Immediate Consequences of Acute Kidney Injury: The Impact of Traditional and Nontraditional Complications on Mortality in Acute Kidney Injury

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Acute kidney injury (AKI) that requires renal replacement therapy is associated with a mortality rate that exceeds 50% in the intensive care unit, which is greater than other serious illnesses such as acute lung injury and myocardial infarction. Much information is now available regarding the complications of AKI that contribute to mortality and may be usefully categorized as "traditional" and "nontraditional". Traditional complications are the long-recognized complications of AKI such as hyperkalemia, acidosis, and volume overload, which may be typically corrected with renal replacement therapy. "Nontraditional" complications include complications such as sepsis, lung injury, and heart failure that may arise due to the effects of AKI on inflammatory cytokines, immune function, and cell death pathways such as apoptosis. In this review, we discuss both traditional and nontraditional complications of AKI with a focus on factors that contribute to mortality, considering both pathophysiology and potential remedies. Because AKI is the most common inpatient consult to nephrologists, it is essential to be aware of the complications of AKI that contribute to mortality to devise appropriate treatment strategies to prevent and manage AKI complications with the ultimate goal of reducing the unacceptably high mortality rate of AKI.

Key Words: Acute kidney injury, Organ cross talk, IL-6, Acute lung injury

INTRODUCTION

Hospital-acquired acute kidney injury (AKI) is a common complication that is associated with significant mortality.[1] AKI occurs in up to 20% of hospitalized patients overall[1] and 30% to 50% of admissions to the intensive care unit (ICU).[2] Increased inhospital morality occurs in patients with either mild[3-5] or severe (requiring renal replacement therapy [RRT]) AKI.[6,7] The inhospital mortality of patients with AKI-requiring dialysis is 33% overall[8] and >50% in patients in the ICU.[9,10]

Before routine use of RRT, patients died of electrolyte abnormalities such as hyperkalemia, complications from uncontrolled uremia such as pericarditis or upper gastrointestinal bleeding from uremic platelet dysfunction, or respiratory failure from volume overload.[11,12] These long-recognized complications may be considered "traditional" complications of AKI.[13] In general, these traditional complications can be medically managed and can be prevented or controlled by RRT; thus, death solely from one of these traditional complications would be considered unusual in modern practice with timely institution of RRT.

Today, it must be acknowledged that AKI is a systemic disease that also predisposes to a wide variety of "nontraditional" complications that are responsible for the high rate of death.[13] These nontraditional complications include sepsis,[5,14] respiratory failure,[6,15] and heart failure.[16] Studies in animal models of AKI support the notion that AKI is a systemic disease, which adversely affects multiple organs including the lung,[17,18] heart,[19] liver,[20,21] brain,[22] and intestine.[23] Reducing the significant mortality of AKI will require preventing and managing its "nontraditional" systemic complications,[19,24,25] which will require management approaches and therapies beyond RRT to correct.

In this review, we discuss both traditional and nontraditional complications of AKI with a focus on factors that likely contribute to mortality, considering both pathophysiology and potential remedies. Because AKI is the most common inpatient consult to nephrologists,[26] it is essential to be aware of the complications of AKI that contribute to mortality to devise appropriate treatment strategies to prevent and manage AKI complications with the ultimate goal of reducing the unacceptably high mortality rate of AKI.

TRADITIONAL COMPLICATIONS OF AKI

Traditional complications of AKI include the following: volume overload; uremic complications such as bleeding, pericarditis, and altered mental status; and electrolyte abnormalities such as hyperkalemia, acidosis, hyperphosphatemia, and hypocalcemia.[27-32] These abnormalities have been recognized as complications of AKI for >50 years[33-36] and are the typical complications of AKI listed in textbooks,[28,31] clinical practice guidelines,[29,32] and review articles.[30] In general, these complications can be managed medically or with RRT, and death from many of these complications—such as uremic pericarditis or uremic bleeding—would be considered unusual today.

We do not suggest, of course, that the clinician become cavalier regarding these traditional complications. Hyperkalemia has the potential to cause life-threatening arrhythmias. Likewise, severe acidosis (generally defined as a pH < 7.10) can impair cardiac contractility, reduce vasopressor responsiveness, and/or contribute to arrhythmias. There are no clear data to guide at what level of potassium or pH that institution of RRT might be beneficial[29,32]; however, RRT for the correction of hyperkalemia may

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reasonably be considered at a level of >6.5 mEq/L, and RRT for the correction of acidosis may reasonably be considered with a pH < 7.10[29,32]. Uremic complications such as pericarditis, encephalopathy, and gastrointestinal bleeding are now relatively rare given recent trends to initiate RRT earlier in the course of AKI, thus avoiding these complications.

Of the "traditional" complications associated with AKI, volume overload is the most well-studied factor that may contribute to patient mortality in the modern era. Volume overload is independently associated with increased mortality[37-39] and increased morbidity such as delayed kidney function recovery.[40] Although poorly studied, fluid overload is associated with a number of adverse effects including increased intra-abdominal pressure, predisposition to sepsis, pulmonary edema, and gut edema.[37] Increased intra-abdominal pressure may delay kidney function recovery, pulmonary edema may predispose to lung inflammation and pneumonia, and gut edema may predispose to sepsis. There is no standard definition of volume overload, but studies have found that fluid overload greater than or equal to 10% of baseline weight is associated with increased mortality in AKI.[38,39] One study found a stepwise increase in mortality for every 1.6 L per day of fluid accumulation.[41]

Although it remains unproven whether fluid overload directly contributes to increased mortality or whether it is simply a sign of more severe disease, we believe that there is enough biologic plausibility and clinical data to conclude that fluid overload is indeed an important causative factor in patient outcomes and should be avoided when possible. Thus, we suggest that meticulous attention to volume status and intake and output be standard practice in patients with AKI. Percent fluid overload (eg, weight increase from baseline) should be monitored and documented. Although an empiric "fluid challenge" is commonly performed to determine whether AKI will improve, we suggest that every effort be made to ascertain whether the patient will indeed be fluid responsive (eg, passive leg raising test[42,43]). Currently, there is insufficient evidence to recommend early initiation of RRT for the purpose of volume management; however, we suggest that volume management and avoidance of volume overload are reasonable considerations in the evaluation of RRT for patients with AKI.

CLINICAL SUMMARY

- AKI is associated with a high mortality that may be due to traditional and non-traditional complications.
- Traditional complications include well recognized complications such as hyperkalemia, acidosis, and volume overload.
- Non-traditional complications include acute lung injury/inflammation, cardiac complications, and sepsis.
- Improving mortality in AKI will require greater attention to and management of the non-traditional complications of AKI.

NONTRADITIONAL COMPLICATIONS

Systemic Inflammation Response Syndrome, Compensatory Anti-inflammatory Response Syndrome, and Immune Dysregulation

Many of the nontraditional complications of AKI may be better understood within the context of the systemic inflammatory response syndrome (SIRS), compensatory anti-inflammatory response syndrome (CARS), and immune dysregulation that also occur in response to a variety of other systemic illnesses. SIRS is the result of pro-inflammatory cytokines that are released in response to a diverse array of infectious and noninfectious insults. The exuberant inflammatory response that results in SIRS may also result in organ injury—most notably acute lung injury (ALI)—and multiple organ dysfunction syndrome. SIRS is normally followed by an anti-inflammatory phase known as the CARS, which is characterized by the elaboration of anti-inflammatory cytokines such as interleukin (IL)-10, which limits pro-inflammatory response. When CARS is inadequate, a period of immune dysregulation can ensue where excessive levels of both pro- and anti-inflammatory cytokines occur.

A wealth of evidence has accumulated to conclude that AKI is associated with both early and sustained elevations of pro- and anti-inflammatory cytokines. For example, IL-6 and IL-8 have been shown to increase in the serum by as early as 2 hours in AKI, rising before serum creatinine.[44,45] IL-6 in particular predicts AKI in a wide variety of clinical settings including sepsis,[46] ALI,[47] and bypass-requiring cardiac surgery.[44,48] Increased levels of IL-6 in AKI are correlated with prolonged mechanical ventilation[44] and increased mortality.[48] Accumulated data in animal models indicate that circulating IL-6 is a mediator of lung inflammation after AKI[49-51]; thus, elevated IL-6 may be both a marker of AKI and a mediator of systemic complications such as lung injury.

Serum levels of IL-6, IL-8, IL-10, tumor necrosis factor (TNF), IL-1β, C-reactive protein, IL-18, macrophage inhibitory factor (MIF), and tumor necrosis factor-receptor inhibitor (TNFR-I) have all been found to be increased in patients with established AKI,[52-54] and increases in IL-6, IL-8, IL-10, IL-18, MIF, or TNFR-I are associated with increased mortality.[52-54] The fact that both pro-inflammatory cytokines (eg, IL-6 and IL-8) and anti-inflammatory cytokines (eg, IL-10) are increased in AKI and predict increased mortality suggests that immune function in patients with established AKI is significantly dysregulated.

Multiple mechanisms are in play that cause the elevations of cytokines observed in patients with AKI. Animal data suggest that both renal and extrarenal production of cytokines is increased in AKI, with prominent cytokine production in the spleen and liver.[51] Animal data also suggest that the kidney plays an important role in cytokine clearance[55] possibly via proximal tubule metabolism.[56] Thus, AKI may be a unique scenario where both cytokine production is increased and clearance is reduced accounting for the high levels of serum cytokines observed in patients with established AKI.