Review

Acute Kidney Injury in Children: Classification, Recognition and Treatment Principles

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Acute Kidney Injury in Children: Classification, Recognition and Treatment Principles

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Abstract: Acute kidney injury (AKI) in children is a critical medical condition characterized by a sudden decline in kidney function. This article provides a comprehensive overview of AKI in pediatric populations, exploring its pathophysiology, the role of various drugs, and the long-term implications for kidney health. Key topics include oliguria, anuria, urine output, hypervolemia and interactions among them as well as role of diuretic nephrotoxicity and glomerular filtration rate. Concepts of electrolytes, acid-base balance and renal perfusion assessment are presented. Basic principles of intensive care unit (ICU) management, renal replacement therapy, and the association with multiorgan failure are described. Additionally, the article discusses the potential long-term outcomes of AKI, including the risk of chronic kidney disease, hypertension, and proteinuria.

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1. Introduction

Acute kidney injury (AKI) is a severe and potentially life-threatening condition characterized by a rapid decline in kidney function. While historically considered an adult-centric concern, AKI is increasingly recognized as a significant issue in pediatric populations. This article aims to explore the pathophysiology of AKI in children, focusing also on recognition and the role of various drugs in its management and the long-term implications for kidney health. AKI in children is defined by a sudden decrease in kidney function, often assessed through parameters like serum creatinine and urine output. The Kidney Disease: Improving Global Outcomes (KDIGO) classification system categorizes AKI based on these criteria, offering a standardized approach to diagnosis and management [1]. It is important to know that serum creatinine is often a late and imprecise test of renal function because it reflects glomerular filtration rate (GFR) in individuals at steady state with stable kidney function. Therefore, it does not precisely reflect the GFR in a patient with changing kidney function. In addition, serum creatinine levels depend upon various extrarenal factors, such as age, sex, muscle mass, associated diseases and the nutritional and hydration status of the child. Nevertheless, elevated serum creatinine level is the most common laboratory parameter used for the diagnosis of AKI in children. However, degree of oliguria affects fluid and electrolyte management and has strong correlation with poor outcomes in children with AKI. Therefore, urine output measurement is very useful, particularly in the critical care setting. But, on the other hand, the presence of a normal volume of urine does not exclude AKI [2]. Oliguria, characterized by reduced urine output, is a hallmark of AKI. Anuria, the absence of urine production, represents a severe form. Both oliguria and anuria signify impaired renal function and inadequate filtration, necessitating prompt intervention [3].

Standardized and widely accepted definitions for pediatric AKI include the KDIGO (Kidney Disease Improving Global Outcomes) and pRIFLE (Pediatric Risk, Injury, Failure, Loss, End-Stage Renal Disease) classifications. The KDIGO AKI definition and staging has been accepted by pediatric nephrology community in order to guide clinical care as well as a standardized measure in AKI pediatric studies. Table 1 presents these definitions [2].

Table 1. Criteria for KDIGO (»Kidney Disease Improving Global Outcomes«) definition of acute kidney injury (AKI) in children and neonates.

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AKI Stage	Serum creatinine	Urine output
1	Increase in serum creatinine by ≥ 0.3 mg/dL from baseline (≥ 26.5 μmol/L) within 48 hours ***or*** Increase in serum creatinine to ≥ 1.5 times baseline within prior 7 days	Urine volume ≤ 0.5 mL/kg/hour for six hours
2	Increase in serum creatinine to 2-2.9 times from baseline	Urine volume < 0.5 mL/kg/hour for 12 hours
3	Increase in serum creatinine to > 3 times from baseline ***or*** creatinine concentration > 353,6 μmol/l (4 mg/dl) ***or*** initiation of RRT ***or*** estimated GFR < 35 ml/min/1.73 m^2	Urine volume < 0.3 mL/kg/hour for 24 hours ***or*** Anuria for at least 24 hours

Abbreviations: AKI - acute kidney injury; GFR - glomerular filtration rate; RRT - renal replacement therapy.

2. Classifications

Several AKI classifications have been developed. The most widely used is the one that separates the causes of AKI into the categories based on the anatomic location of the initial injury which is helpful for understanding the predisposing pathophysiology and treatment approach. Table 2 presents AKI classifications [2].

Table 2. Acute kidney injury classifications.

Causes of AKI		Main characteristics
Anatomic location of the initial injury	Prerenal disease	the most common form of AKI in children
		volume-responsive or functional AKI
		decreased renal perfusion due to hypovolemia (bleeding, GI, urinary or cutaneous losses) or decreased effective circulation (heart failure, septic shock, cirrhosis)
		reduced GFR and normal renal tubular function with increased reabsorption of Na^+ and water, causing oliguria
		urine flow and GFR return to normal after correction of renal perfusion
	Intrinsic kidney disease	structural damage to the renal parenchyma
		most commonly due to prolonged hypoperfusion, sepsis, nephrotoxins or severe glomerular diseases

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	Postrenal disease	Usually due to congenital or acquired anatomic obstructions to the lower urinary tract
Clinical setting or circumstance	Community-acquired AKI	associated with a single predominant insult, such as volume depletion
		often reversible
	Hospital-acquired AKI	usually in the critical care setting
		multifactorial and part of multiorgan failure
		profoundly complicates treatment and outcome
Urine output	Anuria	No urine output
	Oliguria	<1 mL/kg/h in infants <0.5 mL/kg/h in children and adults > 6 h
	Nonoliguria	>1 mL/kg/h in infants >0.5 mL/kg/h in children and adults > 6 h
	Polyuria	>3 mL/kg/h, often in patients with ATN and nephrotoxic AKI, with impaired urinary concentrating defect

Abbreviations: AKI - acute kidney injury; ATN - acute tubular necrosis; GFR - glomerular filtration rate; GI – gastrointestinal; Na^+ - sodium.

3. Clinical Diagnostic Evaluation

Diagnostic evaluation consists of a thorough history, physical examination, laboratory evaluation, imaging of the urinary tract and, and, rarely, a kidney biopsy. The aim of **history** is to uncover a risk factor or cause for AKI, such as vomiting, diarrhea or decreased oral fluid intake, suggestsing prerenal AKI. Bloody diarrhea before the onset of AKI is suggestive of hemolytic uremic syndrome, for example. Pharyngitis or, rarely, impetigo a few weeks prior to macrohematuria or edema is typical for poststreptococcal glomerulonephritis. Nephrotoxic drugs or hypotensive episodes are usually associated with intrinsic AKI, especially in hospitalized patients. But in patients with autoimmune diseases or vasculitides, such as IgA vasculitis (Henoch-Schönlein purpura) or systemic lupus erythematous, systemic signs may be present, such as fever, joint involvement or rash [2].

The physical examination includes blood pressure measurement, assessment for edema and recent weight increase and signs of systemic disease. There are some physical findings, specific for underlying etiology, such as signs of volume depletion in prerenal AKI (dry mucousa, tachycardia, decreased skin turgor), edema in children with nephrotic syndrome or glomerulonephritis (the latter often accompanied by elevated blood pressure) and an enlarged bladder, suggestive of lower urinary tract obstruction. Daily assessment of body weight is crucial, especially for critically ill children, in whom hypervolemia with more than 10 % increase of body weight compared to admission weight is associated with increased morbidity and mortality. Moreover, in children with AKI who need renal replacement therapy (RRT) and with fluid overload above 20 %, mortality is increased above 700 % [2]. In AKI, hypervolemia often occurs due to impaired fluid excretion. For this reason, diuretics, such as furosemide, are commonly employed to address fluid overload. However, their use requires careful consideration, as diuretic nephrotoxicity can exacerbate renal damage [4].

Laboratory studies used to determine the underlying etiology of AKI are urinalysis, blood tests and fractional sodium excretion. Table 3 presents these studies in more detail [2].

Table 3. Laboratory studies used in the evaluation process of acute kidney injury (AKI).

Laboratory test	**Main characteristics of specific findings**
Urinalysis	Muddy brown granular casts and epithelial cell casts suggest intrinsic AKI or ATN

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	red cell casts suggest glomerulonephritis, especially when associated with dysmorphic red cells and marked proteinuria; white cells and white cell casts may be present
	Pyuria with white cell, granular, or waxy casts indicate tubulointerstitial disease or UTI
	A positive test for heme on a urine dipstick without red blood cells in the sediment suggest hemolysis or rhabdomyolysis
	Usually normal in cases with prerenal AKI
	patients with ATN have σ < 1.010 and urine osmolality (more accurate measure of concentrating ability) < 350 mosmol/kg while those with prerenal AKI have σ > 1.020 and urine osmolality > 500 mosmol/kg
Fractional excretion of Na^+	FE_{Na} < 1 (< 2 in neonates): prerenal AKI - majority of the filtered Na^+ is reabsorbed as a response to reduced perfusion
	FE_{Na} > 2 (> 2.5 in neonates): indicates ATN
	FE_{Na} 1 - 2: inconclusive
	Limitations of FE_{Na}: fluid administration prior to measurement, diuretic use, AKI due to contrast nephropathy or pigment nephropathy

Abbreviations: AKI - acute kidney injury; ATN - acute tubular necrosis; Na^+ - sodium; σ - urine specific gravity; UTI - urinary tract infection

Biomarkers, including serum creatinine and urea, play a crucial role in diagnosing and monitoring AKI. Periodic assessments of renal function aid in treatment adjustments and provide insights into the progression or resolution of the condition [5]. Serum creatinine is the most common laboratory test used to detect decreased GFR as a marker of AKI. However, it accurately reflects GFR only in patients with stable renal function. When it is not known if the GFR is decreased according to initial creatinine, subsequent regular measurements revealing a rise in its concentration confirms the diagnosis of AKI. The serum creatinine can be detected only with at least 50 % reduction in GFR in some cases. Some studies suggest that cystatin C has potential to be a laboratory parameter that more accurately predicts AKI in children. It is freely filtered by the kidney with complete reabsorption and catabolism in the proximal tubules with negligible urinary excretion. Therefore, it is less affected by extrarenal factors compared to creatinine except for thyroid dysfunction, corticosteroids and inflammatory diseases. However, unlike creatinine, its measurements are expensive and are not widely available [2].

The ratio between serum blood urea nitrogen (BUN) and creatinine concentrations is significantly increased in patients with prerenal AKI (being over 20) and normal in patients with ATN (between 10 and 15). The reason for a difference is increased urea reabsorption by the proximal tubules, otherwise impermeable to creatinine. But increased BUN is present also in patients with increased urea production (administration of steroids, total parenteral nutrition), catabolic states and gastrointestinal bleeding and, therefore, this ratio has limited utility. In some patients, fluid administation of 10 - 20 mL/kg of normal saline might be both diagnostic and therapeutic. After such a fluid challenge, a decrease of BUN and serum creatinine suggests a prerenal AKI while a lack of their improvement, especially with simultaneous signs of fluid overload, is in favour of intrinsic AKI. Therefore, fluid administation is contraindicated in patients with establishe hypervolemia [2]. In addition, AKI significantly impairs the GFR, leading to electrolyte imbalances and disruptions in acid-base homeostasis. These alterations can contribute to complications and necessitate meticulous management to restore equilibrium [6].

Regarding **imaging**, a renal ultrasound is very useful in children with AKI of unclear etiology. It can detect the presence of renal agenesis, renal size, and can assess the parenchyma. In addition, It is very helpful in diagnosing urinary tract obstruction or occlusion of the major renal vessels and in differentiating AKI (where the size of the kidneys, with increased echogenicity, is normal or increased) from chronic kidney disease (usually small and shrunken) [2].

4. Basic Principles of Pediatric AKI Treatment

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Supportive measures include careful fluid management, maintenance of electrolyte balance, and addressing the underlying cause of AKI. These measures are crucial for optimizing conditions for kidney recovery [7]. Adequate fluid administration in children with hypovolemia, avoidance of hypotension in critically ill children by providing inotropic support if indicated and adjustment of dosing of nephrotoxic medications based on close monitoring of renal function and drug levels whenever possible are the most important measures for prevention of AKI. Routine use of certain drugs (such as loop diuretics, manitol, low-dose dopamine, fenoldopam and others) is not indicated for prevention of AKI in high-risk children. Table 4 presents principles of supportive measures in more detail [8].

Table 4. Principles of supportive measures.

Parameter	Special conditions	Description
Fluid volume	Hypovolemia	immediate i.v. fluid administation in order to restore renal function and prevent progression to intrinsic AKI
	Euvolemia	fluid losses (insensible fluid, urine GI losses) must be balanced with given fluids
	Hypervolemia	fluid removal / restriction needed
		oliguric AKI - consider furosemide to convert AKI to nonoliguric form
		early consideration for RRT in the critically ill child
Electrolytes	Oliguria / anuria	restriction of potassium and phosphorus
		hyperkalemia is the most common electrolyte complication and is potentially life-threatening due to cardiac arrhythmia
		therapy according to severity of hyperkalemia
	Sodium	intake restriction to 2-3 mEq/kg/day to prevent fluid retention and hypertension
	Polyuria	Replacement of electrolyte losses
Acid-base balance	Metabolic acidosis	common abnormality of AKI
		$NaHCO_3$ indicated in life-threatening situations despite possible adverse effects
Hypertension		common complication of AKI
		therapy according to the severity and cause of hypertension
Nutrition		AKI is associated with catabolism
		nutritional support needed to enhance the recovery
		normal nutrition maintenance requirements and supplemental calories to address the catabolic needs

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	Caloric intake: at least 120 Kcal/kg/day in infants and at least 150 % of maintenance needs in older children
Drugs	avoidance of nephrotoxic agents
	dosing adjustment of renally excreted drugs according to renal function

Abbreviations: AKI - acute kidney injury; GI – gastrointestinal; $NaHCO_3$ - Sodium bicarbonate.

In severe cases of pediatric AKI, especially when oliguria or anuria persists, RRT may be initiated. This can include modalities like hemodialysis or continuous renal replacement therapy (CRRT) to provide temporary renal support [9]. AKI is an independent predictor of morbidity and mortality, especially in critically ill children. RRT may prevent and correct the adverse and potentially life-threatening complications and improve survival. Urgent indications for RRT in children with AKI are clinically significant hypervolemia unresponsive to diuretic therapy (especially if associated with increased ventilatory requirements, usually in children with above 15 % degree of fluid overload), hyperkalemia and persistent metabolic acidosis (both unresponsive to medical treatment), complications of uremia (pericarditis, encephalopathy and bleeding) and exposure to toxins that are dialyzable and are inadequately excreted by the kidney. However, RRT should be initiated early according to BUN level and before the development of clinical signs and symptoms of AKI rather than delaying dialysis until the child is symptomatic. It is indicated as well in critically-ill children with oliguria despite diuretic therapy who require high volumes of intravenous fluids for drugs, nutrition or transfusions [10].

Several RRT modalities, including peritoneal dialysis (PD), intermittent hemodialysis and continuous RRT, are available to treat children with AKI. PD is the most common modality utilized in children, especially in infants and small children. There is no enough available data to favour one modality over another. Therefore, the selection of modality of RRT is based on patient chracteristics (size, comorbidity, ability to obtain access), local expertise and experience and available resources. In addition, initiating RRT in a critically ill child requires collaboration among nephrologists and other different subspecialists caring for the child. Early discussion and planning will enhance the therapeutic process and help to improve the outcome. Retrospective data demonstrate the overall survival rates range between 50 and 75 % in children with AKI who needed RRT. Risk factors for mortality include the underlying disease, hypotension, marked hypervolemia at the initiation of RRT, use of inotropic therapy during RRT and age below one year [10].

5. Long-Term Implications of Pediatric AKI

AKI in childhood poses a heightened risk of developing chronic kidney disease (CKD) in later life. The severity and duration of AKI are correlated with the likelihood of CKD development, highlighting the importance of ongoing monitoring [11]. Children who have experienced AKI may be at an increased risk of developing hypertension as well. The disruption in renal function and hemodynamics during AKI may contribute to long-term blood pressure abnormalities [12]. Proteinuria, an abnormal presence of proteins in the urine, is another potential long-term consequence of AKI. This further underscores the need for ongoing monitoring and early intervention to mitigate the risk of progressive kidney damage [13]. In addition, AKI in children is associated with increased mortality, especially in critically ill children and in those in need of RRT. Children with moderate to severe AKI should be followed regularly (at least once a year) to detect signs of CKD, such as hypertension and proteinuria [8].

6. Conclusions

Pediatric AKI is a critical condition that demands prompt recognition and intervention. The pathophysiology involves disruptions in kidney function, fluid balance, and electrolyte homeostasis. Diuretics, while essential in managing fluid overload, should be used judiciously to avoid nephrotoxicity. In the intensive care unit, renal replacement therapy may be necessary for severe cases. The long-term implications of pediatric AKI, including the risk of chronic kidney disease,

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hypertension, and proteinuria, underscore the importance of ongoing monitoring and early intervention to optimize outcomes. Further research and clinical advancements are essential to enhance our understanding and management of pediatric AKI.

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