Acute Kidney Injury: The Road to Recovery

Richard Lafayette

A cute renal failure, increasingly being called acute kidney injury (AKI), is a devastating event, most typically occurring in hospitalized patients. While we teach our students to look for easily reversible causes such as pre-renal and obstructive causes of AKI, or treatable interstitial nephritis or glomerulonephritis, it often follows a progressive course.

Patients with AKI, presently recognized by increasing serum creatinine values or oliguria, have unacceptably high rates of complications demonstrated by increased costs, prolonged ICU stays, and hospitalization, as well as the frequent need for dialysis support. Most notably, hospital mortality rates range from 30 to 80 percent for sustained, dialysis-dependent AKI, depending on the setting (1,2). Recently, there has been increased attention to the fact that survivors of AKI continue to suffer long-term adverse events, including progression to renal failure and increased mortality (3).

In our hospitals, the incidence of AKI is increasing, reaching rates as high as 7 percent of all admissions (4). This is associated with an aging population, sicker inpatients, and more aggressive care for serious illnesses, including cardiovascular disease and cancer. The community-based risk of AKI is also apparently growing, now at as high as 5.2 cases per 1000 patient-years (5). There are some indications that overall outcomes may be improving slightly either due to better reporting of cases or to true improvements in overall supportive care (6). It is also encouraging that there are clear efforts at getting better definitions of disease and of the measures of outcome to set the stage for future discovery (7,8). Fortunately, to date, most studies of specific therapies and interventions have failed to show any benefit on the course of this disease.

Presently, there is great uncertainty as to how best to diagnose this process or to get an early and full appreciation of risk. Furthermore, once identified, there is no clear intervention to help the kidney recover more quickly or completely or to assure that the patient suffers fewer complications. We continue to be uncertain of the appropriate time to intervene with dialysis or with which modality or intensity to supply renal replacement therapy (2).

In this special issue of ASN Kidney News, we are fortunate to have the viewpoints of several leaders in the field of acute kidney injury. They provide evidence that nephrology is trying to develop better, more effective ways to deal with the diagnosis, treatment, and support of patients with AKI. Ranging from efforts to verify novel biomarkers of injury through enhanced basic science understanding of pathophysiology, to specific issues in patient care in terms of fluid support and nondiagnostic and dialytic treatment in the hospital, these insights should pave the way to new avenues of investigation and clinical care. We certainly must hope for improvement in the care and outcome of this very devastating event.

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Fluid Administration in Pediatric AKI: When Is a Patient Being Overdosed?

By Stuart Goldstein

Recent and important advances in acute kidney injury (AKI) research have focused primarily on: (I) derivation and validation of multidimensional AKI definitions and classification systems, e.g., RIFLE (Risk, Injury, and Failure (1)), pRIFLE (2), or the Acute Kidney Injury Network (AKIN) (3) definitions; (ii) demonstrating that even small serum creatinine increases (e.g., > 0.3 mg/dl) can be associated with increased patient mortality (4); and (iii) discovery and validation of novel urinary biomarkers that can detect AKI earlier than serum creatinine changes with the hope that earlier detection may provide clinicians with the opportunity to intervene to prevent or at least mitigate the effects of AKI (5–7). Although these advances will undoubtedly lead to improved patient care by prompting clinicians to be vigilant for early AKI development, they may provide little benefit once patients have already developed AKI.

Care for the critically ill patient with sepsis and AKI is further complicated by the need to manage multi-organ system failure, often requiring complex supportive measures of fluid resuscitation, vasoactive medication administration, and decisions as to timing of renal replacement therapy (RRT).

Clinical research in adults with sepsis and acute respiratory distress syndrome has also focused primarily on the benefits of early and aggressive goal-directed fluid resuscitation to re-establish end-organ provision. Recently attention has been given to conserva- tive late fluid management strategies to limit fluid administration (8–9). However, it has been pediatric studies that have examined the concept of fluid accumulation in the critically ill child with AKI.

Children with AKI provide an informative population for study, as their care is usually not complicated by comorbidities found in adults such as atherosclerotic heart disease, diabetes, or chronic obstructive pulmonary disease. The purpose of this article is to introduce the concept of “fluid overdose” in the critically ill patient with AKI based on pediatric studies from the past decade.

Can fluid be a toxic medication?

All physicians are taught about fluid and electrolyte homeostasis in medical school and early in postgraduate training, with an emphasis on how to respond to pathologic homeostatic disorders such as SIADH or diabetes insipidus. In these instances, physi- cians become quite adept at managing fluid composition and volume rates to correct or minimize the electrolyte de-rangements that accompany these syndromes. In fact, much controversy has arisen recently regarding the potential dangers of prescribing hypotonic solutions to any hospitalized patient (10–12). Clearly the concept that certain fluid compositions in particular settings may be toxic is not new.

In the setting of AKI, physicians are very cognizant to limit the dose of potentially harmful electrolytes (potassium, phosphorus) provided in exogenous fluids, but the concept of a fluid volume dose has been limited for the most part to an acute dose to treat hypotension (e.g., 10 mL/kg of normal saline). Yet the concept of a deleterious degree of positive fluid accumulation, or fluid overdosage, has received no systemic evaluation and certainly has not been defined. For example, neither of the two most recent, comprehensive, randomized, and con- trolled trials comparing small solute dose of RRT has reported to date the positive fluid balance in their patient cohorts at the time of RRT initiation (12–14). Given that these patients had oligosunary AKI and that dosed fluid homeostasis is a primary indication to initiate RRT, our collective ignorance regarding the fluid balance status in patients with AKI is perplexing.

Why has cumulative fluid balance received such short shrift? I suggest that we and AKI investigators have assumed that patients are getting the amount of fluid they need (and maybe too little, but rarely too much), and since it is usually of a relatively isotonic composition (e.g., normal saline or Ringer’s lactate) and can be removed by RRT, fluid can’t really be overdosed. However, lessons from the pediatric AKI literature challenge these assumptions.

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Lessons from the pediatric intensive care unit

The lessons from pediatric nephrologists—disease prevention and medication dosing based on patient size. I am not suggesting that these perspectives are unique to pediatrics and absent in internal medicine, but they are more common in pediatric training and everyday practice.

In the area of pediatric AKI and RRT, a concept of relative fluid accumulation (percent fluid overload) based on ICU admission weight and timing of renal replacement based on percent fluid overload and not BUN concentration has driven extensive pediatric research in the past decade.

Critically ill children often require aggressive fluid and isotropic support to maintain adequate perfusion. Substantial single-center and multicenter pediatric study over this past decade demonstrates that increasing degrees of relative fluid accumulation, or percent fluid overload, at the time of RRT initiation in children with AKI is independently associated with mortality (Table 1) (15–19). Percent fluid overload is calculated by total inflating fluids volume from ICU admission to RRT initiation using the following equation:

\[ \% \text{FO} = \left( \text{Fluid Input (L)} - \text{Fluid Output (L)} \right) / \text{Patient ICU admission weight (kg)} \]

In all of these studies, estimated GFR, renal replacement size, urine output, diuretic use, and severity of illness did not differ between survivors and nonsurvivors. Analysis of different percent thresholds from these studies suggests mortality increases from 40 percent to 60 percent in children with >10–20 percent fluid overload at RRT initiation, independent of patient severity of illness (Table 1). Thus, the pediatric community now has data from over 400 children in five studies that consistently show a potential fluid overload threshold at >20 percent positive accumulation from ICU admission to CRRT initiation.

The Prospective Pediatric Continuous Renal Replacement Therapy (pCRCRT) Registry Group recently conducted an analysis of its entire 340-patient cohort using a tripartite classification for percent fluid overload (FO) at CRRT initiation: <10 percent FO, 10–20 percent FO, and >20 percent FO (Sutherland S. et al, accepted 2019). One could still potentially argue that the patients actually “needed” the fluids they received. However, in a published multicenter study from the pCRCRT, the mean central venous pressure (CVP) for survivors was 16.5 ± 6.1 mm H2O versus 21.2 ± 6.6 mm H2O for nonsurvivors (18). Current recommendations for early goal-directed fluid resuscitation advocate fluid administration until a CVP of 8. Since the mean CVP was two to threefold above target recommendations, it is difficult to support the notion that patients received only the fluid volumes they needed and not an excess amount of fluid.

Limitations and potential rationale

The observational and focused nature of the studies mentioned above cannot be overemphasized. These studies just highlight a potential association between fluid overdose and mortality, yet do not prove causality. In addition, the studies only included children who ultimately received CRRT at the discretion of the local physician; CRRT initiation was not directed by a protocol in any of these studies. Finally, since these studies involved only CRRT cohorts, the ability to generalize the findings to patients without AKI who don’t need RRT is hampered.

Nevertheless, the observations generate some potential provocative hypotheses to explain the associations. For instance, in pediatric practice, almost all medications are prescribed to patient size, in terms of body weight or surface area. One can imagine a scenario in which a child with a gram negative sepsis treated with a third-generation cephalosporin dosed on ICU admit weight or historical dry weight is actually underdosed as a result of a severely increased volume of drug distribution from excess fluid accumulation. In this example, it is possible that the antibiotic concentration is below the pharmacodynamic profile to eradicate the organism. Another obvious potential hypothesis would posit an association between excess fluid accumulation and impaired oxygenation or other pulmonary mechanics, especially in patients with capillary leak syndromes such as sepsis.

Final thoughts

This article promotes a concept of fluid overdose in critically ill children with AKI. Inherent in this concept is the importance of regarding fluid as a medication with respect to both composition and volume (dose). Future research will require prospective evaluation of different fluid dosing strategies beyond the initial resuscitation effort to optimize care for all critically ill patients.

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References