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Renal Disorders in the ICU

NRuba Sarsour[1]* and Tejas Desai[2]

[1]East Carolina University – Brody School of Medicine, Department of Internal Medicine, Greenville, NC 27834, USA

[2]Assistant Professor of Medicine, East Carolina University – Brody School of Medicine, Department of Internal Medicine, Greenville, NC 27834, USA

***Corresponding author:** Ruba Sarsour, DO, East Carolina University – Brody School of Medicine, Department of Internal Medicine, Greenville, NC 27834, USA, E-mail: SarsourR@ecu.edu

Introduction

Acute Kidney Injury (AKI) is a sudden decrease in kidney function due to a reduction in glomerular filtration rate (GFR), increase in creatinine or a decrease in urine output. AKI consists of different etiologies including pre-renal, acute tubular necrosis, interstitial nephritis, glomerular and vasculitic renal diseases, and post-renal obstructive nephropathy [1]. AKI is commonly seen in critically ill patients with important consequences including increased risk of death even in mild and/or reversible AKI [1].

Acute Kidney Injury

Whether the disorder is pre-renal, intrinsic or post-renal, identifying the underlying etiology is imperative in an intensive care unit (ICU) setting. The investigation includes a detailed history, medication reconciliation, assessment for recent exposure to toxins or trauma, and a detailed review of symptoms.

A detailed physical exam should include a careful assessment of patients' volume status. Hypotensive patients are at risk for over-resuscitation after they achieve hemodynamic stability due to a lack of serial fluid status reassessments. Fluid overload may present as peripheral edema, jugular venous distention, and/or crackles on lung auscultation. Evidence of systemic syndromes or vasculitis may be suggested by a rash, arthritis and signs of embolic events. Abdominal distention can direct towards bladder outlet obstruction, ascites, or abdominal compartment syndrome [2].

Laboratory and radiologic tests are key diagnostic modalities in renal disease, regardless of the hospital setting. Providers should inquire prior records for baseline renal functions. A basic metabolic profile is crucial as the rate of rise of serum creatinine can be suggestive of the underlying etiology; a slow rise is mostly seen with pre-renal etiology whereas in ATN serum creatinine tends to rise at a rate of 0.3-0.5 mg/dL per day. A sudden oliguria (urine output <500 mL/day) can also be suggestive of an acute process. Urinalysis and microscopy for urine sediment, quantification of urine protein or albumin and fractional excretion of sodium can be important diagnostic tests that aid in the diagnosis of the underlying origin. A renal ultrasound with Doppler can demonstrate obstructive pathologies or anomalies in renal size or structure. A renal biopsy is often last resort if the non-invasive evaluation is not sufficient for diagnosis [3].

It is essential to identify patients that are at higher risk of developing AKI as this will allow for certain protective and/or preventative measures to be undertaken [4]. High risk individuals and/or susceptibility factors include: dehydration, hypoalbuminemia, advanced age, exposure to nephrotoxic agents, female gender, history of chronic kidney disease (CKD), history of Diabetes Mellitus, history of Heart disease, patients undergoing cardiac surgery, patients with liver disease or malignancy and patients on mechanical ventilation [4,5].

Etiologies of Acute Kidney Injury

Pre-renal acute kidney injury

Pre-renal disorders are responsible for 30-40% of acute renal injury the ICU [6]. Pre-renal diseases result from a decreased arterial blood volume or from any process that reduces renal blood/oxygen delivery [3]. In pre-renal diseases, the decrease in GFR is a physiological response to hypoperfusion rather than tissue damage [2].

In the ICU, certain measurements such as a low central venous pressure (CVP) of 1-2 mm Hg or 10-12 mm Hg in ventilator dependent patients may suggest hypovolemia. In ventilator dependent patients, a decrease in blood pressure shortly after lung inflation can be used as evidence of inadequate cardiac filling. Central venous oxyhemoglobin saturation ($ScvO_2$) below 50% suggests a low cardiac output. If anemia is not the cause of reduced tissue perfusion, a $ScvO_2$ below 25-30% is highly indicative of low cardiac output [6]. Pre-renal disease is seen in multiple scenarios:

-Hypovolemic states (i.e. acute hemorrhage, diarrhea, or insensible losses) [3].

- Hypervolemic states with low arterial blood volume (i.e. acutely decompensated heart failure)[3].

- Acutely decompensated liver disease with portal hypertension [6].

- Alteration in renal vasculature auto-regulation due to non-steroidal anti-inflammatory drugs (NSAIDS) or iodinated contrast [3].

- Rise in intraabdominal pressure >20 mm Hg leading to abdominal compartment syndrome [2].

In the setting of renal hypoperfusion, sodium reabsorption increases and urinary sodium excretion decreases. A urine sodium <20 mEq/L usually indicates a prerenal condition [2]. However urine sodium >40 mEq/L does not rule out pre-renal disease [6]. Fractional excretion of sodium (FE_{Na}) is the most sensitive index for pre-renal disease for patients not exposed to loop diuretics. For patients taking diuretics, the fractional excretion of urea (FEU_{rea}) is superior, with a specificity and sensitivity above 95%. FEU_{rea}<35% suggests renal hypoperfusion. Rapid reversal of renal hypoperfusion is critical, as prolonged ischemia can lead to renal tubular necrosis [2].

Cardiorenal syndrome

Cardiorenal syndrome occurs when one organ dysfunction (heart or kidney) causes another organ dysfunction [7]. Although there are 5 types of cardiorenal syndromes, types 1 and 5 are the most related to acute kidney injury in the ICU. Type 1 (acute) is when AKI is a consequence of acute heart failure. Type 5 is AKI and/or acute heart failure that occurs secondary to a systemic disorder like sepsis [8]. In decompensated heart failure, renal injury can be secondary to decreased cardiac output, increased renal venous pressure or activation of Renin-angiotensin-aldosterone system which leads to systemic vasoconstriction to ensure brain and heart perfusion while decreasing renal perfusion [9].

Hepatorenal syndrome

Hepatorenal syndrome is a diagnosis of exclusion that can be seen with end stage liver disease and fulminant hepatic failures. In this syndrome, effective hypovolemia leads to severe intrarenal vasoconstriction. It can occur spontaneously in advanced liver disease, or develop after a precipitating event such as infection, gastrointestinal bleeding, or large-volume paracentesis without albumin [10]. It carries a poor prognosis [2]. There are 2 main types of hepatorenal syndrome; in type 1 there is a 2 fold increase in serum creatinine to a level >2.5 mg/dL in <2 weeks; while type 2 has a slower increase in serum creatinine and presents with refractory ascites [10].

Acute tubular necrosis

Acute Tubular Necrosis (ATN) is the cause of 50% of cases of acute kidney injury in intensive care unit. Unlike pre-renal disease, in ATN, there is parenchymal damage with sloughing of damaged cells into the renal tubules. These cells create an obstruction that lead to an increased pressure in the proximal tubules and a decrease in the glomerular filtration rate. With urine microscopy, tubular epithelial cells with epithelial cell casts are pathognomonic of ATN. Renal recovery can be expected in >90% of patients who previously had normal baseline function [6] if managed appropriately. There are several phases of ATN:

1. Initiation Phase: oxidative injury secondary to prolonged ischemia [5].
2. Extension phase: inflammatory state secondary to initiation phase leading to medullary congestion and hypoxic injury [5].
3. Maintenance phase: restoration of tubule cells [5]. It can be either oliguric or nonoliguric. Nonoliguric ATN has a better outcome; however, attempts to change from oliguric to non-oliguric have not shown improved outcomes [5].
4. Repair phase: restoration of polarity and function [5].

There are several etiologies that predispose patients to ATN. Common causes include:

- Ischemia from prolonged pre-renal state [11]
- Aminoglycosides can cause ATN in 25% of hospitalized patients receiving therapeutic drug levels. It is more common in patients with higher risks for AKI. It causes a reversible non-oliguric renal injury 5-10 days into treatment. Aminoglycosides can remain in renal tissue for up to a month, thus renal function is not restored immediately after discontinuing the drug. Streptomycin is the least nephrotoxic of the aminoglycosides. Prior to starting an aminoglycoside, experts advocate inquiring into any family history of drug-induced vestibular disorders as well as informed consent that they are aware of the potential nephrotoxicity [11].
- Amphotericin B can have a cumulative nephrotoxic effect. Toxicity leads to a type-I renal tubular acidosis. Liposomal preparations have lower propensity for nephrotoxicity [2].
- Cyclosporine toxicity is dose dependent and can lead to a type-4 renal tubular acidosis from severe vasoconstriction. Blood level monitoring is crucial. In some cases, a renal biopsy is needed to distinguish transplant rejection from cyclosporine toxicity. Renal function usually improves after reducing the dose or stopping the drug [11].
- Acyclovir can potentiate renal disease. Discontinuation of acyclovir usually reverses renal injury [11].
- Cisplatin toxicity is dose-depending and cumulative but can be avoided by hydration prior to the initiation of therapy [11].
- Ethylene Glycol/Methanol poisoning can elevate the osmolar gap and cause an anion gap metabolic acidosis. Urine sediment is usually positive for envelope shaped oxalate crystals [2]. Toxicity may be managed with fomepizole antidote but hemodialysis is indicated for refractory metabolic acidosis/AKI [2].
- Rhabdomyolysis can have several etiologies: trauma (crush injury), infection, immobility, drugs (especially statins), electrolyte abnormalities (hypophosphatemia, hypokalemia), snake venom, and status epilepticus [6]. Dehydration and acidosis can predispose to the development of myoglobin, which can cause direct tubular damage [11]. Rhabdomyolysis of clinical importance commonly occurs with serum creatinine kinase above 20,000-50,000 international units/L [2].
- Hemoglobinuria results from substantial intravascular hemolytic processes due to transfusion reactions or hemolytic anemia [11]. Patients would present with elevated lactate dehydrogenase, decreased haptoglobin, and elevated unconjugated bilirubin [2].
- Cast nephropathy is composed of light chains (myeloma) that can lead to direct tubular injury and intratubular obstruction [2].
- Tumor Lysis Syndrome can be seen 48-72 hours after chemotherapy or from rapid cell turnover in the setting of lymphomas. Renal injury takes place through uric acid precipitation in the acidic environment of the tubules. Serum uric acid levels are often > 15-20 mg/dL and urine uric acid levels >600 mg/24h [11]. Also, hyperphosphatemia can lead to calcium-phosphate crystal formation and renal deposition [2]. A urine uric acid to urine creatinine ratio >1.0 indicates a high risk of acute kidney injury [11].

Iodinated contrastinduced nephropathy

This is the third leading cause of acute renal failure in hospitalized patients and is caused by both renal vasoconstriction and tubular injury [5]. Renal injury becomes apparent as rising serum creatinine within 72 hours after contrast administration [6]. Risk factors include preexisting renal dysfunction, heart failure, diabetes, volume depletion, multiple myeloma, large volume and high osmolarity contrast

administration. Preventative measures include premedication with isotonic saline volume infusion and/or N-acetylcysteine. However, the KDIGO guidelines discourage using N-acetylcysteine to prevent AKI in critically ill or postsurgical patients with hypotension.

Acute interstitial nephritis

Acute interstitial nephritis (AIN) is an interstitial inflammatory process that occurs mostly through cell-mediated immune reactions [11]. It is often caused by medications (70% of cases) or infections (usually viral or atypical pathogens) [6].It usually presents without oliguria and the classic triad of rash, eosinophilia and fever is rarely seen. Urinary sediment is routinely positive for white blood cells, white blood cell casts and eosinophils (detected with Hansel's stain) [6]. Renal biopsy may be needed for a definite diagnosis [2].

Drugs responsible for interstitial nephritis include antibiotics (aminoglycosides, amphotericin B, beta-lactams, fluoroquinolones, sulfonamides, vancomycin), anti-epileptics (carbamazapine, phenobarbital, phenytoin), NSAIDs (aspirin, ibuprofen, ketorolac, naproxen), diuretics (acetazolamide, furosemide, thiazides), acetaminophen, ACE-inhibitors, iodinated dyes, and ranitidine [6].

Obstructive nephropathy

Obstructive nephropathy accounts for 10% of the cases of acute kidney injury [6]. Although obstruction can occur anywhere in the urinary tract, bilateral obstruction (or unilateral obstruction in a single functioning kidney) is necessary for a reduction in glomerular filtration rate to take place [3]. If left untreated, obstructive nephropathy can lead to irreversible tubulointerstitial fibrosis [3].

Staging of AKI

The RIFLE criteria, which is used to define the severity of AKI:

-Risk: 1.5 fold rise in the serum creatinine, a 25% reduction in glomerular filtration rate (GFR), or a urine output below 0.5 ml/kg/hr for six hours.

-Injury: Two fold rise in the serum creatinine, a 50% reduction in GFR, or a urine output <0.5 ml/kg/hr for 12 hours.

-Failure: Threefold rise in serum creatinine, a 75% reduction in GFR, or a urine output <0.3 ml/kg/hr for 24 hours, or anuria for 12 hours.

-Loss: Complete loss of kidney function (e.g., need for renal replacement therapy) for > 4 weeks.

-End stage renal disease (ESRD): Complete loss of kidney function (e.g., need for renal replacement therapy) for >3 months [12].

The Kidney Disease Improving Global Outcomes (KDIGO) foundation does not use GFR for staging:

-Stage 1: serum creatinine of 1.5-1.9 from baseline, ≥ 0.3 mg/dL (≥ 26.5 micromole/L) rise in serum creatinine, or urine output <0.5 mL/kg per hour for 6 to 12 hours.

-Stage 2: serum creatinine of 2.0-2.9 or urine output <0.5 mL/kg per hour for ≥ 12 hours.

-Stage 3: serum creatinine >3.0, urine output <0.3 mL/kg per hour for ≥ 24 hours, anuria for ≥12 hours, renal replacement therapy necessitation, age below 18 years, or a reduction decrease in estimated GFR to <35 mL/min per 1.73m^2 [12]

Patients should be classified according to the criteria that result in the highest (most severe) stage of injury [12]. Nevertheless, there are limitations to these criteria; for example in the early stages of AKI; the serum creatinine level does not correlate with the degree of renal injury [4]. Another example would be patients with sepsis have decreased creatinine production; hence the serum creatinine level will not accurately reflect the degree of renal injury [4]. Also, in patients with rhabdomyolysis, creatinine release from skeletal muscle adds to serum creatinine and therefore will not accurately reflect the degree of renal injury [2].

Management of AKI

In all cases of AKI, treating the underlying cause and discontinuation of all offending agents is the first step in management. However, this may not always be possible in the ICU setting. Secondly, initiation of volume resuscitation is important for volume expansion using isotonic crystalloid fluids, or in the case of hemorrhagic shock, colloid fluids [1]. The early initiation of fluid therapy can also identify patients with pre-renal kidney injury if renal function responds quickly [1]. Fluid resuscitation should be directed towards an objective physiologic endpoint, such as mean arterial pressure or urine output [13]. The KDIGO guidelines recommend using vasopressors in conjunction with fluids in patients with shock irresolute with fluid resuscitation [1]. Norepinephrine is currently the vasopressor of choice, as it raises mean arterial pressure without increasing mortality and without the accompanying arrhythmic events associated with dopamine [1].

Patients with all cases of AKI can develop hyperkalemia, metabolic acidosis, hypocalcemia and hyperphosphatemia. In general, patients with AKI should avoid receiving medications containing potassium. Hyperkalemia should be treated as medically indicated. Patients with refractory hyperkalemic metabolic acidosis in the setting of volume overload or severe acidosis (PH<7.1) often necessitate renal replacement therapy. Bicarbonate infusion in patients with metabolic acidosis and oliguria/anuria should be avoided as it can reduce ionized calcium and increase the partial pressure of carbon dioxide and intracranial pressure in patients with diabetic ketoacidosis. Hypocalcemia and hyperphosphatemia are also commonly seen in AKI, and hypocalcemia should only be treated in symptomatic patients unless the serum phosphate level is >8 mg/dL, in which case the patient should be dialyzed due to the risk of calcium-phosphate binding and deposition in organs and vessels [13].

In the setting of cardiorenal syndrome, optimizing cardiac function is goal. In critically ill patients, treatment is directed at establishing volume hemostasis through the use of intravenous (IV) loop diuretics, even if it leads toa temporary worsening of renal function. Thiazide diuretics can be added in patients who are refractory to loop diuretics. Ultrafiltration is only indicated in cases refractory to IV diuretics, not as first line, as studies have shown better outcomes with the use of diuretics [8].

In the case of hepatorenal syndrome in the ICU, it is usually managed with a combination of norepinephrine and albumin [2]. Norepinephrine is given as a continuous infusion (0.5 to 3 mg/hr) with the goal of raising the mean arterial pressure by 10 mmHg,

and albumin is given as 1 g/kg per day for 2 days (maximum of 100 g per day) [10]. In patients with spontaneous bacterial peritonitis, albumin infusion may prevent development of hepatorenal syndrome [2].

Patients with rhabdomyolysis induced renal failure should be treated with vigorous hydration (may require up to 10 L of normal saline during 24 hr), however, 30% of the patients will require dialysis [6]. Patients with Tumor Lysis syndrome will also require vigorous hydration as well as allopurinol and rasburicase [2].

In the setting of ATN, there are experimental studies that suggest that the administration of growth factors insulin like growth factor-I (IGF-I), epidermal growth factor (EGF), and hepatocyte growth factor may expedite the recovery of renal function [5].

AIN is managed with the removal of the offending agent and/or treating the underlying infection [11]. The use of steroids is controversial, but a treatment dose of methylprednisolone 0.5 to 1 g/d for one to four days or prednisone 60 mg/d orally for 1-2 weeks, followed by a prednisone taper can be used in severe cases [11]. Complete resolution can take months [6].

However, in glomerular disease (which is less commonly seen in the ICU setting), treatment includes immediate intravenous corticosteroids (methylprednisolone at 7 mg/kg/day for 3 days followed by oral prednisone at 1 mg/kg/day up to 60 mg) and with cytotoxic immunosuppressants (cyclophosphamide at 2 to 3 mg/kg/day). Goodpasture's disease often requires plasma exchange for therapy. In TTP, plasma volume exchange is the lifesaving therapy, whereas antibiotics and platelets transfusion are contraindicated [2].

Renal Replacement Therapy

Renal replacement therapy (RRT) is indicated in the setting of refractory fluid overload, electrolyte abnormalities (especially hyperkalemia and hypocalcemia), metabolic acidosis, and uremic encephalopathy, as well as certain drug intoxications [14]. In the ICU setting there are different forms of RRT; intermittent hemodialysis (IHD) and continuous renal replacement therapy (CRRT) but CRRT is becoming more favorable due to it being more physiologic-like and is better tolerated in critically ill patients [6]. There have been studies to suggest that CRRT can also have an advantage in septic patients due to better removal of inflammatory mediators and an advantage in the cases of fulminant hepatic failure and acute brain injury due to hypothesized better cerebral perfusion [14]. Nevertheless, there is no evidence to support that one method is associated with better outcomes compared to the other [15]. The timing for initiation of RRT continues to be controversial; there are no definitive criteria at which RRT should be initiated, however, it is recommended to initiate RRT prior to the development of life threatening symptoms or complications [14]. Once there is evidence of renal function improvement; continuous decrease in creatinine, an increase in urine output, electrolyte stabilization, symptomatic improvement and an improvement in creatinine clearance, then RRT can be discontinued [15].

Conclusion

We present the common causes of acute kidney injury in an ICU setting, from pre-renal to renal and post-renal anomalies. Regardless of the type of renal disease, identifying the underlying disorder is imperative in order to adequately manage the critically ill patient and prevent further complication. Renal disease is an exceptionally common problem in an ICU setting and providers should be familiar with the clinical features and management strategies.

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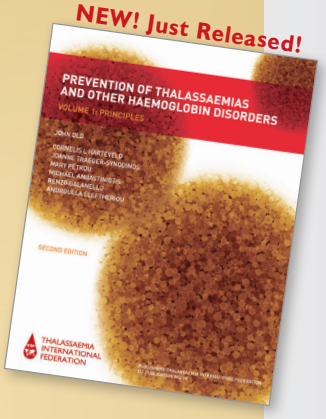

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