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Acute Kidney Injury in the Critically Ill Patient: A Current Review of the Literature

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Abstract

Purpose: A comprehensive review of the literature to provide a focused and thorough update on the issue of acute kidney injury (AKI) in the surgical patient. **Methods:** A PubMed and Medline search was performed and keywords included AKI, renal failure, critically ill, and renal replacement therapy (RRT). **Principal Findings:** A common clinical problem encountered in critically ill patients is AKI. The recent consensus definitions for the diagnosis and classification of AKI (ie, Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease/Acute Kidney Injury Network) have enabled us to standardize the severity of AKI and facilitate strategies for prevention. These strategies as well as treatment modalities of AKI are discussed. We provide a concise overview of the issue of renal failure. We describe strategies for prevention including types of fluids used for resuscitation, timing of initiation of RRT, and different treatment modalities currently available for clinical practice. **Conclusions:** Acute kidney injury is a common problem in the critically ill patient and is associated with worse clinical outcomes. A standardized definition and staging system has led to improved diagnosis and understanding of the pathophysiology of AKI. There are many trials leading to improved prevention and management of the disease.

Keywords

acute kidney injury, renal failure, critically ill, renal replacement therapy

Introduction

Acute kidney injury (AKI) is a significant morbidity encountered in the critically ill patient both in medical and surgical intensive care units (ICUs). Approximately 6% of critically ill patients with AKI are treated with some form of renal replacement therapy (RRT) during their ICU stay.[1] These patients often have a prolonged hospital course; longer days spent in the ICU, and may go on to require dialysis after discharge.[2] The intensivists who care for these patients must have the fundamental knowledge of the principles related to AKI to understand important strategies for both the prevention and treatment of AKI.

This article will aim to provide a review of the pathophysiology of AKI, go over the most recent diagnosis and classification systems, describe specific causes of AKI in the intensive care setting, review fluids chosen for resuscitation, and discuss timing and modes of RRT based on recent evidence.

Epidemiology of AKI

The incidence of AKI varies depending on the population studied. It accounts for 1% of hospital admissions in the United States. This review will focus on hospital acquired AKI, which has an incidence of 5% to 7%.[3,4] There are a number of causes of AKI in the critical care setting, with acute tubular necrosis remaining the most common. The process is often multifactorial including sepsis, nephrotoxic drugs, contrast agents, and postsurgical.[4] Approximately 5% to 20% of ICU patients will develop some AKI, of whom approximately 6% will require some form of RRT during their ICU stay.[1,2] The incidence of ICU-related AKI has increased over the last decades and this is probably due to the increasing incidence of sepsis-related hospital admissions.

Pathophysiology

Intrinsic Causes of AKI

The pathogenesis of AKI involves a complex relationship among vascular, tubular, and inflammatory factors.[2,5] The AKI secondary to septic shock is predominantly thought to involve a

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reduction in renal blood flow secondary to systemic arterial vasodilation and concomitant intrarenal vasoconstriction. This results in renal hypoperfusion and ischemia.

The kidneys receive higher blood flow per unit mass compared to any other organ in the body but the actual fraction of extracted oxygen is less. This makes the kidney very sensitive to conditions of hypoperfusion. Ischemia and toxins result in vasoconstriction, endothelial injury, and the activation of innate and acquired inflammatory immune responses.[2,5] The oxygen supply to the renal tissues can be impaired due to acute blood loss from trauma or during acute hemodilution during resuscitation with large quantities of crystalloids in trauma or septic shock.[6]

The AKI that results then triggers a cascade of inflammatory processes both locally and systemically. This systemic inflammatory response syndrome is initially characterized by a systemic release of proinflammatory cytokines followed by a counter anti-inflammatory response syndrome. This anti-inflammatory response is aimed at controlling and limiting the inflammatory process.[7] Uremia in the setting of AKI can disrupt this natural sequence of events and this has been thought to play a key role in the pathogenesis of multiorgan failure.

Extrarenal Causes of AKI

Intra-abdominal hypertension. The kidneys have a unique relationship with other vital organs. Diseases and processes that affect one organ will often affect another. An example of a process that can lead to the development of AKI is the presence of intra-abdominal hypertension (IAH). In a critically ill patient, normal intra-abdominal pressure (IAP) is approximately 5 to 7 mm Hg. Intra-abdominal hypertension is defined by a sustained or repeated elevation of IAP $\geq$12 mm Hg. A common clinical scenario in which this may occur is with excessive fluid resuscitation due to inflammation.[8,9] The combination of large fluid volumes inflammation-induced capillary leak results in fluid sequestration in extracellular compartments, which leads to visceral edema, and subsequent IAH.

Even lower IAPs (<12 mm Hg) have been found to have some causal relationship with AKI due to decreased renal perfusion. There have been studies looking specifically at renal cortical perfusion based on renal artery resistive index and urine output and have shown decreases in both as the IAPs increase.[7] It has been shown in several studies dating back to the 1940s that an IAP as low as 10 mm Hg can lead to a reduction in renal blood flow and the start of renal dysfunction. An IAP of 20 mm Hg has been shown to have a 20% to 25% decrease in renal blood flow.[10,11]

Mechanical Ventilation and Pulmonary Causes

As renal function is closely related to other organs, it is also affected by interventions used in the critically ill patient. There are very close lung–kidney interactions including renal effects of acute lung injury and mechanical ventilation. There is a known entity called ventilator-induced kidney injury. The ARDSnet investigators demonstrated that those treated with a lung-protective lower tidal volume technique had fewer days with AKI.[12]

The physiologic impact of positive pressure ventilation (PPV) and its effects on renal perfusion are well documented.[12-14] The PPV results in decreased renal perfusion and function by 2 main mechanisms. The first is the hemodynamic effects, which is illustrated by decreased cardiac output as a result of reduced venous return from the increase in intrathoracic pressures. This can also lead to hypotension and fluid responsive shock. All of this has been shown to correlate with decrease in renal blood flow, glomerular filtration rate, and urine output during PPV. A recent review by van den Akker et al showed that invasive mechanical ventilation was associated with a 3-fold increase in the odds of developing AKI in the critically ill patients.[13] The PPV has also been shown to alter various neurohormonal systems including increased sympathetic outflow, which in turn activates the renin–angiotensin axis resulting in decreased renal blood flow, fluid retention, and oliguria.[14]

Definition and Classification

In the past, it was thought that a major impediment to good comparative research in acute renal failure was the lack of a uniform definition. It was believed this might explain differences in reported incidence and outcomes of AKI in the literature. As a result, in 2004, the Acute Dialysis Quality Initiative workgroup developed a consensus definition known as the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) classification.[2,15-17] This classification was based on 2 main parameters, changes in serum creatinine (SCr) from baseline and urine output. The severity of the renal failure was determined by the more severe of the 2 parameters. There are 3 stages described in RIFLE, which include Risk, Injury, and Loss all of which have increasing prognostic significance based on the increase in SCr from baseline (see Table 1).

After data emerged demonstrating that even small alterations in renal function led to adverse outcomes, the Acute Kidney Injury Network (AKIN) modified the RIFLE classification system in 2007.[15,16,18] This network replaced the term acute renal failure with AKI in an attempt to standardize both the definition and staging of kidney injury and it has facilitated improved risk stratification in critical AKI. The AKIN workgroup defined AKI as a reduction in kidney function occurring over no more than 48 hours with an absolute increase in SCr level 0.3 mg/dL or more or a relative increase in SCr 1.5- to 2-fold, or documented oliguria less than 0.5 mL/kg/h for more than 6 hours despite adequate fluid resuscitation.[18] There have been multiple studies, which have shown really no difference between the 2 in predicting mortality, but they have allowed for a more uniform classification[15,19] (see Table 2). The Kidney Disease Improving Global Outcomes Network addresses both of these classification systems within their guidelines as both have been validated. However, they do note that there are

Table 1. RIFLE Classification.

	Cr/GFR Criteria	Urine Output (UO) Criteria
*R*isk	Increased Cr × 1.5 or GFR decreases >25%	UO <0.5 mL/kg/h × 6 h
*I*njury	Increased Cr × 2 or GFR decreases >50%	UO <0.5 mL/kg/h × 12 h
*F*ailure	Increased Cr × 3 or GFR decreases >75% or Cr ≥4 mg/dL (with a cute rise of ≥0.5 mg/dL)	UO <0.3 mL/kg/h × 24 h or anuria × 12 h
*L*oss	Persistent ARF = complete loss of renal function for >4 weeks	
*E*SRD	End-stage renal disease	

Abbreviations: ARF, acute renal failure; Cr, creatinine; GFR, glomerular filtration rate; RIFLE, Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease.

Table 2. AKIN Classification.

	Cr Criteria	Urine Output (UO) Criteria
Stage 1	Increased Cr × 1.5 or ≥0.3 mg/dL	UO <0.5 mL/kg/h × 6 h
Stage 2	Increased Cr × 2	UO <0.5 mL/kg/h × 12 h
Stage 3	Increased Cr × 3 or Cr ≥4 mg/dL (with acute rise of ≥0.5 mg/dL)	UO <0.3 mL/kg/h × 24 h or anuria × 12 h

Abbreviations: AKIN, Acute Kidney Injury Network; Cr, creatinine.

limitations with both and they recommend that patients should be staged according to the criteria that give them the highest stage.[20]

Fluids for Resuscitation and AKI

A major part of the acute management of critically ill patients is centered about fluid resuscitation and the uses of crystalloids versus colloids have been studied and debated both in the medical and surgical literature. Crystalloids and colloids have different benefits and risks related to outcomes including renal dysfunction in the critically ill patients, and in the most recent update for the Surviving Sepsis Guidelines there is a section dedicated to the choice of fluids and how they related to kidney injury.[21] These studies relating to the choice of fluids and how they relate to renal failure will be outlined next.

Studies have shown that Lactated Ringers (LR) solution has proinflammatory effects and can activate leukocytes. Theoretically the potentiation of the inflammatory response including the increase in leukocyte superoxide burst activity can potentiate organ dysfunction including kidney injury.[22,23] In contrast, large volumes of 0.9% sodium chloride during resuscitation may contribute to metabolic acidosis by increasing the plasma chloride concentration relative to the plasma sodium concentration. This excess chloride can cause an osmotic nephrosis, which causes a structural change to the cells within the kidney and is irreversible.[24-26]

Recently there have been a number of published randomized controlled trials (RCTs) trying to address the long debated issue of crystalloids versus colloids.[27] Several studies have shown that colloids lead to an overall reduction in the amount of fluid needed during resuscitation.[7,21,27,28] There is greater intravascular retention, less capillary leak that leads to improved microcirculation with reduced endothelial activation, and less endothelial damage. However, the higher molecular-weight hetastarches (HESs) have been shown to increase the risk of developing renal failure and the need for RRT.[29-31]

Specifically, the Crystalloids Morbidity Associated with severe Sepsis (CRYSTMAS) study was a multicenter RCT that compared the hemodynamic effects and safety of the lower molecular-weight HES to normal saline for hemodynamic stabilization in patients with severe sepsis. They hypothesized that the use of colloids would reduce the amount of fluid required to reach hemodynamic stability.[29] Their safety variables were kidney function categorized according to the RIFLE and AKIN classifications. The study did correlate that less colloid was needed compared to crystalloid to reach hemodynamic stability and there was no difference in mortality. This study was an underpowered study with fewer than 200 patients.

The 6S trial was a Scandinavian multicenter study with 800 patients with severe sepsis. The primary outcomes measured were death and renal failure requiring dialysis. The data revealed an increased risk of death at 90 days and a higher need for RRT with 6% HES compared to LR.[33] Similarly, the Chest study another multicenter trial with 7000 patients enrolled compared 6% HES and normal saline. Their results showed no difference in mortality but again the need for RRT was higher in the HES group.[30-33]

As the aforementioned studies are diverse, have large sample sizes and date back several years, there is still no definitive answer for the ideal choice of fluid in critical illness and how it impacts renal function. These data underscore the following: there is no difference in mortality or renal impairment with crystalloids versus albumin. In sepsis, crystalloids are considered first line and colloids; specifically albumin should be used for large volume resuscitations.[19] The Surviving sepsis guidelines also clearly recommend the use of crystalloids as first line and then, 5% albumin for large volume resuscitations. The use of HESs is not recommended.[27]

Timing of Initiation of RRT

The mainstay of treatment for AKI is RRT and there is a paucity of data to guide the optimal timing to initiate and mode of therapy. There are a number of indications for the initiation of RRT including acid/base derangements, volume overload, various electrolyte abnormalities, and uremia.[2,4,6,16,20] As the primary goal of RRT is to compensate for loss of renal function and the associated sequelae such as fluid overload and clearance of toxins, the conventional markers for the initiation of RRT include SCr, blood urea nitrogen (BUN), and oliguria <200 mL in 12 hours. As a matter of fact, these parameters

traditionally have served to guide our involvement of nephrologists with decisions regarding RRT.

The problem with using the standard criteria of creatinine, BUN, and oliguria is that the physiology related to sepsis and low perfusion can lead to the misinterpretation of these values. For example, the production of creatinine can either be decreased due to changes in volume status, decreased muscle mass, or decreased excretion secondary to toxic effects. In critically ill patients, the dilution of SCr by fluid accumulation may also lead to underestimation of the severity of AKI and increases the time required to identify a 50% relative increase in SCr.[34] Therefore, using the traditional values may be misleading and lead to later initiation of RRT.[15,35]

The use of several biomarkers is being investigated with samples from both urine and plasma. Those which are showing promise include neutrophil gelatinase-associated lipocalin, cystatin C, interleukin (IL) 18, and kidney injury molecule 1. Ischemic injury to the kidney upregulates these proteins in the proximal tubule of the kidney, resulting in increased urine and plasma levels. The combination of urinary and plasma biomarkers may facilitate early detection of AKI over the traditional, less sensitive individual biomarkers.[36-38]

To address this issue, there have been several studies showing a significant reduction in mortality in patients where RRT was started early with just the presence of oliguria rather than waiting for changes in the lab values of BUN or Cr.[35,39] The concept of early or prophylactic hemodialysis was introduced over 50 years ago. The traditional value for BUN of 80 to 100 for the initiation of dialysis was changed to a BUN of 60 to define early versus late.

A recent meta-analysis by Yong et al showed an overall mortality benefit in early RRT. In the majority, a clear survival benefit was demonstrated in diverse populations; however, the studies were underpowered.[35]

A very pivotal study based on military data demonstrated that in burn patients managed with early CVVH versus patients who received no RRT, there was a mortality benefit in the early CVVH group. The early group had significantly improved outcomes based on mortality.[40] Although cytokines were not addressed in the article, one of their potential explanations was that this survival benefit was based on the clearance of cytokines and inflammatory mediators in the group that underwent CVVH.

Similarly The Program to Improve Care in Acute Renal Disease, a multicenter observational study of AKI in ICU patients who required dialysis examined the timing of initiation of dialysis with mortality. They defined early initiation of RRT based on a BUN of <76. They showed that there was an association with a higher degree of azotemia and mortality.[34,41]

The largest cohort study conducted was by the investigators of the Beginning and Ending Supportive Therapy for the Kidney (BEST kidney). This was a multicenter study comparing critically ill patients with septic and nonseptic AKI. This group defined early based on timing from admission to ICU and showed that early initiation of RRT was associated with lower mortality, shorter hospital length of stay, and shorter overall duration of RRT.[42]

Modes of RRT

Renal replacement therapies are categorized by the primary transport process used to remove solutes and toxins. These include ultrafiltration for fluid removal and either diffusion, convection, or a combination of the latter 2 to achieve solute clearance.[43] Options for therapy include intermittent hemodialysis (IHD), various forms of continuous RRT, and newer "hybrid" forms such as sustained low-efficiency dialysis (SLED) and prolonged intermittent therapy.

Intermittent hemodialysis is the standard method of providing RRT in the chronic setting. It is single pass, meaning it is not continuous but typically run over 3 or 4 hours per session and is highly effective for the removal of small molecules. The flow rates are faster than CVVH. The main disadvantage of IHD is the risk of systemic hypotension caused by rapid fluid shifts and removal. This occurs in approximately 20% to 30% of treatments.[44,45]

Continuous venovenous hemofiltration (CVVH) has emerged over the past decade as a viable modality for management of hemodynamically unstable patients with AKI. It is believed that CVVH is better tolerated in hemodynamically unstable patients because it is mimics the native kidney by running continuously, 24 hours/d with slower flow rates. There is better control of fluid shifts and as a result, less episodes of renal and intestinal ischemia.[46] Another potential benefit with regard specifically to sepsis are that during CVVH there is a drop in core body temperature, which results in mild hypothermia, and thus leads to an increase in vascular tone.

An earlier study by Bellomo and colleagues documented a decrease in serum cytokine levels, particularly tumor necrosis factor and IL-1 in patients with sepsis who were managed with CVVH.[47] Since then there have been numerous data to suggest that there is some hemodynamic benefit and protection from organ failure with the removal of inflammatory mediators associated with CVVH. However, it is unclear whether or not mortality is benefited. The Haemodiafe Study Group showed no difference in survival between intermittent and continuous modes of RRT.[48] Lins et al also showed no difference in outcomes in ICU patients with AKI when comparing either mode of RRT.[49]

Some key differences between CVVH and IHD as it relates to critically ill patients are described here. Critically ill patients with hemodynamic instability do not tolerate rapid fluid and electrolyte shifts, and this is particularly true during the resuscitative phase when patients are unstable and acidotic and may require vasopressors. Multiple hypotensive episodes can worsen morbidity and mortality.[40,46] The gradual continuous volume removal makes control of volume status easier and allows administration of medications and nutrition with less concern for volume overload. Critically ill patients are catabolic and often malnourished as a result of their catabolic state. Compared to continuous renal therapy, IHD requires limited

protein and fluid intake between episodes to prevent toxic levels of nitrogen and fluid overload.[43,46]

Although numerous beneficial effects of continuous therapies have been elucidated, multiple studies have shown no difference in outcomes between continuous and intermittent modes of therapy. Newer modified modalities have been introduced which combine the advantages of both intermittent and continuous forms of hemodialysis. These include SLED and extended daily dialysis. These slower dialytic modes run for prolonged periods using conventional hemodialysis machines.[50] This allows for larger volume solute removal but gradually over longer periods of time. Perhaps there is a role for the use of prolonged intermittent RRT in the treatment of critically ill patients with hemodynamic instability.

Conclusions

In summary, AKI has been linked to sepsis and inflammation, as the kidney is very sensitive to hypoperfusion. The kidney is also sensitive to many of our interventions, such as mechanical ventilation and excessive fluid resuscitation. Positive pressure ventilation can lead to hemodynamic changes and also the systemic release of cytokines that can impact renal function.

Fluid therapy during resuscitation can also result in renal impairment, including all forms of fluid therapy. Crystalloids and colloids in the form of albumin are considered equally safe, however. Crystalloids are first-line therapy followed by 5% albumin for large volume resuscitation.

The initiation of RRT should be considered early and there are data supporting early RRT in the setting of oliguria versus the traditional parameters including azotemia, fluid overload, electrolyte changes, and acidosis. The early initiation of CVVH is widely supported with the benefits occurring primarily in hemodynamically unstable patients due to its continuous nature and lack of significant fluid shifts. The benefits may be substantial in sepsis, as the removal of cytokines and perhaps the nutritional benefits, have some theoretical application.

Overall, the knowledge of the renal physiology and of the impact of iatrogenic supportive maneuvers that may impair renal function is pivotal in the provision of good critical care. Renal replacement therapies are a supportive adjunct in the critically ill patients and more research is needed to further elucidate timing and optimal modes of replacement therapy in diverse patient groups.

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