Review Article

Pediatric acute kidney injury: A syndrome under paradigm shift

Mohd Ashraf, Naveed Shahzad, Mohd Irshad, Sheikh Quyoom Hussain, Parvez Ahmed

Abstract

The recent standardization and validation of definitions of pediatric acute kidney injury (pAKI) has ignited new dimensions of pAKI epidemiology and its risk factors. pAKI causes increased morbidity and mortality in critically ill-children. Among the hospitalized patients incidence of pAKI ranges from 1% to 31%, while mortality ranges from 28% to 82%, presenting a broad range due to lack of uniformly acceptable pAKI definition. In addition, cumulative data regarding the progression of pAKI to chronic kidney disease in children is rising. Despite these alarming figures, treatment modalities have failed to deliver significantly. In this review, we will summarize the latest developments of pAKI and highlight important aspects of pAKI management.

Keywords: Acute kidney injury, children, kidney biomarkers, oliguria, serum creatinine

Access this article online

Website: www.ijccm.org

DOI: 10.4103/0972-5229.138156

Quick Response Code:

Introduction

Acute kidney injury (AKI) has supplanted the term acute renal failure (ARF) to allow earlier detection of renal dysfunction and to promote a proactive approach for the real-time management of AKI. AKI is characterized by the abrupt onset of renal dysfunction resulting from injurious endogenous or exogenous processes, leading to decrease in glomerular filtration rate (GFR) with the rise of serum creatinine (SCr), inability to regulate acid and electrolyte balance, and excrete wastes and fluid.[1] Since the kidney is too silent an organ to attract medical attention resulting in scanty clinical evidence for this disorder.[2] These clinically silent kidney attack(s) or subclinical kidney injury may have an important effect on both short-and long-term clinical outcomes and kidney function.[3,4] To overcome these silent/subclinical kidney attack(s) and for the real-time detection of pediatric AKI (pAKI), thorough campaign for awareness and alertness should be undertaken. These include the use of new functional biomarkers like neutrophil gelatinase-associated lipocalin (NGAL), cystatin C (Cys C), kidney injury molecule-1 (KIM-1), interleukin-18 (IL-18), and liver-type fatty acids binding protein (L-FABP).[5] It is hoped that these new biomarkers will be able to diagnose AKI earlier, and differentiate different etiologies and stages of AKI. Until these, biomarkers are adapted functional marker, such as SCr and Cys C are used to diagnose AKI. This review article will summarize the latest developments in the field of AKI in children.

Epidemiology of Acute Kidney Injury in Children

It estimated that over 30 definitions exist in the published literature about the ARF albeit bearing a significant effect on the health of the patients.[6] Most ARF definitions are based on SCr rise, oliguria or anuria or need for renal replacement therapy (RRT). Lack of an uniform definition more than a decade ago was probably the main reason of lack of recognition of significant kidney injury and delay in treatment. Variations in the definitions of ARF, based on changes in SCr levels, fractional excretion of sodium (FENa), urine formation; or the effect of age, sex, race, diet, and technique on the SCr level prompted nephrologists, critical care specialists and allied researchers to reach an international consensus to standardized the definition of AKI using the "risk, injury, failure, loss, end (RIFLE)" criteria in 2004.[6] Based on GFR, SCr values, and urine output plotted against time of admission,

From:
Pediatric Nephrology Division, Department of Pediatrics, GB Pant Hospital, Government Medical College Srinagar, Jammu and Kashmir, India

Correspondence:
Dr. Mohd Ashraf, 8-Green Lane Raj Bagh, Srinagar, J&K 190008, India.
E-mail: aashraf_05@yahoo.co.in

RIFLE stands for 3° of severity-Risk, Injury, and Failure, and two outcomes-Loss and End-stage kidney disease. The RIFLE was later modified[7] in 2007 using the "AKI network (AKIN)" criteria Table 1. Refining further AKIN group replaced the categories of risk, injury, and failure to Stages 1, 2 and 3, respectively, and the outcome categories loss and end-stage renal disease were eliminated. An absolute increase in SCr levels of at least 26.5 μmol/L (0.3 mg/dl) has been added to the minimum requirements for Stage 1. Patients starting RRT are automatically classified as having Stage 3 AKI, regardless of their SCr levels and urine output. Modification, application and validation of adult-derived RIFLE in pediatric population and renaming it as pediatric RIFLE (pRIFLE) was done to stratify AKI in children. Severity of AKI was graded from mild (RIFLE-R, "risk") to severe (RIFLE-F, "failure") based on changes in SCr or estimated creatinine clearance and urine output [Table 2]. One of the first prospective study on AKI in children using the pRIFLE criteria indicated 82% patients had AKI, when AKI criteria were SCr 1.5 times base line and who received invasive mechanical ventilation with at least one vasoactive medication.[8] However, in another prospective study on AKI in children using the pRIFLE criteria when AKI criteria were doubling the SCr level in all pediatric intensive care unit (ICU) admissions incidence rate plummets to 4.5%,[9] indicating the population characteristics and SCr criteria influences the incidence of AKI in children. The AKIN criteria were developed with input from pediatric nephrologists, and preliminary comparisons show that pRIFLE and AKIN lead to similar diagnostic AKI rates.[10] In one of the recent studies authors have proposed the concept of "renal angina equivalent" similar to cardiac angina where chest pain prompts the patients and doctor to intervene, whereas in renal angina case pediatric metrics includes invasive mechanical ventilation, vasoactive substance use, history of recent stem cell transplantation, and/or the development of relative fluid overload (FO).[11]

Setting SCr as a functional marker for AKI is not ideal as rise of SCr will take days and this rise will only occur after 25-50% of the kidney function has already been lost.[12] It is noteworthy that SCr varies by muscle mass, hydration status, sex, age and gender and method of measurement.[13] In addition to this, one should not forget that SCr is dialyzable and after dialysis SCr does not guide about the AKI management, while in neonates, SCr in the first few days of life reflects mother's SCr.[14] In spite of all these contrary evidences, new classifications using SCr have stratified the AKI dimensions making headway for better AKI epidemiology.

Acute kidney injury increases overall mortality, hospital costs, length of stay, and ventilator days,

Table 1: Diagnostic criteria for AKI

RIFLE	AKIN
An increase in SCr of ≥50% developing over <7 days (or) A urine output of <0.5 ml/kg/h for >6 h	An increase in SCr of ≥0.3 mg/dl (or) ≥50 developing over <48 h (or) A urine output of<0.5 ml/kg/h for>6 h

RIFLE stage	Increase in SCr %	Urine output criteria	Increase in SCr %	AKIN stage
Risk	≥50	<0.5 ml/kg/h for>6 h	≥0.3 mg/dl; or≥50	Stage 1
Injury	≥100	<0.5 ml/kg/h for>12 h	≥100	Stage 2
Failure	≥200	<0.5 ml/kg/h for>24 h (or) anuria for>12 h	≥200	Stage 3
Loss	Need for RRT for>4 weeks			
End stage	Need for RRT for>3 months			

AKI: Acute kidney injury; RIFLE: Risk, injury, failure, loss, end; AKIN: Acute Kidney Injury Network; SCr: Serum creatinine; RRT: Renal replacement therapy

Table 2: The modified pediatric version of the RIFLE criteria (pRIFLE)

Stage	eCCl %	Urine output
R=Risk for renal dysfunction	eCCl decrease by 25	<0.5 ml/kg/h for 8 h
I=Injury to the kidney	eCCl decrease by 50	<0.5 ml/kg/h for 16 h
F=Failure of kidney	eCCl decrease by 75 or <35 ml/min/1.73 m^2	<0.3 ml/kg/h for 24 h or anuria for 12 h
L=Loss of kidney function persistent failure>4 weeks		
E=ESRD persistent failure>3 months		

eCCl: Estimated creatinine clearance; ESRD: End-stage renal disease; RIFLE: Risk, injury, failure, loss, end; pRIFLE: Pediatric risk, injury, failure, loss, end

independent of disease severity among pediatric and adult population, specifically when associated with sepsis, trauma, burns, transplant, acute respiratory distress syndrome (ARDS), multi-organ failure, hematopoietic stem cell or solid organ transplant, and extra-corporeal membrane oxygenation.[15-18] Even small changes in SCr, which previously were ignored, are associated with poor outcomes.[15]

Etiology of Pediatric Acute Kidney Injury

The etiology of AKI in children is an important component to the understanding of pattern and distribution of AKI. The diagnostic criteria[19] for AKI in children are framed after thorough evaluation of possible etiological factors. However, various studies have shown a change in trend from primary kidney diseases to secondary renal diseases as the cause of pAKI.[20] Common causes of AKI differed from country to country; in China commonest form of pAKI is intrensic AKI[21] while in India prerenal form is the most common one.[22] However, most of the recent studies have shown that the major causes of AKI were cardiac surgery, sepsis, blood cancer, and respiratory failure of varied etiology. Overall common causes of pAKI are detailed as shown in Table 3.[23]

Risk Factors for Acute Kidney Injury

Various studies are investigating the risk factors associated with the development of adult AKI, both patient and procedure related. Consistent risk factors for AKI were cardiac and noncardiac surgery.[24,25] Patient-related risk factors are age, hypertension, diabetes mellitus, cardiac failure, peripheral vascular disease, cerebrovascular disease and preexisting chronic kidney disease.[25,26] In children, the main risk factors for developing AKI are administration of nephrotoxic medications, veno-occlusive disease in association with hepatorenal syndrome, severe sepsis with shock, cardiopulmonary bypass (CPB) surgery, use of vasopressors along with invasive ventilation, FO, stem cell transplants and tumor lysis syndrome.[27-29]

Approach to a Child with Acute Kidney Injury

Patients with AKI require thoughtful history taking and a meticulous physical examination; followed by evaluation of urinary and blood chemistry; renal imaging, and when appropriate, renal biopsy.[16] A rapid rise of SCr and blood urea nitrogen (BUN) from the previously known value indicates an acute insult. It is important to have knowledge of spurious causes of elevated BUN and SCr, levels such as high-protein intake, gastrointestinal bleeding, catabolic states (fever, steroids, burns), extreme exercise, drug intake like trimethoprim and cemitidine, to avoid misdiagnosis of AKI. When prior BUN and SCr measurements are not available, key findings that may indicate a chronic process include physical manifestations such as growth retardation, developmental delays, rickets, anemia, recurrent infections, malnutrition, mental apathy, in adolescents it could present as features of hyperparathyroidism (resorption of distal phalangeal tufts or the lateral aspect of clavicles), band keratopathy, half-and-half nails, and small echogenic kidneys on radiographic imaging. Once the presence of AKI has been confirmed, attention should focus on patient, urine output, laboratory, and radiographic assessments to differentiate among prerenal, intrinsic, and postrenal processes in order to identify the cause of AKI and guide treatment.

Table 3: Common causes of pAKI

Renal hypoperfusion
Low intravascular volume
Hemorrhage/gastrointestinal losses: Postoperative, trauma, severe dehydration
Third-space losses: Sepsis and capillary leak, burns, hypoalbuminemia (nephrotic syndrome/liver disease)
Decreased effective circulating volume
Cardiac dysfunction: Congestive heart failure, cardiac tamponade/ pericarditis, sepsis-associated Cardiac dysfunction, sepsis-associated diffuse vasodilation
Pulmonary diseases: Pulmonary embolism, sepsis, pulmonary arterial hypertension
Diseases of renal tissue
Glomerular: Glomerulonephritis due to anti-glomerular basement membrane disease, antineutrophil, cytoplasmic autoantibody disease, infection, cryoglobulinemia, membranoproliferative glomerulonephritis, immunoglobulin A nephropathy, systemic lupus erythematosus
Vascular/ Hematological disorders
Hemolytic uremic syndrome, Infections, drug-induced (calcineurin inhibitors), renal vein/artery thrombosis, disseminated intravascular coagulation, thrombotic, disease, malignant hypertension
Interstitial
Acute interstitial nephritis: Drug-induced, infectious, immune-mediated, pyelonephritis
Tubular
ATN: Hypoxic/ischemic injury, drug induced, exogenous toxins (metals, venom, illicit drugs, ethylene glycol, methanol), endogenous toxins hemolysis, tumor lysis syndrome
Urinary tract obstruction
Urethral obstruction: Posterior urethral valves in neonates; urinary catheter obstruction
Obstruction of solitary kidney urinary tract: Congenital (ureteral-pelvic junction, ureteral stenosis, ureterovesical junction, mass), stones, mass
Bilateral ureteral obstruction: Mass, stones

ATN: Acute tubular necrosis; pAKI: Pediatric acute kidney injury

Diagnosis of prerenal AKI is usually based on the prompt resolution of AKI after restoration of renal perfusion. If impairment in kidney function persists or worsens despite restoration of renal perfusion ischemic acute tubular necrosis (ATN) should be suspected. Intrensic AKI due to drugs requires a comprehensive review of all clinical, pharmacy, nursing, radiographic, and procedural notes for evidence of administration of nephrotoxic agents. Hemoglobin or myoglobin induced ATN may be suspected if the clinical assessment reveals risk factors for rhabdomyolysis like excessive exercise, drug abuse, seizures, crush injury or drug/food induced hemolysis.[30] Postrenal AKI is symptomatic only when obstruction is complete, and there is anuria and it is asymptomatic when obstruction develops gradually. Suprapubic or flank pain may be the presenting complaint if there is an acute distention of the bladder or renal collecting system and capsule, respectively. Colicky flank pain radiating to the groin suggests acute ureteral obstruction, most commonly from renal stone disease. History of intake of anticholinergic drug intake, spinal cord trauma, or fever with painful micturition will be useful points in delineating the cause. Postrenal AKI diagnosis becomes certain when postvoid bladder volume and radiographic evaluation of the urinary tract supports the clinical examination, and renal function improves following the relief of the obstruction.

Laboratory Investigations

Urinalysis is essential in patients suspected with AKI and is an inexpensive and useful diagnostic tool.[31]

In prerenal and postrenal AKI, the urine sediment is typically bland but may contain transparent hyaline casts. However, hematuria is common in patients with intraluminal obstruction. Muddy brown granular casts and tubule epithelial cell casts are characteristic of ischemic or nephrotoxic ATN. They may be found in association with microscopic hematuria and mild tubular proteinuria (<1 g/day). Casts may be absent, however, in approximately 20% to 30% of patients with ischemic or nephrotoxic ATN and are not a requisite for diagnosis.[32] Red blood cell (RBC) casts almost always indicate acute glomerular disease but in rare cases may be observed in acute interstitial nephritis. In general, there is poor correlation between the severity of AKI and urinalysis. Urinalysis in prerenal AKI will show FENa <1%, UNa < 10 mEq/L, SG >1.018, while in vascular causes of AKI there will be mild proteinuria, occasionally RBCs, eosinophiluria. In glomerulonephritis or vasculitis, hemolytic uremic syndrome/thrombotic thrombocytopenic purpura, malignant hypertension presence of RBC or granular casts, RBCs, white blood cells (WBCs), proteinuria are not uncommon. In ischemic or nephrotoxic ATN, urinalysis shows muddy brown granular or tubular epithelial cell casts, FENa >1%, UNa >20 mEq/L, SG ~ 1.010. In allergic interstitial nephritis, acute bilateral pyelonephritis, postrenal AKI, WBC casts, WBCs (frequently eosinophiluria), RBCs, rarely RBC casts, proteinuria (occasionally nephritic) are seen.

Role of Biomarkers in Diagnosing Pediatric Acute Kidney Injury

Diagnosing of pAKI with rising SCr, and/or declining urine formation is not reliable indicator,[33] during acute kidney dysfunction as SCr does not increase until the GFR has moderately decreased (about 40 ml/min/1.73 m^2). This obscures the therapeutic window providing the false sense of security and leads to late detection of kidney damage, thus paves the way for estimation of more sensitive biomarkers that will sense real time kidney damage.

Serum Cystatin C

Cystatin C is a 13.3-kDa protein belonging to cystatin protease inhibitors that is fully catabolized in the proximal renal tubule and is not returned to the blood. Concentration of serum Cys C is not affected by gender, age, race, protein intake, and muscle mass, unlike SCr. Cys C was shown to detect AKI 1-2 days earlier than creatinine in critically ill patients,[34] and postoperative Cys C was more effective at predicting AKI in pediatric cardiac surgery patients.[35] Once AKI is established, there is no effective treatment for human AKI, and dialysis merely provides supportive care. However, animal studies have shown that AKI can be prevented or treated if intervention is started in time.[36] New AKI biomarkers are rapid, noninvasive and easy to perform using easily accessible samples such as blood or urine, and are sensitive to facilitate early detection of AKI with a wide dynamic range and able to the identify the AKI sub-types.[37] Among various biomarkers those that hold promise to reach clinical application in the near future, are NGAL, IL-18, and KIM-1.

Neutrophil gelatinase-associated lipocalin

Neutrophil gelatinase-associated lipocalin is a 25-kD lipocalin-protein, made of 178 amino acids, belongs to the lipocalin superfamily. NGAL is expressed at very low levels in human tissues, including kidney, trachea, lungs, stomach, and colon, and its expression increases greatly in the presence of inflammation and injured epithelia.[38] NGAL, like the other lipocalins, is able to bind some ligands, including the siderophores. Interactions with iron binding siderophores are responsible for NGAL's characteristic bacteriostatic effects as it deprives bacteria from iron supply required for their growth and multiplication. The biologic significance of this finding was demonstrated in genetically modified mice, which were deficient for both copies of the NGAL gene.[39] NGAL levels in plasma and urine are increased as NGAL mRNA expression is upregulated in acute renal insults. Increased NGAL urinary levels result from insufficient reabsorption of NGAL from the filtered load. Any decrease in GFR resulting from AKI would be expected to decrease the renal clearance of NGAL, with subsequent accumulation in the systemic circulation.[40] NGAL is rapidly and massively elevated in various tubular and glomerular injuries.[41,42] NGAL has an excellent sensitivity and specificity (90 and 99%), as well as the ability to differentiate between AKI and other causes of elevated creatinine, such as chronic kidney disease and prerenal azotemia.[43] However, certain limitations of NGAL are that plasma NGAL measurements may be influenced by a number of coexisting variables, including chronic kidney disease, chronic hypertension, systemic infections, inflammatory conditions, anemia, hypoxia, and malignancies. Interpreting NGAL levels from improperly stored sample can be misleading, besides being a costly investigation.

In a study of children undergoing CPB, the diagnosis of AKI (defined as a 50% increase in SCr) was only possible 1-3 days after surgery, while NGAL measurements by ELISA revealed a marked increase in the urine and

plasma within 2–6 h of the surgery in these patients who subsequently developed AKI.[44] In a meta-analysis for NGAL, including 24 studies, analysis revealed both urine and serum NGAL levels predictably high within 6 h of renal insult than from 24 to 48 h before the diagnosis of AKI by conventional means. They demonstrated that the overall diagnostic odds ratio for NGAL to predict AKI was 18.6 with an AUC of 0.815, sensitivity of 76.4%, and specificity of 85.1%.[45] Urine NGAL was found to be slightly superior to plasma measurements in the meta-analysis with an AUC of 0.837 versus 0.775 for plasma or serum.

Interleukin-18

In a cross-sectional study, urine IL-18 a pro-inflammatory cytokine levels measured by ELISA were markedly elevated in patients with established AKI, but not in subjects with urinary tract infection, chronic kidney disease, nephrotic syndrome, or prerenal azotemia.[46] In a subsequent study, urinary IL-18 was found to be significantly upregulated prior to the increase in SCr in patients with ARDS who developed AKI.[47] On multivariate analysis, urine IL-18 levels >100 pg/mg creatinine predicted the development of AKI 24 h before the rise in SCr. In patients who developed AKI 2–3 days after surgery, urinary NGAL was induced within 2 h and peaked at 6 h, whereas urine IL-18 levels increased around 6 h and peaked at over 25-fold at 12 h postsurgery. Both IL-18 and NGAL were independently associated with duration of AKI among cases. However, urinary IL-18 measurements may also be influenced by a number of variables, such as endotoxemia, immunologic injury and cisplatin toxicity.[48]

Kidney injury molecule-1

Kidney injury molecule-1 is one of the highly induced proteins in the kidney after AKI in animal models, and a proteolytically processed domain of KIM-1 is easily detected in the urine soon after AKI.[49] In a case-control study of children undergoing CPB, urinary KIM-1 levels were markedly enhanced in subjects who subsequently developed AKI within 12 h.[50] In another cohort study patients with established AKI, both urinary KIM-1 as well as urinary N-Acetyl-β-(D)-Glucosaminidase (NAG) were associated with adverse clinical outcomes, including dialysis requirement and death.[51]

Liver-type Fatty Acids Binding Protein

Liver fatty acid binding proteins are a family of 15-kDa cytoplasmatic proteins. They facilitate the transfer of fatty acids between cell membranes. FABPs are believed to have a role in the reduction of cellular oxidative stress, binding fatty acid oxidation products, and limiting the toxic effects of oxidative intermediates on cellular membranes.[52] L-FABP occurs mainly in the liver, but are also found in kidney and small intestine in small quantities. Urinary L-FABP is undetectable in healthy control urine. Under ischemic conditions the proximal tubular reabsorption of L-FABP is reduced.[53] In one study, urinary L-FABP at the time of admission was significantly higher in the nonsurvivors than in survivors with an AUC for mortality prediction of 0.99.[54] A recent study was performed to evaluate the performance of urinary L-FABP and NAG for AKI diagnosis in cardiac surgery patients. Urinary L-FABP showed high sensitivity and NAG detected AKI with high specificity. When combined; these two biomarkers revealed that this combination panel can detect AKI with higher accuracy than either biomarker measurement alone (AUC-ROC 0.81).[55]

Renal Angina Index

In one of the latest studies,[56] a test scoring system namely renal angina index (RAI) that identifies critically ill-children at risk for developing severe AKI was evaluated. This system relates early decline in kidney function or signs of FO, with the clinical setting to derive a total point score. It was observed that patients who accumulated enough points to meet the criteria for "renal angina" were more likely to double their baseline SCr within 72 h than patients who did not. The RAI scale displayed moderate ability to discriminate between patients developing or not developing severe injury (areas under the curve, 0.74-0.81) that outperformed a validated severity-of-illness scoring system. This study concludes that the RAI can be used to risk-stratify patients and serve as a screening tool to enhance optimal care. However, practice standards should alert the health care providers for the potential development of more severe injury compared with mild injury in patients with FO and declining urine output within the context of clinical severity parameters.[57]

Acute Kidney Injury and Fluid Overload

Continuous RRT(CRRT) is now utilized more frequently to treat the vast complexities of pediatric diseases in the emergency setting, and is a standard therapy for AKI patients. However, various studies[58-62] have shown that FO is associated with increased length of stay in hospital and poor outcome. FO that is more than 10% increase in body weight relative to the base line has been independently associated with increased morbidity and mortality in patients with acute lung injury, ARF, and multi-organ failure. Targeting the FO at the initiation of CRRT will improve the outcome of

the critically ill patients, and this FO is calculated by the description of Goldstein *et al*.[60] formula as under:

FO = Sum of daily (fluid in − fluid out)/ICU admission weight × 100

Drug Induced Acute Kidney Injury

Acute kidney injury that is secondary to medical interventions is iatrogenic AKI. In one of the epidemiologic multicenter ICU study 25% of AKI was attributed to drugs.[63] Conditions such as chronic kidney disease, sepsis, diabetes, hypertension, hydration status, and extreme ages are the risk factors for drug-induced nephrotoxicity. Commonly incriminated drugs are aminoglycosides, vancomycin, amphotericin B, nonsteroidal anti-inflammatory drugs, angiotensin antagonists, anti-viral and anti-cancer drugs. The use of aminoglycosides associated with a 6-26% incidence of nephrotoxicity depending on the patient's population and duration of therapy. Nephrotoxicity from aminoglycosides increases with increased cumulative dose, frequency of dosing, more duration and administration during the bed rest period.[64] Concomitant use of vancomycin and aminoglycosides and other drugs such as cyclosporine, amphotericin B, cephalosporins, and loop diuretics along with their prolonged treatment (>21 days) enhanced the nephrotoxic potential of vancomycin.[65] Frequent courses of aminoglycoside treatment and persistently high trough or peak levels expose kidneys to high concentrations of the drug, resulting in accumulation of aminoglycosides in the renal cortex and predisposing the patient to AKI. General preventive measures for drug-induced nephrotoxicity include, addressing all the modifiable risk factors. Besides correct dosing and reassessment of concomitant medications, assuring adequate hydration is of utmost importance before the administration of nephrotoxic drugs.

Treatment of Pediatric Acute Kidney Injury

Unsettled issue of AKI etiology and epidemiology is creating a major hurdle in pAKI treatment. However, real-time cause directed interventions may prove beneficial. Treatment is subjected to AKI risk stratification and ongoing damage control measures, such as patients with sepsis, exposure to nephrotoxic agents, ischemia, bloody diarrhea, or volume loss, could be helped by optimizing the fluid administrations, antibiotics possessing least nephrotoxic potential, blood transfusion where hemoglobin is dangerously low, limiting the use of nephrotoxic agents including radio contrast use, while maximize the nutrition.

Dopamine infusion

By using low (renal) dose dopamine in children, pAKI outcome remained same.[66] Another dopamine agonist fenoldopam did not show any promising result in treating pAKI although fenoldopam dosed from 0.05 to 0.1 μg/kg/min was shown to improve SCr values in 100 adults matched for severity of illness.[67]

Type of fluid administration

In adults SOAP and SAFE studies did not show any superiority of crystalloid over colloid administration or vice-versa.[68,69] However, similar studies in children are yet to come.

Fluid administration

In a retrospective study of 116 children by (the Prospective Pediatric CRRT Registry Group [ppCRRT], observed, fluid administration to be independently associated with mortality in children started on CRRT,[70] necessitating the patient specific proper dose of preload fluid administration.

Diuretics

Converting oliguric AKI into nonoliguric AKI by use of diuretics did not improve the outcome.[71] There have been no prospective studies on the use of diuretics in pAKI. However, limited data to increase the urine output in pAKI using diuretics is limited to bone marrow transplant and postbypass patients.[28,72]

Nutritional Support

Good nutritional support has been advocated in pAKI, since these patients are generally in a developmental growth phase requiring adequate nutrition than adults. Recent studies have suggested that protein/amino acid supplementation in critically ill-children of the order of 2-3 g/kg/day for children aged 0-2 years, 1.5-2.0 g/kg/day for children aged 2-13 years, and 1.5 g/kg/day for adolescents aged 13-18 years.[73] However, those children requiring RRT may need more than this.[74]

Renal Support for Pediatric Acute Kidney Injury

Accumulation fluid during the hospital stay indicates maladaptive renal response to external fluids and is major determinants for renal support therapy. It has been consistently observed that more than 10-20% of the FO children on CRRT had higher mortality.[58-61] CRRT is now becoming a standard renal support therapy in critically ill-pediatric patients with AKI. As per one of the most authentic data from USA: ppCRRT Registry showed

that, 29% received CRRT to treat isolated FO, 13% to treat isolated electrolyte abnormalities, and 46% to treat FO and electrolyte abnormalities, indicating almost 90% patients received CRRT because of severe FO or solute imbalance.[75] Among patients in the ppCRRT registry, overall mortality was 42%; higher mortality rates were seen in AKI patients with multiple organ failures.[76] It has been observed that outcomes are likely to be superior if CRRT is initiated earlier in the clinical course, rather than later, and at a lesser, rather than greater, degree of FO.[77] Some researchers favor the use of peritoneal dialysis because of its simplicity, less invasiveness, its operability in neonates and hemodynamic instability.[78]

Prevention of Acute Kidney Injury

Pediatric AKI prevention in hospitalized patients mainly depends on the early recognition of at-risk patients. In view of substantial heterogeneity in baseline risk, clinical status, and various procedures performed, strategies to prevent AKI must be individualized. However, following measures will be helpful in pAKI prevention.

(1) Use of invasive/functional hemodynamic monitoring to guide resuscitation, maintenance of fluid and electrolyte homeostasis. In addition, use of balanced crystalloid solutions is of paramount importance to mitigate risk of hyperchloremic acidosis and oliguria in AKI.[79] (2) Recent studies have failed to favor the use of hyperchloremic solutions like normal saline, and use of dopamine in patients with shock.[80] In fact, dopamine may be associated with increased arrhythmic complications.[81] If vasopressor support is required, norepinephrine should be preferred. (3) Management of patients with sepsis and those with perioperative events may benefit with the proper protocol-based treatment. (4) Single dose of theophylline can be provided to neonates at risk of AKI. However no such treatment is valid for adults.[82] (5) Therapeutic drug monitoring for aminoglycosides is should be a part of standard care. (6) Prompt initiation of CRRT should be considered in patients with established and/or worsening AKI that is refractory to conservative therapy.

References

1. Andreoli S. Clinical evaluation and management. In: Avner E, Harmon W, Niaudet P, editors. Pediatric Nephrology. Philadelphia: Lippincott Williams and Wilkins; 2004. p. 1233-12352.
2. Ronco C, McCullough PA, Chawla LS. Kidney attack versus heart attack: Evolution of classification and diagnostic criteria. Lancet 2013;382:939-40.
3. Haase M, Devarajan P, Haase-Fielitz A, Bellomo R, Cruz DN, Wagener G, *et al.* The outcome of neutrophil gelatinase-associated lipocalin-positive subclinical acute kidney injury: A multicenter pooled analysis of prospective studies. J Am Coll Cardiol 2011;57:1752-61.
4. Ronco C, Staeul F, McCullough PA. Subclinical acute kidney injury (AKI) due to iodine-based contrast media. Eur Radiol 2013;23:319-23.
5. Tsigou E, Psallida V, Demponeras C, Boutzouka E, Baltopoulos G. Role of new biomarkers: Functional and structural damage. Crit Care Res Pract 2013;2013:361078.
6. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P; Acute Dialysis Quality Initiative Workgroup. Acute renal failure-definition, outcome measures, animal models, fluid therapy and information technology needs: The Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004;8:R204-12.
7. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, *et al.* Acute kidney injury network: Report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007;11:R31.
8. Akcan-Arikan A, Zappitelli M, Loftis LL, Washburn KK, Jefferson LS, Goldstein SL. Modified RIFLE criteria in critically ill children with acute kidney injury. Kidney Int 2007;71:1028-35.
9. Bailey D, Phan V, Litalien C, Ducruet T, Mérouani A, Lacroix J, *et al.* Risk factors of acute renal failure in critically ill children: A prospective descriptive epidemiological study. Pediatr Crit Care Med 2007;8:29-35.
10. Zappitelli M, Parikh CR, Akcan-Arikan A, Washburn KK, Moffett BS, Goldstein SL. Ascertainment and epidemiology of acute kidney injury varies with definition interpretation. Clin J Am Soc Nephrol 2008;3:948-54.
11. Goldstein SL, Chawla LS. Renal angina. Clin J Am Soc Nephrol 2010;5:943-9.
12. Brion LP, Fleischman AR, McCarton C, Schwartz GJ. A simple estimate of glomerular filtration rate in low birth weight infants during the first year of life: Noninvasive assessment of body composition and growth. J Pediatr 1986;109:698-707.
13. Lolekha PH, Jaruthunyaluck S, Srisawasdi P. Deproteinization of serum: Another best approach to eliminate all forms of bilirubin interference on serum creatinine by the kinetic Jaffe reaction. J Clin Lab Anal 2001;15:116-21.
14. Gallini F, Maggio L, Romagnoli C, Marrocco G, Tortorolo G. Progression of renal function in preterm neonates with gestational age<or = 32 weeks. Pediatr Nephrol 2000;15:119-24.
15. Lassnigg A, Schmid ER, Hiesmayr M, Falk C, Druml W, Bauer P, *et al.* Impact of minimal increases in serum creatinine on outcome in patients after cardiothoracic surgery: Do we have to revise current definitions of acute renal failure? Crit Care Med 2008;36:1129-37.
16. Thadhani R, Pascual M, Bonventre JV. Acute renal failure. N Engl J Med 1996;334:1448-60.
17. Hoste EA, De Waele JJ. Acute kidney injury in the intensive care unit: It's the gene, stupid! Crit Care Med 2008;36:3266-7.
18. Cartin-Ceba R, Haugen EN, Iscimen R, Trillo-Alvarez C, Juncos L, Gajic O. Evaluation of "Loss" and "End stage renal disease" after acute kidney injury defined by the Risk, Injury, Failure, Loss and ESRD classification in critically ill patients. Intensive Care Med 2009;35:2087-95.
19. Sharfuddin AA, Weisbord SD, Palevsky PM, Molitoris BA. Acute kidney injury. In: Taal MW, Chartow GM, Marsden PA, Skoreki K, Yu AS, Brenner BM, editors. Brenners and Rectors the Kidney. 9th ed. John Kennedy Blvd Phildelphia: Elsevier Saunders; 2012. p. 1045-99.
20. Williams DM, Sreedhar SS, Mickell JJ, Chan JC. Acute kidney failure: A pediatric experience over 20 years. Arch Pediatr Adolesc Med 2002;156:893-900.
21. Cao Y, Yi ZW, Zhang H, Dang XQ, Wu XC, Huang AW. Etiology and outcomes of acute kidney injury in Chinese children: A prospective multicentre investigation. BMC Urol 2013;13:41.
22. Srivastava RN, Choudhry VP. Acute renal failure in Delhi. Indian J Pediatr 1982;49:65-70.
23. Zappitelli M. Epidemiology and diagnosis of acute kidney injury. Semin Nephrol 2008;28:436-46.
24. Eriksen BO, Hoff KR, Solberg S. Prediction of acute renal failure after cardiac surgery: Retrospective cross-validation of a clinical algorithm. Nephrol Dial Transplant 2003;18:77-81.
25. Kheterpal S, Tremper KK, Heung M, Rosenberg AL, Englesbe M, Shanks AM, *et al.* Development and validation of an acute kidney injury risk index for patients undergoing general surgery: Results from a national data set. Anesthesiology 2009;110:505-15.
26. Thakar CV, Liangos O, Yared JP, Nelson DA, Hariachar S, Paganini EP.

Predicting acute renal failure after cardiac surgery: Validation and re-definition of a risk-stratification algorithm. Hemodial Int 2003;7:143-7.
27. Van Why SK, Friedman AL, Wei LJ, Hong R. Renal insufficiency after bone marrow transplantation in children. Bone Marrow Transplant 1991;7:383-8.
28. Michael M, Kuehnle I, Goldstein SL. Fluid overload and acute renal failure in pediatric stem cell transplant patients. Pediatr Nephrol 2004;19:91-5.
29. Kist-van Holthe JE, Goedvolk CA, Brand R, van Weel MH, Bredius RG, van Oostayen JA, *et al.* Prospective study of renal insufficiency after bone marrow transplantation. Pediatr Nephrol 2002;17:1032-7.
30. Sever MS, Vanholder R, Lameire N. Management of crush-related injuries after disasters. N Engl J Med 2006;354:1052-63.
31. Szwed JJ. Urinalysis and clinical renal disease. Am J Med Technol 1980;46:720-5.
32. Tsai JJ, Yeun JY, Kumar VA, Don BR. Comparison and interpretation of urinalysis performed by a nephrologist versus a hospital-based clinical laboratory. Am J Kidney Dis 2005;46:820-9.
33. Goldstein SL. Kidney function assessment in the critically ill child: Is it time to leave creatinine behind? Crit Care 2007;11:141.
34. Herget-Rosenthal S, Marggraf G, Hüsing J, Göring F, Pietruck F, Janssen O, *et al.* Early detection of acute renal failure by serum cystatin C. Kidney Int 2004;66:1115-22.
35. Zappitelli M, Krawczeski CD, Devarajan P, Wang Z, Sint K, Thiessen-Philbrook H, *et al.* Early postoperative serum cystatin C predicts severe acute kidney injury following pediatric cardiac surgery. Kidney Int 2011;80:655-62.
36. Devarajan P. The future of pediatric acute kidney injury management – biomarkers. Semin Nephrol 2008;28:493-8.
37. Nguyen MT, Devarajan P. Biomarkers for the early detection of acute kidney injury. Pediatr Nephrol 2008;23:2151-7.
38. Cowland JB, Borregaard N. Molecular characterization and pattern of tissue expression of the gene for neutrophil gelatinase-associated lipocalin from humans. Genomics 1997;45:17-23.
39. Flo TH, Smith KD, Sato S, Rodriguez DJ, Holmes MA, Strong RK, *et al.* Lipocalin 2 mediates an innate immune response to bacterial infection by sequestrating iron. Nature 2004;432:917-21.
40. Grigoryev DN, Liu M, Hassoun HT, Cheadle C, Barnes KC, Rabb H. The local and systemic inflammatory transcriptome after acute kidney injury. J Am Soc Nephrol 2008;19:547-58.
41. Makris K, Rizos D, Kafkas N, Haliassos A. Neurophil gelatinase-associated lipocalin as a new biomarker in laboratory medicine. Clin Chem Lab Med 2012;50:1519-32.
42. Hirsch R, Dent C, Pfriem H, Allen J, Beekman RH rd, Ma Q, *et al.* NGAL is an early predictive biomarker of contrast-induced nephropathy in children. Pediatr Nephrol 2007;22:2089-95.
43. Nickolas TL, O'Rourke MJ, Yang J, Sise ME, Canetta PA, Barasch N, *et al.* Sensitivity and specificity of a single emergency department measurement of urinary neutrophil gelatinase-associated lipocalin for diagnosing acute kidney injury. Ann Intern Med 2008;148:810-9.
44. Mishra J, Dent C, Tarabishi R, Mitsnefes MM, Ma Q, Kelly C, *et al.* Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. Lancet 2005;365:1231-8.
45. Haase M, Bellomo R, Haase-Fielitz A. Neutrophil gelatinase-associated lipocalin. Curr Opin Crit Care 2010;16:526-32.
46. Parikh CR, Jani A, Melnikov VY, Faubel S, Edelstein CL. Urinary interleukin-18 is a marker of human acute tubular necrosis. Am J Kidney Dis 2004;43:405-14.
47. Parikh CR, Abraham E, Ancukiewicz M, Edelstein CL. Urine IL-18 is an early diagnostic marker for acute kidney injury and predicts mortality in the intensive care unit. J Am Soc Nephrol 2005;16:3046-52.
48. Leslie JA, Meldrum KK. The role of interleukin-18 in renal injury. J Surg Res 2008;145:170-5.
49. Vaidya VS, Ramirez V, Ichimura T, Bobadilla NA, Bonventre JV. Urinary kidney injury molecule-1: A sensitive quantitative biomarker for early detection of kidney tubular injury. Am J Physiol Renal Physiol 2006;290:F517-29.
50. Han WK, Waikar SS, Johnson A, Betensky RA, Dent CL, Devarajan P, *et al.* Urinary biomarkers in the early diagnosis of acute kidney injury. Kidney Int 2008;73:863-9.
51. Liangos O, Perianayagam MC, Vaidya VS, Han WK, Wald R, Tighiouart H, *et al.* Urinary N-acetyl-beta-(D)-glucosaminidase activity and kidney injury molecule-1 level are associated with adverse outcomes in acute renal failure. J Am Soc Nephrol 2007;18:904-12.
52. Wang G, Gong Y, Anderson J, Sun D, Minuk G, Roberts MS, *et al.* Antioxidative function of L-FABP in L-FABP stably transfected Chang liver cells. Hepatology 2005;42:871-9.
53. Yamamoto T, Noiri E, Ono Y, Doi K, Negishi K, Kamijo A, *et al.* Renal L-type fatty acid - binding protein in acute ischemic injury. J Am Soc Nephrol 2007;18:2894-902.
54. Doi K, Noiri E, Maeda-Mamiya R, Ishii T, Negishi K, Hamasaki Y, *et al.* Urinary L-type fatty acid-binding protein as a new biomarker of sepsis complicated with acute kidney injury. Crit Care Med 2010;38:2037-42.
55. Katagiri D, Doi K, Honda K, Negishi K, Fujita T, Hisagi M, *et al.* Combination of two urinary biomarkers predicts acute kidney injury after adult cardiac surgery. Ann Thorac Surg 2012;93:577-83.
56. Basu RK, Zappitelli M, Brunner L, Wang Y, Wong HR, Chawla LS, *et al.* Derivation and validation of the renal angina index to improve the prediction of acute kidney injury in critically ill children. Kidney Int 2014;85:659-67.
57. Siew ED, Furth SL. Acute kidney injury: A not-so-silent disease. Kidney Int 2014;85:494-5.
58. DiCarlo JV, Alexander SR, Agarwal R, Schiffman JD. Continuous veno-venous hemofiltration may improve survival from acute respiratory distress syndrome after bone marrow transplantation or chemotherapy. J Pediatr Hematol Oncol 2003;25:801-5.
59. Sutherland SM, Zappitelli M, Alexander SR, Chua AN, Brophy PD, Bunchman TE, *et al.* Fluid overload and mortality in children receiving continuous renal replacement therapy: The prospective pediatric continuous renal replacement therapy registry. Am J Kidney Dis 2010;55:316-25.
60. Goldstein SL, Currier H, Graf Cd, Cosio CC, Brewer ED, Sachdeva R. Outcome in children receiving continuous venovenous hemofiltration. Pediatrics 2001;107:1309-12.
61. Foland JA, Fortenberry JD, Warshaw BL, Pettignano R, Merritt RK, Heard ML, *et al.* Fluid overload before continuous hemofiltration and survival in critically ill children: A retrospective analysis. Crit Care Med 2004;32:1771-6.
62. Bouchard J, Soroko SB, Chertow GM, Himmelfarb J, Ikizler TA, Paganini EP, *et al.* Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. Kidney Int 2009;76:422-7.
63. Guerin C, Girard R, Selli JM, Perdrix JP, Ayzac L. Initial versus delayed acute renal failure in the intensive care unit. A multicenter prospective epidemiological study. Rhône-Alpes Area Study Group on Acute Renal Failure. Am J Respir Crit Care Med 2000;161:872-9.
64. Prins JM, Weverling GJ, van Ketel RJ, Speelman P. Circadian variations in serum levels and the renal toxicity of aminoglycosides in patients. Clin Pharmacol Ther 1997;62:106-11.
65. Malacarne P, Bergamasco S, Donadio C. Nephrotoxicity due to combination antibiotic therapy with vancomycin and aminoglycosides in septic critically ill patients. Chemotherapy 2006;52:178-84.
66. Andreoli SP. Acute kidney injury in children. Pediatr Nephrol 2009;24:253-63.
67. Brienza N, Malcangi V, Dalfino L, Trerotoli P, Guagliardi C, Bortone D, *et al.* A comparison between fenoldopam and low-dose dopamine in early renal dysfunction of critically ill patients. Crit Care Med 2006;34:707-14.
68. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R, *et al.* A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med 2004;350:2247-56.
69. Vincent JL, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, *et al.* Sepsis in European intensive care units: Results of the SOAP study. Crit Care Med 2006;34:344-53.
70. Goldstein SL, Somers MJ, Baum MA, Symons JM, Brophy PD, Blowey D, *et al.* Pediatric patients with multi-organ dysfunction syndrome receiving continuous renal replacement therapy. Kidney Int 2005;67:653-8.
71. Swärd K, Valsson F, Odencrants P, Samuelsson O, Ricksten SE.

Recombinant human atrial natriuretic peptide in ischemic acute renal failure: A randomized placebo-controlled trial. Crit Care Med 2004;32:1310-5.
72. Ricci Z, Stazi GV, Di Chiara L, Morelli S, Vitale V, Giorni C, *et al.* Fenoldopam in newborn patients undergoing cardiopulmonary bypass: Controlled clinical trial. Interact Cardiovasc Thorac Surg 2008;7:1049-53.
73. Mehta NM, Compher C, A.S.P.E.N. Board of Directors. A.S.P.E.N. Clinical Guidelines: Nutrition support of the critically ill child. JPEN J Parenter Enteral Nutr 2009;33:260-76.
74. Zappitelli M, Goldstein SL, Symons JM, Somers MJ, Baum MA, Brophy PD, *et al.* Protein and calorie prescription for children and young adults receiving continuous renal replacement therapy: A report from the Prospective Pediatric Continuous Renal Replacement Therapy Registry Group. Crit Care Med 2008;36:3239-45.
75. Goldstein SL, Somers MJ, Brophy PD, Bunchman TE, Baum M, Blowey D, *et al.* The Prospective Pediatric Continuous Renal Replacement Therapy (ppCRRT) Registry: Design, development and data assessed. Int J Artif Organs 2004;27:9-14.
76. Goldstein SL. Continuous renal replacement therapy: Mechanism of clearance, fluid removal, indications and outcomes. Curr Opin Pediatr 2011;23:181-5.
77. Sutherland SM, Alexander SR. Continuous renal replacement therapy in children. Pediatr Nephrol 2012;27:2007-16.
78. Bonilla-Félix M. Peritoneal dialysis in the pediatric intensive care unit setting. Perit Dial Int 2009;29 Suppl 2:S183-5.
79. Bagshaw SM, Bellomo R, Devarajan P, Johnson C, Karvellas CJ, Kutsiogiannis DJ, *et al.* Review article: Acute kidney injury in critical illness. Can J Anaesth 2010;57:985-98.
80. Palevsky PM, Liu KD, Brophy PD, Chawla LS, Parikh CR, Thakar CV, *et al.* KDOQI US commentary on the 2012 KDIGO clinical practice guideline for acute kidney injury. Am J Kidney Dis 2013;61:649-72.
81. De Backer D, Biston P, Devriendt J, Madl C, Chochrad D, Aldecoa C, *et al.* Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med 2010;362:779-89.
82. Bhat MA, Shah ZA, Makhdoomi MS, Mufti MH. Theophylline for renal function in term neonates with perinatal asphyxia: A randomized, placebo-controlled trial. J Pediatr 2006;149:180-4.

How to cite this article: Ashraf M, Shahzad N, Irshad M, Hussain SQ, Ahmed P. Pediatric acute kidney injury: A syndrome under paradigm shift. Indian J Crit Care Med 2014;18:518-26.

Source of Support: Nil, **Conflict of Interest:** None declared.