Acute Kidney Failure

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OVERVIEW

Alterations in renal function are common after surgical emergencies, trauma, and major operations. In these settings, successful recovery of renal function is dependent on prompt diagnosis and protective management strategies.

Acute kidney injury (AKI) is characterized by an acute decrease in glomerular filtration rate (GFR). The true incidence of AKI and acute renal failure (ARF) has been difficult to define, given the broad and various definitions used to quantify and study altered renal function. Relatively recent introduction of consensus definitions, such as RIFLE (risk, failure, loss, and end-stage renal failure) criteria and AKIN (Acute Kidney Injury Network) staging, have provided standard definitions to facilitate more uniform outcome reporting. With use of these definitions, recent studies suggest that AKI occurs in up to two thirds of patients in the intensive care unit (ICU). Moreover, increasing severity of AKI is associated with increasing mortality. AKI is also associated with increased morbidity, such as increased hospital length of stay and cost of care, and has been linked to other in-hospital complications, such as increased difficulty in weaning from mechanical ventilation. Preoperative risk factors for development of AKI include older age, emergent surgery, hepatic disease, obesity, high-risk surgery, vascular disease, and chronic obstructive pulmonary disease (COPD). Prompt recognition of AKI facilitates effective treatment. Although the incidence rate of AKI appears to be rising, overall outcomes from AKI are gradually improving.

DEFINITIONS

The RIFLE criteria (Table 1), defined in 2004 by the Acute Dialysis Quality Initiative (ADQI) Group, quantifies the severity of AKI. Studies by Hoste and colleagues and by Osterman and Chang found that mortality progressively increased with increasing RIFLE severity and that patients in all of the RIFLE classifications had higher mortality rates than those in the ICU without AKI.

In 2005, the AKIN also formulated consensus diagnostic criteria for AKI (Table 2). The AKIN definition of AKI is "an abrupt (within 48 hours) reduction in kidney function currently defined as an absolute increase in serum creatinine of either ≥0.3 mg/dL or a percentage increase of ≥50% (1.5-fold from baseline) or a reduction in urine output (documented oliguria of <0.5 mL/kg/hr for >6hrs)." These criteria can only be applied in the face of adequate fluid hydration. The AKIN staging system is arguably more inclusive than the RIFLE criteria. Chertow and associates found that an acute absolute change in creatinine of 0.3 or more was associated with increased mortality, length of stay, and cost of care. Barrantes and colleagues found that patients who met the AKIN definition of AKI were three times as likely to die during hospitalization.

In 2007, Coca and colleagues published a review and meta-analysis of eight studies that suggested that even smaller elevations in serum creatinine values than recommended in RIFLE and AKIN (on the order of 10% to 24%) were associated with a twofold risk of short-term death in several clinical settings; the Coca paper hypothesized that poor outcomes from AKI may in part result from delay in diagnosis caused by the lag time of serum creatinine testing.

DIAGNOSIS OF ACUTE KIDNEY INJURY

Comorbidities and potentially nephrotoxic medications should be identified. Identification of signs and symptoms suggestive of urinary tract obstruction is also important. Although physical examination in critically ill patients with AKI has been shown to be of limited accuracy, ascertaining clinical clues to patients' hemodynamic and volume statuses is essential.

Urinalysis with microscopy is useful in determination of the etiology of AKI. Presence of casts or other cells can suggest etiology. Red cell casts suggest glomerulonephritis or vasculitis, and white cell casts may raise the possibility of interstitial nephritis or pyelonephritis. "Muddy brown" casts and renal tubular epithelial cells are pathognomonic for acute tubular necrosis (ATN) and differentiate ATN from prerenal azotemia, which is characterized by normal sediment or occasional hyaline casts. Dark heme-positive urine without red blood cells (RBCs) on microscopy is diagnostic of rhabdomyolysis.

Distinguishing between prerenal azotemia and ATN, the two most common etiologies of AKI, is critical but not always simple. Aside from analysis of urine sediment, response to fluid repletion is frequently used in this distinction. Return to baseline of renal function in 24 to 72 hours after fluid repletion suggests prerenal etiology. Urine chemistries can also aid in the diagnosis. The fractional excretion of sodium (FeNa) measures the ratio of the sodium excreted to the sodium filtered by the formula:

$$\text{FeNa} = (\text{urine sodium} \times \text{serum creatinine}) / (\text{serum sodium} \times \text{urine creatinine}) \times 100$$

Prerenal azotemia is characterized by FeNa less than 1%, and FeNa more than 1% suggests ATN. However, FeNa may be spuriously low in patients with severe sepsis, heart failure, or cirrhosis, despite the presence of ATN. Conversely, FeNa may be falsely elevated in patients on diuretics, with glucosuria, or with preexisting renal insufficiency. In the case of diuretic use, the fractional excretion of urea (FEurea) has been shown to accurately distinguish between prerenal azotemia and ATN with the following formula:

$$\text{FEurea} = (\text{urine urea nitrogen} \times \text{serum creatinine}) / (\text{BUN} \times \text{urine creatinine}) \times 100$$

with *BUN* for blood urea nitrogen. Prerenal azotemia is indicated by FEurea less than 35% and ATN by FEurea more than 50%. Although of variable utility, other serum and urinary measures may also be used in aggregate to distinguish ATN from prerenal azotemia. These tests are summarized in Table 3, in order of general usefulness.

Serologic tests, such as antinuclear antibody, hepatitis B surface antigen, and antiglomerular basement membrane antibody, are useful for distinguishing the etiology of glomerular diseases. Elevated creatinine phosphokinase levels are seen with rhabdomyolysis.

BUN levels reflect the balance between urea production, metabolism, and excretion and frequently rise as renal function declines. Numerous nonrenal sources of BUN exist, including dietary protein intake, parenteral hyperalimentation therapy, catabolism of endogenous proteins, corticosteroid administration, and upper gastrointestinal bleeding. However, a recent study by Beier and colleagues suggests that elevation of BUN value is predictive of long-term mortality, independently of normal creatinine.

Most clinicians rely on changes in serum creatinine and BUN values as indicators of renal function because they are accessible and familiar. However, BUN and creatinine values can be misleading, as serum creatinine levels are influenced by nonrenal factors such as age, gender, race, body weight, muscle mass, protein intake, and drugs; accordingly, changes in creatinine values tend to lag behind actual alterations in GFR. BUN levels are influenced by nutritional intake and the degree of catabolism, independently of renal function. For

TABLE 1: RIFLE criteria

	S_{Cr} criteria	Urine output criteria
Risk	Increased 1.5×-2× baseline	<0.5 mL/kg/h for 6 h
Injury	Increased 2×-3× baseline	<0.5 mL/kg/h for 12 h
Failure	Increased >3× baseline *or* S_{Cr} >4.0 mg/dL with acute rise ≥0.5 mg/dL	<0.3 mL/kg/h for 24 h *or* Anuria for 12 h
Loss	Persistent renal failure for >4 wk	
ESRD	Persistent renal failure for >3 mo	

ESRD, End-stage renal failure; *RIFLE,* risk, injury, failure, loss, and end-stage renal disease; S_{Cr}, serum creatinine.

TABLE 2: Acute Kidney Injury Network staging system

Stage	S_{Cr} criteria	Urine output criteria
I	Absolute increase ≥0.3 mg/dL *or* Increased 1.5×-2× baseline	<0.5 mL/kg/h for 6 h
II	Increased 2×-3× baseline	<0.5 mL/kg/h for 12 h
III	Increased >3× baseline *or* S_{Cr} ≥4.0 mg/dL with absolute increase ≥0.5 mg/dL *or* Need for RRT	<0.3 mL/kg/h for 24 h *or* Anuria for 12 h

RRT, Renal replacement therapy; S_{Cr}, serum creatinine.

TABLE 3: Diagnostic indices that distinguish prerenal azotemia from acute tubular necrosis

Measurement	Prerenal azotemia	ATN
Urinalysis	Normal or hyaline casts	Muddy brown casts
Response to fluid repletion	Within 24-72 h	No response
FeNa	<1%	>1%
FEurea	<35%	>50%
BUN/creatinine ratio	20	10
Urine sodium (mEq/L)	<20	>30
Urine osmolality (mOsm/L)	>350	300

ATN, Acute tubular necrosis; *BUN,* blood urea nitrogen; *FeNa,* fractional excretion of sodium; *FEurea,* fractional excretion of urea.

these reasons, alternatives to serum creatinine and BUN values serve as more specific markers, earlier indicators, and better prognostic tools for kidney injury.

Belcher and associates reviewed one of the most promising of these markers, interleukin-18 (IL-18). A proinflammatory cytokine thought to be released by injured proximal renal tubules, IL-18 is both a mediator and biomarker of AKI and can be reliably measured in the urine. The authors cite research that identifies IL-18 as an early indicator of AKI, as a tool for distinguishing prerenal azotemia and hepatorenal syndrome (HRS) from ATN, and as a prognostic tool to predict mortality and viability of renal transplant.

Belcher and associates also discuss neutrophil gelatinase-associated lipocalin (NGAL), an acute-phase reactant indicative of inflammatory injury that is upregulated and released by proximal renal tubular cells within a few hours of tubular damage. Like IL-18, studies suggest that NGAL can be used as an early indicator, in the differential diagnosis, and as a prognostic tool for AKI.

Kidney injury molecule 1 (KIM-1) is a type 1 cell membrane glycoprotein only expressed by proximal tubular cells in response to injury. It is detectable in urine and has been shown to discriminate ATN from other causes of AKI and is also used as a prognostic tool, as it predicts outcomes.

Cystatin C is a cysteine protease inhibitor secreted by all nucleated cells and is freely filtered by the glomerulus. Although several studies suggest that serum cystatin C is superior to serum creatinine as a surrogate for GFR and thus better for the early detection of AKI, another study suggests urinary cystatin C may be better.

Liver-type fatty acid–binding protein (L-FABP) is an intracellular molecule found in the proximal renal tubules where it binds lipid peroxidation products. Although urinary levels of L-FABP may be affected by liver injury or systemic inflammation, they are largely determined by tubular injury.

RADIOLOGIC IMAGING

Renal ultrasound scan is an important test to differentiate the etiology of AKI. Use of ultrasound scan to determine kidney size and echogenicity, cortical thickness, and the presence or absence of hydronephrosis is convenient and noninvasive. The presence of a thin rim of decreased echogenicity ("renal sweat") may surround the kidneys in patients with kidney injury. The addition of color Doppler technology may also useful in the diagnosis of AKI. Measurement of the resistivity index (RI), an indicator of perfusion based on

measurement of flow at the level of the arcuate or interlobar arteries, may help differentiate between prerenal azotemia (normal RI), ATN (reduced RI), and postrenal obstruction (elevated RI). Another promising ultrasound technique for the diagnosis of AKI is contrast-enhanced ultrasound scan, which makes use of microbubble-based contrast agents to help quantify renal blood flow, which is often decreased early in the progression of AKI. Ultrasound scan is critical for the diagnosis of hydronephrosis, in which it is more than 95% accurate in detecting dilation of the collecting systems and renal pelvis. A postrenal obstructive cause of AKI is suggested when hydronephrosis is present bilaterally. Assessment of bladder volume with ultrasound scan is important in the case of bilateral hydronephrosis. A postvoid residual volume greater than 150 mL is suggestive of bladder-outlet obstruction, and if it is observed in the presence of a urinary catheter, catheter malfunction should be considered. If ultrasound scan results are negative, computed tomographic (CT) scan may be necessary to elucidate the etiology of obstruction, such as obstructing stones or pelvic mass.

MEDICATION REVIEW

Thorough investigation of medications and ingestions is essential in determining the etiology of AKI. Certain medications can elevate serum creatinine levels without affecting GFR, leading to misdiagnosis of AKI. The drugs cimetidine and trimethoprim do this by blocking tubular creatinine secretion, and several drugs and substances interfere with the creatinine assay. The drug tenofovir disoproxil fumarate, used in the treatment of HIV/AIDS, has been shown to elevate serum creatinine levels without affecting measured GFR by an undefined mechanism.

A number of medications and substances can induce AKI (Table 4). The use of nephrotoxic agents should be limited when possible, especially in the presence of shock and decreased renal blood flow. If AKI is already present, medication doses must be adjusted to avoid toxicity.

DIFFERENTIAL DIAGNOSIS

Prerenal Azotemia

Prerenal azotemia is caused by decreased renal perfusion. This can occur as a result of decreased cardiac output for any reason, an absolute decrease in extracellular fluid volume (i.e., hemorrhage, gastrointestinal losses, burns), a decrease in the effective circulating volume (i.e., heart failure, portal hypertension), or shifting volume out of the intravascular space (i.e., third spacing). Prerenal azotemia is reversible if treated early and aggressively with fluid resuscitation, improvement in cardiac output, or correction of the third-space defect. If untreated, however, hypoperfusion of the kidney leads to tissue ischemia and cell death, resulting in progression to renal injury.

Abdominal compartment syndrome has increasingly been recognized as an important cause of prerenal azotemia. High intraabdominal pressures (>20 mm Hg bladder pressure) result in renal venous hypertension, which can lead to renal hypoperfusion and oliguria. If the condition is detected early, medical management with fluid resuscitation may be effective. However, early decompressive laparotomy is usually necessary for definitive reversal of abdominal compartment syndrome; immediate reversal of prerenal azotemia often results.

TABLE 4: Medications associated with direct and indirect nephrotoxicity

Direct nephrotoxicity				Indirect nephrotoxicity		
ATN	*Osmotic Nephrosis*	*Interstitial Nephritis*	*Glomerular Injury*	*Decrease in Intrarenal Blood Flow*		*Volume Depletion*
Iodinated Contrast	Hypertonic Solutions	NSAIDs	NSAIDs	Crystal Deposition (Intrarenal Obstruction)	Retroperitoneal Fibrosis (Ureteral Obstruction)	Diuretics (Loop, Mannitol, Thiazide)
Aminoglycosides	IVIG	Beta-lactams	Zoledronate	Indinavir	Ergotamine	
Amphotericin B		Quinolones	Pamidronate	Sulfadiazine	Sotalol	
Petamidine		Sulfonamides	Ticlopidine	Sulfamethoxazole	Propranolol	
Foscarnet		Phenytoin	Clopidogrel	Methotrexate	Bromocriptine	
Cisplatinum		Allopurinol	Cyclosporine	High-dose acyclovir		
Acetaminophen		Thiazide and loop diuretics	Gemcitabine			
Cidofovir		Indinavir				
Adefovir		PPIs				
Tenofovir		Vancomycin				
Melphalan						
IVIG						
Hetastarch						
Mannitol						

ATN, Acute tubular necrosis; *IVIG,* intravenous immunoglobulin; *NSAIDs,* nonsteriodal antiinflammatory drugs; *PPIs,* proton pump inhibitors.

Postrenal Azotemia

Postrenal azotemia occurs from obstruction of urinary flow at any point in the urinary tract from the renal collecting system to the level of the urethra. Increased backflow builds pressure and decreases filtration. This type of azotemia can be caused by prostatic disease, neurogenic bladder, obstruction of an in-dwelling urinary catheter, abdominal or pelvic tumors, adhesions from prior surgery or radiation, vesicoureteral reflux, ureteral or bladder stones, medications that cause crystals or fibrosis, or myeloma light chains (in multiple myeloma). The obstruction must be corrected to resolve the azotemia. Complications of postrenal azotemia include urinary tract infection from urinary stasis, hyperkalemia caused by impaired excretion, and rarely, postobstructive diuresis marked by significant diuresis that leads to hypotension.

Intrinsic Renal Disease

Intrinsic renal disease results from injury to the parenchyma of the kidney, including the glomeruli, the interstitium, and the renal tubules.

Glomerular Disease

Glomerular disease is classified as nephritic or nephrotic and can have an acute or insidious onset. Nephritic syndrome is characterized by hematuria, proteinuria, hypertension, and edema from pores in the glomeruli allowing leakage of red blood cells and protein into the urine. Etiologies include bacterial endocarditis, systemic lupus erythematosus (SLE), poststreptococcal glomerulonephritis, hepatitis B antigenemia, immunoglobulin A (IgA) nephropathy, and hepatorenal syndrome.

The hallmark of nephrotic syndrome is marked proteinuria with minimal hematuria and anasarca. Frequently, the diagnosis of nephrotic syndrome requires renal biopsy. Etiologies include minimal change disease (MCD), focal segmental glomerulosclerosis, and membranous nephropathy.

Interstitial Disease

Many conditions that affect the renal interstitium have been recognized, including allergic, drug-induced, infectious (bacterial, viral, fungal, parasitic), autoimmune (SLE, Sjögren's disease, Goodpasture syndrome), infiltrative (lymphoma, sarcoid), and idiopathic forms of disease. The most common etiology of acute interstitial nephritis (AIN) is a drug-induced disease; it is thought to underlie 60% to 70% of cases. Illicit drugs, penicillins, cephalosporins, sulfonamides, and nonsteroidal antiinflammatory drugs (NSAIDs) are some of the most common offenders. AIN can cause fever, rash, eosinophilia, and eosinophiluria; however, none of these are reliably diagnostic. Kidney biopsy is the gold standard of diagnosis but is rarely needed. Timely discontinuation of the offending agent is usually effective treatment. The use of steroids in drug-induced AIN is controversial, but a recent study suggests that early administration of steroids (within 2 weeks) may prevent long-term sequelae.

Hyperuricemia, hyperuricosuria, and hyperphosphatemia, seen in tumor lysis syndrome, can cause deposits of crystals in the renal interstitium and tubules, leading to AKI. Similarly, ingestion of oral sodium phosphate solutions in bowel preparations for colonoscopy has been recognized as a cause of AKI resulting from crystal deposition. Allopurinol and rasburicase have been used for the prevention and treatment of tumor lysis syndrome.

Tubular Disease

Acute tubular necrosis was originally thought to be caused by a period of ischemia followed by reperfusion causing extensive necrosis. More recently, investigators have clarified the role of endothelial dysfunction, systemic inflammatory mediators, and oxidative stress in causing AKI. With this in mind, the term ATN currently is more often used to describe a clinical situation with adequate renal perfusion to largely maintain tubular integrity but not enough to sustain glomerular filtration. This is particularly true in the case of sepsis and shock of any etiology.

ATN is also caused by toxins, most commonly the aminoglycoside antibiotics. Other toxins that cause ATN include platinum, antifungals, rhabdomyolysis, hemolysis, and radiographic contrast, to highlight a few (see Table 4). Risk factors for ATN include volume contraction, age, and concomitant use of other nephrotoxins. Prevention of ATN is focused on achieving euvolemia while maintaining renal perfusion and avoiding further renal insults.

Rhabdomyolysis is caused by massive breakdown of muscle, with release of myoglobin, which can result in ATN. Rhabdomyolysis can be precipitated by drugs (heroin, cocaine, statins, alcohol), multiple trauma, crush injuries, seizures, muscle compression, and extreme exertion.

Contrast-induced nephropathy (CIN) is an acute decline in renal function seen after administration of intravenous radiographic contrast, specifically, an increase in serum creatinine of 25% above baseline or absolute increase of 0.5 mg/dL within 48 hours after administration of parenteral contrast. Although not well understood, it is likely the result of several factors. Transient hypotension from osmotic diuresis, vasoconstriction of glomerular vessels, and direct cytotoxic effect have been hypothesized. CIN is the third most common cause of hospital-acquired renal injury and is most prevalent among those with underlying renal disease.

Nephrogenic systemic fibrosis (NSF) is a recently diagnosed disease that occurs in patients with preexisting stage IV and V chronic kidney disease or acute renal failure that has been linked to intravenous administration of gadolinium-based contrast media for magnetic resonance imaging (MRI). Shortly after exposure to gadolinium (2 to 12 weeks) patients have development of skin thickening and fibrosis, similar to scleroderma, and can have rapid progression to joint contractures and severe disability. Systemic involvement may occur, leading to cardiomyopathy, pulmonary fibrosis, pulmonary hypertension, diaphragmatic paralysis, and death. The pathophysiology of the disease still remains unclear, but recent studies have shown gadolinium deposits in tissues of patients diagnosed with nephrogenic systemic fibrosis. Currently, prevention of NSF entails avoidance of gadolinium administration in this population. Several treatment options (steroids, intravenous immunoglobulin [IVIG], ultraviolet light, renal transplant) have been studied and have some benefit, but the evidence is based on small case studies or case reports and further evaluation is needed.

RENAL PROTECTIVE STRATEGIES

Prevention of Contrast-Induced Nephropathy

Contrast-induced nephropathy has historically been a common cause of AKI. Low-volume nonionic low-osmolar or isoosmolar contrast media are now clearly associated with a significantly lower incidence of CIN than high-osmolar agents that were commonly used in the past. For this reason, older high-osmolar contrast agents should be avoided.

Volume expansion is the primary prevention of CIN. Patients who receive fluid administration before radiologic studies have a lower incidence of nephropathy. However, the optimal choice of fluid has been controversial. Several meta-analyses of isotonic sodium bicarbonate show benefit over isotonic saline solution; however, a recent randomized controlled trial (RCT) suggested no difference between the two fluids, both of which were beneficial in preventing CIN.

N-acetylcysteine (NAC) is a free radical scavenger that has been shown in some studies to decrease the incidence of CIN compared with both placebo and saline solution alone. However, more recent studies showed no benefit to NAC in the prevention of CIN. Despite an unproven benefit, because it is safe and inexpensive, NAC is often used as part of a preventive regimen, in addition to volume expansion.

Other Preventive Strategies

The most important priority in renal protection is to maintain renal perfusion. Fluid choice, specifically crystalloid or colloid, for this purpose has been controversial. The landmark SAFE (Saline versus Albumin Fluid Evaluation) study compared saline solution and albumin and found no differences in the need for dialysis or survival between the two groups.

The use of synthetic colloids for volume expansion has been questioned because of studies implicating an increased risk of renal dysfunction. An increased risk of AKI was shown by a recent systematic review of the use of hydroxyethyl starches in patients with sepsis.

When fluid resuscitation is administered in critically ill patients, the amount given is of paramount importance. In general, early and aggressive fluid resuscitation has been associated with a lower incidence of AKI and better survival, particularly after trauma and sepsis. However, an observational study in patients with AKI reported increased mortality associated with a positive fluid balance, and an RCT in patients with acute lung injury reported fewer ventilator days with conservative fluid management, which did not increase the need for renal replacement therapy (RRT). The likely explanation for these conflicting results is that the need for fluid therapy changes during the time course of shock, with aggressive fluid administration essential in early prevention and resuscitation and more measured fluid administration optimal later in the course of AKI.

Erythropoietin (EPO) has shown some promising nonerythropoietic properties, including tissue protection and antiapoptotic effect in animal models of brain, heart, and kidney. Despite preclinical data that show protective effects in AKI, the EARLYARF (early acute renal failure) RCT in humans did not show benefit in EPO administration. However, proponents of EPO cite the use of poorly validated biomarkers, among other flaws in study design that may have been responsible for the apparent failure.

The use of diuretics, such as mannitol and furosemide, in the prevention and treatment of AKI has not been found to shorten the duration of AKI, reduce the need for RRT, or improve overall outcomes. Mannitol has proven beneficial in preventing ATN in patients after renal transplant and after severe crush injury. In a recent study, high-dose furosemide showed a protective effect on mortality in patients with acute lung injury but no significant effect after adjustment for post-AKI fluid balance.

Atrial natriuretic peptide (ANP) dilates afferent glomerular arterioles and constricts efferent glomerular arterioles and may selectively increase GFR. It has also been reported to inhibit agents that reduce renal blood flow. Although a recent RCT shows promising results in reducing the need for dialysis in cardiac surgery patients, prior studies did not show any benefit of ANP. Further studies are needed before its use can be recommended.

Dopamine at low doses increases renal perfusion and GFR; for this reason, dopamine has been evaluated for its role in renal protective strategies. Despite numerous studies on this subject, none have yielded evidence to support the usefulness of dopamine in AKI.

Fenoldopam, a dopamine-1 receptor agonist used in hypertensive emergencies, has been shown at its lowest dose to increase renal blood flow. In a recent meta-analysis of 16 randomized trials in critically ill patients with AKI, fenoldopam appears to reduce both mortality and need for RRT.

A promising study by Heemskerk and associates reports a significant decrease in plasma creatinine after an infusion of alkaline phosphatase (AP) in patients in intensive care with severe sepsis or septic shock. The authors propose that exogenous AP attenuates production of nitric oxide (NO), a systemic vasodilator that causes compensatory renal vasoconstriction, by inhibiting inducible nitric oxide synthase (iNOS), an enzyme that catalyzes production of NO. Reduction in NO may protect renal function; however, larger trials are needed to determine the presence of morbidity or mortality benefit.

Other agents evaluated for potential use in prevention of CIN or ATN include theophylline and prostaglandin E1. Both have shown promising but conflicting results; further study is needed before their use is recommended.

TREATMENT

Both hyperglycemia and hypoglycemia during the perioperative period or during critical illness correlate with adverse renal outcomes. Several studies suggest that aggressive glucose control is associated with decreased incidence of AKI and reduced need for RRT and may be protective of renal function in critically ill surgical patients. However, the largest and most recent RCT that compared intensive insulin therapy with conventional glucose control found no difference in need for RRT. Lung protective ventilation has become a mainstay in the treatment of adult respiratory distress syndrome (ARDS) as a result of the ARDSnet trial, which also suggested that the low-volume ventilation may be beneficial for the kidney as well. High-volume and high-pressure ventilation have been reported to contribute to AKI.

Renal Replacement Therapy

RRT remains the mainstay for treatment of severe AKI. Approximately 4% of critically ill patients with development of AKI go on to need RRT. However, consensus on best practice in regards to initiation, dose, and modality of RRT has not been established.

Timing of Initiation of Renal Replacement Therapy

Accepted indications for initiation of dialysis include severe acidemia, severe hyperkalemia, ingestion of a dialyzable substance that causes renal injury, volume overload in the presence of oliguria, and clinically apparent signs of uremia. Evidence suggests that there is benefit to early initiation of RRT in AKI; however, the literature is confounded by variable definitions of early and late, and differing indications for initiation of RRT. Continued studies are needed to further define when RRT is best initiated.

Frequency and Rate of Renal Replacement Therapy

Currently, wide variations are found in clinical practice in the frequency of RRT. Current studies have conflicting conclusions. A multicenter trial that studied outcomes related to dose of renal support was the Acute Renal Failure Trial Network (ATN) Study. This study assigned patients with hemodynamically stable conditions to the intermittent hemodialysis (IHD) group and patients with hemodynamically unstable conditions to continuous renal replacement modalities. The intensive management strategy underwent IHD 6 times per week or continuous therapy at 35 mL/kg/h. The less intense management strategy underwent IHD 3 times per week or continuous therapy at 20 mL/kg/h. No significant differences were seen between treatment groups in 60-day survival or renal recovery. To date, studies have not defined best practice guidelines for the frequency of RRT.

Modalities for Renal Replacement Therapy

Peritoneal dialysis (PD) is a simple but limited method for clearance of solute and ultrafiltration. Patients must have intact peritoneal cavities for PD to be effective, which is often not the case in critically ill surgical patients. PD has the advantage of being well tolerated hemodynamically, but the dialysate fluid increases intraabdominal pressure and thus can compromise respiratory status. Nonetheless, PD remains a useful option for selected patients with AKI.

Ultrafiltration (UF) is a technique that allows rapid removal of volume without significant solute removal. The ability to regulate the rate of UF allows titration to maintain intravascular volume and therefore maintain hemodynamic stability. UF has the primary application of treating volume overload in the presence of oliguria.

IHD is the most frequently used method for RRT in the United States. This method uses a semipermeable biocompatible synthetic membrane and an electrochemical gradient maintained with continuous dialysate flow to remove solute. The major benefit of IHD is rapid removal of solute. However, intravascular volume removal is frequently limited by hypotension. Another frequent drawback is hypoxia during treatment.

Continuous renal replacement therapies (CRRTs) are the most common methods for RRT internationally but are used less frequently in the United States. Continuous therapies use hemofiltration, a technique that, like ultrafiltration, removes volume but also has equal removal of solute as a result of the high permeability of the membrane used. In this case, solute clearance is dependent on volume filtered, and because the volume filtered is substantial, replacement fluid is infused continuously to avoid hemodynamic instability. Hemodiafiltration adds a dialysate flow to supplement hemofiltration clearance. Whether this addition adds benefit to hemofiltration alone is unclear.

Continuous venovenous hemofiltration (CVVH) and continuous venovenous hemodiafiltration (CVVHDF) are two frequently used methods of CRRT that have been evaluated and compared with IHD. These continuous methods were initially thought to be safer for patients with hemodynamically unstable conditions and more physiologic and thus better for the critically ill. However, studies to determine the optimal method of RRT have yielded contradictory results. In a recent meta-analysis of nine randomized trials, Bagshaw and colleagues found no difference in mortality or renal recovery between continuous and intermittent modalities.

Hybrid therapies also exist but have not yet been evaluated by prospective randomized trials. The most common hybrid modality is slow low-efficiency dialysis (SLED). SLED is a technique that is based on the observation that slower flow and longer treatments of IHD improve hemodynamic stability. SLED is sometimes performed over 8 to 12 hours nightly, avoiding typical daytime interruptions (procedures, radiology, surgery) and allowing for daytime mobilization.

Currently, many questions regarding the optimal choices for RRT remain unanswered; there are no evidence-based best practice guidelines. However, RRT clearly plays an essential role in the support of patients with AKI. A variety of techniques are available, all of which appear to be effective. RRT therapy should currently be selected based on institutional experience and expertise, and individual patient tolerance.

PROGNOSIS

The reported mortality rate of AKI is 30% to 60%. If RRT is necessary, reported mortality rates are over 50%. The reason for such high mortality is that AKI now usually occurs as part of a spectrum of multiple organ failure, most often associated with severe sepsis or septic shock. The mortality in this setting is often determined by the underlying septic syndrome, rather than by complications of individual organ failure. Of surviving patients of AKI, a significant number have development of chronic renal insufficiency, which necessitates chronic dialysis. The precise rate of development of chronic renal failure varies greatly in the literature, depending on the patient populations. A recent review of AKI estimates that overall, the risk of necessary chronic dialysis is approximately 12%.

SUGGESTED READINGS

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