



Acute Kidney Injury: Definitions and Epidemiology

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Case 1

An 11-year-old female with history of acute myeloid leukemia who underwent bone marrow transplant 34 days ago developed fever to 104 °F; her blood pressure was 50/20 and heart rate was 180 beats/min. On physical exam she appeared lethargic, pale, and cold to touch. She was empirically started on broad-spectrum antibiotics and underwent emergency resuscitation with multiple fluid boluses ultimately requiring intubation and pressor support. Her urine output was previously reported as 1 ml/kg/day; however, she made only 30 ml of urine in 6 h after admission to the intensive care unit (ICU). Laboratory studies on ICU admission demonstrated that the electrolytes were normal, the blood urea nitrogen was 50 mg/dl, and creatinine was 0.9 mg/dl (creatinine was 0.6 mg/dl 2 days ago). The urinalysis was unremarkable.

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Case 2

A 14-year-old previously healthy male presented to emergency department for complaints of lower back pain and malaise for which he reported taking ibuprofen in appropriate doses daily last week. Otherwise he did not have fever and reported unchanged amount of urine output. On physical examination the height and weight were normal, the blood pressure was 117/75, and he appeared pale. Laboratory studies demonstrated that the electrolytes were normal, the blood urea nitrogen was 57 mg/dl, and creatinine was 3.2 mg/dl. The urinalysis was unremarkable. Renal ultrasonography demonstrated normal sized kidneys with increased echogenicity and loss of corticomedullary differentiation.

1.1 Acute Kidney Injury: Definition

Acute kidney injury (AKI) is defined as a rapid decline in glomerular filtration rate (GFR) leading to accumulation of waste products. AKI is common, affecting one third of the children admitted to intensive care unit (ICU) and is associated with poor outcomes including increased mortality and morbidity among critically ill children [1]. Severity and progressions of AKI is directly associated with stepwise increase in mortality and other adverse outcomes. Therefore, a standardized definition of AKI is particularly important to diagnose AKI and stratify AKI severity, in order to manage these patients better. In the past, available literature included multiple definitions for renal failure based on different thresholds of serum creatinine or blood urea nitrogen, with or without contribution from urine output, or requirement of renal replacement therapy, which made detection, diagnosis, classification, and study of AKI rather difficult. In an effort to better define AKI, three standardized consensus classifications have been proposed: (1) RIFLE (Risk, Injury, Failure, Loss, End-stage kidney disease) criteria was developed by the Acute Dialysis Quality Initiative (ADQI) in 2004 for adult patients by using changes in serum creatinine levels from baseline and/or decrease in urine output (Table 1.1) [2]. RIFLE definition was adapted for children by using change in estimated creatinine clearance from baseline, which is referred to as pediatric RIFLE (pRIFLE) definition (Table 1.1) [3]. In an adult study, increase of serum creatinine 0.3 mg/dl was found to be associated with 70% increase in risk of death; those results were replicated later in a pediatric study where increase of serum creatinine of 0.3 mg/dl was associated with increased mortality risk in a population with decompensated heart failure [4, 5]. (2) Further refinement of RIFLE criteria was developed by acute kidney injury network (AKIN) in 2007 which included the additional criterion of 0.3 mg/dl increase in serum creatinine in less than 48 h (Table 1.2) [6]. (3) Finally, in 2012 several aspects of RIFLE, pRIFLE, and AKIN criteria were integrated into a single definition for pediatric and adult patients by the Kidney Disease Improving Global Outcomes (KDIGO) classification (Table 1.3) [7].

Table 1.1 RIFLE/pRIFLE criteria for acute kidney injury

	Cr/GFR criteria	Urine output criteria
Risk (R)	Increased Cr \times 1.5 or decreased GFR by 25% eCCL decrease by 25% ^a	Urine output <0.5 ml/ kg/h \times 6 h Urine output <0.5 ml/ kg/h \times 8 h ^a
Injury (I)	Increased Cr \times 2 or decreased GFR by 50% eCCL decrease by 50% ^a	Urine output <0.5 ml/ kg/h \times 12 h Urine output <0.5 ml/ kg/h \times 16 h ^a
Failure (F)	Increased Cr \times 3 or decreased GFR by 75% or Cr >4 mg/dl (with acute rise of >0.5 mg/dl) eCCL decrease by 75% or Cl <35 ml/ min/1.73 m ^{2a}	Urine output <0.3 ml/ kg/h \times 24 h or Anuria \times 12 h
Loss (L)	Persistent failure—complete loss of renal function for >4 weeks	
ESRD (E)	End-stage renal disease-persistent failure >3 months	

^apRIFLE criteria; eCCL estimated creatinine clearance, Cr creatinine

Table 1.2 AKIN criteria for acute kidney injury

	Cr/GFR criteria	Urine output criteria
Stage 1	Increased Cr \times 1.5–1.9 from baseline or increase by \geq 0.3 mg/dl	Urine output <0.5 ml/kg/h \times 6 h
Stage 2	Increased Cr \times 2–2.9 from baseline	Urine output <0.5 ml/kg/h \times 12 h
Stage 3	Increased Cr \times \geq 3 or sCr \geq 4 mg/dl with acute rise of \geq 0.5 mg/dl	Urine output < 0.3 ml/kg/h \times 24 h or Anuria \times 12 h

Table 1.3 KDIGO criteria for acute kidney injury

	Cr/GFR criteria	Urine output criteria
Stage 1	Increased Cr \times 1.5–1.9 from baseline or increase by \geq 0.3 mg/dl	Urine output <0.5 ml/ kg/h \times 6–12 h
Stage 2	Increased Cr \times 2–2.9 from baseline	Urine output <0.5 ml/ kg/h \times 12 h
Stage 3	Increased Cr \times \geq 3 or increase in sCr \geq 4 mg/dl or initiation of renal replacement therapy or, in patients <18 years, decrease in GFR <35 ml/min/1.73 m ²	Urine output <0.3 ml/ kg/h \times 24 h or Anuria \times 12 h

All three definitions have subtle differences and different advantages. Baseline creatinine interpretation differs among definitions; most notably, AKIN uses first creatinine available as the baseline creatinine, whereas pRIFLE requires height to calculate eCCL. Thus, pRIFLE, AKIN, and KDIGO result in different AKI epidemiology. pRIFLE is more sensitive to detect mild AKI. AKIN is less sensitive but more specific to diagnose severe AKI; whereas, pRIFLE and KDIGO detect severe AKI similarly. Since KDIGO is applicable to both pediatric and adult population it has come into wide use. Overall, all three definitions highly correlate with staging of AKI and outcomes [8, 9].

Table 1.4 Modified KDIGO criteria for neonatal acute kidney injury

	Cr/GFR criteria	Urine output criteria
Stage 0	No change in sCr or rise <0.3 mg/dl	Urine output >1 ml/kg/h
Stage 1	sCr rise ≥ 0.3 mg/dl within 48 h or sCr rise ≥ 1.5 to $1.9 \times$ reference sCr within 7 days	Urine output >0.5 ml/kg/h and ≤ 1 ml/kg/h
Stage 2	sCr rise ≥ 2 to $2.9 \times$ reference sCr	Urine output >0.3 ml/kg/h and ≤ 0.5 ml/kg/h
Stage 3	sCr rise $\geq 3 \times$ reference sCr or sCr ≥ 2.5 mg/dl or receipt of dialysis	Urine output ≤ 0.3 ml/kg/h

^aReference serum creatinine, defined as the lowest previous serum creatinine value available

The criteria for the diagnosis of AKI and staging of severity of AKI are based on changes in serum creatinine and urine output. The caveat here is that serum creatinine is a late marker of decreasing GFR. Additionally, serum creatinine concentrations can be influenced by malnutrition, liver dysfunction, decreased muscle mass, and volume overload, which all can cause underestimation of the degree of renal dysfunction. On the other hand, changes in urine output usually precede the changes in serum creatinine [10]. If only creatinine criteria are used, up to 70% of AKI are missed [1]. However, relying on urine output solely will obviously miss nonoliguric AKI, such as presented in Case 2 in the beginning of the chapter. Since urine output may not be measured routinely in non-intensive care settings, early AKI might easily be missed. The worry for catheter associated urinary tract infection has led to a tendency of not placing indwelling bladder catheters or early removal in the intensive care settings. Clinicians need to be aware of when closer monitoring is needed and order this simple intervention accordingly. All patients who get admitted in shock should receive an indwelling bladder catheter until shock is resolved.

Definition of AKI in critically ill neonates has lagged behind that in older populations. Serum creatinine is difficult to interpret in newborns since it may reflect maternal creatinine during first week of life in term neonates and may persist at maternal levels up to 2–3 weeks in preterm infants. Monitoring the trend of the serum creatinine may be more helpful. Progressive increase in serum creatinine or failure to decrease is consistent with decreased renal function. KDIGO AKI definition was adapted and used for study purposes in the neonatal population (Table 1.4). The overall incidence of AKI in neonates and infants is about 30% and is associated with poor outcomes including higher mortality, similar to other age groups [11].

1.2 Acute Kidney Injury: Epidemiology

Although precise incidence of pediatric AKI is not known, overall incidence of AKI is thought to be increasing and depends on the clinical setting and patient's clinical condition. An administrative dataset screening for physician coding revealed AKI rate of 3.9 per 1000 at-risk pediatric hospitalizations [11]. Twenty seven percent of the critically ill children at pediatric intensive care unit (PICU) developed AKI with 10% of them developing severe AKI (AKI stage 2 and stage 3), and 1% requiring renal replacement therapy. Twelve percent of severe AKI develops within 7 days after ICU admission [1].

Multiorgan dysfunction, need for mechanical ventilation, documented infection, extracorporeal membrane oxygenation, and nephrotoxic medication exposure are identified as risk factors for developing AKI in critically ill children, while nephrotoxic medication exposure has the greatest independent risk [12, 13]. Development of AKI is associated with higher mortality, PICU length of stay, and duration of mechanical ventilation [13, 14]. Severe AKI (stage II or III) has the highest association with mortality. Patients with resolved AKI or those who have improvement in their severity of AKI stage tend to have lower mortality; however, patients with any degree of AKI, even mild, despite complete resolution, still have higher rates of mortality than patients who do not develop AKI at all in the ICU setting [15]. Outside of the PICU, 25% of the non-critically ill children who are exposed to three or more nephrotoxic medications developed AKI [16, 17]. AKI rates of 30% have been reported in infants; whereas, 48% of extremely preterm infants (less than 28 weeks of gestation) develop AKI [18]. The incidence increases to 40–65% in the infants undergoing cardiac surgery depending on the definition used, the rate increasing with lower age at surgery, longer cardiopulmonary bypass, type of repair, and lower gestational age [19, 20] (Table 1.5).

Table 1.5 Risk factors associated with AKI [21]

Critical illness
Sepsis
Shock—hypotension, vasopressor requirement
Mechanical ventilation
Extracorporeal membrane oxygenation
Preexisting renal, hepatic, cardiac, neurologic, or respiratory disease
Oncologic disease
Neonates
Low gestational age
Low birth weight
Perinatal asphyxia
Congenital diaphragmatic hernia
Bronchopulmonary dysplasia
Maternal exposure to angiotensin-converting enzyme (ACE) inhibitors
Solid organ transplants
Bone marrow transplants
Intravascular volume depletion—diabetic ketoacidosis, nephrotic syndrome, diarrhea, vomiting
Venous congestion—congestive heart failure, right heart failure, pulmonary hypertension
Post cardiac surgery—prolonged cardiopulmonary bypass
Nephrotoxic medication exposure ^a
Aminoglycosides
Vancomycin
Piperacillin/tazobactam
Amphotericin B
Chemotherapeutics
Immune modulators
Non-steroidal anti-inflammatory drugs
ACE inhibitors
Intravenous contrast media

^aList in not exhaustive

1.3 Acute Kidney Injury: Pathophysiology

1.3.1 Functional AKI

Functional (prerenal) AKI is caused by decreased renal perfusion due to decrease in either absolute or effective circulating volume. Hypotension, decreased cardiac function, renovascular compromise, and volume depletion can all lead to functional AKI. The hallmark is the improvement of renal function with correction of underlying problem, hence the term functional. Systemic hypoperfusion triggers the activation of sympathetic nervous system, renin-angiotensin axis, and nonosmotic antidiuretic hormone secretion leading to compensatory mechanisms that raise blood pressure. GFR is initially preserved by several intrarenal autoregulatory mechanisms including generation of intrarenal vasodilatory prostaglandins and intrinsic myogenic mechanisms [22]. Prolonged duration and increased severity of the trigger lead to decrease in GFR, manifested as functional AKI. During this phase, subclinical intrinsic renal injury may be demonstrated by novel biomarkers, which typically are proteins expressed in cellular stress and repair. Longer duration of this phase can easily transition into intrinsic injury.

1.3.2 Intrinsic Renal Injury

Prolonged duration of processes leading to functional AKI, exposure to nephrotoxins, or sepsis, among other causes, can lead to intrinsic AKI, especially in the setting of critical illness. Though traditionally referred to as acute tubular necrosis (ATN), histological evidence of ATN is exceedingly rare in the critically ill patients suffering from AKI. Endothelial cell injury can promote the initiation and extension of intrinsic AKI via disrupting the microvascular blood flow. Straight segment (S3 segment) of proximal tubule and medullary thick ascending limb of Henle are particularly sensitive to ischemic changes given inherent high cellular energy needs and relative low oxygen tension in the adjoining renal medulla. Cellular injury leads to cell sloughing from disrupted adhesion molecules and cell necrosis which may further cause tubular obstruction with leakage of proteinaceous material (Tamm-Horsfall protein). Inflammatory processes also contribute to the sequence of events in intrinsic AKI [22].

1.3.3 Postrenal AKI/Obstructive Nephropathy

Anatomic abnormalities of the genitourinary system (for example, posterior urethral valves), functional problems (for example, neurogenic bladder, dysfunctional bladder, or other voiding dysfunction), obstruction at the bladder outlet or bilateral ureters, or blockage of tubules with protein and crystals can lead to urinary retention and AKI. Obstruction affecting bilateral collecting systems is the hallmark of obstructive AKI. Backward pressure from obstruction is transmitted up through the

Table 1.6 Determining type of the renal injury

	FeNa: $([U/P] Na)/([U/P]/Cr) \times 100$	FeUrea: $([U/P] Urea)/([U/P]/Cr) \times 100$
Functional AKI	FeNa <1%	FeUrea <35%
	Urine sodium: <20 mEq/l	
	Urine osmolality: >400 mOsm/kg	
	Urine specific gravity: >1020	
	Urine sediment: bland	
Urine protein: none to low		
Intrinsic AKI	FeNa >2%	FeUrea >50 to 65%
	Urine sodium: >30 mEq/l	
	Urine osmolality: <350 mOsm/kg	
	Urine specific gravity: <1012	
	Urine sediment: broad brownish granular cast	
Urine protein: none to low		

Sodium (Na), Creatinine (Cr), Urine (U), Plasma (P)

urinary system, which counteracts the hydrostatic pressure for filtration at the glomerulus. When it eventually overcomes the hydrostatic pressure in the glomerulus, glomerular filtration stops and AKI occurs [22].

1.4 Differentiation of Functional and Intrinsic AKI

Urinary indices are derived from the assumption that tubular integrity is maintained in the setting of functional AKI. In prerenal/functional AKI state, sodium-retaining mechanism is activated, reducing the urinary sodium; whereas tubular cell damage of ATN causes impaired resorptive capacity of proximal tubule leading to urinary sodium rise. Thus, urine sodium is used as an indicator of volume status and renal tubular integrity. Fractional excretion of sodium (FeNa) evaluates urinary sodium excretion. However, diuretic use limits sodium reabsorption and makes FeNa calculation unreliable in patients who have received diuretics. Fractional excretion of urea (FeUrea), based on the same principal, can be used in these instances (Table 1.6).

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