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Evaluation and Management of Critically Ill Children with Acute Kidney Injury

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Abstract

Purpose of the review—Acute kidney injury (AKI) has replaced the term acute renal failure and new definitions have been proposed to allow earlier detection. Recent epidemiology data show that the etiology of pediatric AKI has changed and the indications for initiation of renal replacement therapy have evolved. This review will highlight recent studies on the diagnosis of AKI, review the differential diagnosis, highlight the importance of cumulative fluid overload and provide key management strategies for the pediatric patient with AKI.

Recent findings—Over the last decade serum creatinine based categorical definitions of AKI have been accepted and improve our ability to detect AKI early in the disease process. Evidence based modifications of these definitions have occurred. Higher degree of fluid overload portends poor outcomes in critically ill patients. Significant improvements in our understanding of the pathophysiology of glomerular/vascular causes of AKI have occurred.

Summary—Categorical definitions of AKI have shown that higher that AKI portends poor outcomes even when adjustment of severity of illness and other confounders. As higher degrees of fluid overload are independently associated with poor outcomes, strategies to prevent and/or treat fluid overload are likely to improve outcomes.

Keywords

Fluid Overload; Definition; Etiology; Management

Introduction

Acute kidney injury (AKI) has replaced the term acute renal failure and new definitions have been proposed to allow earlier detection. Clinically, AKI is characterized by a sudden deterioration of normal kidney function. This dysfunction causes abnormal regulation of fluid, electrolytes, blood pressure, and removal of waste products. In addition, growing evidence shows that the kidneys play a key role in the development and regulation of the inflammatory process which occurs in multi-organ failure (1–4). Over the past several years tremendous effort and large number of resources have been placed to improve our ability to diagnose AKI early in the disease state. It is hoped that these new biomarkers will be able to diagnose AKI earlier in the disease state and differentiate different etiologies and stages of AKI. Until these biomarkers are adapted, functional markers, such as serum creatinine (SCr) and cystatin C, are used to diagnose AKI. This review will highlight recent studies that have improved our ability to diagnose AKI, review the differential diagnosis of AKI, highlight the

importance of cumulative fluid status in the assessment of the critically ill child with AKI, and finally provide some key management questions/strategies to the pediatric patient with AKI.

Does this critically ill child have acute kidney injury?

Historically, a substantial rise in SCr and a drop in urine output have been used to determine if a child has AKI. Prior to the 2004, over 30 definitions of AKI existed in the literature which made comparison between studies very difficult. In 2004, the ADKI group proposed the RIFLE (Risk, Injury, Failure, Loss and End-Stage) classification definition of AKI(5). The first 3 categories (Risk, Injury and Failure) staged the degree of AKI based on whether the amplitude of SCr rise (or decrease in estimated GFR) and/or a drop in urine output. The last two categories (Loss and End-stage) defined temporary or permanent loss of kidney function after AKI. In 2007, a similar definition was proposed for pediatric patients and has been used to describe several cohorts (6–11). The RIFLE definition was updated in 2007 by the Acute Kidney Injury Network (12), by many of the same experts who proposed RIFLE. The AKIN definition is similar to the first 3 stages of the RIFLE classification with a couple of changes. Recently, the Kidney Disease Improving Global Outcomes (KDIGO) [www.kdigo.org] has brought together international experts from many different specialties to produce a definition and staging system which will harmonize these recent definitions. It is expected that this definition will be accepted globally in 2011. (See Table 1 for comparison of RIFLE, pRIFLE, AKIN). The adjustments in these definitions over time should be considered gradual evidence-based improvements. These SCr-based classification definitions of AKI have provided great insights; however, when using these definitions, it is important to acknowledge the shortcoming and limitations of using SCr-based AKI definitions.

The use of changes in function markers such as SCr to define AKI is not ideal as SCr concentrations may not change until 25–50% of the kidney function has already been lost and thus it may take days after an injury before a significant rise in SCr is seen(13). At lower GFR, SCr will overestimate renal function due to tubular secretion of creatinine(13). SCr varies by muscle mass, hydration status, sex, age and gender and method of measurement(14, 15). Once a patient receives dialysis, SCr can no longer be used to assess kidney function since SCr is easily dialyzed. In neonates, SCr in the first few days of life reflects mother's; thereafter, the SCr improve at different rates depending on the degree of gestational age (16). In addition, SCr based definitions fails to delineate the severity, timing and cause of the injury.

Despite the above concerns about these AKI definitions, these new SCr-based classification definitions of AKI have allowed for valuable comparisons among different studies, which have shed new light about the epidemiology of AKI. Using these definitions, we have learned that AKI is an independent predictor of mortality in critically ill neonates(17), children(6, 11), and adults(18–22) even after controlling for co-morbidities, interventions and demographics. Even small changes in SCr, which previously were ignored, are associated with poor outcomes(9) (23).

Hopefully, as research on novel AKI biomarkers and therapies continue, these definitions can be adapted such that patient risk can be stratified, pathophysiologic etiology can be determined and clear time points for interventions can be deduced.

What is the etiology of AKI in this critically ill child?

With advancements in the field of critical care medicine and other fields of pediatrics, the etiology of AKI has changed in large tertiary centers, whereby less than 10% of those with

AKI (24) and those who receive continuous renal support(25) have a primary renal diagnosis. The approach to uncovering the etiology of AKI has not changed much over the last decade although future biomarker and radiologic studies may help delineate the cause of AKI. Until then, critically ill children with AKI should have an evaluation of the following:

- Risk factors for AKI (chronic kidney disease, cardiac disease, liver failure, nephrotoxic medications)
- Assessment for potential causes of AKI (decrease intake, increased losses, urinary tract symptoms, drug exposure, presence of sepsis, fever, rashes, joint pains)
- Clinical exam findings: rash, uveitis, joint swelling, fever, skin perfusion, heart rate, blood pressure, audible renal bruits, and a palpable bladder.
- Laboratory/radiologic tests will depend on the history and physical exam. They include: serum electrolyte, blood urea, SCr, cystatin C, urinalysis, microbiology, urinary electrolytes, chest x-ray, electrocardiogram, renal ultrasound (to evaluate for congenital abnormalities and obstruction), and kidney biopsy

AKI is commonly multi-factorial. Classically, the underlying cause of rising SCr/drop in urine output has been divided into pre-renal azotemia, renal injury, and post-renal obstruction.

Pre-renal Azotemia—Pre-renal azotemia (sometimes referred to “pre-kidney failure” but perhaps better termed “acute kidney success”) occurs in response to decreased renal blood flow (RBF). Causes of pre-renal azotemia are listed in (Table 2). When low RBF occurs, renal autoregulation preserves glomerular filtration rate (GFR) by increasing renal sympathetic tone, activation of the renin-angiotensin-aldosterone system, and increased activation of hormones such as vasopressin and endothelin which enhance proximal tubular sodium and water reabsorption in those with intact tubular function. These renal hemodynamic changes lead to decrease water and sodium losses, so as to maintain systemic volume expansion and blood pressure.

In those with pre-renal azotemia and intact tubular function, increased sodium and urinary urea reabsorption occurs. This is reflective by low urine sodium concentrations ($FE_{Na} < 1\%$), low urine urea concentration ($FE_{Urea} < 35\%$) and increased blood urea:creatinine ratios. These renal indices should be interpreted with caution in patients on diuretics, those with salt-losing state, and those with chronic kidney disease. In a recent study of children with AKI, FE_{Urea} was found to be a more useful index (26).

This period of renal hypoperfusion, which has been recently referred to as “renal angina” is critical to recognize and treat to prevent cellular damage to occur(27). Correction of the underlying cause of hypoperfusion restores GFR unless renal hypoperfusion is severe enough to cause renal tubular and endothelial damage. Once parenchymal damage occurs, renal tubular cell damage occurs even if renal perfusion is restored.

Intrinsic Acute Kidney Injury—Although disease process can affect more than one part of the kidney, intrinsic kidney injury can be divided into tubular, intrinsic, vascular, and glomerular.

Ischemic Acute Kidney Injury—Pre-renal azotemia and ischemic AKI are a continuum of physiologic responses. Prolonged or severe hypoperfusion causes injury to renal parenchymal cells, particularly to tubular epithelium of the terminal medullary portion of the proximal tubule (S3 segment) and of the medullary portion of the thick ascending limb of the loop of Henle. In contrast to pre-renal azotemia, renal function abnormalities in intrinsic

AKI are not immediately reversible. The severity of intrinsic AKI ranges from mild tubular dysfunction, to acute tubular necrosis, to renal infarction and corticomedullary necrosis with irreversible renal damage.

The course of ischemic AKI may be subdivided into the prerenal, initiation, extension, maintenance, and recovery phases (28). If restoration of renal blood flow occurs during the pre-renal azotemia stage, GFR can return promptly to normal. The initiation phase includes the original insult and the associated events resulting in a drop in GFR. Tubular dysfunction with low GFR represent the maintenance phase. The duration of the maintenance phase depends on the severity and duration of the initial insult. The recovery phase is characterized by the gradual restoration of GFR and tubular functions which can take months to occur. Recognition of the different phases of intrinsic AKI is helpful in the diagnosis, clinical management, and prognostication of the disorder.

Not only are tubular epithelial cells critical in the pathophysiology of ischemic AKI, but damage to the innermost lining of the renal vascular system, endothelial cells, has a critical role in the initiation, extension, maintenance and recovery phases of ischemic AKI (29–31). Damaged endothelial and tubular cells not only lead to dysfunction within the kidney, but they produce a systemic inflammatory response which leads to distant organ dysfunction in brain, lung, heart, liver, bone marrow and gastrointestinal tract. (32–34).

Nephrotoxic Acute Kidney Injury—Pharmacologic agents are one of the most common cause of nephrotoxic AKI although endogenous substances like hemoglobin, myoglobin and uric acid can also be harmful. These toxins can cause AKI by decreasing renal perfusion (NSAID's, diuretics, ACE-inhibitors), direct tubular injury (aminoglycosides, cephalosporins, amphotericin B, rifampin, vancomycin, NSAIDs, contrast media, myoglobin/hemoglobin), interstitial nephritis, or tubular obstruction (acyclovir, uric acid). A recent study by Zappatelli shows that children treated with aminoglycosides for at least 5 days had a 33% incidence of AKI (by AKIN criteria), longer length of stay and substantial added hospital expenditures(10).

Acute Obstruction—The most common cause of obstructive induced kidney dysfunction in pediatrics are secondary to congenital malformations including imperforate prepuce, urethral stricture, prune-belly syndrome, and posterior urethral valves. Other causes of acute obstruction include neurogenic bladder, extrinsic compression, and intrinsic obstruction from renal calculi or fungal balls. Depending on the cause and associated damage to the kidneys, relief of the obstruction is imperative to restore renal function.

Primary Renal Etiologies of AKI – Glomerular/Vascular cause or AKI—in large tertiary centers, multi-organ failure and nephrotoxic medications make up a large portion of AKI cases, while primary renal conditions make up a small proportion of pediatric AKI. Nonetheless, the ability to diagnose these conditions is very important as the overall management of the patients will differ considerably and may include specific therapies such as plasma exchange and immunosuppressive therapies.

Glomerulonephritis/vascular diseases should be suspected when a child presents with AKI without an identifiable cause. Clinical signs and symptoms dictate the work-up in these patients. Those with pulmonary hemorrhage should be evaluated for glomerular/vascular cause. Examination of the urine sediment for red blood cell casts can differentiate glomerular/vascular from tubular injury. Laboratory evaluation for autoimmune antibodies (such as p and c-ANCA antibodies, anti-GBM, anti-nuclear antibodies), complement fragments (C3, C4 and CH50) and a diagnostic kidney biopsy may be helpful to unmask the cause, stage the disease, and determine the extent of active (treatable) disease.

Children with microangiopathies may present with AKI, thrombocytopenia, hemolytic anemia, elevated LDH and low haptoglobin. These microangiopathies arise from underlying damage to the endothelial cells. In the case of diarrhea associated hemolytic uremic syndrome (HUS), this endothelial damage comes from bacterial endotoxin such as the toxin expressed by E-Coli 0157. Secondary causes of atypical HUS/thrombocytopenia purpura include disorders of complement regulation (Factor H deficiency, Factor I deficiency, C3-Nephritic Factor and membrane co-factor protein), inherited or acquired ADAMTS-13 deficiency, defects in cobalamin metabolism, and secondary to medications. Strep pneumonia associated HUS, and thrombocytopenia associated multi-organ failure are unique entity that require special consideration. Excellent reviews of the evaluation and management of these conditions have recently been published. (25, 35–37).

Assessment for Cumulative Fluid overload – the forgotten vital sign

When evaluating a critically ill child with AKI, one must determine whether renal support therapy is indicated. The phrase “renal support” may be better than “renal replacement” as partial dysfunction may be an indication for technologic interventions. This is analogous to the use of “cardiac/ventilator support” as opposed to “cardiac/ventilator replacement”. Studies in pediatrics show that prevention and treatment of fluid overload are two of the most common reasons for initiation of renal support therapy(25). When Goldstein et al (38) first published on the potential detrimental effects of cumulative fluid overload, there was a lot of resistance from the critical care community about their conclusions as there was new data on the importance of aggressive goal-directed use of fluids in the early course of sepsis (39–41). Fluid overload can be calculated as follows:

$$[(\text{fluid input in liters}) - (\text{fluid output in liters})]/\text{ICU admission weight in kg}$$

Since the initial description of the potential detrimental effects of fluid overload, pediatric(38, 42–46) and adult studies(47, 48) consistently show that children and adults who accumulate a higher cumulative percent fluid overload have worse outcomes even after controlling for severity of illness. For example, using the prospective pediatric continuous renal replacement therapy (ppCRRT) registry, Sutherland et al(44) showed that those with who initiated renal replacement therapy with cumulative % fluid overload < 20% had better survival than those who had cumulative fluid excess > 20% (46% vs. 68% p<0.01). After controlling for potential confounders, the adjusted mortality odds of death was an alarming 8.5 (95% CI, 2.8, 25.7; p<0.01). Similar study of a large adult database(48) shows the same effect for not only those who received renal support therapy, but also in those who did not receive renal support. This effect may be even greater in critically ill bone marrow transplant recipients (49–52).

Management of AKI in critically ill patients

Although the definition of AKI may change over time as newer biomarkers are tested, if renal injury is indeed confirmed, several interventions should be commenced. These interventions can help determine the underlying cause, eliminate further damage to the injured kidney, and the response to therapies may help uncover the underlying etiology.

- Diagnostic evaluation to uncover the underlying etiology
 - Does this individual have risk factors for AKI?
 - Does the patient have oliguric or anuric renal failure?
 - Is there exposure to sepsis, nephrotoxic agents, ischemia, bloody diarrhea or volume loss?

- Is there urine obstruction?
- Are there signs of glomerulonephritis/vasculitis syndromes?
- Optimization of hemodynamics
 - What happens to hemodynamics, and urine output when fluid challenge is prescribed?
- Minimize exposure to nephrotoxic medications agents including radiocontrast material
- Initiation of goal directed therapy with conservative fluid management after an initial resuscitation.
- Maximize nutrition – if fluid issues hinder the ability to adequately provide nutrition, renal support therapy should be strongly considered.
- One of the most important determinants for receipt of renal support therapy is cumulative fluid overload. This value should be recorded at least daily to provide a sense of how the patient is handling fluids over the course of the hospitalization. This important vital sign is very informative to the critical care team when balancing the potential benefits and risk of renal support therapy.
- If the patient is fluid overloaded consider diuretics and/or ultrafiltration to optimize the support for the dysfunctional kidney.
- If continuous renal support is prescribed, supply an extra 1 g/kg/day of protein to make up for losses typical of continuous renal support therapies.
- Based on recent dialysis dose recommendation for critically ill patients, a minimum of 20 ml/kg/day of effluent clearance should be provided to children need continuous renal support. A KT/V clearance of 1.2 is the minimum amount of dialysis critically ill children should be provided to children receiving intermittent thrice-weekly hemodialysis(53, 54)

Conclusion

Categorical definitions of AKI have been created to detect AKI early in the disease process. Until, interventions to treat AKI are found, clinical evaluation, strategies to prevent and/or treat fluid overload, avoiding nephrotoxin medications and adequate renal support are keys to maximize outcomes in critically ill children with AKI.

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KEY BULLET POINTS

1. New categorical serum creatinine-based definitions of pediatric AKI have been devised
2. Evaluation of the pediatric patient with acute kidney injury should focus on determining the underlying cause and evaluation for renal support therapy.
3. Cumulative fluid overload is strongly associated with poor clinical outcomes in critically ill children; therefore, monitoring this important “vital sign” is essential to determine optimal time for renal support therapy.

Table 1

Classification Definitions of Adult and Pediatric AKI

AKIN			Adult			pRIFLE		
Stage	Serum Cr	Urine Output	Class	Serum Cr or GFR	Class	eCCl by Schwartz	Urine Output	Class
I	↑ SCr >0.3 mg/dl or ↑ SCr >150–200% from baseline	<0.5 ml/kg/hr × 6 hr	Risk	↑ SCr by 150% or GFR decrease by 25%	Risk	eCCl decrease by 25%	<0.5 ml/kg/h × 8 hrs.	
II	↑ SCr to >200%–300% from baseline	<0.5ml/kg/hr>12 hr	Injury	↑ SCr by 200% or GFR decrease by 50%	Injury	eCCl decrease by 50%	<0.5 ml/kg/h × 16 hrs.	
III	↑ SCr of >300 % from baseline or SCr> 4.0 mg/dl with an acute rise of at least 0.5 mg/dl	<0.3ml/kg/hr>24 hr or anuria for >12 hr	Fail	↑ SCr by 300% or SCr>4.0 mg/dl with acute rise of 0.5 mg/dl or GFR decrease by >75%	Fail	eCCl decrease by 75% or <35 ml/min/1.73m ²	<0.3 ml/kg/h for 24 or anuric for 12 hrs	
			Loss	Failure > 4wks	Loss	Failure > 4wks		
			ESRD	Failure >3 mo	ESRD	Failure >3 mo.		

Adapted from references [5],[6] and [12]

Table 2

Differential Diagnosis of Pediatric AKI

Prerenal Azotemia	Intrinsic AKI		Obstructive AKI
Loss of effective blood volume	Renal Artery Damage	Interstitial Nephritis	Congenital malformations
Absolute loss	Renal Vein damage	Drugs	Imperforate prepuce
Hemorrhage	Acute tubular necrosis	Virus/Bacteria	Urethral stricture
Gastrointestinal losses	Severe renal ischemia	Infiltration	PUV
Renal losses	Nephrotoxins	Lymphoma	Urethral diverticulum
Skin losses	Aminoglycosides	Sarcoid	Ureterocele
Relative loss – capillary leak	Indomethacin	Glomerular Causes	Megaureter
Sepsis	Amphotericin B	Post-Infections	UPI obstruction
hypoalbuminemia	Calcineurin inhibitors	IGA nephropathy	Extrinsic compression
Extra-corporeal Membrane	Radiocontrast dyes	Membranoproliferative	Intrinsic obstruction
Oxygenation			
Heart Failure	Myoglobinuria	Lupus	Renal calculi
Pharmacologic agents	Hemoglobinuria	ANCA Ab Associated	Fungus balls
Indomethacin	Heavy Metals/Poison	Pauci-immune GN	Neurogenic bladder
Tolazoline	Intra renal obstruction	Goodpasture's disease	
ACE inhibitors	Acyclovir	(anti-GBM)	
ARB	Uric acid	Microangiopathies	
	Infections	Renal vascular causes	
	Pyelonephritis	Renal artery thrombosis	
	Radiation/Chemotherapy	Renal vein thrombosis	

ACE = angiotensin converting enzyme; ARB=angiotensin 2 receptor blocker; IGA = immunoglobulin A; ANCA = anti neutrophil cytoplasmic antibody; anti GBM = anti glomerular basement membrane antibody;