

CHAPTER 200

Treatment of Acute Kidney Injury in Children: Conservative Management to Renal Replacement Therapy

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OBJECTIVES

This chapter will:

1. Review the cause of pediatric acute kidney injury, correlated with reversibility and outcome.
2. Outline the components of conservative management of pediatric acute kidney injury.
3. Present an approach to dialytic management of pediatric acute kidney injury.

Management of acute kidney injury (AKI) in a child should begin with a thorough etiologic evaluation to pinpoint the underlying cause or causes and an assessment of the potential for reversibility of the renal impairment, as well as its likely duration. This information is crucial in predicting severity and outcome of AKI.

This chapter describes conservative (preventive and medical option) and dialytic management of children with AKI.

CAUSE

The initial evaluation is straightforward, with assessment of patients' anamnesis, recent medical or surgical procedures,

and received drugs. In the same line, volume status, cardiac output, and careful examination of volume depletion should be performed. Evaluation by hemodynamic monitoring as well as determination of the fractional excretion of sodium (FeNa) may be helpful to diagnose renal dysfunction in this etiologic category.¹

Other possible causes of AKI can be evaluated readily by renal ultrasound imaging at the bedside to look for an obstructive pattern, at the level of either the bladder or the ureters. Identifying whether the patient has solitary or bilateral kidneys or other major renal congenital malformations also is helpful.

The remaining causes of AKI are intrinsic processes. With advances in technology and medical care in Western medical centers, intrinsic kidney disease often is related to drug toxicity, sepsis, acute tubular necrosis (ATN), or an acute process with underlying chronic kidney disease (CKD).² Another primary cause of intrarenal AKI continues to be hemolytic uremic syndrome.³ The diagnosis of hemolytic uremic syndrome can be made easily by evaluation of a peripheral smear, looking for subnormal cell counts and presence of schistocytes, with worsening anemia and uremia. This clinical picture should be distinguished from that in sepsis or disseminated intravascular coagulation (DIC), which can include the same findings. In the absence of hemolytic uremic syndrome, drug-induced AKI, or ATN, renal biopsy is indicated to identify the AKI cause and perhaps to direct therapy; however, this is rarely the case in the pediatric intensive care unit (PICU) setting.

GENERAL APPROACH TO CONSERVATIVE MANAGEMENT

Removal or Correction of the Offending Cause

With intrarenal or intrinsic disease, it is important to look for all possible offending causes. Many of the newer agents that are useful for pain management (e.g., nonsteroidal antiinflammatory drugs [NSAIDs]), in transplantation (e.g., calcineurin inhibitors), or for general medical care may be beneficial in relief or prevention of symptoms but detrimental to renal function. A review of the patient's current medications therefore potentially can identify an etiologic factor that can be adjusted or removed to minimize the AKI. It is well known that certain combinations of medications, including angiotensin-converting enzyme inhibitors/angiotensin receptor blockers plus diuretics plus nonsteroidal antiinflammatory drugs (NSAIDs), known as the "triple whammy," are associated with increased rates of AKI.⁴ Furthermore, a combination of two of these classes of medications was associated with an increased risk of AKI. Thus, in the setting of AKI and in patients at risk for AKI, such as those with dehydration or acute infection, clinicians must balance the risk of nephrotoxicity versus the therapeutic benefit that led to their prescription in the first place. The prospective Nephrotoxic Injury Negated by Just-in-time Action (NINJA)⁵ study has been described. NINJA uses an automated program to extract data in near real time from electronic health records to flag non-critically ill hospitalized children exposed to three or more nephrotoxic medications simultaneously or an intravenous aminoglycoside for 3 or more consecutive days. Exposed patients underwent systematic surveillance with a daily serum creatinine measurement. In the first year, NINJA revealed that 25% of exposed patients developed AKI and that more than 50% experienced severe AKI, defined as a doubling of serum creatinine from baseline. In the first 3 years of the NINJA project a 38% decrease in the rate of three nephrotoxic medication exposures and a concomitant 64% decrease in AKI rates was observed, which was associated with more than 600 exposures and nearly 400 AKI episodes avoided.⁶ Although the NINJA is a surveillance program for non-critically ill hospitalized children, it is not unreasonable to expect that the contribution of nephrotoxic medications to AKI acquired in the intensive care unit likely would be lessened as well with systematic surveillance of nephrotoxic medication burden.

Enhancement of cardiac output also is in order. Evidence from studies in adult patients has shown that renal-dose dopamine is not beneficial for preservation of urine output or recovery of renal function.⁷ This aspect of management of AKI has never been looked at adequately in the pediatric population, however. Data from adult critical care and animal models now support the concept of "renal-dose norepinephrine." In human studies and septic animal models, low-dose norepinephrine has been shown to improve splanchnic blood flow, improve renal perfusion, and enhance urine output by maximizing cardiac output and vascular tone.^{8,9} The result of this beneficial effect may be avoidance of the need for renal replacement therapy (RRT). Nesiritide and fenoldopam were introduced in the past decade and have been touted as drugs that have renal-protective mechanisms while enhancing urine output.¹⁰ These agents have yet to be found to be beneficial in the pediatric population, although interesting studies have been conducted recently in cardiac surgery patients.^{11,12}

The use of albumin versus saline to preserve intravascular volume integrity is the subject of ongoing debate. The sentinel

study by Finfer et al., involving a hypovolemic comparison of 4% albumin versus saline, showed no difference in AKI or a need for RRT between the two treatment groups.¹³ In the subset of patients with sepsis or burns, a preferential benefit was observed in the albumin treatment group. In a recent study, Dubois et al. noted that in patients with a low plasma albumin, replacement of albumin as compared with saline will improve splanchnic blood flow, as evidenced by the patient's ability to tolerate enteral feedings.¹⁴ Therefore enhancement of cardiac output by balancing volume replacement and use of norepinephrine have now become common practice in the management of AKI in adults. None of this has been studied adequately in the pediatric population; however, there is a strong rationale to optimize hemodynamics and enhancing of vascular tone by means of vasoactive drugs to restrict the amount of administered fluids.

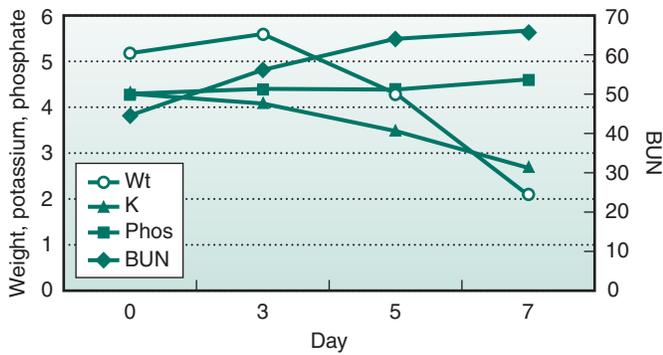
Attention to Nutrition

To avoid the need for RRT in a patient with AKI, consideration of solute and fluid status is essential. Specific attention to nutrition delivery based on renal clearance is in order. Nutrition is important in patients with AKI as part of ongoing care. Either the parenteral or the enteral route can be used for delivery of nutritional formulas. The evidence in adult and pediatric patients has shown clearly an advantage of enteral nutrition over parenteral nutrition.^{15,16} As supported by clinical experience in many programs, specialized formulas can be delivered to patients with AKI to maximize nutrition and minimize solute and fluid excess. To this end, the use of "adult-based formulas" such as Renalcal (Nestle, Glendale, CA), Suplena (Ross, Columbus, OH), Nepro (Ross, Columbus, OH), or Magnacal (Novartis, East Hanover, NJ) can provide high-calorie nutrition, with either low or high protein and low or no electrolytes. All of these formulas deliver 2 cal/mL, with either no electrolytes (Renalcal) or low electrolytes (specifically, potassium and phosphorus) for nutritional supplementation. These formulas can be given either orally or by feeding tube to provide adequate caloric intake. Because these formulas are hyperosmolar (600 mOsm), they may induce a hyperosmolar diarrhea that may be detrimental to nutrition absorption. If the patient can tolerate these feedings, then adequate dietary supplementation can be provided easily with a reduced fluid balance intake, optimal calories amount, and corrected elements in case of renal dysfunction (Fig. 200.1).

Volume Status

Attention to the patient's volume status is essential throughout the hospital stay. Many programs focus exclusively on intake and output measurements as a way to monitor volume status. This approach, however, does not take into account insensible losses. Therefore obtaining daily weight measurements on the same scale is paramount and, in combination with vital signs, heart rate, and blood pressure, will give the clinician a better sense of the patient's volume status.

Fluid overload has been associated repeatedly with renal dysfunction as either a cause or a consequence. Different threshold of cumulative weight gain with respect to patient body weight has been described. However, excessive fluid accumulation in the range of 10% to 20% has been associated unanimously with worsened lung, heart, and kidney function and patients' prognoses.¹⁷ However, in patients with other (independent) reasons for fluids requirements



Calories/kg/day = 107; Protein/kg/day = 2.1 g

FIGURE 200.1 “Invisible loss” nutrition with an “adult-based formula” (Renalcal) in an anuric infant. *BUN*, Blood urea nitrogen (mg/dL); *K*, potassium (mmol/L); *Phos*, phosphate (mg/dL); *Wt*, weight.

and poor outcomes (e.g., renal dysfunction, low cardiac index, residual surgical defects, infection, intraoperative bleeding with massive transfusion), we cannot know whether aggressive fluid administration is the cause of organ dysfunction, or if it is an associated factor with no direct causal relationship.¹⁷ The possibility of setting fluids infusion according to predefined hemodynamic targets (goal-directed therapy) to correctly tailor every milliliter of administered intravenous fluid is a research priority in current intensivists’ agendas.

Diuretics

Diuretics can be used to augment urine output but will not enhance solute clearance. Comparison of loop diuretics given as an intermittent bolus or by continuous infusion shows that the use of continuous infusion involves less exposure to these potentially toxic agents with the same amount of urine output.^{18,19} Thiazide-like diuretics (e.g., oral metolazone or intravenous chlorothiazide) can be given to enhance the effectiveness of loop diuretics.²⁰ Urinary flow does not reflect effective solute clearance. Accordingly, increased urine output does not correlate with improvement of renal function or with improvement of solute clearance. However, optimization of fluid balance with the administration of aggressive diuretic therapy in overloaded patients has shown in post-cardiac surgery infants potentially to improve hard outcomes (i.e., ventilation and PICU stay).²¹

DIALYTIC THERAPIES

If the blood urea nitrogen (BUN) level rises above 70 mg/dL, or if volume excess is greater than 10%, or if a classic indication for RRT, such as metabolic acidosis, hyperkalemia, or pulmonary edema, is present, intervention with dialytic therapy should be considered.^{22–26}

RRT in a critical care setting can be carried out using intermittent hemodialysis, continuous peritoneal dialysis, or a continuous hemofiltration protocol.^{27,28} Hemodialysis can be done in either a convective or a diffusive mode, or a combination of both. The evidence does not suggest that one modality is superior to another in terms of outcome. In patients who are less hemodynamically compromised and are receiving primarily enteral feedings, intermittent

hemodialysis may be the most appropriate form of RRT. If patients are hemodynamically compromised, then a continuous form of dialysis (peritoneal dialysis or hemofiltration) may be the preferred method for RRT.²⁹ Peritoneal dialysis may be contraindicated in patients with intraabdominal pathology. Another contraindication to peritoneal dialysis is presence of a ventriculoperitoneal shunt, for it may add a low risk of shunt infection.

Comparable data for children are limited regarding outcome based on RRT modality in pediatric patients. Work by Fleming et al. showed no difference in mortality rate between peritoneal dialysis and hemofiltration in postoperative pediatric cardiac patients. In those patients on hemofiltration, delivery of a higher calorie load was possible, but this had no impact on mortality rate.³⁰

In later work, Maxvold et al. used a retrospective database to compare hemodialysis and hemofiltration. These investigators found that mortality rate was not related to the modality of RRT but was influenced by the severity of illness as measured by pressor use.³¹ Another study looked at a large series of children on intermittent hemodialysis, peritoneal dialysis, or hemofiltration, extending the work of Maxvold’s group. Again, this report demonstrated that the modality had minimal impact on outcome, but the severity of illness predicted survival versus nonsurvival in this population.²⁹

Thus, with use of RRT in patients with AKI, work as early as 1994 by Lane et al. demonstrated that volume excess may be a predictor of nonsurvival.²³ These investigators demonstrated that in bone marrow transplant recipients with a volume excess greater than 10%, those with a higher volume excess at the initiation of RRT had a worse survival. In hemofiltration-specific studies, Goldstein et al. in 2001,²⁴ Foland et al. in 2004,²⁵ Gillespie et al. in 2004,³² and the Prospective Pediatric Continuous Renal Replacement Therapies (pPCRRT) study group in 2005²⁶ demonstrated the same effect of higher volume excess in patients at the initiation of RRT: a negative impact on survival. Interestingly, a recent study comparing peritoneal dialysis to diuretics in post-cardiac surgery neonates found that the former, being effective in early control of fluid balance in the studied cohort, turned out to reduce the number of patients with prolonged ventilation time and PICU stay.³³

In summary, no controlled studies in pediatric patients have compared modality differences in outcome or have assessed the relative benefits of convection versus diffusion in hemofiltration modalities. Although no prospective evidence is currently available, in certain patient subgroups, such as bone marrow transplant recipients, the use of a convective modality may be beneficial.

Finally, long-term follow-up evaluation of patients who had recovered from AKI demonstrated evidence of ongoing risk of progressive loss of kidney function over time in a small subset of patients. In a group of children who had survived acute renal failure and RRT with clinical recovery, Askenazi et al. found evidence of microalbuminuria, increased glomerular filtration rate such as hyperfiltration syndrome, and hypertension. Resolution of AKI after RRT is no longer needed does not mean that these patients are left with no long-term risk factors.³⁴

CONCLUSION

The care of the child with AKI need not begin with RRT, but initiation of specific interventions is indicated at the earliest identification of the renal impairment. Attention to volume status, nutrition, and drug delivery, as well as

avoidance of nephrotoxins, has to be considered the first line of therapy in patients with AKI. Some form of RRT should be instituted in patients with a rising BUN or a BUN in excess of 70 mg/dL, a volume status greater than 10% excess, or one of the more classic indications, which include malignant hypertension, pulmonary edema, hyperkalemia, and metabolic acidosis.

Key Points

1. The cause of acute kidney injury in children can be divided into prerenal, intrarenal, and postrenal causes.
2. For management of children with acute kidney injury, enhancement of cardiac output is essential, as is specific attention to drug dosing and nutrition delivery based on renal clearance.
3. Diuretics can be used to augment urine output in these patients but will not enhance solute clearance.
4. Intervention with dialytic therapy may be indicated for patients with blood urea nitrogen in excess of

70 mg/dL or greater than 10% of volume excess, or if metabolic acidosis, hyperkalemia, or pulmonary edema is present.

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