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Acute Kidney Injury: Quoi de Neuf?

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ABSTRACT

Background: Acute kidney injury (AKI) is frequently encountered in the nephrology practice. Serum creatinine, with its many shortcomings, is still the main biomarker used to detect AKI.

Methods: This review focuses on recent advances in definition, diagnosis, risk factors, and molecular mechanisms of AKI. In addition, specific AKI syndromes such as contrast-induced AKI, hepatorenal syndrome, and acute decompensated heart failure are discussed. The connection between AKI and subsequent chronic kidney disease and recent developments in renal replacement therapy are also covered.

Results: Novel biomarkers such as cystatin C and neutrophil gelatinase–associated lipocalin (NGAL) are being investigated to replace serum creatinine in the detection of AKI. Recent studies suggest that intravenous (IV) fluid use is beneficial for the prevention of contrast-induced AKI, while N-acetylcysteine use is not as well established. Diuretics are clearly beneficial in the treatment of acute decompensated heart failure. Ultrafiltration is less promising and can lead to adverse side effects. Although terlipressin use in hepatorenal syndrome is associated with reduced mortality, it is not available in the United States; combination therapy with midodrine, octreotide, and albumin provides an alternative. Fluid resuscitation is frequently used in critically ill patients with AKI; however, overly aggressive fluid resuscitation is frequently associated with an increased risk of mortality. A 3-step approach that combines guided fluid resuscitation, establishment of an even fluid balance, and an appropriate rate of fluid removal may be beneficial. If fluid resuscitation is needed, crystalloid solutions are preferred over hetastarch solutions. Renal replacement therapy is the last resort in AKI treatment, and timing, modality, and dosing are discussed. Research suggests that AKI leads to an increased incidence of subsequent chronic kidney disease. However, this relationship has not been fully established and additional studies are needed for clarification.

Conclusion: Despite major advances in AKI research, serum creatinine remains the major biomarker for the detection of AKI. The following interventions have shown to be beneficial: IV fluids for contrast-induced AKI; diuretics for acute decompensated heart failure/cardiorenal syndrome; and combination therapy with midodrine, octreotide, and albumin for hepatorenal syndrome. Fluid resuscitation in a patient with AKI should be used with caution because too liberal use of fluids can be associated with increased mortality. AKI appears to be related to increased rates of subsequent chronic kidney disease, and patients with AKI should therefore be monitored closely. Recent studies on renal replacement therapy have neither revealed an optimal timing for initiation of dialysis nor a clear advantage for a specific dialysis modality.

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INTRODUCTION

Acute kidney injury (AKI), a rise in serum creatinine that occurs within hours to days, is frequently encountered in the nephrology practice and is traditionally divided into 3 categories: prerenal, intrinsic, and postrenal.[1,2]

Prerenal disease is usually seen in the context of decreased blood delivery to the kidneys. Severe diarrhea, decreased oral intake for prolonged periods, shock, and acute hemorrhage are examples of prerenal disease. In addition, disruption of renal vascular regulation via nonsteroidal antiinflammatory drugs, iodinated contrast, and acute calcineurin-inhibitor toxicity via vasoconstriction of the afferent glomerular arteriole can also lead to prerenal kidney injury.[1]

Intrinsic renal disease can be further divided into vascular, glomerular, interstitial, and tubular subcategories. Thrombotic thrombocytopenic purpura, nephrotic syndrome, acute interstitial nephritis, and acute tubular necrosis (ATN) are examples of intrinsic renal disease, as is multiple myeloma via tubular injury from excess light chains.[1]

Table. Definition of Acute Kidney Injury According to Kidney Disease Improving Global Outcomes Guidelines[4]

Stage	Serum Creatinine Increase	Urinary Output
1	1.5-1.9 × baseline in up to 7 days or ≥0.3 mg/dL in <48 hours	<0.5 mL/kg/h for 6-12 hours
2	2-2.9 × baseline	<0.5 mL/kg/h for ≥12 hours
3	3 × baseline or increase in serum creatinine ≥4 mg/dL or initiation of renal replacement therapy or in patients <18 years, decrease in eGFR to <35 mL/min per 1.73 m^2	<0.5 mL/kg/h for ≥24 hours or anuria ≥12 hours

eGFR, estimated glomerular filtration rate.

Postrenal or obstructive disease is most frequently caused by prostatic disease (hyperplasia or cancer) and metastatic cancer.[1]

According to a recent study, the most frequent causes of AKI in the hospital setting include ATN, prerenal disease, acute on chronic disease, and obstruction.[3] Other causes are much less frequently represented.

Common presenting symptoms for patients with AKI include volume depletion (diarrhea, vomiting, decreased oral intake), shock, anuria, edema, and unilateral flank pain. However, patients can also present without any clear signs of renal insufficiency, and laboratory evaluation is needed to reveal AKI.[1]

Once kidney disease has been discovered, a comprehensive history, medication review, and physical examination likely will indicate the underlying cause. In addition, laboratory tests for serum creatinine, urinalysis, and protein/creatinine are needed.

A renal ultrasound is done if the evaluation suggests obstruction. Serologies are usually ordered for patients who have nephritic or nephrotic glomerular disease. Indications for renal biopsy include nephritic syndrome, nephrotic syndrome, rapidly progressive glomerular nephritis, and unexplained AKI.[1]

I would like to emphasize that this review is not complete and many AKI entities are not covered (for further details, see reference 1). I also would like to apologize to all my colleagues whose important publications could not be cited because of space limitations. Rather, I focus on recent advances in definition, diagnosis, risk factors, and fluid management in AKI. In addition, updates on specific AKI syndromes, information about studies that investigated a possible relationship between AKI and chronic kidney disease (CKD), recent work on the molecular biology of ATN, and a discussion of renal replacement therapy (RRT) are covered in this review.

DEFINITION OF AKI

In 2012, the Kidney Disease Improving Global Outcomes (KDIGO)[4] organization published new guidelines for the definition of AKI (Table) that simplify past definitions and unify the previously used Acute Kidney Injury Network (AKIN) and Risk, Injury, Failure, Loss of Kidney Function, and End-Stage Kidney Disease (RIFLE) guidelines.[5,6] According to the KDIGO system, AKI stage 1 is defined as either an increase of serum creatinine ≥0.3 mg/dL occurring in <48 hours or a 1.5-fold increase in the baseline creatinine in <7 days.

Whether this new system will offer advantages over previous systems remains to be seen, but the criteria have several drawbacks.

First, the KDIGO urine output criteria cannot be applied to morbidly obese patients. A urine output of 75 mL/h in a patient weighing 150 kg can hardly be considered AKI; however, this patient would qualify as having AKI according to the guidelines.

Second, the KDIGO definition of AKI relies on a baseline creatinine level, but baseline levels are frequently unavailable. Using a baseline creatinine value that corresponds to a normal glomerular filtration rate (GFR) of about 75 mL/min per 1.73 m^2 would likely lead to frequent overestimation of AKI, as pointed out by Pickering and Endre.[7] A possible solution to this problem would be to perform several creatinine clearance measurements, separated by 4-6 hours, to obtain a better estimate of the real-time renal function.[8]

Third, using creatinine as a biomarker for AKI has shortcomings. The detection of AKI in the perioperative setting is frequently impeded by a dilutional effect that is the result of fluid/volume overload, and as a result, a dilutional decrease in the creatinine level is often seen after surgical intervention. Englberger et al and Ho et al found that using the AKIN guidelines to detect AKI (increase of creatinine by ≥0.3 mg/dL in <48 hours) often provided misleading results because the creatinine increases were not caused by genuine AKI but rather by rebound increases from dilutional values.[9,10] By the same token, the dilutional decrease in the creatinine levels can mask genuine AKI events, leading to a delayed detection of AKI.

To avoid these misleading results, the following

formulas were developed to correct serum creatinine levels for volume overload:[11,12]

$$\text{Adjusted serum creatinine} = \text{serum creatinine} \times \text{correction factor}$$

$$\text{Correction factor} = [\text{hospital admission weight (kg)} \times 0.6] + \Sigma[\text{daily cumulative fluid balance (liter)}]/[\text{hospital admission weight (kg)} \times 0.6]$$

Initial studies suggest that application of the formula leads to improved AKI detection.[11]

NEW BIOMARKERS AND RENAL ULTRASOUND IN THE PREDICTION AND DIAGNOSIS OF AKI

The accuracy of using serum creatinine to predict AKI is severely limited because kidney injury occurs before creatinine levels rise. Because of this disadvantage, new biomarkers have been studied that may lead to an earlier detection of AKI.

Preoperative cystatin C has been shown to be a better predictor of AKI in patients undergoing cardiac surgery than serum creatinine or creatinine-based estimated GFR (eGFR).[13] Preoperative urinary protein/creatinine is also predictive of perioperative AKI in adults.[14] In addition, the biomarkers urine neutrophil gelatinase-associated lipocalin (NGAL), plasma NGAL, and urine interleukin-18 (IL-18) are associated with both the development of AKI and poor outcomes in adult patients who have had cardiac surgery.[15]

Similar results have been observed in the emergency room setting. Nickolas et al[16] observed that among several biomarkers measured at hospital admission, urinary NGAL performed best as a predictor of intrinsic AKI. Urinary concentrations of IL-18, cystatin C, kidney injury molecule 1 (KIM 1), and liver-type fatty acid binding protein were also predictive of intrinsic AKI.

An interesting observation in the Nickolas et al study is that the combined use of serum creatinine with biomarkers of renal damage, such as NGAL, potentially can be used to differentiate between CKD, ATN, and prerenal azotemia. Higher levels of NGAL are associated with progression to more severe AKI and the requirement for dialysis.

The use of novel biomarkers in the intensive care setting has been less promising. A 2011 report by de Geus et al showed that using NGAL to predict AKI produced results similar to using serum-creatinine derived eGFR.[17]

Although biomarker use is largely experimental, renal ultrasound is frequently used in the workup of AKI patients. To avoid unnecessary ultrasound procedures, Licurse et al developed a risk-stratification protocol that uses 7 factors to identify low-risk patients who may not require an ultrasound.[18] According to their results, 32 members of this low-risk population would have to be evaluated to identify 1 case of hydronephrosis, and 223 members would have to be screened to detect 1 case of hydronephrosis that warrants subsequent intervention. The authors suggest that substantial cost savings can be realized through using their risk-stratification protocol.

NOVEL RISK FACTORS FOR AKI

Recent studies have identified several novel risk factors for the development of AKI. Soto et al implicated body mass index (BMI) as a risk factor.[19] They showed that in patients with acute respiratory distress syndrome, obesity is linked to an increased risk of AKI that cannot be explained by shock or severity of illness. Another connection between AKI and BMI was found in the observational cohort study by Plataki et al.[20]

Proteinuria is also a risk factor for AKI.[21] Initial publications revealed a connection between dialysis-requiring AKI and proteinuria,[22] and recent studies have extended this observation: even low-grade proteinuria is associated with an increased risk of developing AKI.[23]

In the Veterans Affairs Nephropathy in Diabetes trial, patients with type 2 diabetes who had macroalbuminuria and an eGFR of 30.0-89.9 mL/min per 1.73 m^2 of body surface area received an angiotensin receptor blocker (ARB) (losartan) with or without an angiotensin-converting enzyme (ACE) inhibitor (lisinopril).[24] Although ARB/ACE inhibitor combination therapy led to improved blood pressure control and a more pronounced decrease in albuminuria than monotherapy, these protective effects were outweighed by increased levels of hyperkalemia and acute renal injury, and the trial was terminated prematurely.

CONTRAST-INDUCED AKI

Contrast-induced AKI (CI-AKI) is a common complication of many diagnostic and therapeutic procedures and can lead to prerenal impairment, as well as ATN. The latest KDIGO guidelines recommend the use of intravenous (IV) fluids, either sodium bicarbonate or isotonic sodium chloride, for the prevention of CI-AKI based on level 1A evidence (strong recommendation with high quality of evidence).[4] In addition, KDIGO suggests the use of oral N-acetylcysteine (NAC) with isotonic IV fluids based on level 2D evidence (weak recommendation with very low quality of evidence).[4] Although no good evidence supports the use of NAC, we routinely use both IV fluids and NAC in the prevention of CI-AKI. On

the other hand, in the Acetylcysteine for the Prevention of Contrast-Induced Nephropathy trial, which was not included in the KDIGO guidelines, 2,308 patients were given either NAC or placebo the day before and the day after their angiogram.[25] No difference was seen in the development of AKI (defined as a >25% increase of creatinine above baseline within 48-96 hours after angiography) between the NAC group and the placebo group. Despite this negative outcome, the prevention of CI-AKI by NAC warrants additional studies.

Using forced diuresis to prevent CI-AKI has been the subject of many studies. This approach combines the use of diuretics to maintain increased urinary output with crystalloid solutions to maintain euvolemia. KDIGO guidelines recommend against the use of diuretics in the prevention of CI-AKI.[4] However, 2 recent studies have investigated the benefits of forced diuresis using the RenalGuard system (PLC Medical Systems, Inc.), a fluid-management device that tries to minimize the development of volume depletion by balancing fluid replacement and diuretic-induced volume loss. In both trials, forced diuresis and matched volume replacement led to a decreased incidence of CI-AKI.[26,27] Nevertheless, a number of issues limit the universal application of the RenalGuard system. For example, volume overload and hypokalemia may develop in vulnerable patients.

Statins have properties that make them attractive candidates for the study of CI-AKI prevention: they improve endothelial function and reduce inflammation and oxidative stress. Several observational and small randomized trials have suggested that statin use may be beneficial in the prevention of CI-AKI.[28,29] However, a randomized trial with 304 patients showed no benefit of atorvastatin compared with placebo.[30] Because statin-related trials are limited and have led to conflicting data, the use of statins in the prevention of CI-AKI may be premature.

CONGESTIVE HEART FAILURE AND THE CARDIORENAL SYNDROME

Diuretic therapy is a mainstay in the treatment of acute decompensated heart failure (ADHF), and studies have compared the effect of continuous vs bolus use. A metaanalysis conducted by Salvador et al analyzed the use of continuous diuretic infusion and compared it to bolus diuretic administration in 221 patients with ADHF.[31] Although continuous infusion led to increased fluid removal and less tinnitus compared to the bolus infusion, the study was not large enough to provide any data on renal safety or survival benefits.

In the Diuretics Optimization Strategies Evaluation trial, a prospective, double-blind, placebo-controlled, randomized study, 308 patients with ADHF were randomly assigned to receive intravenously administered furosemide either via bolus or continuous infusion.[32] The data showed no significant difference between the 2 regimens in terms of efficacy (global assessment of symptoms over 72 hours) or safety (change in serum creatinine from baseline). Overall, no trials in patients with ADHF clearly favor continuous diuretic infusion over bolus therapy or vice versa.

Vaptans, a family of vasopressin receptor 2 inhibitors, have been studied extensively in the treatment of ADHF. These compounds, in contrast to traditional diuretics, induce a free water diuresis that makes them ideal drugs for the treatment of ADHF with hyponatremia. The large Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan trial investigated the effect of tolvaptan in 4,133 patients who were hospitalized for ADHF. Patients were randomly assigned to treatment with tolvaptan vs placebo for a minimum of 60 days. Although tolvaptan use resulted in greater weight loss and improvement of dyspnea, no difference in all-cause mortality was seen after a follow-up of 10 months.[33,34]

Ultrafiltration is frequently used in the clinical setting to treat patients with ADHF who are developing renal insufficiency or patients who are resistant to diuretic therapy. The efficacy of ultrafiltration has been studied in randomized trials.

The Ultrafiltration vs Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure trial randomly assigned 200 patients with ADHF to ultrafiltration or IV diuretic therapy.[35] Renal dysfunction was not an entry criterion, making this group of ADHF patients a rather heterogeneous population. Patients in the ultrafiltration arm had much greater fluid loss after 48 hours and fewer heart failure readmissions after 90 days than patients assigned to the diuretics arm. Although the rates of adverse events were similar in both groups, no significant difference was seen in serum creatinine increases.

The Cardiorenal Rescue Study in Acute Decompensated Heart Failure trial studied 188 patients with ADHF, worsened renal function, and persistent congestion.[36] The patients were randomly assigned to either ultrafiltration or a stepped pharmacological therapy that included an IV diuretic plus selective use of inotrope and vasodilator therapy. The pharmacological regimen was superior to ultrafiltration and was associated with a decrease in serum creatinine. In contrast, the ultrafiltration group showed an increase in serum creatinine. Although no significant difference in weight loss at 96 hours was seen between the 2 groups, the rate of adverse events (heart failure, renal

failure, and sepsis) was significantly higher in the ultrafiltration group. Because of this outcome, trial enrollment was halted early.

In summary, ultrafiltration was inferior to pharmacological treatment in patients with ADHF and renal impairment and was associated with a higher rate of adverse effects. Ultrafiltration should be reserved for patients who are resistant to diuretic therapy.

HEPATORENAL SYNDROME

Hepatorenal syndrome (HRS) is characterized by a progressive increase in serum creatinine level, minimal proteinuria (<500 mg/d), a low rate of sodium excretion (urine sodium often <10 mEq/L), oliguria, and an often normal urine sediment.[1]

Two types of HRS have been described. Type 1 HRS is defined by a more than 2-fold increase in serum creatinine to a level >2.5 mg/dL in <2 weeks. It often develops after a trigger event (eg, infection) and has an associated median survival of <2 weeks if no treatment is initiated. Type 2 HRS is defined as renal impairment that is less severe than type 1. It is often seen in refractory ascites and is associated with a median survival of 4-6 months if no treatment is initiated.[1]

Previous definitions of AKI in cirrhosis lacked standardization and sensitivity and were limited to narrow clinical settings. These shortcomings are further complicated by the fact that using serum creatinine to estimate GFR is likely to result in an overestimation because cirrhotic patients frequently have reduced creatinine production rates or reduced muscle mass. To overcome these shortcomings, new AKI definitions have been developed. Supposedly, a better AKI definition in cirrhotic patients should lead to earlier detection of AKI and initiation of therapy at an earlier phase.

Several groups have studied the use of the AKIN classification[5] to better define AKI in patients with liver disease. Belcher et al conducted a multicenter, prospective observational cohort study of patients with liver cirrhosis and associated AKI.[37] The authors used the AKIN definition system for AKI and showed that AKI in cirrhosis frequently progresses to a worse stage of renal insufficiency. Tsien et al determined the prevalence and outcomes of AKI as defined by the AKIN classification.[38] They found that cirrhotic patients with AKI had an increased mortality rate compared to cirrhotic patients without AKI. A similar correlation was found by de Carvalho et al.[39] These studies suggest that the AKIN classification is able to detect early AKI in cirrhotic patients. These patients frequently progress to a worse stage of renal insufficiency and are associated with increased mortality rates.

In 2012, Gluud et al published an updated Cochrane metaanalysis that evaluates the results of terlipressin treatment in HRS.[40] Their review revealed that terlipressin reduced mortality compared with albumin alone or no therapy. In addition, terlipressin increased the number of patients who achieved reversal of HRS (defined as achieving a serum creatinine <1.5 mg/dL in most reviewed trials). Although terlipressin did not increase the risk of gastrointestinal side effects, it was associated with an increased rate of cardiovascular adverse events. Altogether, these studies suggest that terlipressin may lead to improved kidney function and reduced mortality. Terlipressin is not available in the United States, but combination therapy with midodrine, octreotide, and albumin provides an alternative.[41]

FLUID REPLACEMENT STRATEGIES

Fluid resuscitation is a common practice in critically ill patients. However, overly aggressive fluid replacement is often deleterious and associated with an increased risk of mortality, as demonstrated in 2 studies published in 2011. Maitland et al performed a randomized trial with children in Africa who suffered from shock and life-threatening infections.[42] The trial was stopped early because fluid resuscitation with albumin or saline was associated with increased 48-hour mortality in children with impaired perfusion. Boyd et al investigated the effects of a positive fluid balance in adult patients with septic shock both early in resuscitation and after 4 days.[43] The authors found that a strongly positive fluid balance is associated with increased risk of mortality. However, best survival in these patients was seen with a moderately positive fluid balance of approximately 3 liters at 12 hours. Three studies published in 2012 investigated fluid management in dialysis-requiring AKI in adults.[44-46] All 3 studies demonstrated that positive fluid balance is associated with an increased risk of death. Altogether, these analyses suggest that positive fluid balance may be deleterious in sepsis as well as in AKI and should be dealt with promptly.

Although volume resuscitation might be required to maintain cardiac output, the resultant fluid accumulation can considerably contribute to organ dysfunction, particularly in patients with AKI. To resolve this dilemma, a new fluid management protocol has been proposed.[47] This protocol relies on a 3-step approach that involves guided fluid resuscitation, establishment of an even fluid balance, and an appropriate rate of fluid removal.

With regard to fluid preparations, previous studies that evaluated the use of hetastarch (HES) documented an increased risk of AKI in septic patients who were treated with HES.[2] These findings have been corroborated by more recent large-scale trials. The

Scandinavian Starch for Severe Sepsis/Septic Shock trial revealed that HES use is linked to an increased risk of mortality, as well as the need for RRT.[48] A large clinical trial randomized about 7,000 critically ill patients to receive HES or normal saline.[49] Although no difference in mortality was seen between the 2 groups, the rate of RRT was higher in the HES group. These studies suggest that HES-containing fluids should be avoided for fluid resuscitation because of associated adverse events such as AKI.

Finally, some investigations indicate that certain types of crystalloid solutions may be beneficial when used in fluid resuscitation. Animal studies suggest that hyperchloremia can lead to vasoconstriction and a concomitant decrease in GFR.[50] This observation has prompted investigators to compare chloride-rich to chloride-poor solutions in fluid resuscitation studies. Yunos et al reported that chloride-poor solutions such as Plasma-Lyte 148 (Baxter), when compared to chloride-rich solutions such as normal saline, led to a reduction in the peak rise of creatinine, as well as a reduction in the incidence of AKI requiring RRT.[51] However, the study was not randomized, and randomized clinical trials are needed to confirm these interesting results.

CONNECTION BETWEEN AKI AND CKD

In the past few years, a number of reports on the long-term consequences of AKI have been published. Some of these studies suggest that AKI is associated with an increased risk of developing CKD and end-stage renal disease (ESRD).[52,53] A metaanalysis by Coca et al found that in patients with AKI, the incidences of CKD and ESRD were 25.8 per 100 person-years and 8.6 per 100 person-years, respectively.[54] More severe AKI and repeated episodes were, not surprisingly, associated with an increased risk.[54,55] Even recovered AKI (defined as a 50% rise in creatinine from baseline and subsequent recovery within 3 months to within 10% of baseline eGFR) is associated with an increased risk of developing CKD.[56] Given these observations, follow-up of patients after AKI is critical. KDIGO recommends evaluating patients 3 months after AKI for resolution, new onset, or worsening of preexisting CKD.[4] In contrast, data from the United States Renal Data System indicate that only 13.2% of patients with AKI saw a nephrologist within 3 months of the initial episode.[57] Clearly, a better effort needs to be made to provide these patients with appropriate follow-up.

Despite the large amount of evidence that points to a causal relationship between AKI and CKD, this relationship is far from clear cut. Potential problems that put the relationship between AKI and CKD in question include residual confounding, ascertainment bias, misclassification of exposure, and misclassification of outcome.[58] Until these problems have been resolved, a causal relationship between AKI and CKD cannot be concluded with certainty.

MOLECULAR BIOLOGY OF ATN

ATN, a common form of AKI, usually develops in the context of prolonged hypotension (eg, as a result of surgery or sepsis). ATN's multiple stages include prerenal, initiation of injury, maintenance of injury, and repair. Histologically, ATN is associated with the loss of proximal tubule brush border, loss of tubule cells, proximal tubule dilatation, distal tubule casts, and areas of cellular regeneration that are seen during the recovery/repair period.[1] Investigations focusing on the molecular events that occur during ATN have identified a number of genes that are intimately involved in the stages of injury and repair.

For example, damage to the endothelial cells of the microvasculature plays a critical role in renal injury by reducing renal blood flow. Increased concentrations of endothelin (a vasoconstrictor) and reduced amounts of nitric oxide (a vasodilator) worsen the initial ischemic insult.[59,60] Increased expression of intercellular adhesion molecule 1 is another factor involved in endothelial cell-mediated kidney damage.[61]

Damage to the epithelial cells of the renal tubules is another hallmark of ATN. Animal studies have implicated toll-like receptors (TLR) 2 and 4.[62] The proteins are involved in the immune response to pathogens and are expressed in immune cells and renal epithelial cells. Increased expression of TLR 2 during AKI leads to subsequent activation of ischemia-related cytokines and renal damage at the epithelial level. Reduced expression of TLR 2, on the other hand, leads to reduced cytokine release and mitigates renal injury.[62] Peroxisome proliferator-activated receptor (PPAR) is a ligand-activated transcription factor that appears to play a role in the protection against renal ischemia. Mice deficient in PPAR beta are more sensitive to ischemia-induced renal injury. Activation of PPAR with its corresponding ligand leads to a reduction in ischemia-induced injury.[63]

Renal damage that occurs during ATN is clearly mediated by various arms of the immune system, and neutrophils, natural killer T cells, and macrophages are activated during this process.[62] These cells become aware of ischemia-mediated renal injury via receptor-mediated detection of intracellular factors that are released by dead cells. Ultimately, this renal damage leads to strong activation of immune and inflammatory responses, as well as the complement system, and various adhesion molecules are induced during this process.[61,64] Tumor necrosis factor-alpha, IL-6 and IL-8, chemokines, and bone morphogenetic protein-7 are among the many factors that have been

implicated in the immune-mediated response to renal injury.[65-67]

In contrast, few studies deal with the promotion of renal repair. Renal tubular epithelial cells have the remarkable potential to regenerate after an ischemic or toxic insult. Renal stem cell populations that may be useful in the regeneration of injured kidney cells have been identified.[68]

RRT

RRT is indicated to treat volume overload (not responsive to diuretics), uremia, severe acidosis, hyperkalemia, and drug overdose (eg, aspirin).

The optimal timing for initiation of RRT is currently not known. A metaanalysis published in 2011 suggests that early dialysis is associated with an improvement in 28-day mortality.[69] However, this analysis was flawed because of the low number of randomized trials and the heterogeneity of the observational studies. An adequately powered randomized clinical trial is needed to provide a satisfactory answer.

In terms of modalities, no studies currently suggest a clear benefit of intermittent hemodialysis (IHD) vs continuous renal replacement therapy (CRRT).[70] The Kidney Disease Outcomes Quality Initiative suggests that CRRT should be used instead of IHD in patients who are hemodynamically unstable and in patients with cerebral edema.[2] CRRT may also be the modality of choice in patients with chronic hyponatremia to avoid overly rapid correction. Patients who suffer from intoxication should be treated with IHD because it provides more rapid clearance.

Dialysis dosing recommendations by the Acute Renal Failure Trial Network study suggest a minimum Kt/V of at least 1.2 for intermittent hemodialysis.[71] For patients on CRRT, KDIGO guidelines recommend an effluent volume of 20-25 mL/kg/h.[4]

Observational studies have suggested that the actual effluent volume delivered during CRRT is substantially less than the prescribed dose, so the recommendation is to increase the prescribed dose by 20%-25%.[2] Two metaanalyses found that more intense therapy (effluent volume >20-25 mL/kg) did not improve survival compared with less intensive regimens.[72,73]

CONCLUSION

AKI is commonly encountered in the renal practice and its molecular details are beginning to be unraveled.

Although biomedical research has identified several promising new biomarkers (eg, NGAL, cystatin C) for the detection of AKI, serum creatinine, with its many shortcomings, remains the most important biomarker for the prediction and diagnosis of AKI. Using serum creatinine in the context of volume overload for the diagnosis of AKI is usually misleading, and creatinine levels need to be corrected under these circumstances.

Several new risk factors for AKI have recently been identified. Increased BMI, proteinuria, and combined ACE inhibitor/ARB use are all linked to increased levels of AKI.

A number of interventions have been shown to be beneficial for the prevention and treatment of AKI. While IV fluids are clearly advantageous for the prevention of CI-AKI, no convincing evidence currently supports the use of statins and/or NAC. ADHF and associated AKI are best treated with diuretic therapy. Currently, no good evidence favors continuous over bolus therapy. Ultrafiltration appears to be inferior compared to diuretic use in patients with ADHF. Several studies suggest that terlipressin leads to reduced mortality and improved renal function in patients with HRS. Unfortunately, this medication is not available in the United States, but combined therapy with midodrine, octreotide, and albumin provides a promising alternative. Aggressive fluid resuscitation is frequently seen in patients who also suffer from AKI. A number of recent investigations indicate that this practice is detrimental and should be avoided. RRT is the last resort in the treatment of patients with AKI. Despite several large-scale studies, currently no consensus exists for the optimal timing of dialysis initiation. In addition, no clear advantage has been shown for intermittent vs continuous dialysis, and the optimal dosing has not yet been established.

A number of reports suggest that AKI is associated with an increased risk of developing subsequent CKD and ESRD. Although the causality of this correlation has not been fully established, it appears reasonable to follow all patients with AKI and monitor them closely for renal function worsening.

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