EPIDEMIOLOGY AND MANAGEMENT OF ACUTE KIDNEY SYNDROME

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Abstract- **Acute renal failure (ARF), commonly referred to as Acute kidney injury (AKI), is a brief episode of kidney damage or failure that continues for a few hours or days. Waste products accumulate in the blood as a result of AKI, which also makes it more difficult for the kidneys to preserve the proper fluid balance in the body. AKI can also impact the heart, lungs, brain, and other organs. Hospitalized patients, those in critical care units, and older persons in particular frequently suffer from acute renal injury. Numerous studies have demonstrated the rising prevalence of AKI in the elderly, who are typically characterized as those over 65, as well as the age-dependent association between AKI and advanced age. The majority of this has been ascribed to anatomical and physiological alterations in the ageing kidney, and a portion to different comorbidity, such as hypertension, cardiovascular disease, and chronic kidney disease (CKD), which may necessitate remedies and/or drugs that act as kidney stressors, change renal haemodynamics, or are nephrotoxic. The underlying cause of AKI is intricate and multifaceted. Ischemia is the most frequent cause of AKI and can arise for several reasons. Reductions in blood flow can be partially compensated for by physiological adaptations; nonetheless, organ dysfunction results from insufficient delivery of oxygen and metabolic substrates, which causes cellular damage.**

Key words: **Acute renal failure (ARF), acute kidney injury (AKI), Anatomical and physiological alterations in kidney.**

1. INTRODUCTION

Acute kidney injury (AKI) is a frequent condition that can be costly to treat, lengthen hospital stays, and raise fatality rates. An investigation examining the treatment of patients who passed away with an AKI diagnosis was released in 2009 by the National Confidential Enquiry into Patient Outcome and Death (NCEPOD). The percentage of patients who received "good" care was only 50%. According to the NCEPOD analysis, patients who were at risk of AKI were not adequately assessed, and 21% of AKI cases that occurred after admission were preventable. Before a diagnosis was made, two-thirds of the patients had a considerable level of AKI, and these patients received insufficient senior evaluation. Higher mortality is correlated with more severe AKI. According to reports, the in-hospital mortality rate for AKI is 24% and rises as AKI severity worsens. An audit of dialysis-dependent patients with severe AKI in Northern Ireland revealed a death rate of up to 40% after 90 days (personal communication). AKI guidelines were released in 2013 by the National Institute for Health and Care Excellence (NICE). According to NICE's calculations, if AKI was identified and treated with careful consideration for medicine and hydration, up to 42,000 fewer fatalities may occur each year, and 100,000 cases could be avoided [1].

Renal function abnormalities are common in critically ill and wounded patients. Numerous illnesses can induce abnormalities in urine output or blood chemistry, and because these clinical symptoms are crucial to serious illness, they are frequently examined hourly alongside other "vital signs." In addition to causing organ malfunction, many critical illness types can cause organ harm as a result of their treatments or the illnesses themselves. Organ protection is necessary, even though dysfunction might call for assistance. Although the origins of this notion are as old as intensive care units themselves, it is relatively new in the field of critical care. Our mentality has been shaped by the ideas of brain protection, heart preservation, and, more recently, protective lung ventilation. Yet, the idea of acute kidney damage (AKI) has only recently emerged. If all one observes is organ dysfunction, then organ support is only necessary when organ failure occurs; on the other hand, the idea of organ injury prompts one to look for ways to minimize organ harm [2].

2. FUNCTION OF KIDNEY:

The maintenance of equilibrium is the kidneys' primary function. They control electrolyte balance, fluid levels, and other elements that maintain a stable and comfortable internal environment for the organism [3].

These organs perform a multitude of physiological tasks.

a.   Waste excretion

Numerous waste materials are eliminated by the kidneys and excreted in urine. Among the principal substances eliminated by the kidneys are:

✓   Urea is produced when proteins break down.

✓   Uric acid produced when nucleic acids break down.

✓   Medications and their byproducts [4].

b.   Reabsorption of nutrients

Through the use of tubules, the kidneys reabsorb nutrients from the blood and deliver them to the optimal locations for health support. To aid in preserving homeostasis, they also reabsorb more substances. Among the reabsorbed products are Glucose, Aminoacids, water, phosphate, sodium, magnesium, and potassium ions as well as bicarbonate [5].

c.   Maintaining of pH

Appropriate pH ranges for humans are 7.35-7.45. The body goes into an acidemia or alkalemia state, depending on the level, at which it is. Enzymes and proteins degrade and become incapable of functioning in these conditions. The lungs and kidneys aid in maintaining a steady pH in the body [6].

d.   Osmolality of regulation

The body's electrolyte-water balance, or the proportion of fluids to minerals, is measured by osmolality. One of the main causes of electrolyte imbalance is dehydration. The brain's hypothalamus reacts to an increase in blood plasma osmolality by communicating with the pituitary gland. Anti-diuretic hormone is released by this gland (ADH). Urea is retained in the kidney's medulla rather than being eliminated because it sucks in water [7].

e.   Regulation of blood pressure

The kidneys regulate blood pressure when necessary, but they are responsible for slower adjustments. They adjust long-term pressure in the arteries by causing changes in the fluid outside of cells. The medical term for this fluid is extracellular fluid. These fluid changes occur after the release of a vasoconstrictor called Angiotensin II. Vasoconstrictors are hormones that cause blood vessels to narrow. This absorption effectively increases the size of the extracellular fluid compartment and raises blood pressure. Anything that alters blood pressure, including excessive alcohol consumption, smoking, and obesity, can damage the kidneys trusted source over time [8].

f.   Secretion of active compounds.

The kidneys release several important compounds.

•   *Erythropoietin* is regulated by the process of erythropoiesis, or the generation of red blood cells. In adults, the kidneys are the primary producers of erythropoietin, while the liver also generates some of it.

•   *Renin* is an enzyme that aids in controlling the growth of arteries as well as the amounts of lymph, interstitial fluid, and blood plasma. White blood cells, which boost immune function, are found in lymph, and the major extracellular fluid component is interstitial fluid.

•   *Calcitriol* is the vitamin D metabolite that is hormonally active. It enhances phosphate reabsorption in the kidney and increases the quantity of calcium that may be absorbed by the intestines [9].

3.   DEFINITION OF AKI

Acute kidney injury (AKI) is a brief episode of kidney damage or failure that continues for a few hours or days. Waste products accumulate in the blood as a result of AKI, which also makes it more difficult for the kidneys to preserve the proper fluid balance in the body. **Table 1** provides an overview of the features of this diagnostic system. This method defines two outcome classes (loss and end-stage renal disease (ESRD)) as well as three severity ratings (risk, injury, and failure) [10].

Serum urea (sUr), sCr, urinalysis, and UO values were the main instruments used to identify AKI. To distinguish between transient and chronic AKI, urine indicators, including fractional excretion of sodium (FeNa) and urea (FeUr), were also used. The organization that came first was the Acute Dialysis Quality Initiative (ADQI). Based on changes in sCr or UO, where the worst of each criterion is used, the severity criteria of AKI are developed. The length of renal function deterioration determines the outcome criterion [11].

Pickering etal.'s study from 1957 demonstrated that the descriptions of Risk and Failure severity categories did not correspond with increases in sCr concentration and reductions in GFR (calculated using the MDRD or Cockroft-Gault equations). A one-third (not a 25%) drop in GFR is correlated with a 1.5-fold rise in sCr, and a two-third (not a 75%) fall in GFR is correlated with a three-fold increase. Results may also vary depending on the formula employed if the GFR is approximated rather than explicitly measured. According to the MDRD formula, a three-fold rise in sCr and a 1.5-fold increase in GF equal to a 37% drop in GFR and a 72% drop in GFR accompanied by a three-fold rise in sCr [12].

4.   CLASSIFICATION AND STAGES AKI:

The organization that came first was the Acute Dialysis Quality Initiative (ADQI) **Table 1** provides a summary of this diagnostic system's features. With this method, two outcome class loss and end-stage renal disease (ESRD) and three severity grades risk, injury, and failure are identified. The AKI severity criteria are established by utilizing the worst of each criterion when defining changes in sCr or UO. The length of renal function deterioration determines the outcome criterion [13].

A modified version of the Risk Injury Failure Loss End Stage Kidney Disease (RIFLE) criteria was proposed in 2007 by the Acute Kidney Injury Network (AKIN) group in an effort to increase the sensitivity of the AKI diagnostic criteria. Changes included the addition of an absolute rise in SCr of at least 0.3 mg/dL (26.5 μmol/L) to stage 1, the removal of the GFR requirement, the classification of patients beginning RRT as stage 3, regardless of sCr readings, and the elimination of outcome classes. **Table 1** provides a summary of this system's attributes.

Table 1:

RIFLE criteria for classification /Staging AKI			AKIN criteria for classification /Staging AKI		
Stage	**GFR Criteria**	**Urine Output Criteria**	**Stage**	**Serum Creatinine criteria**	**Urine output criteria**
Risk	1.5 fold increase in sCr or >25% decrease in GFR	UO <0.5ml/kg/h for 6 hr	**Stage 1**	Absolute increase in sCr ≥ 0.3mg/dl (≥26.5 μmol/L) or ≥ 1.5 to 2.0 folds from baseline.	UO <0.5ml/kg/h for 6 hr
Injury	2 fold increase in sCr or >50% decrease in GFR	UO <0.5ml/kg/h for 12 hr	**Stage 2**	Increase in sCr ≥ 2.0 to 3.0 folds from baseline.	UO <0.5ml/kg/h for 12 hr
Failure	3.0 fold increase in sCr or >75% decrease in GFR (or) sCr>4.0mg/dl with an acute increase of 0.5mg/dl	UO <0.3ml/kg/h for 24 hr (or) anuria for 12 hr	**Stage 3**	Increase in sCr ≥ 3.0 folds from baseline or increase of sCr to ≥ 4mg/dl (≥354 μmol/L) with n acute increase of at least ≥ 0.5mg/dl (44 μmol/L).	UO <0.3ml/kg/h for 12 hr (or) anuria for 12 hr
Loss	Complete loss of kidney function for >4 weeks				
ESKD – End Stage Kidney Disease for > 3months					

Stage 3 includes a rise in sCr up to three times baseline, sCr greater than 4.0 mg/dL (354 μmol/L), and the start of RRT. In order to identify stage 3, KDIGO eliminates the 0.5 mg/dL rise for sCr >4 mg/dL **(Table 2).**
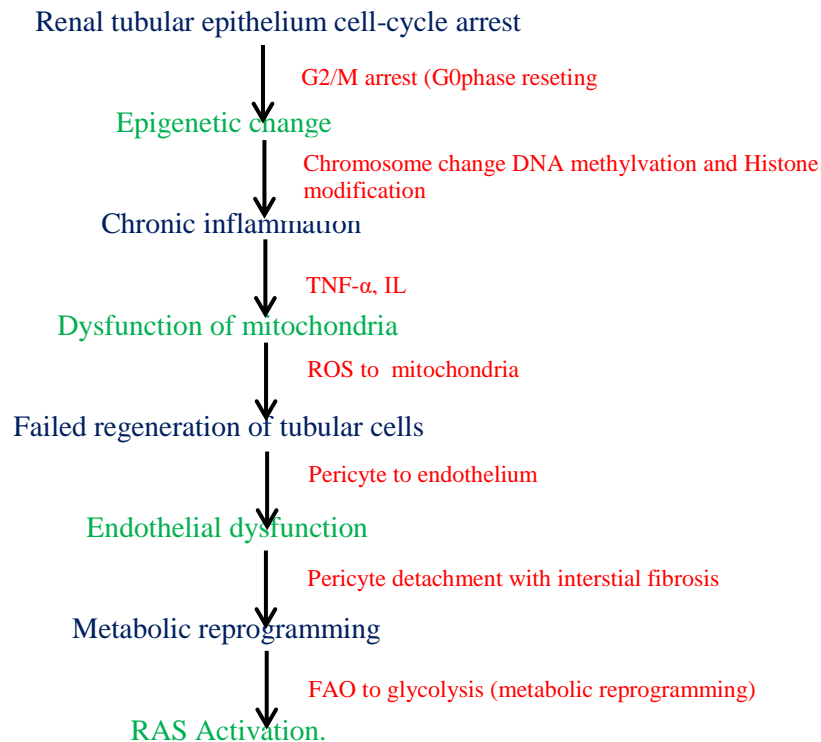
Table 2:

AKI is defined as any of the following:		
1	Increase in sCr ≥ 0.3mg/dl (≥26.5 μmol/L) within 48 hrs or	
2	Increase in sCr ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days, or	
3	Urine volume <0.5 ml/kg/h for 6 hours	
AKI is staged for severity according to the following criteria:		
Stage 1	1.5-1.9 times baseline or ≥ 0.3mg/dl (≥26.5 μmol/L) absolute increase in sCr	Urine volume <0.5 ml/kg/h for 6-12 hours
Stage 2	sCr ≥ 2.0-2.9 times baseline sCr ≥ 3.0 times from baseline (or) Increase in sCr to ≥ 4.0mg/dl (≥353.6 μmol/L) or	Urine volume <0.5 ml/kg/h for ≥12 hours
Stage 3	Initiation of renal replacement therapy or In patients <18 years, decrease in eGFR to <35ml/min per 1.73 m^2	Urine volume <0.3 ml/kg/h for ≥ 24 hrs or anuria for 12 hours
sCr-Serum Creatinine, eGFR-estimated glomerular filtration rate		

5.   MECHANISM OF AKI

Numerous credible pathways that contribute to acute kidney injury (AKD) have been suggested. These pathways include cell-cycle arrest of the renal tubular epithelium, epigenetic modifications, the inability to recover from AKI-induced inflammation, malfunctioning mitochondria, ineffective proximal tubule regeneration, endothelial dysfunction, metabolic reprogramming, and activation of the renin-angiotensin system (RAS). Studying these systems may lead to the development of novel treatment drugs and monitoring techniques.

Angiotensinogen (AGT), renin-angiotensin system (RAS), reactive oxygen species (ROS), FAO(fatty acid β-oxidation), interleukin (IL), ANG I (angiotensin I) and ANG II (angiotensin II), acute kidney disease (AKI), and TNF-α (tumor necrosis factor α) [14].

Renal tubular epithelium cell-cycle arrest
↓ G2/M arrest (G0phase reseting
Epigenetic change
↓ Chromosome change DNA methylvation and Histone modification
Chronic inflammation
↓ TNF-α, IL
Dysfunction of mitochondria
↓ ROS to mitochondria
Failed regeneration of tubular cells
↓ Pericyte to endothelium
Endothelial dysfunction
↓ Pericyte detachment with interstial fibrosis
Metabolic reprogramming
↓ FAO to glycolysis (metabolic reprogramming)
RAS Activation.

6.   PATHOPHYSIOLOGY

AKI has a complicated and multiple pathogenesis. Ischemia, which can happen for a variety of causes, is the most frequent cause of AKI. Although some degree of compensation can be achieved by physiological adjustments to the reduction in blood flow, organ dysfunction results from insufficient supply of oxygen and metabolic substrates, which causes cellular harm. The kidney is particularly vulnerable to ischaemia-related damage, which can lead to endothelial damage, vasoconstriction, and the initiation of inflammatory processes [15].

Partially explaining this sensitivity are anatomical links between renal tubules and blood vessels in the kidney's outer medulla, where ischemia lowers blood supply to vital nephron structures. The reduction in effective renal perfusion causes the epithelial cells to lose the capacity to sustain the intracellular ATP levels necessary for vital physiological functions. When a cell's ATP supply runs out, it may undergo damage and ultimately die via necrosis or apoptosis. Although any part of the nephron might be damaged by an ischemic insult, the proximal tubular cells bear the majority of the damage. Lethal quantities of various chemicals may be produced for the surrounding epithelial cells due to the nephron's natural capacity to filter, concentrate, and reabsorb a wide spectrum of substances from the tubular lumen. AKI is also quite prevalent when sepsis is present. Sepsis is characterized by hyperdynamic circulation, altered blood flow though not always in the ischemic range and a rapid decline inGFR. The pathogenesis of septic-AKI is extremely complicated and includes tubular cell release of cytokines, inflammation, oxidative stress, and microvascular dysfunction. The conventional division of AKI into pre-renal, intrinsic-renal, and post-renal categories has lately been contested due to the rarity of histological diagnosis and the inability to definitively demonstrate the difference between tubular injury and pre-renal azotemia [16].

7.   DIAGNOSIS

Analyses of serum albumin, blood cell counts, electrolytes, SCr, standard bicarbonate, and dipstick urine analysis should be performed using blood and urine samples. Urinary sediment analysis may potentially be used as a reference to identify the cause of AKI. Because oliguria and anuria are prevalent and indicate progressive AKI earlier than SCr, urine output should constantly be checked in patients with AKI [17].

8.   EPIDEMIOLOGY OF AKI

After coronary angiography, contrast-induced AKI (CI-AKI) is very frequent, occurring in 2.61-13% of cases. Several medications, including nonsteroidal anti-inflammatory medicines (NSAIDs), antimicrobials, and chemotherapeutic agents, are linked to AKI [1819]. In patients undergoing surgery, there is controversy over the relationship between angiotensin-Converting Enzyme (ACE) inhibitors, Angiotensin receptor blockers, and acute kidney injury (AKI) [20]. Most of the time nephrotoxic drugs may be substituted with less nephrotoxic ones, or delivery techniques can be altered to reduce drug-induced AKI [21,22]. It is believed that, compared to cardiac surgery, noncardiac surgery carries a decreased risk of AKI.AKI is, however, mainly unstudied in individuals undergoing non-cardiac surgery [23]. In one study, 7% of patients experienced AKI, which was defined as a rise in SCr levels of more than 50% following noncardiac surgery. Sepsis patients frequently have AKI, and those who also have septic shock have almost double the in-hospital death rate [24].

9.   PRERENAL ACUTE KIDNEY INJURY

When intraglomerular pressure and plasma flow are insufficient to sustain filtering capacity, prerenal AKI develops. The most frequent reason is hypovolemia, which is followed by lower NSAIDs and may cause a decrease in cardiac output or a disturbance in autoregulation. In terms of returning baseline SCr to normal, prerenal AKI is often reversible; however, damage may still be present [25].

10.   POSTRENAL ACUTE KIDNEY INJURY

Urinary flow blockage is the cause of postrenal AKI. There are several reasons for this, including urethral stricture, benign prostatic hyperplasia, malignancies of the pelvis or abdomen, neurological conditions including multiple sclerosis, kidney stone blockage in the ureter, and ureter damage from trauma or surgery. The first step is to rule out blockage of the urine outflow. Next, an ultrasound should be done to rule out hydronephrosis [26].

11.   ACUTE RENAL INJURY

Renal ischemia, infection, sepsis, nephrotoxic medications, malignant hypertension, and inflammation (such as glomerulonephritis, vasculitis, or allergic response) are all possible causes of renal AKI. Inflammatory disorders of the renal parenchyma, such as glomerulonephritis and vasculitis, should be considered in the absence of a definite etiology of AKI, an insufficient response to therapy, or observations of both hematuria and proteinuria in patients with AKI [27].

12.   DRUG FOR ACUTE KIDNEY INJURY

AKI has been treated with a number of medications, but none of them has been proven to be effective in clinical settings. Numerous investigations lacked sufficient power, and the outcomes were uneven. The therapies that have been investigated the most for AKI are included here [28].

a.   Diuretics

There are many renoprotective properties of furosemide, such as obstructing the tubules' oxygen-consuming sodium channels, promoting diuresis, which lowers the kidney's oxygen demand, and eliminating kidney-toxic compounds. But aside from individuals with fluid overload, clinical trials have not been able to show that furosemide improves the prognosis in AKI [29].

b.   Stains

It has been assumed that statins, which are used to prevent cardiovascular events, may prevent AKI since they are considered to lower free oxygen radicals in the renal tubules and modify inflammatory responses. A high dosage of atorvastatin (80 mg) prior to the injection of a contrast agent was found to be related to a decreased incidence of CI-AKI in a 2012 publication. In relation to CI-AKI, a recent meta-analysis of research on patients receiving statin Negative and Positive coronary angiography suggested that statin therapy prior to contrast exposure may offer some protection. Statin treatment is not currently advised for the prevention of AKI due to these contradictory findings. In another RCT, Rosuvastatin was associated with persistent AKI as a secondary outcome in patients who had sepsis-associated acute respiratory distress syndrome [30].

c.   Dialysis

Life-threatening alterations in fluids, electrolytes, the acid-base balance, or uremic consequences are the current criteria used to determine whether to initiate rapid replacement therapy (RRT). There is nevertheless debate regarding the advantages of starting dialysis later on versus earlier, before potentially fatal problems arise. Renal replacement therapy (RRT) was initiated in critically ill patients with acute kidney injury (ELAIN) study, which showed that early RRT beginning decreased hospital length of stay, RRT duration, and mortality as compared to late RRT initiation [31].

d.   NAC - N Acetyl Cysteine

Acetylcysteine's antioxidant qualities are thought to be primarily responsible for its beneficial effects, although it also causes vasodilation in the renal medulla by blocking ACE and stabilizing nitric oxide. It hasn't been demonstrated that

acetylcysteine prevents AKI in individuals undergoing heart surgery or sepsis. Results in the context of CI-AKI have been inconsistent; nonetheless, a number of meta-analyses indicate that acetylcysteine may offer some protection against CI-AKI, particularly in high-risk individuals [32].

13. TREATMENT OF AKI

To reach normovolemia and hemodynamic stability, there are a few important guidelines to abide by. The advancement of AKI and hyperkalemia should be prevented by stopping the use of ACE inhibitors and potassium-sparing diuretics. In moderate-to-severe AKI (stages 2 and 3), where treating the underlying causes is the major goal, acid-base abnormalities, primarily in the form of metabolic acidosis, are common. Monitoring urine output and, initially, heart rate multiple times a day is a fundamental component of the care of all patients with acute kidney injury [33].

a. Fluid Overload

Large fluid infusions have long been thought to cure or prevent AKI by preserving renal perfusion and urine production. This was reinforced by research that came out fifteen years ago, which revealed that patients with severe sepsis who received so-called "early goal-directed therapy," which included giving them copious quantities of fluids, had a higher chance of surviving. The Acute Dialysis Quality Initiative has developed a novel four-phase technique for fluid resuscitation to prevent fluid overload. These stages include rescue, optimization, stability, and de-escalation. The rescue phase involves giving fluid boluses to patients experiencing life-threatening hemodynamic instability; the optimization phase involves carefully administering fluids to hemodynamically stable patients; the stabilization phase involves aiming for a zero or negative fluid balance when the patient is in a stable condition; and the de-escalation phase involves removing excess fluid [34].

b. Fluid Therapy

The goal of restoring fluid balance is to raise cardiac output, normalize hemodynamics, and restore renal blood flow without causing fluid overload in any scenario where hypovolemia is thought to be the cause of acute kidney injury (AKI). Determining one's level of hydration can be challenging, but a number of techniques have recently entered clinical use, including Bioimpedance measurement and Ultrasonography-based measurements of the left ventricle and vena cava. Every person's rate of rehydration needs to be determined [35].

c. Selection of fluid

Numerous investigations have demonstrated that high-chloride crystalloid solutions may be hazardous and cause renal function to deteriorate. High concentrations of chloride in the macula densa are hypothesized to promote tubuloglomerular feedback, which in turn causes preglomerular vasoconstriction and reduced renal perfusion. Reuscitation using fluids with a high chloride concentration has been linked to a higher risk of AKI, metabolic acidosis, and length of stay on mechanical breathing, according to a recent meta-analysis. Research involving the use of synthetic colloid hydroxyethyl starch in patients with sepsis and critical illness has revealed an elevated risk of AKI, prompting discontinuation of its application [36].

d. Vasoactive medications

Vasoactive medications cause elevated blood pressure and systemic vasoconstriction, which enhance renal perfusion. Patients with vasodilated shock may be able to lower their risk of AKI by taking a modest dosage of norepinephrine. Administering norepinephrine has been shown to enhance GFR and renal blood flow in animal experiments.Renal blood flow is increased by dopamine, a renal vasodilator that acts on both the pre- and postglomerular arterioles. It has been suggested that administering a small dosage of dopamine might improve renal perfusion [37].

14. SUMMARY

AKI is widespread and connected to unfavorable results. There is currently no proven way to prevent or cure AKI, despite several interventions and research studies. Consequently, attempts should be made to minimize harm in AKI patients by using crystalloid solutions rather than fluids with a high chloride content, avoiding fluid overload, and stopping or reducing the dosage of nephrotoxic medications. To avoid additional kidney injury, postrenal outflow obstruction and medication-induced AKI must be ruled out if the cause of AKI is not immediately apparent [38].

15. CONCLUSION

Poor clinical outcomes for hospitalized patients are linked to AKI, a significant clinical condition. Improvements have been made to the diagnosis of this illness and the understanding of the pathophysiologic processes underlying the various clinical manifestations. It is evident that no one pathophysiologic mechanism can account for all clinical manifestations of AKI. AKI promotes distant organ damage and organ cross-talk. These developments will facilitate the creation of randomized trials for therapeutic and preventative treatments, as well as epidemiological investigations [39].

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