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Review Article

Progress in the Diagnosis and Management of Acute Kidney Injury in Children

Progrès dans le diagnostic et la prise en charge des lésions rénales aiguës chez les enfants

Song Mei Fang[1], Suzy Hamo[2], Andreas Chiabi[2]

[(1)]The 20th Chineese Medical Team from Shan Xi, Yaounde Gynaeco- Obstetric and Pediatric hospital, Cameroon
[(2)]Yaounde Gynaeco-Obstetric and Pediatric hospital, Cameroon

Corresponding author:
Andreas Chiabi, Yaounde Gynaeco-Obstetric and Pediatric hospital, Cameroon
Mail: andy_chiabi@yahoo.co.uk

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ABSTRACT

Pediatric acute kidney injury (PAKI) is a critical renal syndrome with multiple causes and multiple pathogenic mechanisms, and might have a poor prognosis if misdiagnosed or poorly managed. So early diagnosis is imperative to avoid delays in treatment. In recent years, some biomarkers have been developed, to predict the early occurrence of AKI, such as Neutrophil gelatinase associated lipocalin (NGAL), Kidney injury molecule-1 (KIM-1), Liver-type fatty acid binding protein (L-FABP), and Interleukin-18 (IL-18). Currently, PAKI lacks effective drug therapy, and renal replacement therapy (RRT) is the main treatment for AKI. Choosing the type of renal replacement therapy（RRT), must consider the patient's primary disease, clinical status, and the advantages and disadvantages. This article reviews the different most recent diagnostic markers of PAKI, and therapeutic interventions used.

RÉSUMÉ

La lésion rénale aigue en pédiatrie est un syndrome rénal grave avec de multiples causes et de multiples mécanismes pathogéniques qui pourraient avoir un mauvais pronostic si le diagnostic n'est pas posé ou mal traité. Un diagnostic précoce est donc impératif pour éviter les retards de traitement. Au cours des dernières années, certains biomarqueurs ont été développés pour prédire la survenue précoce de la lésion rénale aigue comme Neutrophil Gelatinase associated lipocalin (NGAL), Kidney injury molecule 1(KIM-1), Liver type fatty acid binding protein (L-FABP) et l'interleukin 18(IL-18). A l'heure actuelle, les lésions rénales aigues pédiatriques n'ont pas de traitement médicamenteux efficace et la thérapie de transplantation rénale est le principal traitement des lésions rénales aigues. Le choix du type de thérapie de remplacement rénal doit tenir compte de la maladie primaire du patient, de son état clinique, des avantages et inconvénients. Cet article passe en revue les différents marqueurs diagnostiques les plus récents de MRAP et les interventions thérapeutiques utilisées.

INTRODUCTION

Acute kidney injury (AKI) is a clinical syndrome which includes which includes a rise in SCr ⩾ 26.5 μmol/L within 48 hours or the original SCr value increases by ⩾ 50% and/or urine output <0.5 mL/kg/h for 6 hours. [1]. Acute kidney Injury is associated with high morbidity and fatality. The use of the term acute renal failure was confusing, both clinically as well as in medical publications, because just a slight fluctuation in blood creatinine could influence renal function.

Studies showed that the incidence of AKI in adult hospitalizations is 21.6%, but it can be as high as 33.7% in children [2]. The incidence in newborns is 8% to 24% [3-4], and the mortality rate is 10% to 61% [5]. In addition, it is also an independent risk factor that affects prognosis in children and a major health disorder in children [6-8].

Since there is no specific drug for treating AKI, most patients who survive would develop chronic kidney disease and require renal replacement therapy. Therefore, early diagnosis and timely interventions are very important. But previous studies of AKI have mostly focused on adult patients, and AKI in children (PAKI) is rarely reported, so the purpose of this review, which is aimed at providing useful information for the treatment and prevention of early AKI.

ETIOLOGIES OF PEDIATRIC ACUTE KIDNEY INJURY (PAKI)

According to the location of the disease, AKI is divided into three categories: prerenal, renal, and postrenal.

In addition, epidemiological studies have shown that the main causes of AKI vary from country to country, and renal disease especially acute glomerulonephritis, is the most common cause of AKI [10,11]. Also, AKI may be caused by different diseases at different ages, and renal cortical necrosis and renal venous thrombosis are common in newborns.

Table I: Etiologic classification of PAKI [89]

Classification	Etiology
1. Prerenal injury	
• Hypovolemia	Bleeding, severe dehydration from gastrointestinal losses (diarrhea, vomiting), nasogastric tube drainage of body fluids, third lacuna fluid losses (burns, trauma, nephrotic syndrome, capillary leakage syndrome), central or nephrogenic diabetes insipidus, sodium loss (renal or adrenal disease),drug-related diuresis or osmotic diuresis
• Insufficient effective	Congestive heart failure, cardiac tamponade, pericarditis,
• Blood volume	Liver failure
2. Kidney Parenchymal Injury	
• Acute tubular necrosis	Ischemic hypoxic injury: due to the development of prerenal renal injury factors. Drugs and exogenous toxins: Nephrotoxic antibiotics (aminoglycosides, amphotericinB, rifampicin, sulfa, etc.), nephrotoxic anticancer compounds (ifosfamide cisplatin,etc.),non-steroidal anti-inflammatory drugs (acetaminophen), angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, fluorine compound anesthetics(methoxyflurane, halothane, etc.), contrast agents, heavy metals (lead, mercury, lithium), organic solvents (Ethylene glycol), bee sting venom, snake venom, Endogenous toxins: hemolytic uremic syndrome, intravascular hemolysis (hemoglobinuria), rhabdomyolysis, crush syndrome (myoglobinuria), tumor lysis syndrome (uric acid)
• Severe glomerulonephritis	Acute nephritis, rapidly progressive nephritis, allergic purpura nephritis, lupus nephritis
• Acute interstitial nephritis	Drug-related, infection-related
• Renal vascular disease	Renal cortex necrosis, renal artery/venous thrombosis or embolism, Polyarteritis nodosa
• Congenital **kidney disease**	Abnormal kidney development, polycystic kidney disease, infantile polycystic kidney, polycystic kidney dysplasia
3. Post renal obstructive injury	Urethral obstruction (urethral valves), isolated renal urinary tract obstruction, bilateral ureteral obstruction

Table II: Pediatric acute kidney injury diagnosis and staging standards [1]

Staging	SCr		Urine volume	
	2005	2012	2005	2012
I	SCr higher than the baseline value≥1.5 times or increase in absolute value ≥ 26.52 μmol /L	1.5-1.9 times the baseline value Or increase≥0.3 mg/dL(≥26.5 μmol /L)	＜0.5mL /(kg·h) lasts 6 h	＜0.5mL /(kg·h) lasts6～12 h
II	SCr higher than the baseline value ≥ 2 times	2.0-2.9 times the baseline value	＜0.5mL /(kg·h) lasts 12 h	＜ 0.5mL /(kg·h) lasts≥12 h
III	SCr higher than the baseline value≥3times or Acutely increase more than 44.2 μmol/L on the basis of SCr≥353.6 μmol/L	3.0 times the baseline value; or increase in SCr≥4.0mg/dL (≥353.6μmol /L); or start renal replacement therapy; or＜18-year-old patient, eGFR decline ＜ 35mL /(min·1.73m2)	＜0.3mL /(kg·h) lasts 24h or anuria lasts 12 h	＜ 0.3mL/(kg·h) lasts≥24h;or anuria lasts≥12 h

In infants and young children, the most common causes are low blood volume (gastrointestinal fluid loss, sepsis), and hemolytic uraemic syndrome. Rapidly progressive glomerulonephritis is the most common cause in children and adolescents [12,13]. Another important cause of neonatal AKI include, some drugs taken by the mother during the fetal period, such as angiotensin-converting enzyme inhibitors (ACEI) and non-steroidal anti-inflammatory drugs (NSAIDs) [14-16]. Other studies have suggested that genetic factors exist in children with AKI. Polymorphisms of TNF-, TL-1B, TL-6 and TL-10 genes, can initiate strong inflammatory responses and thus predispose to AKI [17].

DIAGNOSIS

Traditional diagnostic indicators

Serum creatinine (SCr) and Urine volume are mainly used to evaluate glomerular filtration rate. The diagnosis of Pediatric acute kidney injury (PAKI) still refers to the 2005 Global Acute Kidney Injury Network (AKIN) [18], and the 2012 Global Kidney Disease Prognosis Organization (KDIGO) [1]. Staging is based on changes in creatinine and urine output. However, the traditional diagnostic indicators as SCr and Urine volume will not immediately increase during AKI, and are not always proportional to kidney damage. Moreover, SCr is affected by non-renal factors such as age, individual

muscle capacity, eating habits and metabolism. Because different people's normal creatinine values vary greatly [19], the urine volume is also easily affected by blood volume, urinary tract obstruction, drugs, etc. Therefore, the diagnostic sensitivity and specificity of AKI based on SCr and urine volume is poor and may cause delays in diagnosis and treatment [20]

Recent indicators

Currently, there are four kinds of AKI biological markers namely: neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), liver fatty acid binding protein (L-FABP), Interleukin-18 (IL-18) [21]. The expression of these indicators at different time points in urine was earlier than that of SCr and urine volume, which could improve the predictive power of AKI [22-28].

Neutrophil gelatinase associated lipocalin (NGAL) belongs to the lipocalin super family, which is covalently bound to neutrophil gelatinase [30]. When AKI occurs in newborns and children, renal tubular epithelial cells will be expressed in large quantities and released into plasma and urine. The results of clinical studies have shown that blood and urine NGAL are independent predictors of secondary AKI, and are sensitive and specific early biomarkers for the diagnosis of AKI [31].

Kidney injury molecule-1 (KIM-1) is a type I transmembrane glycoprotein expressed in the renal proximal convoluted tubule cells [30]. Its expression level is very low in normal kidney, and it increases sharply after ischemic injury, and participates in the elimination of necrotic cells in the kidney injury site and inhibits the activation of pro-inflammatory factors [32]. The urine level of KIM-1 increases significantly 12 hours after ischemia [33]. The diagnostic accuracy of urine KIM-1 for infants and children with AKI is better than for adult patients [33].

Liver-type fatty acid binding protein (L-FABP), is a fatty acid binding protein with a molecular mass of 14 000 [30]. It can be expressed in the proximal convoluted tubule epithelial cells. When toxic peroxides accumulate, L-FABP binds to it, and is secreted into the lumen of the renal tubules. The level of urine L-FABP is detected earlier than SCr, which can be used as an early marker of AKI. Ivaniševic et al. [34] showed that the urine L-FABP levels in children with AKI was significantly higher compared to children without AKI ($P<0.05$), and it occurred earlier than SCr.

Interleukin-18 (IL-18) is a pro-inflammatory cytokine produced in proximal tubules. Parikh et al, .reported a significant rise in the urine of ischemic AKI, and it was positively correlated with the severity of AKI, and the higher the IL-18 level was, the more severe the AKI was[35].

To sum up , during cardiopulmonary bypass AKI, NGAL increases at a 2 hour interval, IL-18 and L-FABP increase at a 6 hour interval, and KIM-1 increases after a 12 hour interval [30-35].

Table III: AKI-related new biomarkers and its secreted site in the kidney [29]

Category	Biomarker	Location
Functional biomarkers	Cystatin C	Glomeruli
	Retinol binding protein	Proximal tubules
	NAG	Proximal tubule
	KIM-1	Proximal tubule
	L-FABP	Proximal tubule
	NGAL	Distal convoluted tubule、thick ascending branchof, medullary loop, collecting tube
Up-regulated protein of renal tubular injury related enzymes	IL-18	Renal tubular epithelial, cells, Collecting tube
	IGFBP7	Renal tubular epithelial cells
	TIMP-2	Renal tubular epithelial cells
	Cysteine Rich Heparin Binding protein61 Clump protein	proximal convoluted tubule distal convoluted tubule
	Na+ /H+Exchanger isozyme3	Proximal tubule
	FetuinA	Proximal tubule

However, SCr does not increase during the 36-48 hours of NGAL increase, so monitoring of IL-18, KIM-1, L-FABP, and NGAL can provide an earlier opportunity for AKI treatment [29]. A test of NGAL, IL-18, KIM-1, L-FABP in urine of 150 children undergoing cardiopulmonary bypass (CPB) surgery at 2, 6, 12, 24 h, noted that NGAL appeared 2 h after surgery; the other markers (IL-18, KIM-1, L-FABP) increased after 6 hours, and the diagnostic value of urine NGAL at each time point was the highest (AUC>0.9)[31].

ASSADI et al. showed that urinary KIM-1 was superior to IL-18 and NGAL in the diagnosis of circulatory failure [36]. The monitoring of L-FABP noted that L-FABP had the best predictive value for the occurrence of AKI after CPB. It was also observed, that urinary NGAL and L-FABP increased significantly in the early stage of AKI after cardiac surgery in children, which is significantly earlier than the change in SCr, so can predict the occurrence of AKI faster [37].

TREATMENT OF PEDIATRIC ACUTE KIDNEY INJURY

The management of AKI, includes etiologic treatment, controlling hydro-electrolytic and acido-basic disorders, restriction of dietary proteins, and vigorous treatment of hyperkalemia. Dialysis is only indicated if the above measures fail to give satisfactory results.

Drug therapy

The most commonly used drugs are diuretics and dopamine. Furosemide has been widely used in the

treatment of AKI, but a recent meta-analysis **[38]** showed that loop diuretics can not improve the survival rate of AKI patients and the probability of renal replacement therapy. It is currently not recommended for routine use by the guidelines of KDIGO in 2012**[1]**

Dopamine at a renal dose of 0.5 μg/(kg ·min) to 3-5 μg/(kg ·min), can improve ischemic renal perfusion, but there is no evidence to prove that it can reduce the need for AKI dialysis and increase survival time [**39-43**]. The most commonly used drug is fenoldopam, a short-acting, selective dopamine receptor 1 antagonist, which can increase renal blood flow, and reduce the incidence and mortality of AKI **[44].** However, clinical observations have noted that the drug lowers blood pressure, and has the potential to aggravate AKI. Guidelines of KIDOG (2012) also do not recommend its use in AKI **[45].**

Other drugs, such as insulin-like growth factor-1 (IGF-1), epithelial growth factor, hepatocyte growth factor, in animal models have been shown to promote renal function repair, and reduce the degree of renal damage. In addition, oxygen free radical scavengers and anti-adhesion molecules, can also reduce the degree of damage **[46,47**], and pluripotent mesenchymal stem cells (MSCs) can promote the loss and repair of AKI **[48].** Clinical studies have not achieved these results in animal models.

Natriuretic peptides, including atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) have also been experimentally tried. A meta-analysis showed that the use of ANP or BNP can increase urine output and glomerular filtration rate, reduce the use of diuretics, reduce serum creatinine levels, and shorten the total length of hospital stay. Moreover, ANP can significantly reduce the peak blood creatinine, the number of dialysis treatments and the incidence of arrhythmias **[49].**

Other treatments, include calcium channel blockers and N-acetylcysteine. On the average, calcium channel blockers like diltiazem and nifedipine cannot significantly improve the renal function of AKI after cardiac surgery, but diltiazem may have a protective effect on renal tubules after surgery. [50]. N-acetylcysteine has been shown to have no protective effect on renal function, nor can it prevent the occurrence of AKI **[50].**

Blood purification treatment

This is the process of removing certain metabolic wastes or toxic substances from the blood after the patient's blood is drawn out of the body using professional instruments and equipment, and then returned to the body.. **[51]**. At present, clinically commonly used techniques for blood purification treatment in children include hemodialysis, hemoperfusion, plasma exchange, immunoadsorption, and continuous blood purification technologies **[52].** In recent years, with the continuous development and improvement of technology, it has been clinically used to remove inflammatory mediators, immune factors and toxins, for nutritional supplements and to improve hemodynamic conditions **[53].**

- Hemodialysis (HD): The rate of hemodialysis is controlled at 3~5ml/kg per minute, and the special dialyzer and vascular access are selected according to the weight of the child, and the parameters of the dialyzer are set in combination with the blood volume of the child **[54]**.
- Hemoperfusion (HP): The patient's blood is introduced into a perfusion device equipped with a solid adsorbent, and the adsorbent is used to remove various poisons in the blood to purify the blood. With high safety and few adverse reactions, it is suitable for both adults and children. Hemoperfusion in patients with acute drug poisoning, and poisoning from uremia, sepsis, hepatic encephalopathy and hyperlipidemia can also give good clinical results **[55].**
- Plasma exchange:It uses plasma separation technology to remove macromolecular substances in the blood, remove immune complexes and other toxic substances. The purpose of plasma exchange in children is to regulate the immune system of the child's body. It can be used in children with diffuse intravascular coagulation, idiopathic thrombocytopenic purpura and other blood system diseases. It helps children to establish a normal coagulation system and supplement the protein content in the body's plasma **[56].**
- Immunoadsorption: Its principle is to purify the blood and alleviate the disease by selectively removing the negative factors in the blood. At present, the technology is not widely used in pediatrics. Relevant studies have shown that the clearance rate of pathogenic factors in children's plasma may be higher, and the incidence of adverse reactions caused by plasma infusion may be reduced **[57].**
- Peritoneal dialysis (PD): PD is the use of the human peritoneum as a dialysis membrane to exchange solute and water between the dialysate poured into the abdominal cavity and the plasma components in the capillaries on the other side of the peritoneum to remove the metabolites retained in the body. The operation is simple and effective, and it is the first intention treatment of AKI in infants and young children **[58].** For children with severe PAKI or excessive volume, when it is difficult to establish vascular access, PD has obvious advantages over other blood purification methods in the treatment of AKI.
- Continuous Renal Replacement Therapy (CRRT): It is the process of removing water and toxic substances in the blood continuously and slowly, to correct disorders in the body. It is more suitable for newborns and children with small blood volumes and unstable hemodynamics. This includes, continuous intravenous hemofiltration technology, continuous intravenous hemodialysis technology, continuous intravenous hemodiafiltration technology, etc. Due to the complicated operation of this technique and difficulty in establishing vascular access, it is not widely used in pediatrics. Studies show that the survival rate of infants and children

weighing less than 3kg using CRRT is low, so the technique is not widely used in pediatrics. **[59].**

CONCLUSION

In summary, PAKI has a high morbidity and mortality rate, and early diagnosis is the key to early intervention, early treatment and reduction of mortality. Although the above biologic markers which essential for early diagnosis of AKI, have been used above biologic markers, which are essential for a long time in developed countries, their accessibility and use in developing and low resource countries is still limited. As concerns management, in addition to adjuvant drug treatment, the main effective treatment is an appropriate blood purification treatment.

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