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

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,
RIFLE stands for 3° of severity-Risk, Injury, and Failure, and two outcomes-Loss and End-stage kidney disease. The RIFLE was later modified in 2007 using the “AKIN 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. 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%, 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. 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).

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. It is noteworthy that SCr varies by muscle mass, hydration status, sex, age and gender and method of measurement. In addition to this, one should not forget that SCr is dialyzable and after dialysis SCr does not increase in SCr % for >6 h

### Table 1: Diagnostic criteria for AKI

| RIFLE | AKIN |
|-------|------|
| An increase in SCr of ≥50% developing over <7 days (or) ≥50 developing over <48 h (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 |

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

| Stage | eCCI | Urine output |
|-------|------|--------------|
| R= Risk for renal dysfunction | eCCI decrease by 25 | <0.5 ml/kg/h for 8 h |
| I= Injury to the kidney | eCCI decrease by 50 | <0.5 ml/kg/h for 16 h |
| F= Failure of kidney | eCCI decrease by 75 or <35 ml/min/1.73 m² | <0.3 ml/kg/h for 24 h |
| L= Loss of kidney functionality persistent failure >4 weeks | ESRD persistent failure >3 months | anuria for 12 h |

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

### 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 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. Common causes of AKI differed from country to country; in China commonest form of pAKI is intrinsic AKI while in India prerenal form is the most common one. 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.

Table 3: Common Causes of pAKI

| Cause | Description |
|-------|-------------|
| Cardiac surgery | Cardiac surgery, sepsis, blood cancer, and respiratory failure of varied etiology. |
| Sepsis | Sepsis, blood cancer, and respiratory failure of varied etiology. |
| Blood cancer | Sepsis, blood cancer, and respiratory failure of varied etiology. |
| Respiratory failure | Sepsis, blood cancer, and respiratory failure of varied etiology. |

Indian Journal of Critical Care Medicine August 2014 Vol 18 Issue 8
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.\textsuperscript{[24,25]} Patient-related risk factors are age, hypertension, diabetes mellitus, cardiac failure, peripheral vascular disease, cerebrovascular disease and preexisting chronic kidney disease.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[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.

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. Intrinsic 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.\textsuperscript{[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.\textsuperscript{[31]}

### Table 3: Common causes of pAKI

| Renal hypoperfusion |
|--------------------|
| 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/periocarditis, sepsis-associated Cardiac dysfunction, sepsis-associated diffuse vasodilatation |
| Pulmonary diseases: Pulmonary embolism, sepsis, pulmonary arterial hypertension |

| Diseases of renal tissue |
|-------------------------|
| Glomerular: Glomerulonephritis due to anti-glomerular basement membrane disease, antineutrophil, cytotoxicplasmic autoimmune 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 |
| Intersitial |
| 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
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. 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, eosinophilia. 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, during acute kidney dysfunction as SCr does not increase until the GFR has moderately decreased (about 40 ml/min/1.73 m²). 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 and postoperative Cys C was more effective at predicting AKI in pediatric cardiac surgery patients. 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. 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. 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. 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. 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. NGAL is rapidly and massively elevated in various tubular and glomerular injuries. 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. 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. 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%. 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. 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. 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.

**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. 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. 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.

**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. 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. 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. 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).

**Renal Angina Index**

In one of the latest studies, 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.

**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 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:

\[ \text{FO} = \frac{\text{Sum of daily (fluid in}}{-\text{fluid out})/\text{ICU admission weight \times 100}} \]

**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, cephalexins, 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. Among patients in the pCRRT registry, overall mortality was 42%; higher mortality rates were seen in AKI patients with multiple organ failures. 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. Some researchers favor the use of peritoneal dialysis because of its simplicity, less invasiveness, its operability in neonates and hemodynamic instability.

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. Recent studies have failed to favor the use of hyperchloremic solutions like normal saline, and use of dopamine in patients with shock. In fact, dopamine may be associated with increased arrhythmic complications. 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 events may benefit with the proper protocol-based treatment. (5) Therapeutic drug 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. (6) Prompt initiation of CRRT should be considered 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.

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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.