



# ACUTE KIDNEY INJURY (AKI)

Acute kidney injury (formerly known as acute renal failure) is a syndrome characterized by the rapid loss of the kidney's excretory function. It is the clinical manifestation of several disorders that affect the kidney acutely.<sup>1</sup>

## ACUTE KIDNEY INJURY<sup>2</sup>

- Acute kidney injury (AKI) is a **global public health concern** associated with high morbidity, mortality, and healthcare costs.
- AKI often has a **very rapid onset in hours or days**, in contrast with chronic kidney disease (CKD) which takes months or years to develop.
- In the **developed world**, AKI tends to manifest in older patients **in the Intensive Care Unit (ICU)**.
- In **lower- to middle-income countries**, which represent 85% of cases of AKI, **young adults and women** are particularly prone and at risk of death.
- Among those patients who survive, **long-term outcomes of AKI** can include the development of **CKD and end-stage renal disease (ESRD)**, or **exacerbation of pre-existing CKD accelerating the progression to ESRD**.
- Although previously thought to have a benign course in patients who recovered, **AKI can lead to poor quality of life and high long-term costs**.
- **Early detection is important** as some 20-30% of cases of AKI may be partially or fully preventable.

## THE BURDEN OF AKI<sup>3,4</sup>

AKI occurs in about **13.3 million people** per year

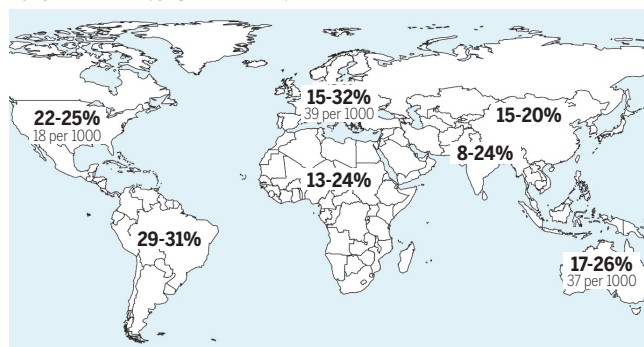
AKI contributes to about **1.7 million deaths** every year

It affects **7-18%** of hospital in-patients and **30-70%** of critically ill patients

**±5%** of Intensive Care Unit admissions require renal replacement therapy (RRT)

## Epidemiology of AKI per hospital admission and corresponding incidence by region<sup>5</sup>

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## CAUSES OF AKI<sup>6-9</sup>

AKI may be caused by a variety of conditions including disease, injury, toxins, drugs or major surgery (especially cardiac surgery). It is common for patients developing AKI to have multiple etiologies at once.

### Common conditions leading to AKI<sup>6, 8, 9</sup>

- Severe infections: sepsis, malaria, COVID-19
- Cardiac surgery (especially with cardiopulmonary bypass)
- Critical illness
- Major non-cardiac surgery
- Circulatory shock
- Nephrotoxic drugs
- Burns
- Radiocontrast agents
- Trauma
- Poisonous plants and animals

### In patients with critical illness<sup>7</sup>

- Sepsis and hypovolemia are the most frequent reported etiologies for AKI.
- Nephrotoxic drugs were reported as the etiology for AKI in 14.4% of patients.
- At the time of AKI diagnosis, one-third of patients were treated with diuretics and 11.9% with non-steroidal anti-inflammatory drugs.
- Aminoglycosides, glycopeptides and contrast media were administered in less than 10% of AKI patients.
- Half of AKI patients were treated with vasoactive therapy at the time of AKI diagnosis.
- One-third were mechanically ventilated.

## STAGES OF AKI<sup>6</sup>

AKI is defined by the **Kidney Disease: Improving Global Outcomes (KDIGO)** consensus classification and is staged for severity according to the following criteria.

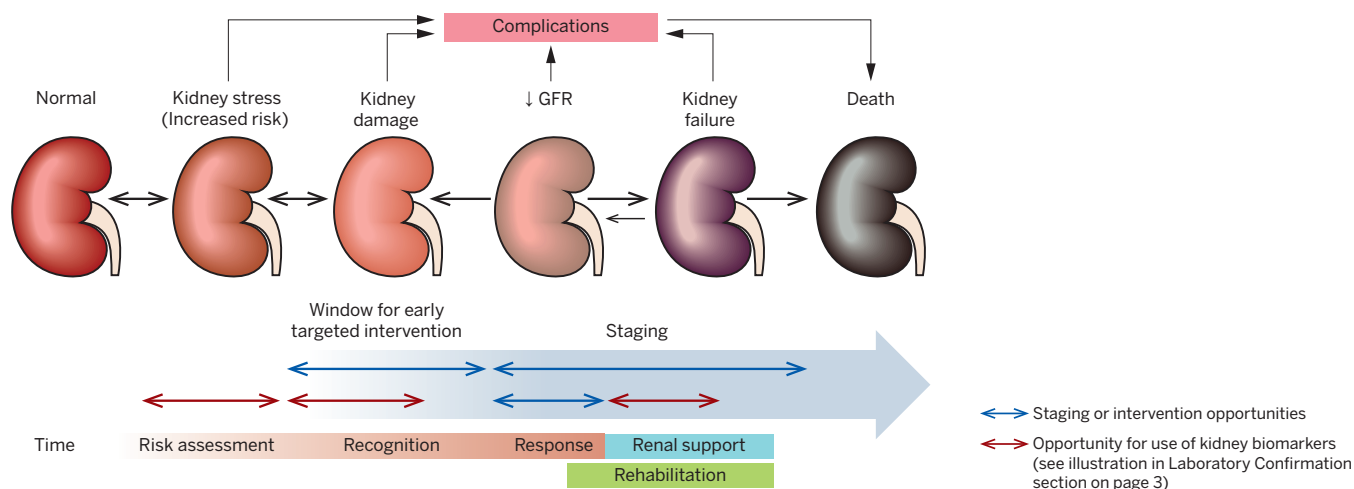
### KDIGO staging of AKI<sup>6</sup>

Stage	Serum creatinine	Urine output
1	1.5-1.9 times baseline OR ≥0.3 mg/dL (≥26.5 μmol/L) increase	<0.5 mL/kg/h for 6-12 hours
2	2.0-2.9 times baseline	<0.5 mL/kg/h for ≥12 hours
3	3.0 times baseline OR Increase in serum creatinine to ≥4.0 mg/dL (≥353.6 μmol/L) OR Initiation of renal replacement therapy OR In patient <18 years, decrease in eGFR to <35 mL/min per 1.73 m <sup>2</sup>	<0.3 mL/kg/h for ≥24 hours OR Anuria for ≥12 hours

eGFR: estimated Glomerular Filtration Rate

### Conceptual framework and targeted approach for raising awareness of AKI<sup>4</sup>

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## CLINICAL PRESENTATION<sup>4,6</sup>

- AKI is a process that evolves from early injury through severe damage, resulting in kidney failure and the need for RRT. The natural course can vary from complete renal recovery to dialysis dependency or death.
- Unlike myocardial infarction and stroke, **kidney disease is largely asymptomatic**, and kidney injury may be discovered only late in the course.
- For this reason, the Kidney Disease: Improving Global Outcomes (KDIGO) guideline begins with patients at high risk of AKI, and not with patients who already have the condition.
- Although a number of susceptibilities (e.g. advanced age, underlying chronic disease) and exposures (e.g. sepsis, critical illness, shock, burns, trauma, cardiac surgery, major non-cardiac surgery, nephrotoxic drugs, radiocontrast agents) for AKI have been identified, there is no reliable way for a clinician to use this information to establish a clear risk profile.

### Risk groups for AKI<sup>6</sup>

- Dehydration or volume depletion
- Advanced age
- Female gender
- Black race
- Chronic kidney disease (CKD)
- Chronic diseases (heart, lung, liver)
- Diabetes mellitus
- Cancer
- Anemia

## DIAGNOSTIC APPROACH<sup>10</sup>

- Clinical diagnosis of AKI is guided by standard criteria based on **changes in serum creatinine (SCr), urine output (UO) or both**.
- Severity of acute kidney injury is determined by the **magnitude of increase** in serum creatinine or decrease in urine output.

## LABORATORY CONFIRMATION

### CLASSICAL AND NOVEL BIOMARKERS<sup>5, 11, 12</sup>

**SCr and UO are classical biomarkers** used to diagnose AKI, but both have serious limitations in defining the presence and severity of AKI.

- **SCr lacks sensitivity** and only starts to increase when approximately 50% of glomerular filtration rate (GFR) is lost. It is also influenced by confounders such as muscle mass, fluid therapy and muscle injury.
- **UO lacks specificity** and is also affected by confounders such as intravenous fluid therapy, diuretics and hemodynamic status.

Recently, **novel AKI biomarkers** have been discovered, which can be measured in blood or urine and can predict the subsequent development of AKI. Several molecules have been identified as potential markers for early detection of kidney damage before serum creatinine rises. To date, clinical trials have been completed, and some biomarkers have gained official regulatory approval. Current evidence from clinical studies supports the use of these new biomarkers in the prevention and management of AKI.

- **Stress biomarkers** indicate cell stress; cell stress can resolve or progress to damage or alter kidney function.
- **Damage biomarkers** indicate structural damage that may or may not be associated with reduced kidney function.

### Characteristics of acute kidney injury biomarkers<sup>5</sup>

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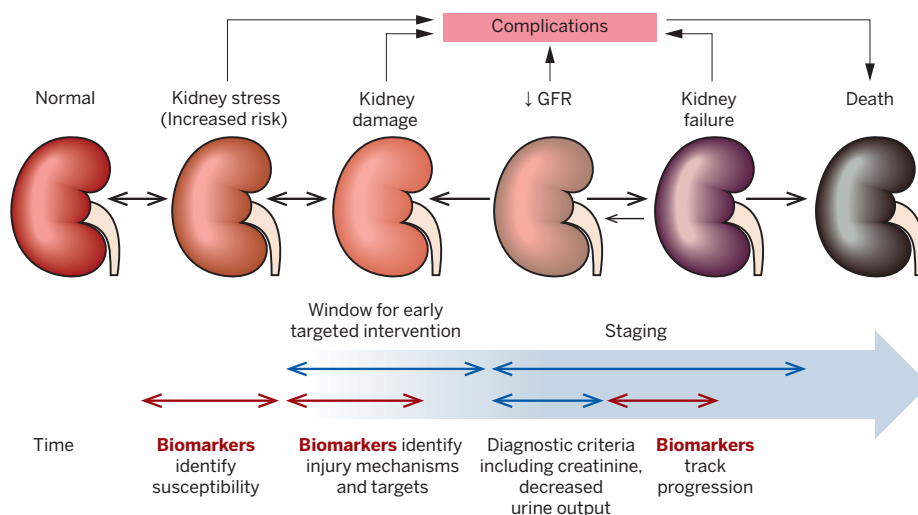
Biomarker	Sample type	Class	Appearance or peak after injury*	Functional role in the kidney
Tissue inhibitor of metalloproteinases-2 (TIMP-2) and Insulin-like growth factor-binding protein 7 (IGFBP-7)	Urine	Stress	Immediately after cardiopulmonary bypass; peaks at 6-24 h	Cell-cycle arrest: can induce cell-cycle arrest - thought to be a protective mechanism
Neutrophil gelatinase associated lipocalin (NGAL)	Urine or plasma	Damage	<4 h after cardiopulmonary bypass; peaks at 4-6 h	Iron trafficking: binds to iron-siderophore complexes in renal tubular epithelial cells; tubular epithelial genesis: forms an iron-siderophore complex (holo-neutrophil gelatinase associated lipocalin), which is secreted by the ureteric bud, and can induce the genesis of tubular epithelium; anti-inflammatory and anti-apoptotic
Kidney injury molecule-1 (KIM-1)	Urine	Damage	12-24 h; peaks at 2-3 days	Renal recovery and tubular regeneration: clearance of apoptotic bodies; anti-inflammatory effect
Liver-type fatty acid binding protein (L-FABP)	Urine	Damage	Unknown	Fatty acid uptake and intracellular transport: mobilises lipid peroxides from cytoplasm of tubular epithelial cells to tubular lumen; L-FABP gene expression is increased by peroxisome proliferator activated receptor- $\alpha$ and hypoxaemia
Cystatin C	Serum or urine	Function	NA	None, filtration marker: cystatin C is normally taken up by renal tubular epithelial cells; as such its appearance in the urine indicates tubular dysfunction
Pro-enkephalin	Urine	Function	NA	None, filtration marker

NA: not applicable.

\* Available evidence for the time from injury to detection of the marker. Filtration markers have a variable relationship to injury so specific times are not possible to establish.

### Opportunities for timed and targeted therapy in AKI<sup>13</sup>

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Surveillance could be initiated for high-risk individuals on the basis of clinical and biomarker criteria. Sequential assessment of biomarkers may permit identification of a window of opportunity in which kidney injury has been initiated but has not progressed to renal functional change. The duration of this window is inherently dependent on the type and site of injury and the nature and specificity of the biomarkers to determine the targets for intervention. Progression of kidney injury would be determined by development of functional changes staged on the basis of the severity of kidney injury. Biomarkers could further define progression, determine need for additional interventions, and predict prognosis. GFR, glomerular filtration rate.

- ↔ Staging or intervention opportunities
- ↔ Opportunity for use of kidney biomarkers

## PROPOSED NEW DEFINITION OF ACUTE KIDNEY INJURY<sup>12, 14, 15</sup>

The **23<sup>rd</sup> Acute Disease Quality Initiative (ADQI)** recently developed consensus statements for biomarker use. The ADQI expert panel suggested that **a combination of damage and functional biomarkers**, along with clinical information, be used to:

- Identify high-risk patient groups
- Improve the diagnostic accuracy of AKI
- Recognize the different pathophysiological processes
- Discriminate AKI etiology
- Assess AKI severity
- Improve processes of care
- Assist the management of AKI

In addition, the **23<sup>rd</sup> ADQI recommends using validated biomarkers to identify patient populations** for whom preventive interventions have been shown to improve outcomes. This recommendation received a grade of A, strong. Trials have demonstrated that timely initiation of preventive strategies in patients with positive stress biomarkers after a kidney insult, i.e. tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP-7), were effective at preventing AKI.

In the table below, stage 1S identifies an early stage when there is evidence of kidney injury that is not detected by creatinine and urine output criteria. TIMP-2 and IGFBP-7 have been shown to improve risk stratification in critically ill patients with AKI stage 1.

### Proposed new definition of Acute Kidney Injury<sup>12</sup>

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Functional criteria	Stage	Damage criteria
No change or SCr level increase <0.3 mg/dL and no UO criteria	1S	Biomarker positive
Increase of SCr level by ≥0.3 mg/dL for ≤48 h or ≥150% for ≤7 days and/or UO <0.5 mL/kg/h for >6 h	1A	Biomarker negative
	1B	Biomarker positive
Increase of SCr level by >200% and/or UO <0.5 mL/kg/h for >12 h	2A	Biomarker negative
	2B	Biomarker positive
Increase of SCr level by >300% (≥4.0 mg/dL with an acute increase of ≥0.5 mg/dL) and/or UO <0.3 mL/kg/h for >24 h or anuria for >12 h and/or acute KRT	3A	Biomarker negative
	3B	Biomarker positive

KRT: kidney replacement therapy.

## MANAGEMENT OF AKI<sup>6</sup>

- **Early detection of AKI is critical as up to one-third of cases may be partially or fully preventable.**
- There is no definitive treatment for AKI. Treatment will be based on addressing the cause of the kidney injury.
- Other than dialysis, no therapeutic interventions reliably improve survival, limit injury, or speed recovery.
- Supportive care is the main management, regardless of AKI etiology.

### KDIGO Consensus Guideline for AKI: Stage-based management of AKI.<sup>6</sup>

Acute Kidney Injury Stage			
High Risk	Stage 1	Stage 2	Stage 3
	Discontinue all nephrotoxic agents when possible		
	Ensure volume status and perfusion pressure		
	Consider functional hemodynamic monitoring		
	Monitor serum creatinine and urine output		
	Avoid hyperglycemia		
	Consider alternatives to radiocontrast procedures		
	Non-invasive diagnostic workup		
	Consider invasive diagnostic workup		
		Check for changes in drug dosing	
		Consider renal replacement therapy	
		Consider ICU admission	
			Avoid subclavian catheters if possible

Shading of boxes indicates priority of action - solid shading indicates actions that are equally appropriate at all stages whereas graded shading indicates increasing priority as intensity increases from Stage 1 to Stage 3.

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