant condition affecting critically ill patients on the ICU. It is a systemic process affecting all organs, and has a major impact on patient morbidity and mortality. It is, therefore, important to be able to promptly recognize its development and institute the appropriate investigations to guide treatment.

Table 4.1. History and examination in AKI

A full history should be take with reference to the following:
- Presence of risk factors: known chronic renal disease, advanced age, diabetes mellitus, ischemic heart disease, hypertension, peripheral vascular disease, liver disease, recent high-risk surgery
- Previous episodes of renal failure
- Family history of renal disease
- Rashes, joint aches, sinusitis, and hemoptysis suggesting a systemic condition
- Review blood pressure and anesthetic charts for periods of profound or prolonged hypotension in relation to the patients usual blood pressure
- Review fluid balance charts considering hidden losses, such as sweating or "third spacing." The sudden onset of anuria suggests obstruction or a catastrophic vascular event. Remember that diuretics can make the urine output look "artificially good"
- Drug charts should be reviewed for intravenous contrast, chemotherapeutic agents, analgesics, antibiotics, and herbal remedies, including any new medications taken in the past month
- Determine baseline creatine and pattern of change (i.e., sudden jump or gradual decline). The rate of change may be more important than the absolute value
- Review any previous urinalyses for previous hematuria or proteinuria that may suggest chronic disease

A full examination should be performed with reference to the following:
- Pressure: mean arterial pressure in relation to the patients usual readings
- Flow: cardiac output studies and/or markers of end organ perfusion (e.g., lactate)
- Volume: overall volume status as well as intravascular volume status
- Patent vessels: evidence of generalized vascular disease
- Rashes or splinter hemorrhages suggesting vasculitis, cholesterol emboli, or infective endocarditis
- Palpable bladder or kidney, suggesting obstruction
- Raised intra-abdominal pressure or tense limbs, suggesting compartment syndrome

Table 4.2. Laboratory investigations for AKI

Finding	Comment
Anemia	Normochromic, normocytic suggests chronicity
Thrombocytopenia + microangiopathic hemolytic anemia	Consider hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation (DIC)
Neutrophilia, "left shift" + thrombocytopenia	Consider sepsis
Eosinophilia	Consider vasculitis, allergic interstitial nephritis
Abnormal coagulation profile	Sepsis, DIC, hepatorenal syndrome, systemic lupus erythematosus (SLE)
Elevated urea and creatinine	Will rise with any cause of renal failure. A normal serum creatinine does not exclude the presence of renal dysfunction, and conversely an elevated creatinine may underestimate the degree of renal dysfunction
Elevated serum Cystatin C	A newer marker of renal dysfunction, but needs further evaluation on ICU patients. Freely filtered at the glomerulus, and fully metabolized by proximal tubular cells, if GFR falls, levels rise
Hypercalcemia	Elevated in malignancy (including hematological). Calcium may be high, low, or normal in chronic kidney disease (CKD)
Hyperphosphatemia	Extremely elevated in rhabdomyolysis and tumor lysis syndrome, but will rise with any cause of low GFR. May be normal or high in CKD
Elevated creatinine kinase	Rhabdomyolysis
Abnormal liver function tests	Consider hepatorenal syndrome; sepsis; vasculitis; and hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome
Elevated uric acid	Seen in preeclampsia but will rise with any fall in GFR
Abnormal immunoglobulins	Look for myeloma and other hematological malignancies
Elevated antinuclear factor, double-stranded DNA, antineutrophil cytoplasmic antibodies (ANCA), antiglomerular basement membrane antibodies, and low complement	Investigate further for systemic diseases, such as SLE and vasculitis
Positive virology/serology/microbiology	Certain forms of renal injury seen with specific infections, e.g., hepatitis B/C, HIV, leptospirosis, verotoxin-producing *Escherichia coli*

Table 4.3. Urinary findings in prerenal failure and ATN[a]

	Prerenal	Intrinsic
Urine Na	<20 mmol/L	>40 mmol/L
Urine : plasma (U : P) urea ratio	>20	<10
U : P creatinine ratio	>40	<10–20
U : P osmolality	>2.1	<1.2
Specific gravity	>1.020	<1.010
Urine osmolality	>500	<400
Urine osmolality	High (>serum + 100 mOsm/L)	Low (<serum + 100 mOsm/L)
FE sodium[b]	<1%	>1–2%

[a]These results should be interpreted with caution in patients who have had diuretics, large volume resuscitation, the elderly, or patients with chronic renal failure.

[b]FE, fractional excretion of sodium: in a prerenal state, sodium is actively reabsorbed by working tubules to maintain intravascular volume. The kidney will, therefore, produce concentrated urine with a low concentration of sodium. Creatinine is still excreted, but relatively less sodium appears in the urine. Hence, if the tubules are intact, the amount of sodium excreted compared with creatinine (fractional excretion) falls.

$$\text{FE Na} = \frac{\text{Urine Na} \times \text{plasma creatinine}}{\text{Plasma Na} \times \text{Urine creatinine}} \times 100$$

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