Review Article

Acute Kidney Injury Associated with Uremia: Pathophysiological Mechanisms, Clinical Progression, and Management Strategies

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ABSTRACT

Acute kidney injury, also known as AKI, leads to sudden loss of renal function and is associated with a high mortality rate, morbidity, and potential for chronic kidney disease. Uremia is caused by the accumulation of metabolic byproducts, which affect many organs and systems. Acute kidney injury (AKI) in the presence of uremia is a serious medical condition characterised by abrupt impairment of the kidneys, resulting in the buildup of nitrogenous waste and systemic metabolic disruption. The aetiology of uremic AKI is complicated, involving haemodynamic changes, tubular damage, inflammation, and oxidative stress, which are frequently aggravated by underlying medical conditions. Treatment choices include both supportive measures and renal replacement therapy (RRT) when needed, with a focus on prompt treatment to avoid permanent kidney impairment and decrease morbidity and mortality. Early detection and appropriate management, such as medical support and renal replacement therapy, are critical for avoiding complications. This review focusses on the pathogenesis, clinical development, diagnostic shortcomings, and therapeutic methods of AKI in uremic patients.

Keywords: Acute Kidney Injury (AKI), Uremia, Renal Failure, Renal Replacement Therapy, Critical care.

INTRODUCTION

Acute kidney injury (AKI), which is characterised by a deterioration in renal function, is associated with a high rate of mortality and morbidity as well as a higher chance of developing chronic renal failure (CKD). Changes in urinary output and serum creatinine are often used to identify and grade AKI[1], and standardised frameworks for assessment are provided by KDIGO, AKIN, and RIFLE[2]. The buildup of metabolic waste products that are usually eliminated by healthy kidneys, such as urea, creatinine, guanidine, and homocysteine, causes uremia. These toxins have the ability to impair cellular functions, vascular endothelium, and neurological activity [3].

Uremia arises in AKI as a result of neurohormonal imbalances, endothelial damage, tubular dysfunction, decreased glomerular filtration, and systemic inflammation. It continues to be a significant cause of morbidity and death even with improvements in supportive care and renal replacement treatment. Particularly in patients with previously diagnosed CKD, sepsis, or exposure to nephrotoxins, early diagnosis of uremic symptoms is essential for prompt therapies, such as dialysis [4].

This review gives a comprehensive summary of the pathogenesis, clinical characteristics, diagnostic problems, and treatment options for AKI-associated uremia.

1. PATHOPHYSIOLOGY OF AKI

Etiological classification

Prerenal failure happens when the glomerular filtration rate (GFR) is lowered due to decreased blood supply to the nephrons, which causes a disparity between the oxygen and nutrients that the nephrons get and their metabolic needs. Prerenal AKI can be brought on by any medical condition that reduces renal perfusion or systemic blood flow. Cirrhosis, heart failure, long-term diuretic usage, hypotension, sepsis, shock, and blood loss are among the frequent causes. ACE inhibitors, calcineurin inhibitors, NSAIDs, diuretics, and other medications might aggravate prerenal AKI and additionally impair renal perfusion, particularly in individuals with bilateral renal artery stenosis or a single functioning kidney [5].

Intrarenal failure occurs when the renal parenchyma is directly injured, especially the glomeruli or tubules, as observed in acute tubular necrosis (ATN) or acute interstitial nephritis. Through efferent pathways, these injuries cause renal vasoconstriction, which subsequently impairs perfusion. Sepsis, persistent ischaemia, and nephrotoxic medications are common causes. Notably, if cellular injury takes place, neglected prerenal injury can develop into intrarenal damage [6].

a) **Acute interstitial nephritis (AIN)** 15–27% of kidney biopsy findings in AKI are due to AIN. The majority of instances are caused by drugs, particularly NSAIDs and antibiotics such ampicillin, cephalosporins, ciprofloxacin, cloxacillin, and methicillin. Less frequently occurring infectious triggers include Salmonella, Legionella, as well as E. Coli, Brucella, and Campylobacter [7]

b) **Glomerulonephritis** This category of conditions is characterized by inflammation of the glomerulus and frequently manifests as edema, arterial hypertension, nephrotic or nephritic syndromes, and deteriorating kidney functioning [8].

c) **Acute Tubular Necrosis (ATN)** results from damage to renal tubular cells, which causes the cells to lose their capacity to survive. Ischemia, sepsis, rhabdomyolysis, nephrotoxins and renal blockage are among the main causes. Amphotericin B, calcineurin inhibitors (tacrolimus, cyclosporine), sulfa medicines, radiocontrast media, cisplatin, mTOR inhibitors (everolimus, temsirolimus), foscarnet, ifosfamide, cidofovir, acyclovir, and IV immunoglobulin containing sucrose are among the medications linked to ATN [9].

Post-renal AKI Acute blockage of urine flow causes elevated intratubular pressure and an associated decrease in glomerular filtration rate, which results in post-renal AKI. In addition to structural blockage, obstruction can worsen kidney function by reducing renal supply of blood and inducing inflammatory reactions. Nephrolithiasis, intraluminal blood clots, prostatic enlargement, and improperly positioned urinary catheters are common causes [10].

Cellular & Molecular Mechanisms

Acute kidney injury (AKI) can proceed to chronic damage if repair fails to occur, resulting in fibroblast proliferation, extracellular matrix buildup, and end-stage renal disease. Ischaemia and inflammation are the main causes of renal cell apoptosis. When sepsis-induced AKI occurs, innate immune activation sets off a cytokine storm that releases IL-1, TNF-α, and IL-6. In experimental models, TNF binding to glomerular and tubular cell receptors has been demonstrated to induce apoptosis [11].

Ischemia–Reperfusion-Induced Renal Injury

One of the main causes of AKI is ischemia-reperfusion injury (IRI), which is brought on by decreased oxygen and nutrition delivery as well as poor waste product clearance in renal cells. Oxidative stress is fuelled by hypoxia and ischaemia, which impair mitochondrial function, microcirculation, and enzyme activity, ultimately resulting in structural and functional harm in IRI induced AKI. Ferroptosis has become a crucial process in IR-AKI, surpassing these routes. ROS produced by the Fenton reaction cause lipid peroxidation and further tissue damage, which in turn causes this type of iron-dependent, nonapoptotic cell death [12].

Podocyte Injury

Attached to the glomerular basement membrane (GBM), podocytes are highly specific epithelial cells that coat the glomerular capillaries' exterior. They are essential for both the synthesis of GBM proteins and the control of glomerular permeability. Albuminuria is caused by the loss of podocytes, and increased albumin absorption by tubular epithelial cells increases tubular damage and interstitial fibrosis. Loss of podocytes frequently causes irreversible kidney injury because of their poor ability to recover [13].

Sepsis Associated AKI

Sepsis causes altered renal blood flow and microcirculatory dysfunction due to sympathetic nervous system activation, endothelial damage, and the production of vasoactive mediators like endothelin, vasopressin, and angiotensin II. Through intricate molecular mechanisms, these alterations cause acute kidney injury (AKI) and damage to renal tissue. Thus, sepsis is a significant contributor to AKI, causing between 45 and 75% of cases. Sudden decline in the kidney's functioning, damage to tubular epithelial cells, buildup of inflammatory cytokines in the kidney, along with concurrent multiorgan dysfunction are the hallmarks of sepsis-induced AKI [14].

Nephrotoxin Exposure

Acute kidney damage (AKI) caused by drugs is responsible for roughly 19–26% of hospitalised cases. There are three primary ways that drugs can cause nephrotoxicity: (1) proximal tubular injury that results in acute tubular necrosis (ATN), of which is a dose-specific process brought on by drugs or their metabolites coming into direct contact with the apical membrane, being transported from the apical surface, or secreting from the basolateral side into the tubular lumen; (2) tubular obstruction due to crystals or casts formed by drugs and their metabolites, which is also dose-dependent; and (3) drug-induced interstitial nephritis, which is usually dose-independent [15].

2. MECHANISMS OF UREMIA

Uremia is a medical condition that includes a variety of signs and symptoms. It develops after extensive renal damage and is distinguished by the buildup of various organic compounds that would typically be eliminated by functioning kidneys [16].

i. Accumulation Of Middle and Protein-Bound Uremic Toxins

As kidney function deteriorates, the evacuation of many organic solutes is compromised, resulting in their buildup in the body. Protein-bound uremic toxins make up around 25% of all known uremic toxins. Indoxyl sulphate (IS) causes nephrotoxicity by producing reactive oxygen species, depletes antioxidant defences, and promotes fibrosis and inflammation. likewise, p-cresyl sulphate (pCS) causes oxidative stress, renal fibrosis, and inflammation, and appears to be clinically associated to both acute kidney injury (AKI) and chronic kidney disease progression. These toxic substances also promote adhesion molecules like E-selectin, VCAM-1, and ICAM-1, which increases leukocyte recruitment and contributes to atherosclerosis. Higher concentrations of these proinflammatory substances in advanced CKD raise the chance of cardiovascular mortality [17].

ii. Immune Dysfunction and Oxidative Stress

One of the many ways that uremia causes oxidative stress is by reducing the synthesis of antioxidant enzymes in the kidneys. Reactive oxygen species (ROS)

are produced more easily when urea builds up, which damages blood vessels and also induces insulin resistance. This oxidative environment increases the buildup of uremic toxins by damaging endothelial cells, rupturing myelin, and altering brain proteins. Moreover, excessive urea exacerbates endothelial dysfunction and metabolic disorders by inducing the generation of ROS in the mitochondria, activating the NF-κB signalling system, and upregulating the expression of MCP-1 and VCAM-1. By encouraging oxidative stress, exacerbating insulin resistance, and eliciting cardiomyocyte apoptosis through calpain-1 activation and endoplasmic reticulum stress, simultaneous hyperuricemia intensifies these effects and eventually affects cardiac function and mortality [18].

iii. Dysregulation of electrolyte and acid-base balance

Given the critical role renal tubular cells play in preserving acid-base balance, acidosis is another serious metabolic consequence linked to uremia and AKI. As renal failure progresses, the body's capacity to release hydrogen ions and eliminate ammonium declines, which causes phosphate and organic acids including lactic, sulphuric, and hippuric acids to build up. Therefore, hyperkalaemia, metabolic acidosis, hyperphosphatemia, and hypocalcaemia frequently accompany uremia. The broad impacts of diminished renal homeostasis are highlighted by the fact that these disruptions can result in arrhythmias, muscular weakness, and compromised neurological functioning [19].

iv. Link to AKI

Uremia develops from acute kidney injury through a complicated interaction of clinical signs and physiological alterations. AKI is characterised by an abrupt deterioration in kidney function that is normally curable with prompt treatment. Uremia, which is characterised by the buildup of metabolic waste products and electrolyte imbalances brought on by compromised kidney function, can develop from severe or chronic AKI. The number of protein-bound solutes gradually rises as renal function diminishes. Haemodialysis can still be used to eliminate unbound toxins in the initial stages, when these solutes are only slightly raised. However, when the condition worsens, haemodialysis is no longer enough to stop further buildup, and the consequences of these residual solutes start to show themselves in extrarenal tissues [20].

3. UREMIC TOXINS IN THE AKI-TO-CKD TRANSITION

Preclinical research in AKI and CKD models shows that, regardless of the damaged renal compartment—tubules, glomeruli, or endothelium post-injury cellular defence and adaptive mechanisms can propel the development from AKI to CKD. Proinflammatory and profibrotic mediators are released when the immune system is activated after AKI, resulting in a harmful setting that modifies the cellular processes of tubular cells, glomerular cells, and endothelial cells. Reactive oxygen species (ROS), organelle stress, activation of NF-B, cellular death, the epithelial-to-mesenchymal transition (EMT), the creation of extracellular matrix (ECM), and fibrosis are all encouraged by these conditions. Uremic toxins (UTs) contribute to tubular fibrosis, chronic inflammation, and the onset of chronic kidney disease (CKD) by taking part in these physiological processes in all renal compartments. It is difficult to investigate distinct mechanisms independently because of the significant interconnections between these cellular and molecular pathways. For example, endoplasmic reticulum (ER) stress and mitochondrial dysfunction are both severely produced under hypoxic settings. The significance of UTs regarding the AKI-to-CKD transition has only been specifically investigated in one preclinical study at present, emphasising the need for additional investigation to determine whether UTs serve as risk factors or viable therapeutic targets in this scenario [21].

4. DIAGNOSIC APPROACH

A. Staging And Grading Of AKI

Kidney Disease: Improving Global Outcomes (KDIGO) Practice Guideline for AKI

The 2023 KDIGO Clinical Practice Guideline for Acute Kidney Injury (AKI) revises the 2012 guidelines, offering guidance on AKI definition, assessment, prevention, and treatment as shown in Table-1. The following characteristics are indicative of AKI: urine output <0.5 mL/kg/h for at least 6 hours; an elevation in serum creatinine to ≥1.5 times baseline within the previous 7 days; or a spike of ≥0.3 mg/dL (≥26.5 µmol/L) within 48 hours [22].

Table 1: KDIGO Guideline for AKI[22]

Stage	Serum creatinine	Urine output
I	1.5- 1.9 times baseline OR ≥ 0.3 mg/dl increase	< 0.5 ml/kg/h for 6-12 hours
II	2.0 – 2.9 times baseline	< 0.5 ml/kg/h for ≥ 12 hours
III	3.0 times baseline	< 0.3 ml/kg/h for ≥ 25 hours
	OR	OR
	Increase in Sr. creatinine to ≥ 4.0 mg/dl	Anuria for ≥ 12 hours
	OR	
	Initiation of RRT (in pts < 18 y, decreases in eGFR to < 35ml/min/1,73m2)	

RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) classification

To describe and differentiate the severity of acute kidney injury (AKI), the RIFLE classification (Risk, Injury, Failure, Loss of renal function, and End-stage kidney disease) as shown in Fig-1 was adopted in May 2004. Changes in urine output, glomerular filtration rate, as well as serum creatinine serve as the foundation for this approach. It has been demonstrated that the RIFLE criteria can reliably predict patient outcomes, identify a significant percentage of hospitalised AKI patients, and enable assessment of disease progression [23].

The AKIN criteria, sometimes known as the "modified RIFLE" criteria, are derived from the RIFLE criteria. All three methods have comparable prediction capacities for in-hospital mortality, however the RIFLE and KDIGO approaches are more sensitive than AKIN[25].

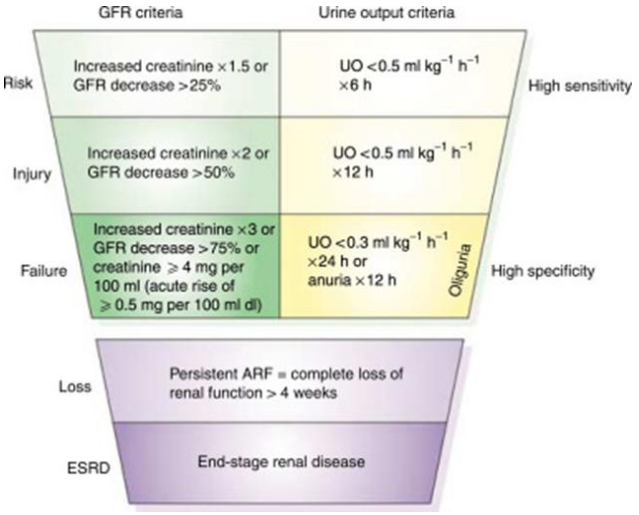

Figure 1: RIFLE classification [24]

B. Lab Investigations

i. Urinalysis: Urinalysis aids in the targeting and identification of the starting point of acute kidney injury (AKI) when used in conjunction with urine microscope. Red blood cell casts and dysmorphic red blood cells signify glomerular injury; muddy brown granular casts and renal tubular epithelial cells represent tubular damage; and white blood cell casts and eosinophils represent interstitial nephritis [25].

ii. Urine Dipstick Testing: All patients with possible or confirmed AKI should have a rapid dipstick assay for blood, protein, leukocytes, nitrites, and glucose [26].

iii. Creatinine Clearance: compared to serum creatinine alone, creatinine clearance offers a more precise and effective evaluation of kidney health since it directly evaluates glomerular filtration rate (GFR). Over time, continuous measurements enhance monitoring. Although longer collection times raise the possibility of mistakes due to faulty scheduling or insufficient sample collection, clearance can be evaluated throughout collection intervals ranging from one to twenty-four hours [27].

iv. Estimated glomerular filtration rate (eGFR) uses serum creatinine, age, and sex to assess kidney function. It is not accurate for evaluating acute kidney injury (AKI), but it is helpful for evaluating chronic kidney disease (CKD).

v. Serum (blood) creatinine: SCr evaluates how well the kidneys remove the metabolic waste product creatinine from the blood. A rise in SCr is indicative of acute kidney injury (AKI), and it is a crucial indicator of glomerular filtration rate (GFR). AKI is identified in accordance with KDIGO recommendations when SCr increases by ≥0.3 mg/dL in 48 hours or by ≥1.5 times baseline in 7 days.

vi. Electrolyte and other tests: In AKI, it is crucial to measure the values of minerals and electrolytes such as sodium, potassium, and bicarbonate. Serum potassium concentrations greater than 6.0 mEq/L can cause potentially fatal cardiac arrhythmias, making hyperkalaemia a serious consequence.

vii. Blood Urea Nitrogen (BUN) monitors the degree to which the renal system can remove urea nitrogen from bloodstream. Although increased BUN is seen in AKI, SCr is more specific. AKI types can be distinguished by the BUN:creatinine ratio; a ratio of about 20:1 shows prerenal causes (such as hypovolemia), while a ratio of around 10:1 indicates intrinsic renal injury.

viii. Arterial blood gas (ABG) analysis: when evaluating acid-base disruptions in AKI, ABG testing is essential. Metabolic acidosis is caused by a buildup of uremic toxins and poor urinary elimination of acids (such as phosphates and sulphates). High anion gap metabolic acidosis (HAGMA), which results from uremic toxin accumulation, lactic acidosis, and hydrogen ion shifts brought on by hyperkalaemia, is the most common finding [28].

C. Imaging Studies

i. Renal ultrasound: To assess kidney size, function, and chances of obstructive causes of AKI, ultrasonography is frequently used. It is especially helpful for evaluating anatomical renal dysfunction and identifying blockage of the urinary tract. Results like decreasing kidney size and diminished corticomedullary differentiation are more indicative of chronic kidney disease (CKD) than acute processes [29].

ii. Renal Doppler ultrasound and contrast-enhanced ultrasound are diagnostic methods that enable assessment of renal perfusion and cortical microcirculation include renal doppler ultrasound and contrast-enhanced ultrasound. Their benefits include availability, precision, and minimal invasiveness. Doppler investigations can show decreased renal blood flow, but they can't pinpoint the precise cause of AKI [30].

iii. Computed Tomography: Non-contrast CT is the gold standard for identifying kidney calculi when ultrasonography is ambiguous, whereas contrast CT detects tumors or artery stenosis but has a nephrotoxicity risk. Brain CT is recommended following trauma because uremic individuals with BUN >150–200 mg/dL are at risk for spontaneous subdural hematomas. Assessing hydronephrosis is aided by pelvic CT [31].

iv. Magnetic resonance imaging (MRI) is useful in identifying vascular factors contributing to renal failure that can be reversed, such as dissection, embolism, or renal artery stenosis. Although a kidney biopsy is usually avoided in patients with small kidneys due to the increased risk of haemorrhage and the limited diagnostic outcome, it is still a useful technique for differentiating AKI from CKD and determining treatability [32].

D. Novel biomarkers

Because of the high morbidity related to acute kidney injury in hospitalised patients, the identification of new biomarkers for enhancing timely identification, diagnosis, and prognosis is of great therapeutic importance [33].

Novel biomarkers of AKI include the following:

- Neutrophil gelatinase-associated lipocalin (NGAL)
- Interleukin-18 (IL-18)
- Kidney injury molecule 1 (KIM-1)
- Liver-type fatty acid–binding protein (L-FABP)
- tissue inhibitor of metalloproteinases–2 (TIMP-2)
- Calprotectin
- Cystatin C
- CXCL9
- Matrix metalloproteinase 7 (MMP7)

5. CLINICAL PRESENTATION AND SYMPTOMATOLOGY OF AKI AND UREMIA

Mild to moderate instances are typically undetectable and can only be identified by laboratory testing. More obvious clinical symptoms appear when the condition worsens due to the accumulation of uremic toxins, changes in fluid balance, and electrolyte imbalances.

i. Decreased urinary output: one of the prominent signs of AKI is decreased urine production. Urine output under 400 millilitres per day is known as oliguria, and in more serious cases, anuria may develop, with output below 100 millilitres per day.

ii. Volume Overload: Fluid retention brought on by decreased kidney function shows up as oedema in the face, legs, the ankles, and feet. Toxin and waste product buildup leads to weakness and exhaustion, and pulmonary oedema can result in difficulty breathing and dyspnoea.

iii. Hyperkalaemia is particularly harmful since it predisposes individuals to potentially fatal arrhythmias. Severe electrolyte imbalances can cause neurological signs such as confusion, disorientation, and coma. Metabolic acidosis also leads to respiratory compensation, which manifests as Kussmaul breathing.

iv. Fluid depletion associated particularly with severe diuretic usage or dehydration. Clinical characteristics include dry mucous membranes, ocular pruritus, decreased skin elasticity, oliguria, and arrhythmias [34].

Clinical Manifestations of Uremia

Uremic symptoms often emerge when creatinine clearance goes below 10-20 mL/min, unless the kidney impairment is severe. Patients may feel nausea, vomiting, exhaustion, anorexia, weight loss, changed taste, chest discomfort, palpitations, dyspnoea, muscular pain, restless legs, pruritus, excessive bleeding, or cognitive problems [35].

i. Anorexia: Uremia-related loss of appetite and altered taste/smell are exacerbated by restricted diets, medicines, and complications such as diabetic gastroparesis.

ii. Anemia: Kidney related anaemia is often normocytic, normochromic, and hypoproliferative, caused by diminished erythropoietin production. It usually happens when GFR is <50 mL/min (<60 mL/min in diabetes) or serum creatinine levels surpass 2 mg/dL [36].

iii. Neurological signs: Cognitive decline can vary from mild defects to coma, including tremor, asterixis, or hyperreflexia. EEG typically reveals slow-wave dominant patterns, and amyloid accumulation can result in neuropathies or nerve compression syndromes [37].

iv. Pericarditis: Uremic pericarditis may occur prior to or right after dialysis, manifesting with serous or hemorrhagic effusions; typical ST elevation on ECG is unusual.

v. Uremic pruritus: A condition characterised by uncontrollable itching that can be localised or generalised and is generally severe at night or during dialysis.

vi. Nausea vomiting: these symptoms are often linked with anorexia and are often the reason for starting dialysis. Uremia has an effect on both the central nervous system (CNS chemoreceptors) and the digestive system (delayed stomach emptying).

vii. Uremic coagulopathy: Marked by reduced platelet adhesion, raised platelet cell turnover, and moderate thrombocytopenia, leading to haemorrhage risks [16].

viii. Uncommon Uremic Manifestations: Because of early dialysis, uremic frost (cutaneous urea elimination), uremic foetor (ammonia odour from saliva), delirium, coma, and death are no longer prevalent. Oral symptoms such as gingival hyperplasia, petechiae, and enamel hypoplasia can last in unmanaged severe situations [38].

6. COMPLICATIONS.

Cardiovascular complications

Acute kidney injury (AKI) increases cardiovascular morbidity and mortality by causing comorbidities such congestive heart failure, arrhythmias, and myocardial infarction. These include the typical consequences of renal failure, such as hyperkalaemia, acidosis, uremia, volume overload, and kidney failure, as well as unconventional sequelae caused by systemic inflammation started or aggravated by AKI [39]. Uremic toxins, like cardiotoxins, have been linked to cardiovascular problems, including an increased risk of pericarditis [40].

Neurological effects.

Uremia and AKI can produce CNS symptoms as fatigue, somnolence, altered sleep-wake cycles, and mental retardation. AKI may also affect the blood-brain barrier permeation, which can lead to brain and hippocampus problems. Uremic encephalopathy, an established toxic condition that manifests as delirium, can occur in individuals with untreated or improperly managed chronic or acute renal disease [41].

Pulmonary Complications

Reduced urine production in AKI causes fluid retention, which may give rise to pulmonary oedema and respiratory failure. In unmanaged uremia, higher pulmonary capillary hydrostatic pressure and toxin-driven capillary leakage led to "uremic lung." Pleural effusions are normally transudative, but they may turn exudative in the context of uremic inflammation [42].

Metabolic complications

Prominent AKI abnormalities include hyperkalaemia, which can result in potentially fatal arrhythmias (e.g., ventricular fibrillation, peaked T waves); hypocalcaemia, which may trigger cramps, tetany, and QT prolongation; and hyperphosphatemia, which is frequently treated with phosphate binders or dietary restrictions. Systemic bicarbonate or citrate treatment may be essential in metabolic acidosis.

Others.

Secondary hyperparathyroidism, renal osteodystrophy, bone fractures. Normocytic normochromic anemia. Gastrointestinal ulcers, pancreatitis, and delayed gastric emptying etc [43].

7. MANAGEMENT STRATEGIES

The goals of AKI management include haemodynamic stabilisation, early recognition of complications, and timely medical treatment. Stabilization is crucial as self-regulation fails in AKI. In cases of uremic emergencies such as encephalopathy, hyperkalaemia, severe acidosis, or pericardial effusion with symptoms, dialysis must be started immediately but cautiously to prevent dialysis disequilibrium syndrome. Timely removal of nephrotoxic drugs is also crucial [44].

A. Fluid Management and Vasopressors

In order to prevent and treat AKI, intravascular hypovolemia must be corrected. After a thorough clinical evaluation, patients should be categorised as hypovolemic, euvolemic, or hypervolemic. Although there isn't a gold standard, postural BP decline with tachycardia, poor peripheral blood supply, decreased skin elasticity, dry mucous membranes, and hypotension (SBP <110 mmHg) all imply hypovolemia. There may also be concentrated urine (SG >1.020) and oligouria (<30 mL/hr).

Initially, 250–500 mL crystalloid boluses are administered repeatedly (up to 2 L in 2 hours). While excess saline might result in hyperchloremic acidosis, Hartmann's or 0.9% saline can be utilised; however, Hartmann's should be avoided in cases of hyperkalaemia. Increased JVP, peripheral oedema, or lung congestion are indicators of hypervolemia. If perfusion pressure is adequate (MAP >65 mmHg, SBP >110 mmHg), a brief trial with loop diuretics may be useful in cases of pulmonary oedema; if not, immediate dialysis or ultrafiltration is necessary [45].

Vasopressors could be necessary if shock continues even after volume is optimised. Although dopamine causes more arrhythmias, studies have shown no morbidity or renal advantage of dopamine over norepinephrine. Although the data is still ambiguous, vasopressin is a treatment option for norepinephrine-refractory shock and may be beneficial in septic shock. The current guidelines stress that vasopressors should not be stopped when necessary, since maintaining perfusion can enhance renal improvements, but they do not suggest any one drug over another. In fact, proper administration of vasoactive drugs can enhance renal perfusion in volume-resuscitated individuals with vasomotor shock [46].

B. Hyperkalemia management

Hyperkalaemia is acknowledged as a key risk factor for potentially fatal cardiac arrhythmia consequences. When an abrupt loss in renal function occurs, both in individuals with chronic kidney disease (CKD) and in individuals with originally regular renal function, HK is the primary rationale for immediate medical care and the use of extracorporeal restoration treatments [47].

i. *Calcium salts:* IV calcium (10-20 mL of 10% solution; 1-2 g gluconate or chloride) quickly regulates cardiac

myocytes by raising the threshold potential and improving impulse conduction. This quickly normalises hyperkalemia-associated ECG abnormalities, with results lasting 30-60 minutes.

ii. *Insulin–dextrose:* Insulin activates Na^+/K^+-ATPase in skeletal muscle, causing an intracellular potassium change. A regimen of 5 U insulin and 25 g dextrose is efficacious and lowers the chance of hypoglycemia when weighed against higher-dose regimens. High blood sugar levels can cause severe hyperglycemia, leading to organ failure and vascular damage.

iii. *β-2 agonists:* β_2-agonists, including inhaled or IV salbutamol, quickly reduce serum potassium levels by transferring it to cells. The typical dose regimen is 2.5 mg nebulised once every 15 minutes (up to 10-20 mg) or 0.5 mg IV. Metered-dose inhalers may also be utilised. Side effects, such as tachycardia, could restrict its usage in individuals with cardiac disease or unstable angina [47, 48].

iv. *Sodium polystyrene sulfonate (SPS):* SPS is a cation-exchange resin which eliminates potassium from the intestinal tract whether taken orally or rectally. It processes sodium to potassium, which is then expelled in faeces. However, significant GI problems, generally associated with sorbitol co-administration, have been identified [49].

C. Hyperphosphatemia treatment.

Excessive phosphate levels produce hypocalcaemia by calcium binding and soft tissue deposits, which may cause coronary artery disease. It also inhibits $1,25(OH)_2D_3$ production, resulting in secondary hyperparathyroidism. Phosphate binders like calcium carbonate or calcium acetate (3-6 g/day), sevelamer (1.5-6 g/day), or lanthanum carbonate (200-1200 mg/day) are often given in split doses with or shortly before meals [50].

D. Management of acidosis.

Acidemia is common in AKI patients, mostly because of increased strong ion gap (SIG), hyperphosphatemia, hyperkalaemia, and a reduced strong ion difference. Sodium bicarbonate can cure severe acidosis by maintaining serum HCO_3^- levels above 8 mmol/L or arterial pH above 7.2. The therapy may cause hypercapnia, hypokalaemia, ionised hypocalcaemia, and QTc prolonging. [52].

E. Use of diuretics.

Diuretics are only advised in AKI to treat fluid retention or electrolyte abnormalities. Although loop diuretics were formerly assumed to protect the loop of Henle against ischaemia, research has revealed that they have no advantage in mitigating AKI, reducing the requirement for renal replacement therapy, improving renal recovery, or lowering mortality from hospitalisation. High dosages may produce ototoxicity, and some studies relate diuretic usage to an elevated mortality, probably due to delayed RRT onset. As a result, KDIGO recommendations do not prescribe diuretics for AKI prophylaxis. [44, 53].

F. Uremia Treatment & Management

The last resort for uremia is kidney replacement therapy, which can be accomplished by peritoneal dialysis, haemodialysis, or kidney transplantation. Dialysis should be initiated when symptoms of uremia (such as nausea, vomiting, fluid overload, hyperkalaemia, or severe acidosis) arise and cannot be controlled with standard medical treatments. Dialysis must be initiated as soon as symptoms appear in individuals with uremia, regardless of their current glomerular filtration rate (GFR). Urgent treatment is necessary for uremia-related disorders include uremic encephalopathy, metabolic acidosis, hyperkalaemia, and pericardial effusion with symptoms. In order to prevent dialysis disequilibrium syndrome, which might result in neurologic symptoms due to cerebral oedema that happens during or after the procedure, dialysis should be begun cautiously [31, 51].

RENAL REPLACEMENT THERAPY

One of the most important aspects of treating extensive acute kidney damage with uremia is renal replacement therapy (RRT). Many patients eventually need RRT using different dialysis or hemofiltration modalities to sustain renal function, even though early conservative treatments are the foundation of AKI therapy [54].

A. Indications of RRT in AKI

Table 2: Indications of RRT in AKI 55.

Absolute indications	Refractory hyperkalemia (K >6.5 mEq/L). Refractory acidemia (metabolic or mixed acidosis with pH <7.15). Signs and symptoms of uremia (bleeding diathesis, pericarditis, encephalopathy). Refractory volume overload with organ edema.
Relative indications	Toxicity or overdose of easily dialyzable medications or drugs. Progressive oliguria/anuria (UO <200 mL/24 hours) unresponsive to medical management. Progressive azotemia; BUN >100 mg/dL unresponsive to medical management. Hyperthermia refractory to regular cooling techniques. Anticipating worsening electrolyte problems with AKI (tumor lysis syndrome, rhabdomyolysis).

Timing Of Initiation.

There is ongoing discussion on the best time to start RRT in critically sick patients, and it mostly relies on clinical opinion[56].

Rationale for early RRT

Justification for Early RRT: Toxic compounds can be eliminated early on before they cause organ failure, including:

- Urea, an underlying cause in platelet malfunction, pericarditis, and encephalopathy
- Metabolic acidosis caused by non-volatile acids
- accumulated medications that might be harmful

Disease-specific substances including intracellular toxins from rhabdomyolysis, ammonia in liver failure, and cytokines in sepsis.

Rationale for delayed RRT

According to studies like the AKIKI trial, up to 50% of patients who are randomized to delayed RRT never need treatment; there are no improvements in their ICU or hospital stay or survival. Delaying RRT helps to prevent possible issues like:

- Includes Risks associated with fluid/electrolyte management, coagulation therapy, and the extracorporeal circuit
- Risks with vascular catheters, such as infection, blood loss, or air embolism
- Increased workload, personnel needs, expensive prices, and specialized equipment

  Possible elimination of helpful chemicals (drugs, endogenous mediators) or delayed renal recovery from hypotension.

RRT does not treat AKI or its underlying cause; rather, it is a supportive intervention. In spite of removing helpful compounds like endogenous mediators and therapeutic medicines, it can also sometimes hinder renal recovery, for example, by causing hypotension from fluid loss or exposures to the extracorporeal circuit [57].

B. Principles of RRT

Diffusion and convection are the two main methods that RRT uses to transfer solutes and fluids. Solutes travel across a semi-permeable membrane in diffusive clearance, also known as dialysis, along a concentration gradient from region of high to low concentration. The balance of solute concentrations, which can potentially add or remove solutes based on how much is present in plasma and dialysate, is made possible by the countercurrent movement of dialysate and blood.

Hemofiltration or ultrafiltration, also known as convective clearance, uses a pressure gradient to transport water while "dragging" solutes along (convective mass transfer). While tiny solute clearance is comparable to diffusion, this approach efficiently eliminates fluid and bigger compounds.

The elimination of solutes and fluids is complicated in practice, even though these methods seem simple. While convection allows the expulsion of bigger solutes together with water, improving total solute removal, diffusion efficacy is dependent on plasma and dialysate flow rates as well as concentration gradients [58].

C. Modalities

Renal replacement therapy (RRT) techniques can be classified based on their access route, treatment period, and major solute clearance mechanism as shown in table-3.

- Duration: hybrid, continuous, or sporadic methods.
- Veno-venous or arterio-venous access.
- Mechanism: convective ultrafiltration, diffusive dialysis, or a mix of the two, also known as the "method" of RRT [55].

Table 3: modalities of renal replacement therapy (RRT) [55].

Continuous therapies	Continuous renal replacement therapy (CRRT) • Continuous venovenous hemofiltration (CVVH) • Continuous venovenous hemodialysis (CVVHD) • Continuous venovenous hemodiafiltration (CVVHDF) Peritoneal dialysis (PD)
Intermittent therapies	Intermittent hemodialysis (IHD)
Hybrid therapies	Sustained low-efficiency hemodialysis (SLED) • Sustained low-efficiency hemodiafiltration (SLED-f)

D. Monitoring and complication

Table 4: complications of renal replacement therapy (RRT)[60].

Respiratory	Hypoxia hypercapnea
Circulatory	Haemodynamic instability Hypothermia
Catheter placement	Hematoma Pneumothorax Pericardial tamponade
Hematologic	Bleeding Metabolic alkalosis Heparin induced thrombocytopenia Hemolysis
Electrolytic and acid-base	Hypocalcemia Hypomagnesemia Hypokalemia Hypernatremia Hypophosphatemia Normoglycemic ketoacidosis.
Renal	Haemodynamic instability Haemofilter membrane-induced complement and cytokine activation septic nephropathy Trophic hormone depletion
Gastrointestinal	Malnutrition due to dialytic nutrient loss Poor glycemic control Vitamin deficiency Amino acid and protein loss

RRT has the risk to cause excessive bleeding, hemodynamic instability, infections, embolism, and, in certain situations, impaired renal recovery, even though it frequently improves lives (table-4) [59]. Dialysis disequilibrium syndrome is a prominent consequence that arises from the excessive removal of tiny solutes, resulting in a significant concentration gradient within the extracellular fluid and the brain itself. Cerebral edema, which starts as disorientation and can lead to seizures or coma, is brought on by this osmotic shift, which pulls water inside the brain [60].

9. PREVENTION

Because established AKI has few available treatments and a high incidence of morbidity and death, prevention and early identification continue to be the best ways to lessen its effects. Although some contend that risk assessment is useless since high-risk patients may not receive certain therapies, new research shows that patient stratification can allow for more focused preventive therapy, which lowers the incidence of AKI while having no effect on long-term renal outcomes. Approximately 50% of AKI cases originate in the community, making it essential for healthcare providers to identify at-risk individuals and implement preventive strategies. High-risk patients should undergo a Kidney Health Assessment (KHA) annually, at least 30 days before any high-risk exposure, and again 2–3 days afterward. The KHA should evaluate AKI and CKD history, blood pressure, serum creatinine, urine dipstick, and medications. Maintaining hemodynamic and volume status, evaluating medicines (including temporarily stopping ACE inhibitors, ARBs, and metformin), and reducing nephrotoxic exposure are the key components of AKI prophylaxis. Speedy recovery to baseline kidney activity is the main objective for patients with AKI in order to reduce the extent and duration of the condition, highlighting the need of early detection and prompt treatment [44].

CONCLUSION

Acute kidney injury linked to uremia is a complicated and often fatal condition requiring immediate detection and treatment. Clinical choices must be guided by an understanding of its multifaceted aetiology, which includes direct tubular damage, inflammatory pathways, and haemodynamic instability. Although uremic AKI progresses differently in each person, serious systemic consequences and a higher death rate might result from delayed diagnosis and treatment. In addition to treating the root cause and closely monitoring metabolic abnormalities, supportive care and the prompt start of kidney replacement therapy continue to be the cornerstones of management. Future developments in targeted medicines, early biomarkers, and individualised treatment plans might improve prognosis and lessen the impact of uremic AKI.

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