Acute Kidney Injury (AKI)

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Introduction

Kidneys perform a multitude of essential functions within the human body. Of these the most important are (1) maintaining pH through regulation of acid/base levels and (2) excreting end products of metabolism. These functions are especially important for healing following trauma and/or surgery. The essential functions of the kidney take place in two distinct yet connected microscopic entities within the renal parenchyma—glomerulus and the tubules. The process of removing the end products of metabolism starts with the glomerular capillaries filtering the blood and passing the filtrate onto the renal tubules. One of the measures of renal function is the glomerular filtration rate (GFR)—volume of fluid passing from the glomerulus onto the renal tubules per minute. Within the renal tubules two processes control what is excreted in the urine: (1) selective reabsorption by which almost 99% of the filtrate volume is reabsorbed back into the circulation and (2) active secretion from the blood into the tubules of substances that are to be excreted, creatinine being one of them. Through glomerular filtration and tubular active secretion, nearly all

the creatinine in the renal artery blood is removed with hardly any present in the renal veins. Thus creatinine clearance rate (CCR) defined as the volume of blood cleared of creatinine per minute closely approximates the GFR and is commonly used as a measure of GFR, which is more difficult to directly measure. Normal values of CCR are given in Table 39.1. There are gender differences in CCR, being lower in females likely due to their lower average muscle mass, which is the principal source of creatinine.

There are major morphologic changes that occur in the kidney with increasing age (Table 39.2). These morphologic changes directly affect renal function. The renal blood flow declines to half by age 80 from its peak at age 20 with a progressive decline in GFR. This decline in GFR is manifested by decrease in CCR that is maximum at age 20 and, on average, declines by about 6.5 mL/min per decade post age 20 [1].

Table 39.1 Normal values for renal function measurements by age and gender

Parameter	Value
Serum creatinine	Adult males: 0.6–1.2 mg/dL
	Adult females: 0.5–1.1 mg/dL
	Teen: 0.5–1.0 mg/dL
	Child: 0.3–0.7 mg/dL
Creatinine Clearance Rate (CCR)	Adult male (<40 years): 107–139 mL/min
	Adult female (<40 years): 87–107 mL/min

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Table 39.2 Morphologic changes in the kidney with age

Morphologic change	Quantification
Loss of renal mass	20–25% loss by age 80
Loss of functioning glomeruli and glomerulosclerosis	30–50% loss by age 70
Decreased tubular number and size and increased fibrosis	
Thickened basement membranes of capillaries and tubules	
Increased arteriosclerosis and decreased afferent arteriolar lumen	

Table 39.3 RIFLE criteria for renal dysfunction

Category	Serum Cr/GFR criteria	Urine output criteria
Risk	Cr increase ×1.5 above baseline	<0.5 mL/kg/h for 6 h
	GFR decline by >25%	
Injury	Cr increase ×2 above baseline	<0.3 mL/kg/h for 24 h
	GFR decline by >50%	
Failure	Cr increase ×3 above baseline	<0.3 mL/kg/h for 24 h or anuria
	GFR decline by 75%	
Loss	Persistent AKI for >4 weeks	
End stage	AKI for >3 months	

Sensitivity for AKI is highest for "risk" category and specificity highest for "end stage" category

The overall impact of these changes is loss of renal concentrating and diluting ability, decreased ability to conserve sodium, lower levels of renin and aldosterone with decreased prostaglandin production and an enhanced vasoconstrictive response leading to increased susceptibility to ischemia and nephrotoxic medications [2]. One of the important reasons of poorer tolerance to injury and surgery among elderly is the decline in renal function and reserve.

Acute renal failure is the term that was utilized in the past to describe injury to the kidney resulting in the kidney unable to perform its essential functions. Usually renal failure is associated with oliguria (urine output <20 mL/h—oliguric renal failure), though it can be observed with more normal or even excessive urine output (non-oliguric renal failure). Multiple studies demonstrated that the development of acute renal failure was associated with a 50% increase in the relative risk of inhospital mortality. More recently it has been realized that even smaller insults to the kidneys that do not result in overt acute renal failure can adversely affect outcomes [3, 4]. Hence the concept and term acute renal failure has been replaced by RIFLE criteria, which encompasses a spectrum of renal dysfunction from "risk" of damage to overt "end stage" renal failure with AKI in the middle of that spectrum. RIFLE includes both urinary output criteria and metabolic criteria (Serum creatinine or GFR) (Table 39.3) [5]. At the "risk" category, the sensitivity for injury is high though the specificity relatively poor. Hence patients diagnosed at risk *may* have suffered renal injury, but if not meeting

the risk criteria, the probability of renal injury is very low. These criteria have been shown to correlate with outcomes [6, 7].

While the outcome of any patient who develops AKI is worse, multiple studies and meta-analysis have demonstrated that the incidence of AKI is higher and the degree to which AKI adversely impacts outcomes is more pronounced in the elderly [8, 9].

Causes of AKI

Causes of AKI are multitude and are classified into prerenal, renal, and post-renal (Table 39.4). Prerenal denotes a reduction in renal perfusion either total perfusion in terms of volume and/or reduction in perfusion pressure. This leads to the kidney being unable to perform its function even though there is no inherent renal pathology. Renal causes are those where the kidney does not perform its function due to inherent renal disease either acute or chronic. Post-renal includes any disease or condition causing an obstruction to the free flow of urine from the renal collecting system down to the external urethral meatus. Large majority (>75%) of patients with AKI encountered in the surgical intensive care unit (ICU) are either hypovolemia causing prerenal AKI, or acute tubular necrosis (ATN) causing renal AKI.

Table 39.4 Cases of various forms of AKI—prenal, renal and post-renal

Prerenal	Hypovolemia from blood/fluid losses
	Hemorrhage
	Gastro-intestinal: Vomiting, diarrhea, GI fistula, etc.
	Urinary: Diuretics, salt wasting states, adrenal insufficiency, etc.
	Cutaneous: Burns, excessive sweating, etc.
	Third spacing: Sepsis, pancreatitis, postoperative, etc.
	Reduced "effective" circulating volume
	Hypoalbuminemia
	Cirrhosis
	Cardiac failure
	Failure of "auto-regulation"
	Use of NSAIDS or ACE inhibitors
Renal	Vascular
	Large vessel: occlusion of bilateral renal artery/vein
	Small vessel: intrarenal micro-angiopathic occlusions
	Thrombotic-thrombocytopenic purpura, hemolytic uremic syndrome, etc.
	Glomerular dysfunction: glomerulonephritis
	Acute tubular necrosis (ATN)
	All prerenal causes when prolonged
	Nephrotoxic agents
	Acute interstitial nephritis (AIN)
	Allergic reactions to medications
	Certain infections: Brucellosis, Epstein–Barr virus, etc.
Post-renal	Genitourinary malignancy: prostate, urinary bladder
	Urinary stone disease
	Acute papillary necrosis, e.g., due to NSAID use

Prerenal AKI

In surgical patients with prerenal AKI, the cause is most often related to reduction in effective circulating volume either due to blood loss or redistribution. The later occurs in ill patients from systemic inflammation and loss of intravascular volume into the interstitial space. It can also occur in patients with heart failure where, while there is overall fluid retention, the intravascular volume is depleted. Auto-regulatory mechanisms present within the kidneys allow them to function despite reduced perfusion, but these mechanisms too are less effective with age, can be overwhelmed by extreme reduction in perfusion, and can be interfered with. These auto-regulatory pathways are dependent upon chemical signaling involving prostaglandins and renin–angiotensin II pathway. Thus use of nonsteroidal anti-inflammatory medications affecting the production of prostaglandins and ACE inhibitors interfering with the renin pathway adversely affect auto-regulation and can cause severe AKI in an at-risk patient [10, 11].

Reduced renal perfusion directly leads to a reduction in GFR. Less filtrate reaching the tubules results in increased reabsorption of urea causing an increase in blood urea nitrogen (BUN). Since creatinine is principally secreted into the tubular lumen and is less dependent upon glomerular filtration, creatinine rise is limited in prerenal AKI. This leads to a higher BUN/creatinine ratio (>20) in prerenal AKI. Although this elevated ratio is a strong pointer to prerenal AKI, by itself it is not diagnostic since it could be elevated in hyper-catabolic states as well. The sine qua non of prerenal AKI is the intense conservation of Na and water by the kidneys. This is demonstrated by oliguria, highly concentrated urine (urine osmolality >500 mOsm/kg) with very low Na concentration (usually <10 mEq/L) and low fractional excretion of Na (FE_{Na} < 1%—see below).

Renal AKI

Renal AKI results from reduced renal function as a result of renal parenchymal disease. These states may be classified as vascular, glomerular, and tubulointerstitial. Vascular causes include bilateral occlusions of the major renal vessels (renal artery and/or vein) or widespread microscopic thrombosis of intrarenal vasculature occurring in a variety of syndromes (thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, etc.). Glomerular dysfunction is seen in the multiple types of acute glomerulonephritis that lead to renal dysfunction. Glomerular and

vascular causes of renal AKI are quite rare in the surgical ICU and beyond the scope of this text. The large majority of renal AKI observed in this setting are caused by tubulointerstitial disease—acute tubular necrosis (ATN) and acute interstitial nephritis (AIN).

ATN is by far the most common form of renal AKI. Pathologically ATN is associated with (1) necrosis and sloughing of the epithelial cells lining the lumen of the tubules causing obstruction; (2) back leak of the filtrate into the circulation through the disrupted tubular epithelium; and (3) reduced glomerular blood flow likely due to afferent arterial vasoconstriction. These three together result in severe renal dysfunction associated with significant rise in the serum BUN and creatinine with a BUN/Cr ratio of <20. Additionally, the sloughed off epithelial cells from the tubular lumen make their way down the urinary passage and can appear on urinalysis as cellular casts. Since renal function is directly affected, the urine is usually not concentrated and has osmolality that is similar to plasma. For the same reason, the kidneys fail to conserve Na and hence FE_{Na} is elevated to >3%. As noted above, reduction in renal perfusion leads to prerenal AKI that is often rapidly reversible by improving renal perfusion. When the reduced perfusion is severe it leads to ATN where recovery is slower since the epithelial lining of the tubules has to be regenerated [12]. A rare but very severe form of AKI is caused by bilateral acute cortical necrosis (ACN). Unlike ATN, where the tubules are primarily affected and glomeruli spared, in ACN both the tubules and glomeruli are affected by the necrotic process. The inciting event is usually very severe shock from any cause though majority of cases are seen in association with obstetric emergencies—placental abruption, amniotic fluid embolism, toxemia of pregnancy, etc. Pathologically there are fibrin thrombi within the capillary beds of the kidney with necrosis. Severe oliguria is the norm with CAN and unlike ATN recovery is uncommon.

AIN can be caused by multiple disorders and is characterized by acute inflammation of the renal interstitium and tubules. The nature of the interstitial infiltrate is dependent upon the primary condition. Since AIN is often seen as an allergic reaction to medications, it is associated with eosinophilic infiltrate within the renal parenchyma and cutaneous manifestations. It can also be caused by some rare infections such as brucellosis and Epstein–Barr viral infection.

Post-renal AKI

Post-renal AKI is also known as "obstructive uropathy." It is caused by complete obstruction to urinary outflow. For a patient to develop post-renal AKI, the obstruction needs to be complete or near complete and affect both kidneys. Long-standing partial obstruction can lead to inability of the kidneys to concentrate urine and an acquired form of nephrogenic diabetes insipidus [13]. The common causes of complete bilateral obstruction leading to post-renal form of AKI include genitourinary malignancy, enlarged prostate, and urinary stone disease. A sometime missed cause is papillary necrosis caused by NSAID use where the renal papilla undergo necrosis, slough off and causes obstruction. Such patients can present with painless hematuria. A complete or near complete cessation of urinary flow should prompt consideration of post-renal AKI, since with prerenal and renal causes, the decrease in urinary output is rarely complete. While renal and prerenal AKI is diagnosed in the appropriate settings by laboratory tests of blood and urine, post-renal AKI requires imaging to arrive at the correct diagnosis.

Approach to AKI in the Surgical ICU (Fig. 39.1)

Prevention

Even relatively mild degrees of renal dysfunction are associated with worse outcomes; hence, preventing AKI from occurring in the first place must be an important goal of all critical care in the ICU. Since in most instances AKI is, or at
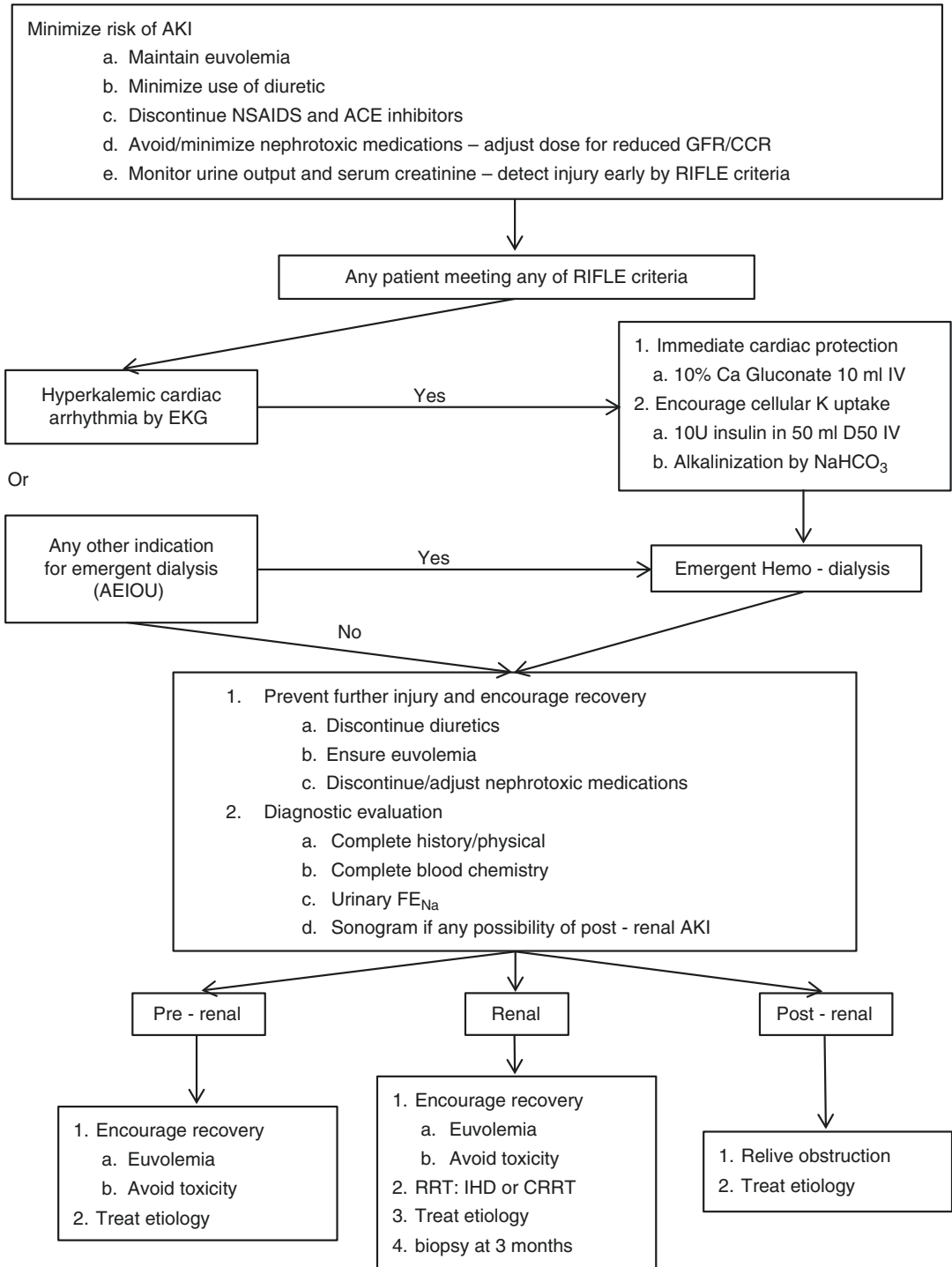
Minimize risk of AKI
- a. Maintain euvolemia
- b. Minimize use of diuretic
- c. Discontinue NSAIDS and ACE inhibitors
- d. Avoid/minimize nephrotoxic medications – adjust dose for reduced GFR/CCR
- e. Monitor urine output and serum creatinine – detect injury early by RIFLE criteria

Any patient meeting any of RIFLE criteria

Hyperkalemic cardiac arrhythmia by EKG

Yes

1. Immediate cardiac protection
   a. 10% Ca Gluconate 10 ml IV
2. Encourage cellular K uptake
   a. 10U insulin in 50 ml D50 IV
   b. Alkalinization by $NaHCO_3$

Or

Any other indication for emergent dialysis (AEIOU)

Yes

Emergent Hemo - dialysis

No

1. Prevent further injury and encourage recovery
   a. Discontinue diuretics
   b. Ensure euvolemia
   c. Discontinue/adjust nephrotoxic medications
2. Diagnostic evaluation
   a. Complete history/physical
   b. Complete blood chemistry
   c. Urinary FE_{Na}
   d. Sonogram if any possibility of post - renal AKI

Pre - renal

Renal

Post - renal

1. Encourage recovery
   a. Euvolemia
   b. Avoid toxicity
2. Treat etiology

1. Encourage recovery
   a. Euvolemia
   b. Avoid toxicity
2. RRT: IHD or CRRT
3. Treat etiology
4. biopsy at 3 months

1. Relive obstruction
2. Treat etiology

Fig. 39.1 Stepwise algorithm for any ICU patient at risk of AKI

least starts as, prerenal from loss of effective circulating volume, keeping a patient euvolemic is extremely important. In the past in the surgical ICUs, in an attempt to prevent the development of AKI, patients were often given too much volume especially in the form of crystalloids. This was directly related to development of multiple complications related to too much volume, namely ARDS, abdominal compartment syndrome, etc. The current understanding is that while hypoperfusion due to hypovolemia should be avoided to prevent organ dysfunction such as AKI, hypervolemia is to be avoided as well and the goal should be euvolemia. Instead of relying completely on provider judgment in assessing the intravascular volume status of a patient, more objective criteria—stroke volume/systolic pressure variation; intensivist performed point of care Echocardiogram and passive leg raise tests, etc.—should be utilized. Secondly when using nephrotoxic medications a careful risk/benefit analysis should be performed to ensure that the benefit of the medication clearly outweighs the risk of nephrotoxicity. If such nephrotoxic medications are utilized, the dose should be carefully adjusted for the individual patient to account for age or other factors related to poorer clearance.

While general principles of prevention outlined above apply to almost all patients admitted to the ICU, they are especially important in patients that have conditions placing them at greater risk of developing AKI. Surgical patients at particular risk of developing AKI are (1) patients suffering hemorrhagic shock due to trauma or any other surgical condition, e.g., ruptured aneurysm and severe necrotizing pancreatitis; (2) postoperative patients following major abdominal, vascular, or open heart surgery; (3) traumatized patients with massive crush injury releasing myoglobin and causing pigment induced nephropathy (see below); (4) major burn patients; (5) patients with preexisting renal disease; (6) patients suffering from systemic sepsis; and (7) geriatric patients. There have been attempts to quantify risk in specific populations but these remain imprecise and of moderate sensitivity at best [14]. There have also been attempts at developing interventions that could prevent the

development of AKI in these at-risk patients. These include use of low dose Dopamine, diuretics, renal protective agents such as Mannitol, and alkalinizing agents such as sodium bicarbonate. To date no such strategy has proven effective in preventing AKI [15, 16]. The best strategy for prevention as mentioned above is maintenance of euvolemia, and strict attention to the use of nephrotoxic agents.

Diagnostic Approach to AKI in the ICU

Despite all preventative measures, some critically ill patients will develop AKI. All patients at risk should be carefully monitored with hourly urine output and at least once daily checking of BUN and serum creatinine. If there is an abrupt decrease in urinary output, the catheter should be checked for blockage. If no blockage is found patients meeting "at risk" RIFLE criteria should have another careful evaluation of (1) intravascular volume; (2) mean arterial pressures; (3) use of diuretics and nephrotoxic agents. In addition, patients should be evaluated by checking FE_{Na} to differentiate prerenal from renal AKI and microscopic urine analysis to detect presence and type of casts. The presence and type of casts seen on microscopic examination can help determine the cause of the AKI. A 24-hour urine collection is necessary to accurately determine FE_{Na} by the following formula:

FE_{Na}=[Urinary Na×Plasma Creatinine/Plasma Na×Urinary Creatinine]×100.

In a patient in prerenal AKI, all diuretics should be suspended and intravascular volume replenished to euvolemic levels. After adequate volume resuscitation, pressors should be utilized to increase the renal perfusion pressure. In most cases of prerenal AKI, these measures should suffice in reversing the process. In specific patients where post-renal AKI is suspected, a sonogram should be performed to evaluate any dilatation of the urinary passage suggesting obstruction. If such an obstruction is found, it will need to be relieved to reverse the AKI. In patients where the

prerenal AKI does not reverse, obstruction has been ruled out, or renal AKI is diagnosed, the treatment of AKI should be as outlined below.

AKI Therapy

Treatment for AKI should be done in the following stepwise fashion (Fig. 39.1):

1. Evaluation for immediate threats to life: The most immediate threat to life from AKI is from acute increase in serum K. Patients should have a serum K measured immediately and frequently. Patients with AKI due to pigment nephropathy are especially prone to hyperkalemia. Patients demonstrating hyperkalemia should have an immediate EKG performed to check for cardiac effects of hyperkalemia. If such effects are detected, immediate therapy consists of calcium gluconate that is cardioprotective from hyperkalemia. Along with cardioprotection, measures to reduce serum K by driving the K from the extracellular compartment intracellularly should be undertaken—alkalization with sodium bicarbonate, and infusion of dextrose with insulin. While these immediate measures are carried out, preparations should be made for urgent dialysis (see renal replacement therapy below).
2. Evaluation for other indications for urgent dialysis: Even in the absence of immediate threat to life from hyperkalemia, patients may have other indications for urgent dialysis (see below). If any of these exist, preparations should be made for urgent dialysis.
3. In the absence of immediate threat to life, and any indication for urgent dialysis, supportive expectant therapy is appropriate:
   (a) Intravascular volume: Maintaining euvolemia
   (b) Drugs: Avoiding nephrotoxic drugs as much as possible and modifying the dose of all renally excreted drugs
   (c) Diet: In the past protein restriction to <40 g daily was the norm. However in this day and age of easy availability of renal replacement therapy restricting pro-

teins and placing patients at risk of protein calorie malnutrition is not considered appropriate. Patients should be provided with adequate calories and proteins as per their needs preferably via the enteral route.
   (d) Fluids: As with diet, in the past patients were strictly restricted to 1–1.5 L of fluid per day. This created problems with essential therapeutic drugs and also led to severe thirst. Now with relative ease of renal replacement therapy, fluid restriction is not necessary and patients should get adequate fluids to maintain euvolemia, get appropriate medications, and be supplied with adequate calories and proteins.

Common Syndromes Associated with AKI

Pigment Induced Nephropathy

Increased plasma levels of oxygen transporting pigments—myoglobin and hemoglobin—can lead to AKI. Myoglobinemia, seen with injuries involving muscle crush and sometimes after heavy use of street drugs [17, 18], is the more common form since its low molecular weight of ~17,000 Daltons allows it to be filtered by the glomerulus and form proteinaceous casts within the tubular lumen. The pigment is directly toxic to the tubular cells via free oxygen radicals. Serum levels of creatine kinase are elevated to >5000 U/L though often run much higher. Free hemoglobin is a less common cause of AKI since the molecule is much larger and is usually not filtered through the glomerulus. Additionally, free hemoglobin binds to haptoglobin forming a large complex that cannot be filtered. Only when there is massive hemolysis that exhausts the supply of haptaglobin does free hemoglobin appear in the circulation and cause hemoglobinuric AKI. The pathophysiology is the same for both the pigments.

Therapy for pigment nephropathy follows the same general principles outlined. The major difference is the addition of forced

diuresis with volume expansion and use of furosemide. Mannitol can also be used though judiciously since it can acutely increase the circulating volume and if diuresis does not occur, lead to volume overload [19]. Both pigments tend to be more soluble in alkaline urine, hence using sodium bicarbonate to alkalinize the urine to pH > 6.5 is also recommended, especially to prevent the development of AKI in at-risk patients.

Contrast Induced Nephropathy (CIN)

Intravenous radiocontrast agents can lead to AKI that has been termed CIN. With rapid expansion of diagnostic and therapeutic radiologic interventions coupled with an aging population with significant comorbidities, the incidence of CIN is rising. Risk factors for CIN are presented in Table 39.5. The actual incidence even in prospective studies varies from a low of <5% to a high of 50%. This is likely due to different study populations and differing definitions of CIN. The most commonly accepted definition is an absolute increase in serum creatinine of 0.5 mg/dL or increase of 25% above baseline. The increase commonly occurs 48–72 h post contrast exposure [20]. The proposed mechanism CIN likely involves vasoconstriction within the renal parenchyma leading to AKI with prerenal type of presentation though there is some evidence of direct toxicity mediated by free radicals [21]. A number of interventions have been studied to reduce the incidence of CIN. Interventions that have shown benefit at least in some, though not all, studies are: volume expansion, alkalanization, use of

Table 39.5 Risk factors for contrast induced nephropathy (CIN)

| Age > 60 years |
| Hypovolemia |
| Use of diuretics |
| Preexisting renal insufficiency |
| Diabetic nephropathy |
| Congestive heart failure |
| Hepatic failure |
| Large volume of contrast (>2 mL/kg) |

N-acetylcystein, limiting volume of contrast agent, using lower osmolarity agents, and discontinuing other nephrotoxic medications [22–27]. Hemodialysis either before or after radiocontrast administration to dialyze out the agent has not been shown to be beneficial [28].

HepatoRenal Syndrome (HRS)

HRS is a unique form of AKI that is seen in patients with advanced hepatic disease. The onset can vary from fairly acute to quite insidious. The typical clinical presentation is very similar to prerenal forms of AKI likely due to severe intrarenal vasoconstriction rather than inherent renal parenchymal disease. This is supported by the observation that HRS rapidly resolves if the hepatic disease is reversed or a functioning liver is transplanted. The pathophysiology likely involves vasodilatation in the splanchnic circulation caused by portal hypertension. This vasodilatation results in pooling of the blood volume within the splanchnic circulation especially in the large dilated mesenteric veins. This in turn leads to poor venous return to the heart and reduced perfusion to the rest of the body including the kidney. The kidneys respond to this relative hypo perfusion by afferent arteriolar vasoconstriction that leads to reduced GFR. Patients with HRS are prone to developing hepatic encephalopathy. Electrolyte disturbances—hypokalemia and hyponatremia—and acid-base disorders are more often seen in HRS as compared to other causes of AKI. While the principles of care are similar in this form of AKI, fluid balance becomes much more challenging since for the AKI a relatively full intravascular compartment and avoidance of diuretics is preferred, while to prevent ascites and peripheral edema from hepatic insufficiency, a mild degree of hypovolemia with diuretic use is preferred. Drainage of ascites especially if causing abdominal compartment syndrome (see below), either externally or internally via a peritoneovenous shunts may offer partial relief. Portal-systemic shunts too may ameliorate the AKI, but AKI in and of itself is not an indication to perform such shunts [29–32].

Abdominal Compartment Syndrome (ACS) Associated AKI

Over the past two decades ACS has been accepted as a distinct nosologic entity where an increase in intra-abdominal pressure leads to organ system dysfunction [33]. Kidneys, along with the lungs, are the most sensitive organs to elevated intra-abdominal pressures. Initially renal function is affected by the elevated intra-abdominal pressure compressing the renal veins. In later stages as the ACS progresses and cardiac output falls due to diminished venous return, this further contributes to AKI. Initially the presentation is that of oliguric with a prerenal picture, but if the ACS progress, ATN sets in. The only effective therapy is rapid relief of the intra-abdominal hypertension usually by surgical decompression [34].

Prognosis and Outcome

The majority (~80%) of the patients that develop AKI and survive will have return of renal function and be dialysis free [35]. While that maybe so, the prognosis for renal function is dependent upon the severity of the initial insult that caused the AKI. Patients with brief vascular insults will likely recover near baseline function within 72 h, while those with more severe and prolonged insults requiring dialysis for the AKI will likely have some long term effect where the serum creatinine remains 1–2 mg/dL above the pre-insult baseline value [36, 37]. During the recovery phase it is extremely important to avoid a second insult in the form of hypovolemia and nephrotoxic medications, etc. Recovery from AKI is heralded by increasing urine output and lack of rise or decrease in serum creatinine despite not getting dialysis. Differing functions of the kidney may recover at different time intervals. Urine output may increase first followed by reduction in serum creatinine and finally the ability to regenerate bicarbonate and maintain body pH. During the recovery phase electrolyte imbalances are common, hence careful monitoring is essential to avoid life-threatening abnormalities from developing.

It has long been known that the development of AKI is associated with a higher mortality. The reasons for this remain a bit unclear and maybe related to the adverse impact of AKI on the immune function [38]. Reported mortality rates range from 25 to 64% [39, 40]. The variation likely represents differing study populations. Overall mortality rates are lower for non-oliguric forms of AKI and AKI due to CIN, while very high rates are reported for HRS. The exact contribution of AKI as an independent risk factor for mortality among critically ill patients is debated. In a prospective study by Hoa et al. on post-cardiac surgery patients, 145 of 843 (17%) developed AKI and AKI was found to be an independent risk factor for mortality with a hazard ratio of 7.8. The overall numbers in terms of outcome for patients developing AKI in the ICU have not changed significantly for the past five decades [41].

As mentioned in the early part of the chapter, multiple studies and meta-analysis have demonstrated that the overall outcomes in general and the return of renal function after AKI in particular are adversely affected by age [8, 9].

Renal Replacement Therapy (RRT)

In critically ill patients with rapidly deteriorating renal function coupled with a hyper-catabolic state from the primary illness, unless renal replacement therapy is provided, the patient will likely die. In broad terms RRT can be provided in two forms—hemodialysis (HD) and peritoneal dialysis (PD). In both types of dialysis the principle of solute and fluid removal is the same. In both blood and dialysate fluid are separated by a semipermeable membrane. Solutes and fluid moves across this membrane following concentration and osmotic gradients. The two main processes are convection, where hydrostatic pressure serves as the driving force and diffusion where concentration gradients and osmotic pressure serve as the driving forces. By manipulating flow rates of blood and dialysate, and the composition of the dialysate, it is possible to control what gets removed—fluid or solute—and, in the

case of solute, what types of solute—high molecular weight or low/medium molecular weight. In the case of HD the semipermeable membrane is in a cartridge called the hemofilter or hemodialyzer, while in case of PD, the peritoneal surface serves as the semipermeable membrane. For the most part, in the ICU setting PD is not used, and the focus of RRT in this chapter will be HD.

There are two forms of HD—intermittent (IHD) and continuous (CRRT). IHD is the main form of RRT utilized for the large majority of patients with end stage renal disease and is also utilized in the ICU for more stable patients. CRRT is less taxing to the hemodynamics of the patient and hence is often utilized for critically ill more unstable patients that need fluid and or solute removal due to AKI. RRT is associated with a host of complications. The complete discussion of all the complications and their management is beyond the scope of this chapter and discussed elsewhere in the text. The common complications are—thrombosis of the access or dialysis circuit, infection, hypotension, and electrolyte imbalances. The decision to initiate RRT should be taken with a careful evaluation of risks and benefits, and if initiated, meticulous attention to detail is paramount to minimize complications.

Indications

Indications for dialysis maybe divided into emergent and non-emergent. Emergent indications are those where without dialysis the patient may die probably within a very short period of time. These can be summarized by the mnemonic AEIOU: A—acidosis; E—electrolytes principally hyperkalemia; I—ingestions or overdose of medications/drugs; O—overload of fluid causing heart failure; U—uremia leading to encephalitis/pericarditis. The principal non-emergent indication for dialysis is ESRD where the renal function has deteriorated to the point that without dialysis, the patient cannot survive long term. In between these two extremes is the use of dialysis for AKI where there is an expectation of return of renal function sufficient for

the patient to live without dialysis. Despite AKI being a very common disorder encountered in the ICU, surprisingly there is little consensus on the indications for dialysis. Some units start dialysis quite early with the expectation that by doing so, the ultimate outcome is improved. Other units tend to delay dialysis till the uremia leads to encephalopathy or an emergent indication emerges. The results of studies to determine the ideal indication and timing of initiating dialysis for AKI are mixed. Combining the results of multiple studies by meta-analysis is hampered by differing studies using differing definitions of early and late dialysis, and also that the older studies were performed with IHD, while the more recent ones have been done with CRRT [42, 43]. In an attempt to provide some objective guidance, the AKI Network has published guidelines [44]. The guidelines emphasize: (1) the indications maybe taken as absolute and relative. Absolute indications are such that by itself each absolute indication would merit dialysis. On the other hand, relative indications are such that while by itself the individual indication may not merit dialysis, however when taken with the entire clinical scenario, the patient merits dialysis. The latter occurs most often in the face of MSOF. The indications are summarized in Table 39.6; (2) fluid overload in critically ill patients is associated with worse outcomes, hence in critically ill patients with fluid overload early CRRT may help with fluid management and possibly improve outcomes [45]; and (3) in line with #2, there is a tendency towards initiating dialysis early in patients with oliguric AKI as opposed to non-oliguric AKI. The above discussion notwithstanding, all agree that dialysis should be administered to treat severe uremia even in the absence of any of the emergent indications. Severe uremia is usually defined as BUN of >100 mg/dL. Lastly the panel did not critically evaluate some emerging evidence of the early use of CRRT in patients with sepsis where the investigators claim that by dialyzing early and vigorously, inflammatory cytokines are removed and outcomes improved. The hypothesis while intriguing remains unproven [46, 47].

Table 39.6 Indications for renal replacement therapy in patients with acute kidney injury as per Acute Renal Failure Trial Network

Indication	Parameter	Absolute/Relative
Metabolic abnormality	BUN >76 mg/dL	Relative
	BUN >100 mg/dL	Absolute
	Hyperkalemia >6 mEq/L	Relative
	Hyperkalemia >6 mEq/L with EKG changes	Absolute
	Dysnatremia	Relative
Acidosis	pH > 7.15	Relative
	pH < 7.15	Absolute
	Lactic acidosis related to Metformin use	Absolute
Anuria/oliguria	Urine output <0.5 mL/kg/h × 6 h	Relative
	Urine output <0.5 mL/kg/h × 12 h	Relative
	Urine output <0.3 mL/kg/h × 24 h	Relative
	Anuria × 12 hours	Relative
Fluid overload	Diuretic sensitive	Relative
	Diuretic resistant	Absolute

Access

In patients with ESRD, dialysis is often anticipated and planned for by creation of an arteriovenous fistula or graft even before the patient actually needs dialysis. In patients with AKI encountered in the ICU, dialysis is usually performed via large (12-15Fr) dual lumen catheters inserted percutaneously into a large vein or directly into the right atrium. These catheters are of two types—cuffed, tunneled and un-cuffed, non-tunneled. Un-cuffed non-tunneled catheters are placed in the unit just as central venous lines. The commonly used ones are made of polyurethane and usually placed acutely for urgent dialysis in the internal jugular or femoral veins. Insertion into the subclavian vein is avoided to prevent stricture of vein that may hamper future placement of fistula or graft in the ipsilateral upper extremity. When placed with appropriate antiseptic precautions, they are safe to use for 2–3 weeks duration. If it is anticipated that dialysis maybe required for a longer duration, a cuffed tunneled catheter is preferred. These are made of silicone usually inserted with fluoroscopic guidance and have a cuff that sits in a subcutaneous tunnel. The tunnel and cuff tend to prevent catheter infection and hence these can be used for longer periods of time.

Dose

As is the case with exact indications and timing, there is also no consensus regarding the ideal dose or intensity of dialysis. While a number of smaller and usually retrospective studies suggest that higher intensity dialysis is associated with improved outcomes [48–50], larger prospective studies failed to demonstrate that [51, 52]. Guidelines as to how much dialysis should be administered to patients with AKI are published by the Acute Renal Failure Trial Network (ATN Trial) [52]. Most centers tend to keep the BUN at about 70 mg/dL. Besides solute reduction, the other component of dialysis is intravascular volume management. In patients that are septic and in the state of systemic inflammation, the capillaries remain hyper-permeable and any removal of fluid from the intravascular compartment leads to hemodynamic instability even though the total body water is increased. On the other hand, in patients that are recovering and the state of inflammation is subsiding, the capillaries regain their selective permeability and removing fluid from the intravascular compartment does not lead to hemodynamic compromise, rather there is resorption of the "third" space fluid from the interstitial compartment. Objective measures of intravascular volume should be utilized in determining how much volume should be removed.

Modality

As in other issues related to AKI, there is ongoing debate as which modality—IHD or CRRT—is superior. It is generally accepted that CRRT is better tolerated specially by critically ill patients that may have some degree of hemodynamic compromise. The results of studies are mixed in terms of overall mortality and return of renal function [53–57]. The modalities can be difficult to directly compare since it is difficult to dialyze the same amount of solute and volume with IHD when it is performed a few hours usually on alternate days, as with CRRT that can be performed round the clock. In the largest randomized prospective study to date, the outcomes were similar for the two forms of dialysis [58]. One surprising result of that study, unlike many others, was that even critically ill patients could tolerate IHD if the dialysate had a very high concentration of Na. In the US most ICUs will opt for CRRT in critically ill patients especially those with unstable or tenuous hemodynamic status, and utilize IHD for the stable patients. In UK and Australia, CRRT is the modality of choice for AKI in the ICU.

Summary

The large majority of patients admitted to the surgical ICU are at risk of AKI as defined by the RIFLE. Due to a host of anatomic and physiologic changes within the kidney that occur with age, the risk of AKI is significantly higher. The occurrence of even mild AKI adversely affects overall outcomes with the elderly often having the worst outcomes of all. Meticulous attention to fluid management and minimizing the use of nephrotoxic medications can help reduce the incidence. All at-risk patients that do develop AKI should have a reexamination of intravascular volume and discontinuation or adjustment of dosage of nephrotoxic medications. RRT therapy is often required for managing patients that do develop AKI.

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