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The ICU Book on RENAL REPLACEMENT THERAPY



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CHAPTER 2

Phenotypes and Subphenotypes of Acute Kidney Injury

Sagar Chandrakant Kulkarni

INTRODUCTION

Acute kidney injury (AKI) is one of the most common organ dysfunctions in critically ill patients. More than 50% patients admitted to the intensive care unit (ICU) have AKI, and it is an independent risk factor for increased mortality.[1] The impact of an episode of AKI extends beyond the acute phase as it increases the risk of subsequent chronic kidney disease (CKD), higher cardiovascular complications, and mortality.[2]

Hence, AKI needs to be managed across all stages of prevention. Primary prevention includes identifying risk factors for AKI and targeting them, e.g., adequate hydration, drug dose adjustments, etc. Secondary prevention aims at early detection and treatment. Tertiary prevention includes measures to hasten recovery and to prevent long-term complications. Recent research in biomarkers of AKI can be applied to improve management in all these areas. Although most of the biomarkers are projected for early detection of AKI, it is not their only utility. Traditional and newer biomarkers when used in appropriate context can help to identify risk, determine pathomechanism, and assess long-term impacts.

The objective of this chapter is to elaborate newer concepts in understanding of AKI based on phenotypes and subphenotypes. It will also take a brief overview upon the development of definitions of AKI, biomarkers, and their application in clinical practice.

CONCEPT OF PHENOTYPE AND SUBPHENOTYPE

The phenotype of a disease means the observable traits that are physical expressions of the underlying process. While subphenotype is a distinct group of patients within a broad cohort or phenotype, who share common features, risk factors, biomarker positivity, response to treatment, or outcomes that separate this subphenotype from other groups of patients within the phenotype.[3] subphenotyping is a strategy to overcome heterogeneity in order to advance clinical research and eventually identify treatable traits.[4] Phenotype depends on the cause of the disease while subphenotype depends on the pathophysiological mechanism driving the injury. Before going into details of phenotypes in AKI, we will take a look at the evolution of various definitions and terminologies of AKI.

DEFINITIONS OF ACUTE KIDNEY INJURY

Acute renal failure (ARF) was the initial terminology in vogue for many decades without any structured definition. In 2004, Acute Dialysis Quality Initiative (ADQI) came up with Risk, Injury, Failure, Loss, and End-Stage Renal Disease (RIFLE) criteria for ARF which moved forward the concept of three stages of renal dysfunction, i.e., risk, injury, failure, and two stages of outcome,

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i.e., loss and end stage. Later the term ARF was replaced by acute kidney injury, which encompassed patients having functional impairment with respect to physiological demands but without actual kidney damage. By 2007, the Acute Kidney Injury Network (AKIN) proposed a modified version of RIFLE criteria with the addition of an absolute rise in serum (Sr.) creatinine of 0.3 mg/dL to diagnose the early stage of AKI. In 2012, Kidney Disease: Improving Global Outcomes (KDIGO) proposed a singular definition that can be used for practice, research, and public health purposes **(Table 1)**.

These definitions are broad and functional but are not characterized to have practical application in patient management. There are two important limitations, firstly, Sr. creatinine is not a sensitive marker of AKI.[6] Secondly, in AKI, Sr. creatinine rises irrespective of the etiology or mechanism; therefore, it does not provide clues about the etiopathology of AKI. This heterogeneity not only has implications in patient management but also poses a significant challenge for designing clinical trials. For example, in a study of an intervention to prevent contrast-induced AKI, cardiac failure and low

TABLE 1: Definition and classification of AKI by RIFLE, AKIN, and KDIGO criteria.[5]

RIFLE		*AKIN*		*KDIGO*		*Urine output criteria (common)*
Class	***Sr. creatinine or GFR***	***Stage***	***Sr. creatinine***	***Stage***	***Sr. creatinine***	
Risk	Increase in Sr. creatinine 1.5 times baseline or GFR decrease >25%	1	>0.3 mg/dL or 1.5–2.0 times rise from baseline	1	>0.3 mg/dL in less than 48 hours or 1.5–1.9 times rise from baseline	<0.5 mL/kg/h for 6–12 hours
Injury	Increase in Sr. creatinine 2 times baseline or GFR decrease >50%	2	2.0–3.0 times rise from baseline	2	2.0–2.9 times rise from baseline	0.5 mL/kg/h for >12 hours
Failure	Increase in Sr. creatinine 3.0 times baseline or ≥4.0 with an acute rise at least 0.5 mg/dL or GFR decrease >75%	3	>3.0 times rise from baseline or ≥4.0 mg/dL with an acute rise at least 0.5 mg/dL or initiation of RRT	3	3.0 times rise from baseline or ≥4.0 mg/dL or initiation of RRT or in patients <18 years, decrease in eGFR to <35 mL/min per 1.73 m^2	<0.3 mL/kg/h for >24 hours or anuria for >12 hours
Loss	Persistent ARF for more than 4 weeks					
End stage	End-stage kidney disease for >3 months					

(AKI: acute kidney injury; AKIN: Acute Kidney Injury Network; eGFR: estimated glomerular filtration rate; GFR: glomerular filtration rate; KDIGO: Kidney Disease: Improving Global Outcomes; RIFLE: Risk, Injury, Failure, Loss, End-stage Renal Disease; RRT: renal replacement therapy; Sr.: serum)

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TABLE 2: ADQI classification of AKI.[7]

Functional criteria	*Damage criteria*	
	Biomarker negative	***Biomarker positive***
No change or Sr. creatinine increase <0.3 mg/dL and no urine output criteria	–	1S
Increase of Sr. creatinine level by ≥0.3 mg/dL for ≤48 hours or ≥150% for ≤7 days and/or urine output <0.5 mL/kg/h for 6 hours	1A	1B
Increase of Sr. creatinine level ≥200% and/or urine output <0.5 mL/kg/h for >12 hours	2A	2B
Increase of Sr. creatinine level by >300% or ≥4.0 mg/dL (with an acute increase of ≥0.5 mg/dL) and/or urine output <0.3 mL/kg/h for >24 hours or auria for >12 hours and/or acute RRT	3A	3B

(ADQI: Acute Dialysis Quality Initiative; AKI: acute kidney injury; RRT: renal replacement therapy; Sr.: serum)

perfusion can also be an ongoing process and may give false negative results of the intervention. Therefore, it is necessary to identify exact phenotypes and subphenotype which will help to select a patient population in which the proposed intervention may actually be useful.

So far, all definitions considered only Sr. creatinine and urine output as markers of AKI. But in 2020, the 23rd ADQI meeting released a consensus statement that incorporated the use of other biomarkers in the prevalent KDIGO definition **(Table 2)**. It introduced a new stage called 1S which will have patients without increase in creatinine or decreased urine output but with positive biomarkers. Also, it subdivided each stage of AKI into A and B depending on the presence or absence of biomarkers.[7]

BIOMARKERS OF ACUTE KIDNEY INJURY

The identification of etiology and pathophysiologic mechanisms need sensitive and specific tools called biomarkers. A biomarker is a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention.[8] It can be a clinical tool or biochemical test. Over the last few decades, multiple biochemical markers of kidney injury have been discovered. Although detailed discussion of each biomarker is beyond scope in this chapter, **Table 3** gives a brief description of some important biomarkers of AKI.

PHENOTYPES OF ACUTE KIDNEY INJURY

The combination of conventional knowledge and novel biomarkers can be used to develop a new approach to AKI with respect to phenotype and subphenotype that will help in early identification and therapeutic intervention.

Traditionally, AKI has been described in three phenotypes, namely prerenal, intrarenal, and post renal. Although this classification has an etiologic connotation, it is an oversimplification of the complex processes involved in AKI. Five phenotypes of AKI have been described as listed here:[16]

1. Low perfusion
2. Immune mediated
3. Infection/sepsis related
4. Obstruction
5. Nephrotoxic

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TABLE 3: Biomarkers in AKI and their role in pathophysiology.

Biomarker	*Comment*
IGFBP-7/TIMP-2	Cell-cycle arrest biomarkers in blood and urine[9]
PAPPA-2	A metalloproteinase secreted by the ThAL which targets the IGFBP system and permits cell survival[10]
KIM-1	A transmembrane protein expressed on tubular epithelial cells acts as a scavenger receptor and converts the normal proximal tubule cell into a phagocyte. Urine levels increase during ischemic or toxin-induced kidney damage[11]
NGAL	NGAL is involved in the iron transport to and from cells, it acts as a bacteriostatic agent which may be important for the local defense against infections. Urine levels increase in tubular stress or injury but not in prerenal AKI[12]
IL-8, IL-6, and sTNFR	Markers of generalized inflammation[13]
MCP-1	It is expressed by mesangial cells and podocytes and may reflect glomerular injury[14]
Angiopontin-1	Vascular endothelial growth factor agonist to Tie-2 receptor stabilizes vascular endothelium and prevents capillary leaking[13]
Angiopontin-2	Vascular endothelial growth factor that antagonizes Tie-2 receptor promotes endothelial dysfunction and inflammation[13]
L-FABP	Endogenous antioxidant with high affinity binding to long-chain fatty acids. It is expressed in proximal tubules with ischemia and oxidative stress. Elevated levels in urine and plasma have been linked to the severity of renal injury[15]

(AKI: acute kidney injury; IGFBP-7: insulin-like growth factor binding protein-7; IL: interleukin; L-FABP: liver-type fatty acid binding protein; KIM-1: kidney injury molecule-1; MCP-1: monocyte chemoattractant protein; NGAL: neutrophil gelatinase-associated lipocalin; PAPPA-2: pregnancy-associated plasma protein-A2; sTNFR: soluble tumor necrosis factor receptor; TIMP-2: tissue inhibitor of metalloproteinase-2; ThAL: thick ascending limb of loop of Henle)

Low-perfusion phenotype includes all causes of AKI which lead to reduced blood flow to the kidneys. The previous grouping called prerenal AKI is referred only to hypovolemia. But low-perfusion AKI includes other causes of reduced blood flow such as ventricular failure or vascular occlusion along with hypovolemia.

Hypoxia is the major mechanism, which leads to injury in this particular phenotype. Tubular epithelial cells have very high oxygen demand, and hypoxia leads to stress on these cells. In this situation, the body tries to arrest the cell cycle and keep tubular function intact. Tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth factor binding protein-7 (IGFBP-7) are cell cycle arrest biomarkers that can be detected in the blood and urine of these patients much ahead of actual tubular injury and rise in Sr. creatinine.[9] When actual tubular injury or necrosis sets in, proximal tubular cells release proteins such as kidney injury molecule-1 (KIM-1), gamma-glutamyl transferase (GGT), alkaline phosphatase (AP), alpha-glutathione S-transferase (α-GST), and neutrophil gelatinase-associated lipocalin (NGAL), and damaged proximal tubules are unable to reabsorb filtered biomarkers such as liver-type fatty acid binding protein (L-FABP), TIMP-2, and IGFBP-7.[16] Glomerular filtration may not reduce significantly till this stage, and Sr. creatinine may remain in the normal range.

In the setting of severe volume depletion without ischemia, a specific set of differentially expressed genes (DEGs) are activated

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which regulate metabolism, transport, and osmoregulatory functions. These gene products, e.g., pregnancy-associated plasma protein-A2 (PAPPA-2) can be detected in patients with prerenal AKI. Interestingly in patients with ischemic AKI, fragments of PAPPA-2 were detected in urine indicating cleavage of PAPPA-2 released during the early phase by a new set of metabolites produced after ischemia.[10]

Next two phenotypes, i.e., infection and immunological diseases have inflammation as a major mechanism, leading to kidney injury. Although endothelial injury and microvascular ischemia play a role in sepsis/infection-related AKI, inflammation remains a major driver of injury. Various damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) are released in circulation as a result of infection and inflammation. They have an amplifying effect on inflammatory processes by cytokine release. Cytokines such as interleukin 6 (IL-6), IL-18, and soluble tumor necrosis factor receptor (sTNFR) can be detected in blood and/or urine of these patients.

Monocyte chemoattractant protein (MCP)-1 is secreted by mesangial cells and podocytes. Urinary detection of MCP can indicate glomerular disease,[14] also *PYCARD* gene pathway is upregulated in autoimmune crescentic glomerulonephritis[17] and can help to diagnose immune-mediated AKI phenotype.

The next phenotype is obstruction in the urinary tract. Here obstruction to urinary flow leads to pressure necrosis of tubules and back-leak of ultrafiltrate into interstitium. Vanin 1 level in the renal pelvis of an obstructed kidney is highly sensitive and specific biomarker and also correlates with degree of severity.[18]

Nephrotoxic AKI due to substances including drugs, poisons, and venoms leads to apoptosis, necroptosis, and ferroptosis and causes tubular injury. Cytochrome C is released in urine during mitochondrial damage and apoptosis. Hence, it can be used as a biomarker in this particular setting.

SUBPHENOTYPES OF ACUTE KIDNEY INJURY

It is important to identify specific pathophysiologic mechanisms that are set in due to the insult. It can be transient hypoxia, persistent hypoxia, endothelial injury, inflammation, or apoptotic process. Even with similar mechanisms, different sets of genes are activated in order to defend the insult or repair the system. This leads to the transcription of certain proteins which can be detected to identify ongoing processes.

In 2018, Bhatraju et al. identified two novel AKI subphenotypes in patients with sepsis and AKI, by using the latent class analysis method.[19] In their study of 794 patients admitted to the ICU with systemic inflammatory response syndrome (SIRS) and suspected infection with AKI, two molecularly distinct subphenotypes were identified, namely AKI-SP-1 and AKI-SP-2. Subphenotype-1 is characterized by low angiopoietin 1 (Ang-1), angiopoietin 2 (Ang-2) ratio, and low sTNFR-1 level, which signifies quiescent vascular bed and low inflammatory state. While subphenotype 2 is characterized by an elevated Ang-1/Ang-2 ratio and higher sTNFR-1 level, which signifies increased capillary permeability and hyperinflammatory state. AKI-SP-1 had a lower mortality rate than AKI SP-2.[13] This model was applied to a subset of patients from the VASST study (n = 328) in which Ang-1, Ang-2, and IL-8 were measured. In this model, s-TNFR is replaced by IL-8 as a marker of inflammation. Out of 328 patients, 271 had AKI with 113 having AKI-SP-1 and 148 having

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AKI-SP-2. It was found that in AKI-SP-1, early addition of vasopressin significantly lowered 90-day mortality compared to a similar intervention in AKI-SP-2.[13] This model highlights the importance of parsing AKI syndrome to identify treatment-responsive subtypes. A similar method of latent class analysis was applied for post hoc analysis of the FINNAKI study, which also identified two subphenotypes of AKI using four biomarkers, namely heparin-binding protein (HBP), neutrophil elastase-2 (Ela-2), proteinase-3 (PRTN-3), and matrix metalloproteinase-8 (MMP-8), with significantly different short-term renal recovery and 90-day mortality.[20]

Another interesting example of how individual subphenotypes within a phenotype improve outcomes with targeted therapy is thrombotic microangioangiopathies in pregnancy-associated AKI. Hemolysis, elevated liver enzymes, low platelet count (HELLP), hemolytic uremic syndrome (HUS), and thrombotic thrombocytopenic purpura (TTP) all have a common clinical picture with thrombocytopenia, hemolytic anemia, and AKI due to microvascular thrombosis, yet the pathophysiology of these conditions is very much different. HELLP syndrome occurs because of placental ischemia caused by altered soluble Fms-like tyrosine kinase-1 (sFLT) to placental growth factor (PLGF) ratio and recovers with delivery. TTP is caused by excess ultralarge Von Willebrand factor multimers due to decreased activity of the ADAMTS-13 and the treatment is plasma exchange with fresh-frozen plasma. HUS is driven by the overactivation of alternate complement pathways, and it requires treatment with complement inhibitors such as eculizumab.

Table 4 elaborates on the phenotypes, subphenotypes, and biomarkers that can be used to develop a new approach toward managing AKI patients. Some biomarkers are bedside clinical tools that have conventionally been used in practice, while others are novel molecules that are done in specialized laboratories. This classification is evolving further with more research in pathophysiology and the discovery of newer biomarkers.

TABLE 4: Phenotypes and subphenotypes of AKI.[21]

Phenotype	*Subphenotype*	*Clinical condition*		*Biomarkers*
Low perfusion	Transient hypoxia (cell-cycle arrest)	Volume depletion without tubular injury		Plasma copeptin levels and urine PAPPA-2
	Hypoxia	Volume depletion with tubular injury		Lactate, malate dehydrogenase, KIM 1, NGAL, L-FABP, and cytochrome C
		Hypoalbuminemia		Sr. albumin
		Vasodilatory states	Hepatorenal syndrome	Portal venous pressure, low NGAL, and LFTs
		Vasoconstriction	Contrast and drugs	
			Hypercalcemia	Sr. ionic calcium

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Phenotype	*Subphenotype*	*Clinical condition*		*Biomarkers*
		Thrombotic microangiopathy	Preeclampsia	s-FLT/PlGF
			Malignant HTN	Papilledema
			HUS	PS-schistocytes, LDH, and low C3
			TTP	Low ADAMTS-13 activity
		Vascular flow interruption	Kidney transplant/ aortic surgery	KIM-1, NGAL, L-FABP, and cytochrome-C
			Raised abdominal pressure	Measurement of abdominal pressure
		Reduced left ventricular output		BNP, Trop I, 2D echo, and angiotensinogen levels
		Reduced right ventricular output		IVC-diameter, liver enzymes, IL-6, and TNF-α
Infection	Inflammation + microvascular injury + hypoxia	Sepsis, and septic shock		Procalcitonin, DAMPs, PAMPs, netrin 1, sTREM 1, Ang-1/Ang-2 ratio, IL-18, IL-6, thrombo-modulin, TNF-α1, and TNF-α2
Immunological	Inflammation	Autoimmune diseases		ANCA, anti-GBM Ab, anti-ds-DNA antibody, C3, C4, *PYCARD* gene
Obstructive	Pressure necrosis			Vanin-1 and cytochrome C
Nephrotoxic	Ferroptosis	Hemolysis		Urine Hb, PS-schistocytes, and LDH
		Rhabdomyolysis		Sr. CPK, urine Mb, NAG, and NGAL
	Necroptosis	Drugs and contrast agent		KIM-1 and cystatin-C
		Toxins		Clusterin
	Inflammation	Acute interstitial nephritis		TNF-α and IL-9

(ANCA: antineutrophil cytoplasmic antibody; Ang-1: Angiopontin-1; Ang-2: Angiopontin-2; BNP: brain natriuretic peptide; CPK: creatine phosphokinase; HTN: hypertension; HUS: hemolytic uremic syndrome; IL: interleukin; IVC: inferior vena cava; KIM-1: kidney injury molecule-1; LDH: lactate dehydrogenase; L-FABP: liver-type fatty acid binding protein; LFT: liver function test; NAG: N-acetyl-beta-D-glucosaminidase; NGAL: neutrophil gelatinase-associated lipocalin; PAPPA-2: pregnancy-associated plasma protein-2; PlGF: placenta growth factor; s-FLT: soluble Fms-like tyrosine; Sr.: serum; TNF: tissue necrosis factor; TTP: thrombotic thrombocytopenic purpura; Urine Hb: urine hemoglobin; Urine Mb: urine myoglobin)

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CONCLUSION

It can be summarized that AKI is a heterogeneous syndrome with various causes and pathophysiological mechanisms. Traditional systems of defining and classifying AKI need to be revised in the context of recent advances in molecular biology. Biomarkers are crucial as they can help to identify the etiology and pathophysiology of AKI, leading to more accurate diagnosis and targeted treatment. In order to refine the practical understanding of AKI, five AKI phenotypes have been proposed. Subphenotypes can be identified within each phenotype with respect to specific mechanisms. The latent class analysis method has been used to identify distinct subphenotypes based on biomarker profiles. There are studies which have shown that different sub-phenotypes have varying responses to treatment and clinical outcomes. This approach will also help for clinical research to analyze specific cohorts of AKI patients which will have more homogenous pathophysiology. In conclusion, phenotyping and subphenotyping of AKI using biomarkers, clinicians can develop more precise and personalized treatment strategies to improve patient outcomes. This area is constantly evolving, and there is a need for further research to uncover additional biomarkers in order to improve AKI management.

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MULTIPLE CHOICE QUESTIONS

1. A 48-year male admitted with acute myocardial infarction underwent primary percutaneous coronary intervention (PCI). He had hypotension on admission, which got resolved post-PCI. On day 3 of admission, he developed raised creatinine value. Urine output is normal. All are true, *except*:

a. The patient seems to have developed prerenal AKI
b. The patient is at risk for contrast-associated AKI
c. The patient needs close monitoring with judicious use of intravenous fluids
d. The patient requires urgent RRT

Ans. d

2. A 70-year-old man is admitted to the ICU with AKI post-chemotherapy. Urine routine examination shows renal tubular epithelial cells and muddy brown casts. What is this phenotype type of AKI?

a. Prerenal AKI
b. Acute tubular necrosis
c. Functional renal impairment
d. Postrenal AKI

Ans. b

Comment: Urinalysis of acute tubular necrosis shows muddy brown casts or renal tubular epithelial cells secondary to the sloughing of tubular cells into the lumen due to ischemia or toxic injury.

3. Cell-cycle arrest biomarkers for AKI in blood and urine include:

a. IGFBP-7 (insulin-like growth factor binding protein-7)
b. TIMP-2 (tissue inhibitor of metalloproteinase-2)
c. L-FABP (liver-type fatty acid-binding protein)
d. a and b

Ans. d

Reference: Rodrigues CE, Endre ZH. Definitions, phenotypes, and subphenotypes in acute kidney injury-moving towards precision medicine. Nephrology (Carlton). 2023;28(2):83-96.

4. In AKI subphenotyping, identifying, and cohorting patients likely to have a high risk for requiring RRT is:

a. Prognostic enrichment
b. Predictive enrichment
c. Personalization
d. Postrenal AKI

Ans. a

Reference: Vaara ST, Bhatraju PK, Stanski NL, McMahon BA, Liu K, Joannidis M, et al. Subphenotypes in acute kidney injury: a narrative review. Critical Care. 2022;26:251.

5. A patient is admitted to the ICU with urosepsis and develops AKI. The Sr. creatinine trajectory shows a rapid rise in Sr. creatinine followed by a plateau. Which of the following AKI recovery subphenotypes can best explain this?

a. Resolving AKI
b. Persistent AKI
c. Nonresolving AKI
d. Transient AKI

Ans. c

Reference: Vaara ST, Bhatraju PK, Stanski NL, McMahon BA, Liu K, Joannidis M, et al. Subphenotypes in acute kidney injury: a narrative review. Critical Care. 2022;26:251.

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The ICU Book on
RENAL REPLACEMENT THERAPY

Salient Features

- This book is designed as a practical guide for beginners in intensive care and nephrologists who are dealing with critically ill patients on renal replacement therapy on a day-to-day basis
- It is compiled by experts from both intensive care and nephrology based on latest literature evidence and experience
- It is equipped with illustrations/flowcharts
- A special section on renal replacement therapy (RRT) in special situations, which is case based, has been included
- Multiple Choice Questions (MCQs) at the end of each chapter are given to assess the understanding of the subjects covered.

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