INVITED ARTICLE

Epidemiology and Pathogenesis of Acute Kidney Injury in the Critically Ill Patients

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History

It is fascinating to read the history of uremia, described painstakingly by Richet.[1] Though urea was recognized and was crystallized between 1797 and 1808, it took another 50 years before it was recognized as a substance produced in the body, and that its excess in the blood could lead to specific problems. Acute tubular necrosis was first described during the Second World War, during London Blitz in 1940, as a result of crush injuries.

Background

Traditionally, acute decline in renal function, which was abrupt involving decreased renal function and due to structural damage and impairment, was termed acute renal failure (ARF). However, this decline in function, was a large spectrum, ranging from minimal decrease in the glomerular filtration rate (GFR) ending with a patient becoming dependent on renal replacement therapy (RRT) due to complete loss of renal function. The term "ARF" has now been replaced by acute kidney injury (AKI). Kidney is one of the first organs to develop dysfunction in the presence of hypoperfusion. The commonest cause of AKI in the critically ill patients is sepsis, followed by the use of nephrotoxic drugs.

The acute dialysis quality initiative (ADQI) was created in 2002 to develop consensus and evidence-based guidelines for the treatment and prevention of AKI. For this, it was necessary to define AKI acceptable to all stakeholders, clinicians, and researchers alike. Thus, the RIFLE (risk–injury–failure–loss–end-stage kidney disease) criteria were created (Table 1).

There were two major shortcomings with the RIFLE criteria, that it needed a value of baseline creatinine for the patient, which is often not available in the critically ill patients, and there was no mention at which stage RRT was required. To overcome this, the ADQI group developed the Acute Kidney Injury Network (AKIN) criteria (Table 2).

The AKIN criteria did not need baseline serum creatinine (sCr) but requires at least two values of sCr obtained within a period of 48 hours. Here, stage I corresponds to risk class and considers an absolute increase in sCr ≥ 26.5 µmol/L (0.3 mg/dL). Stages II and III correspond to injury and failure classes, respectively, and stage III also considers patients requiring RRT independently of the stage [defined by sCr and/or urine output (UO)]. The last two outcome classes (loss of kidney function and end-stage kidney diseases) were removed from AKIN criteria (Table 3).

Kidney Disease: Improving Global Outcomes (KDIGO) thus covers both the AKIN and the RIFLE criteria, taking into account changes in creatinine within 48 hours or a decline in the GFR over 7 days.

Since AKI now has a proper definition, it is easier to properly identify its presence in the critically ill patients and therefore its epidemiology in the critically ill patients.

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Epidemiology of AKI

Overall Incidence of AKI

Waikar et al. described the trends in incidence of AKI, patients requiring RRT after hospital discharge (AKI-D), and related mortality.[5] They found that though the incidence of AKI increased

Table 1: RIFLE classification system for acute kidney injury*[2]

Class	*sCr or GFR*	*UO*
Risk	↑ sCr × 1.5 or ↓ GFR >25%	<0.5 mL/kg/hour × 6 hour
Injury	↑ sCr × 2 or ↓ GFR >50%	<0.5 mL/kg/hour × 12 hour
Failure	↑ sCr × 3 or ↓ GFR >75% or if baseline sCr ≥ 353.6 µmol/L (≥4 µg/dL) ↑ sCr > 44.2 µmol/L (>0.5 µg/dL)	<0.3 mL/kg/hour × 24 hour or anuria × 12 hour
Loss of kidney function	Complete loss of kidney function >4 weeks	
ESKD	Complete loss of kidney function >3 months	

*Acute kidney injury defined as sCr > 50% within 7 days
ESKD, end-stage kidney disease

Table 2: Network criteria for acute kidney injury*[3]

Stage	*sCr*	*UO*
1	↑ sCr ≥ 26.5 µmol/L (≥0.3 µg/dL) or ↑ sCr ≥ 150–200% (1.5–2×)	<0.5 mL/kg/hour (>6 hour)
2	↑ sCr > 200–300% (>2–3×)	<0.5 mL/kg/hour (>12 hour)
3	↑ sCr > 300% (>3×) or if baseline sCr ≥ 353.6 µmol/L (≥4 µg/dL) ↑ sCr ≥ 44.2 µmol/L (≥0.5 µg/dL)	

*Acute kidney injury defined as sCr ≥0.3 µg/dL increase in 48 hours or > 50% within 48 hours

Table 3: Kidney Disease: Improving Global Outcomes staging for acute kidney injury*[4]

Stage	*sCr*	*UO*
1	1.5–1.9 times baseline or ≥0.3 µg/dL increase	<0.5 mL/kg/hour for 6 hour
2	2–2.9 times baseline	<0.5 mL/kg/hour for 12 hour
3	3 times baseline. Increase in sCr to ≥4 µg/dL or initiation of RRT	<0.3 mL/kg/hour for 24 hours or anuria for ≥12 hour

*Acute kidney injury defined as sCr ≥0.3 µg/dL increase in 48 hour or > 50% within 7 days

over the 15 years of study period (1988–2002) from 61 to 288 per 100,000 population, the incidence of ARF-D increased from 4 to 27 per 100,000 population, and the mortality decreased from 40.4 to 20.3% ($p < 0.001$), over time. Another study of Medicare beneficiaries over a 10-year period (1992–2001) showed 11% increase in incidence of AKI per year in hospitalized patients. The incidence of AKI increased with increasing age (18.5, 20.8, 25.8, and 28.6 cases per 1,000 discharges for age groups ≤64, 65–74, 75–84, and ≥85 years, respectively). They also found a decline in mortality due to AKI over the years and concluded that AKI was a major contributor to morbidity and mortality.[6] A meta-analysis looked at the world incidence of AKI, reclassifying it as per the RIFLE, AKIN, and later using KDIGO criteria, in hospitalized patients from 2004 to 2012. The overall incidence of AKI was 23.2% (154 studies involving 3,585,911 patients, 573,424 patients with AKI). The incidence of AKI in adults (130 studies) was 21.6%, while it was 33.7% in children (24 studies). In 7 studies, the incidence of community-acquired AKI was 8.3%, while in 52 studies, the incidence of hospital-acquired AKI was 20.9%. In the critical care setting (41 studies), every third patient developed AKI (31.7%). Most of the data were from high-income countries (spending >5% gross domestic product on health). There were a small number of studies from the Asian regions, and the incidence in these regions was variable (Eastern Asia: 17 studies—14.7%, Western Asia: 2 studies—16.7%, and South Asia: 2 studies—23.7%).[7]

AKI in the Critically Ill Patients

There have been many studies looking at incidence, predictors, and outcomes of patients having AKI in critical care. Two studies are worth mentioning here: the large multinational studies called the AKI-EPI study and the Intensive Care Over Nations (ICON) study.[8,9] As the name suggests, the AKI-EPI study was a multicenter cross-sectional study on the epidemiology of AKI in 1,802 critically ill patients admitted in 97 intensive care units (ICUs) across the world. Acute kidney injury was seen on day 1 in 1,032 patients [57.3%; 95% confidence interval (CI): 55.0–59.6]. In nearly 650 patients, baseline creatinine was not available so either a calculated sCr [Modification of Diet in Renal Disease (MDRD) equation] or sCr value obtained was taken as the baseline value. Once these patients without baseline sCr were removed, the incidence of AKI increased to 62.5% (95% CI: 59.7–65.3; $p = 0.005$). The etiology of AKI in descending order was as follows: sepsis, hypovolemia, drug related, cardiogenic shock, hepatorenal syndrome, and obstructive uropathy. The mortality of the patients increased with an increase in severity of AKI, so that the unadjusted odds ratio for dying for patients with KDIGO stage I was 2.19 (95% CI: 1.44–3.35), in those with stage II was 3.88 (95% CI: 2.42–6.21), and for patients in the third stage of KDIGO stage was nearly 8 (7.18; 95% CI: 5.13–10.04). Nearly 24% AKI patients needed RRT, i.e., 13.5% of all ICU patients. After adjustment for baseline variables, the incidence of AKI and related mortality was similar across all regions.[8]

The ICON was a large multinational study which included 10,069 patients from 730 ICUs from 84 countries.[9] The patients were adults (age > 16 years), and the data were collected between May 8 and May 18, 2012. From this cohort, 9,579 patients were included (excluded patients lacked either sCr or UO data). Acute kidney injury occurred in 4,727 patients within 72 hours (AKIN criteria). The data for patients with chronic renal failure (nearly 850 patients) were analyzed separately and are not discussed here. The incidence of AKI was higher in patients with sepsis (68%) when compared with those without sepsis (57%, $p < 0.001$), and therefore, as expected, the use of RRT was higher in those with sepsis (20%) than those without (5%, $p < 0.0001$). Patients with sepsis who did not have AKI within 3 days were less likely to develop AKI subsequently when compared with other patients. The ICU and hospital length of stay (LOS) and ICU and hospital mortality were higher in patients admitted with sepsis and increased further if AKI occurred. These increases were seen to keep pace with increasing severity of AKI. They concluded that AKI is more frequent in sepsis patients and severe and less likely to resolve once AKIN stage 3 is reached. Also occurrence of AKI leads to higher mortality in patients with sepsis than in those without.

AKI in Critically Ill Patients—the Indian Perspective

There is no nationwide data of the incidence of AKI in Indian ICUs. The data are very fragmented and come from various single-center studies. The definitions used for AKI also vary; in some studies, the denominator is missing. However, certain findings stand out from the studies available. The incidence of AKI in the Indian ICU seems to be equally high, in keeping with the global data. The causation of AKI seems to be different, from the Western ICUs, apart from the common element of sepsis. Tropical illnesses such as malaria, leptospirosis, acute undifferentiated febrile illnesses, and toxins and envenomation seem to be more predominant causes of AKI in some of ICU studies quoted here (and some data of AKI in hospitalized patients—not admitted to the ICUs, which we have not quoted here). For the convenience of the readers, we have summarized the data in Table 4.

Pathogenesis of AKI

The pathogenesis of AKI is quite complex, since it has multiple etiologies and risk factors. It can occur in various different settings, such as major cardiac or transplant surgeries, shock, and sepsis.[20] The process is poorly understood but primarily depends on vascular, tubular, and inflammatory injury mechanisms and

subsequent repair processes that can restore normal function or cause progressive fibrotic changes leading to chronic kidney disease (Table 5).

Our traditional understanding of the etiology of AKI are prerenal, intrinsic, and obstructive, which is more anatomical in nature; however, the immune mechanisms play a vital role in injury or regulation of the inflammatory response and in repair of the epithelial layer.

There are some differences in the mechanism of AKI depending on the etiology causing AKI. Renal ischemia remains the primary modality of AKI and can be due to various mechanisms such as production of oxygen-free radicals, cytokines, and enzymes; endothelial activation and leukocyte adhesion; activation of coagulation; and initiation of apoptosis. Common understanding is that decreased renal perfusion from any cause leads to reduced GFR, whereas renal ischemia and diseases of glomerulus or tubule may be responsible for intrinsic renal failure. Renal perfusion is extremely well autoregulated by the afferent and efferent arterioles that maintain a constant blood flow and filtration fraction within a range of mean arterial blood pressure of 80–180 mm Hg. The tubuloglomerular feedback mechanism through macula densa, the renin–angiotensin–aldosterone system, and the myogenic activity of the afferent arterioles are the mainstay of autoregulation mechanisms of renal blood flow (RBF).[21]

In response to hypotension, to maintain the glomerular filtration, the afferent arteriolar vasodilation occurs from secretion of vasodilators such as prostaglandins and nitric oxide and stimulation of the renin–angiotensin–aldosterone system. During hypertension, the afferent arteriolar vasoconstriction occurs due to various mediators such as endothelin-1, angiotensin II, thromboxane A2, prostaglandin H2, leukotrienes (all a part of family of lipids known as eicosanoids), adenosine, and sympathetic nerve stimulation along with efferent arteriole dilatation to stabilize

Table 5: Etiology of acute kidney injury (AKI)

Prerenal acute kidney injury (AKI)	*Renal*	*Postrenal*
Hypovolemia (bleeding, vomiting, diarrhea)	Ischemic tubular injury, sepsis	Extrarenal or intrarenal obstruction (urinary stones, urethral strictures, ureteric and bladder tumors, benign prostatic hypertrophy, etc.)
Congestive heart failure	Glomerulonephritis, interstitial nephritis	
Liver failure	Drugs and toxins	
Renal artery stenosis, abdominal compartment syndrome	Diseases such as rhabdomyolysis, tumor lysis syndrome, multiple myeloma, Microangiopathies	

Table 4: Epidemiology of acute kidney injury (AKI) in the critically ill patients in India[10–19]

Authors, year	*No. of patients*	*AKI definition*	*Incidence*	*Outcomes*	*Remarks*
Paudel et al., (2012)[10]	100, all patients	AKIN	33%	67% hospital mortality, 93.9% AKI group, and 53.7% non-AKI group	Sepsis-AKI 66%
Gurjar et al., (2013)[11]	323 sepsis	RIFLE	31%	52% ICU mortality	Sepsis patients only, 34 excluded
Eswarappa et al., (2014)[12]	500 AKI	RIFLE criteria (CA-AKI, HA-AKI)	5.8%	37.2% needed RRT, hospital mortality 37.6%	AKI patients only, total ICU admissions 8,621
Reddy et al., (2014)[13]	250 AKI, 8 excluded	RIFLE, AKIN	*R: 34.3%, *A: 45.9%	ICU mortality, *R: 30.1% vs. 3.1% non-AKI, ICU mortality, *A: 23.4% vs. 3.1% non-AKI	Need for RRT, *R: 19.3%, *A: 13.5%
Bhadade et al., (2016)[14]	836	KDIGO	37.7%, 10% ICU-AKI@	ICU mortality 51.9%	Tropical illness, malaria—most common cause
Korula et al., (2016)[15]	715 patients	sCr > 1.6 mg/dL or 25% increase from baseline	16.1%	39.1% patients with AKI needed RRT 28-day mortality 49.5%	
Anghan et al., (2018)[16]	79 severe malaria patients only	AKIN	45.6%	Overall mortality 13.9%, AKI mortality 25%	52.7% #*P. falciparum*, 47.2% #*P. vivax*
Saxena and Meshram, (2018)[17]	245 AKI patients, 16 excluded	KDIGO	6.8%	Hospital mortality 28.4% for AKI patients	3584 ICU admissions
Priyamvada et al., (2018)[18]	236 AKI patients	KDIGO (CA-AKI, HA-AKI)	Denominator not given	30-day mortality was 52.54%	Total ICU admissions unknown
Mathew and Radha, (2019)[19]	150 AKI patients	AKIN	Denominator not given	ICU mortality 41%	Leptospirosis, $UAFI commonest causes of AKI

CA-AKI, AKI present < 48 hour of hospital admission; HA-AKI, AKI present > 48 hour of hospital admission; *RIFLE and *AKIN criteria, @developed AKI during ICU stay, rest had AKI at ICU admission, #P., Plasmodium, $UAFI, undifferentiated acute febrile illness.

RBF and GFR.[22,23] Risk of AKI increases when these autoregulatory mechanisms are inhibited by any mechanism such as use of angiotensin-converting enzyme inhibitors (ACEI) and nonsteroidal anti-inflammatory drugs.

Acute kidney injury is commonly seen with hypotension secondary to hemorrhage, fluid loss, sepsis, or poor cardiac function and use of vasoactive drugs. However, it may not always be necessary to have systemic hypotension, since regional renal hypoperfusion can occur with changes on regional renal flow. The kidneys normally receive approximately 25% of cardiac output. The kidney has a peculiar arrangement of glomerular afferent and efferent arterioles, branching into the peritubular arteries and vasa recta renis, which are vital for the reabsorptive function. The reabsorptive function is a highly energy-dependent function. The adenosine triphosphate (ATP) production that occurs within the cortex is by oxidative metabolism, whereas in medulla, nearly 33% of energy comes from glycolysis, which makes it susceptible to ischemia. The partial pressure of oxygen drops from 70 mm Hg in the cortex to 20 mm Hg in the medulla, with high oxygen demand from the tubular saltwater reabsorption function. Both of these functions make the medulla very sensitive to hypoxia and injury.

The tubular ischemic injury or necrosis leads to disruption of tight junctions between cells, allowing back leak of glomerular filtrate and further depressing effective GFR. The proximal tubules are more vulnerable to mitochondrial dysfunction, as they depend on aerobic metabolism in comparison with the distal tubular cells which can use glycolysis for metabolism. Other suggested mechanisms of tubular injury are endothelial cell activation, endothelial swelling, upregulation of adhesion molecules with denuding of glycocalyx. In addition, there is leukocyte activation, platelet aggregation, red cell trapping, and activation of the coagulation pathway which leads to vascular congestion and further ischemic injury. The dying cells slough off with shedding the cellular debris into the tubules, forming obstructing casts, which further decrease GFR and lead to loss of functional nephrons.[24] Induced autophagy has also been proposed as a mechanism of tubular injury.

Ischemia–reperfusion hypothesis suggests that ischemic injury leads to loss of polarity of the epithelial cells, with alterations in the location of adhesion molecules and Na/K ATPase, and subsequent cell death by either necrosis or apoptosis. Due to this alteration in the location of adhesion molecules, the viable epithelial cells fail to effectively adhere to the basement membrane and eventually fail in the repair process. Some investigators suggest that when injury is severe and prolonged, the epithelial cell may transform to a fibroblast and lead to repair by fibrosis. Fibrosis will decrease the ability of oxygen and nutrients to get to the tubules and hence enhance tubular stress and epithelial cell injury.

Sepsis-induced AKI

Acute kidney injury in sepsis can occur with or without obvious renal hypoperfusion. Various techniques used to measure RBF, such as para-aminohippurate clearance and renal vein catheter thermodilution, suggest that in sepsis-induced systemic vasodilation, the RBF is not decreased and, in fact, may even be increased.[25–27]

Theories suggest that in sepsis, there are various mechanisms interplaying such as (a) hypoperfusion or malperfusion at the microcirculatory level or maldistribution of blood flow to medulla, (b) inflammation/infection/cytokine-mediated apoptosis, and (c) possibly sepsis-induced renal mitochondrial downregulation or hibernation (described as cellular bioenergetic response to injury).

Endothelial injury results in increased permeability of the endothelium and leakage of fluid into the interstitium in the outer medulla, subsequently leading to further congestion of the outer medulla and reduction in blood flow. Activation of thromboxane A2 causes platelet adhesion, capillary thrombosis and further ischemia. Sepsis-induced damage of the endothelial glycocalyx also leads to breakdown of the vascular barrier and contributes to microcirculatory changes in septic AKI. Pathological evidence shows the presence of complex injury findings such as glomerular and tubular necrosis, microvascular thrombosis, interstitial edema with tubular apoptosis, and formation of micro-abscesses.[28]

Nephrotoxic Agents

Direct nephrotoxic parenchymal injury has been implicated as possible pathological mechanism caused by drugs, toxins, and ischemia in approximately 25% of AKI.[29] The proposed mechanism is activation of epithelial and endothelial cells and upregulation of chemokines and cytokines leading up to inflammatory cell infiltration and proximal tubular epithelial injury.[30]

The risk factors for nephrotoxicity are age, preexisting renal dysfunction, ICU patients with multiorgan failure, and multiple concomitant nephrotoxic drugs such as antibiotics, ACEI and angiotensin II receptor blockers, hypovolemia, hypoalbuminemia, and associated hyperbilirubinemia.

Immune and Inflammatory Mechanisms

The mechanism of renal recovery is again interplay of injury, abnormal repair, and the development of fibrosis. Acute kidney injury can result from incomplete repair and persistent tubulointerstitial inflammation, with proliferation of fibroblasts and excessive deposition of extracellular matrix which is a key determinant of progression to end-stage renal failure. Apoptosis occurs primarily by inflammatory mediators and ongoing ischemia. Activation of pro-inflammatory and anti-inflammatory mechanisms has a major role in sepsis-induced AKI. Activation of the innate immune response leads to activation and secretion of various cytokines such as interleukin (IL)-1, tumor necrosis factor (TNF)-α and IL-6 causing cytokine storm. Tumor necrosis factor by binding with TNF receptor 1 on glomerular cells and the TNF receptor 2 sites on renal tubular cells has been shown in animal models to upregulate renal apoptosis.[31,32]

Lipopolysaccharide activates leukocytes, monocytes, and macrophages and causes significant upregulation of toll-like receptor activation of nuclear factor-κB and other pro-inflammatory mediators such as IL-1, IL-6, IL-8, and TNF.[33] Various cells that also take part in the repair process such as neutrophils, dendritic cells, macrophages, and lymphocytes contribute significantly to the ischemia–reperfusion injury.[34] Few studies that targeted prevention of neutrophil accumulation did show reduction in tissue injury. Another interesting finding in animal models indicates that animals, which lack CD4 and CD8 cell adhesion receptors on T lymphocytes, are protected from ischemia–reperfusion injury. Evidence suggests that inhibition of leukocyte infiltration into the kidney may prevent renal injury, cell death, and long-term fibrosis.[35] Macrophages and dendritic cells also likely play an important role in the inflammatory response to ischemia–reperfusion.

The immune mechanism of tubular injury is suggested as the disruption of cell–matrix adhesion that is dependent on β1-integrin is an important aspect that induces cell shedding into the lumen. Inflammatory mediators, including cytokines, chemokines, eicosanoids, and reactive oxygen species, recruit leukocytes and upregulate adhesion molecules that bind on the activated endothelium. The endothelial cells themselves upregulate integrins, selectins, and some immunoglobulins, such as intercellular adhesion molecule-1 and vascular cell adhesion molecule.

The activated leukocytes generate pro-inflammatory cytokines such as IL-1 and TNF-α. Tumor necrosis factor-α, IL-1, and interferon-γ produce a variety of injurious changes in proximal tubular epithelial cells. There is also some evidence that with hypoxia, the inducible nitric oxide synthase (iNOS) protein expression is increased in ischemic kidneys, and this overexpression may contribute to tubular injury.[36] It has been shown that measures to block this upregulation of iNOS was protective against ischemia-induced renal injury in animal models.[37] Nitric oxide inhibits the adhesion of neutrophils to endothelial cells, stimulated by TNF-α, which would also be protective. Another mechanism is hypoxia-induced increased activity of phospholipase-A2 that hydrolyzes the phospholipids generating free fatty acids. It has been studied that phospholipase-A2 can be inhibited with arachidonic acid and thus may prevent hypoxia-induced renal injury.[38] Postinfectious glomerulonephritis is also an immune-mediated renal injury with immune-complex deposition leading to inflammation. This is commonly associated with streptococcal or viral infections.

Conclusion

The available data from global studies and also Indian studies suggest that AKI is common in critically ill patients. It leads to increased morbidity, increased ICU and hospital LOS, costs of hospitalization, and mortality. The data from India is fragmented and there is no national database. The etiology from Indian data suggest that apart from sepsis (similar to global data), the tropical infection may be the predominant etiological factor in our country.

The exact underlying pathophysiology AKI remains poorly understood. We understood that the epithelium plays an important role in abnormal repair with pathological profibrogenic cytokine production. The roles of innate and acquired immunity in the injury phase are vitally related to repair of the epithelium and restoration of the nephron function.

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