REVIEW ARTICLE

Newer Insights Into Acute Renal Failure In Children

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Introduction

Acute renal failure (ARF) is now being more often referred to as acute kidney injury (AKI) and will be done so for the rest of this paper. AKI is defined as an abrupt or rapid decline in glomerular filtration rate (GRF) usually accompanied by a rise in serum creatinine and blood urea nitrogen (azotaemia). It is important to note that a rise in creatinine and urea may not be present immediately after kidney injury and that the only sign of AKI may be decreased urine production. Other factors may result in increased creatinine levels due to inhibition of renal tubular secretion such as medication (e.g. cimetidine, trimethoprim). Similarly blood urea levels may rise from gastrointestinal or mucosal bleeding, steroid use, protein loading and rhabdomyolysis [1, 2].

Although the majority of children with AKI recover completely after appropriate therapy, children who have suffered AKI from any cause are at risk for late development of kidney disease several years after the initial insult [3]. Recent studies show that the incidence of AKI in hospitalised children is increasing worldwide [4-13] particularly in the setting of post-cardiac surgery and in children undergoing stem cell transplantation.

Paediatric retrospective studies have reported incidences of AKI in paediatric intensive care units of between 8-30% [4,5,12,14]. Most studies have shown that neonates have higher rates of AKI, especially following cardiac surgery, severe asphyxia, or premature birth [6,13]. Other factors linked to the development of AKI in neonates include very low birth weight (less than 1500g), a low Apgar score, a patent ductus arteriosus, and maternal receipt of antibiotics or non-steroidal anti-inflammatory drugs during pregnancy [9]. The incidence of AKI in newborns in a developing country was 3.9 /1000 live births and 34.5/1000 newborns admitted to the neonatal unit [10].

Children with AKI due to acute interstitial nephritis, nephrotoxic renal insults including aminoglycoside nephrotoxicity, and contrast nephropathy usually have normal urine output. On the other hand oliguria (urine output less than 500ml per 24 hours in older children or urine output less than 1ml/kg per hour in younger children and infants) or anuria (urine output less than 100ml/day in older children or less than 0.5ml/kg per hour in younger children and infants) is more likely to be present in children with AKI due to hypoxia or ischemic insults, haemolytic uremic syndrome, acute glomerulonephritis and other causes [15].

Classification and Aetiology of Acute Kidney Injury in Children

The lack of a uniform definition of AKI in adults and children has lead to the adoption of a new classification system entitled the RIFLE criteria as a standardize criteria for AKI in adults [16] and has been adapted for paediatric patients [17]. The paediatric RIFLE (pRIFLE) classification better reflects the course of AKI in children admitted to the intensive care unit [Table 1]. The new classification system aims to standardize the definition of AKI based on changes in serum creatinine from baseline, a decrease in urine output, as well as the length of renal replacement at later stages. In adults, the RIFLE criteria were shown in a multinational and multicentre study to independently predict length of stay, cost, morbidity, and mortality [18]. However no similar paediatric studies are available. To aid in the differential diagnosis of AKI, in general terms, AKI may be classified as pre-renal, intrinsic renal, and post-renal. However many pathophysiological features are shared among the different categories [Table 2,3,4].

Table 1: Paediatric-modified RIFLE (pRIFLE) criteria

	Estimated CCI	Urine Output
Risk	**eCCI decrease by 25%**	**<0.5 ml/kg/h for 8 h**
Injury	**eCCI decrease by 50%**	**<0.5 ml/kg/h for 16 h**
Failure	**eCCI decrease by 75%** **eCCI <35ml/min/ 1.73m2**	**<0.3 ml/kg/h for 24 h or Anuric for 12 h**
Loss	**Persistent failure> 4weeks**	
End stage	**End-stage renal disease**	
	(persistent failure >3 months)	

eCCI estimated creatinine clearance, prifle pediatric risk, injury, failure, loss and end-range renal disease. eCCI was calculated using the Schwartz formula. Adapted with permission [17].

Table 2: Aetiology of common causes of pre-renal acute kidney injury in children

Decreased true intravascular volume	Decrease effective intravascular volume
• Haemorrhage	Congestive heart failure
• Dehydration due to gastrointestinal losses	Cardiac tamponade
• Salt wasting renal or adrenal diseases	Hepatorenal syndrome
• Central or nephrogenic diabetes insipidus	
• Increased insensible losses e.g. burns	
• In disease status associated with third space losses e.g. sepsis, nephrotic syndrome, traumatized tissue and capillary leak syndrome	

Table 3: Aetiology of common intrinsic renal disease in children

- **Acute renal necrosis (vasomotor nephropathy)**
  - Hypoxic / ischemic insults
  - Drug induced
  - Toxin mediated
    Endogenous toxins- haemoglobin, myoglobin
    Exogenous toxins- ethylene glycol, methanol
- **Uric nephropathy and tumour lysis syndrome**

- **Interstitial nephritis**
  - Drug induced
  - Idiopathic
- **Glomerulonephritis - Rapid progressive glomerulonephritis**
- **Vascular lesions**
  - Renal artery thrombosis
  - Renal vein thrombosis
  - Cortical necrosis
  - Hemolytic artery syndrome
- **Hypoplasia/ dysplasia with or without**
  - Obstructive uropathy
  - Idiopathic
  - Exposure to nephrotoxic drug in utero

Table 4: Aetiology of common causes of post renal acute kidney injury in children

- Obstruction in solitary kidney
- Bilateral ureteral obstruction
- Uretheral Obstruction

Pathophysiology of Acute Kidney Injury

AKI may develop in 3 clinical patterns: (1) as an adaptive response to severe volume depletion and hypotension, with structurally intact nephrons; (2) in response to cytotoxic, ischemic, or inflammatory insults to the kidney, with structural and functional damage; and (3) with obstruction to the passage of urine.

Pre-renal injury is reversible once blood volume and hemodynamic conditions have been restored. Failure to do this can result in intrinsic AKI due to hypoxic/ischemic acute tubular necrosis (ATN). When renal perfusion is compromised, the afferent arterioles relax their vascular tone to decrease renal vascular resistance and maintain renal blood flow. Intra-renal generation of vasodilatory prostaglandins including prostacyclin mediates vasodilatation of the renal microvasculature to maintain renal perfusion. Administration of cyclo-oxygenase inhibitors such as aspirin or non-steroidal anti-inflammatory drugs can inhibit this compensatory mechanism and precipitate AKI [19]. During pre-renal injury the tubules respond to decreased renal perfusion by appropriately conserving sodium and water such that the urine osmolality is greater than 400-500 mosmol/l, urine sodium is less than 10-20Eq/l and the fractional excretion of sodium is less than 1%. In newborns and premature infants the relative immaturity of the renal tubules need to be taken into account. Thus corresponding values are a urine osmolality greater than 350mosmol/l, urine sodium less than 20-30mEq/l and fractional sodium excretion of less than 2.5% [20,21]. The use of these values to differentiate pre-renal injury from ATN requires that the patient have normal tubular function initially. However, newborns with immature tubules and children with pre-existing renal disease or salt-wasting adrenal disease, as well as other diseases might have urinary indices suggestive of ATN but in fact have pre-renal failure. In addition, the fractional excretion of sodium may be falsely increased in patients receiving diuretic therapy [3].

In children with intrinsic renal disease due to hypoxic/ischemic AKI, there is early vasoconstriction followed by patchy tubular necrosis. The exact mechanism of cellular injury in this condition is unknown but the following are thought to play a role: alterations in endothelin or nitric oxide regulation of vascular tone, ATP depletion and alterations in the cytoskeleton, changes in heat shock proteins, inhibition of the inflammatory response and the generation of reactive oxygen and nitrogen molecules [22,23]. In children with multi-organ failure, the systemic inflammatory response is thought to contribute to AKI as well as other organ dysfunction by the activation of the inflammatory response, including increased production of cytokines and reactive oxygen molecules, activation of polymorpho-nuclear leukocytes, and increased expression of leukocyte adhesion molecules [24].

Nephrotoxic AKI from medications is at least in part due to toxic tubular injury. Aminoglycoside nephrotoxicity typically presents with non-oliguric AKI, with urinalysis showing minimal urinary abnormalities. Factors influencing the development of AKI from amino-glycoside use include the dose and duration of therapy as well as the level of renal function prior to the commencement of treatment. There is disruption of lysosomal function in the proximal tubular and this is reversible once the amino-glycoside has been discontinued. However the serum creatinine may continue to increase for several days due to ongoing tubular injury from continued high parenchymal levels of the aminoglycoside [3]. Other common agents include intravascular contrast, Amphotericin B, chemotherapeutic agents such as ifostamide and cisplatin, acyclovir and acetaminophen.

Table 5 illustrates a classification of various drugs known to cause AKI based on pathophysiological mechanisms [25].

Table 6 illustrates a list of common biological nephrotoxic produced by animals that cause AKI [26].

Table 5: Classification of various drugs based on pathophysiological categories of acute kidney injury

Pathophysiology	Drugs known to cause acute kidney injury.
Prerenal failure	Non-steroid anti-inflammatory drugs, angiotensin converting enzyme, cyclosporine A, norepinephrine, antiogensin-2 receptor antagonists, diuretics, interleukins, cocaine, mitomycin C, tacrolimus, estrogen, quinine.
Acute tubular	Antibiotics: aminoglycosides, cephalosporins, Amphotericin B, rifampicin, vancomycin, foscarnet, pentamidine, Non-steroid anti-inflammatory drugs, glaphenin, contrast media, acetaminophen, cyclosporine A, cisplatin, IV immunoglobulin, dextran, maltose, sucrose, mannitol, heavy metals
Acute interstitial nephritis	Antibiotics: ciprofloxacin, methicillin, penicillin G, ampicillin, cephalosporins, oxacillins, rifampicin. Non-steroid anti-inflammatory, glaphenin, acetylsalicylic acid (ASA), fenoprofen, naproxen, phenylbutazone, piroxicam, tolmetin, zomepirac, contrast media, sulphonamides, thiazides, phenytoin, furosemide, allopurinol, cimetidine, omeprazole, phenindione, zomeporic

Tubular obstruction	Sulfonamides, methotrexate, methoxyflurane, glaphenin, triameterene, acyclovir, ethylene glycol, protease inhibitors
Hyperse -nsitivity angitis	Pencillin G, ampicillin, sulphonamides
Thrombotic microang- iopathy	Mitomycin C, cyclosporine A, oral contraceptives

Adapted with permission from reference [1].

Table 6: Common biological nephrotoxics produced by animals

Animal	Biologic nephrotoxins
Snake	Phospholipase A2, myotoxins, Procoagulant-activating factors V and X
Spider	Sphingomyelinase D, neurotoxins
Bee	Melittin, phospholipase A2, Mast-cell Degranulation protein
Wasp	Antigen 5, mastroparans
Murines animal (carp, jellyfish, sea anemone)	Ichthyogallotoxin, cyprinol

Modified by Chisney and Jones [Reproduced with permission from 1].

Children with AKI caused by nephrotoxic agents have a significant risk for development of chronic kidney disease. Although drugs are an infrequent cause of AKI in children in the general population, drugs and hypoxia are the leading cause of hospital-acquired AKI, with significant morbidity and mortality. The judicious use of nephrotoxic drugs and their combinations, together with adequate hydration, are still the most important measures to take in minimising nephrotoxicity.

Haemolysis and rhadomyolysis from any cause can result in sufficient hemoglobinuria or myoglobinuria to induce tubular injury and precipitate AKI. The mechanisms of AKI are complex but may be related to vasodilation, precipitation of the pigments in the tubular lumen, and/or haeme-protein-included oxidant stress [27].

Uric acid nephropathy and tumour lysis syndrome are most common in children with acute lymphocytic leukaemia and B-cell lymphoma [39]. The pathogenesis of uric acid nephropathy is complex but a potentially important mechanism of injury is related to the precipitation of crystals in the renal tubules leading to obstruction of urine flow and in the renal microvasculature, obstructing urinary blood flow severely [39,40]. AKI during tumour lysis syndrome can also result from extreme hyperphosphataemia from rapid breakdown of tumour cells and the precipitation of calcium phosphate crystals [28].

In children with AKI due to acute interstitial nephritis, the clinical features include rash, fever, althralgias, eosinophilia, and pyuria with or without eosinophiluria. Acute interstitial nephritis is most often due to a reaction to a drug but may be idiopathic. Withdrawal of the offending agent together with corticosteroid therapy may aid in improving renal function.

Any form of glomerulonephritis, including rapidly progressive glomerulonephritis, can progress to AKI. Whilst post-infectious glomerulonephritides are less likely to progress to chronic kidney disease, the other forms of glomerulonephritis presenting with AKI may progress to chronic kidney disease, with or without treatment. Clinical features include hypertension, oedema, haematuria, and a rapidly using blood urea nitrogen and serum creatinine. Since therapy is largely dependent on biopsy findings in rapidly progressive glomerulonephritis, a biopsy should be performed early in the course of the disease [3].

Cortical necrosis as a cause of AKI is most common in neonates and presents with microscopic haematuria, oliguria, hypertension, and elevated levels of blood urea nitrogen and creatinine. Thrombocytopenia may also be present due to microvascular injury. As the disease progresses, ultrasound may show decreased kidney size due to atrophy. Children with cortical necrosis may partially recover or not at all. Haemolytic uremic syndrome in older children may lead to cortical necrosis with substantial morbidity and mortality [29].

Post renal AKI arising from obstruction of the urinary tract occurs if there is obstruction in a solitary kidney, if it involves the ureters bilaterally, or if there is urethral obstruction. In unilateral obstruction, the rise in serum creatinine levels may not be apparent due to intact contralateral renal function. Although the serum creatinine may remain low with unilateral obstruction, significant loss of glomerular filtration occurs, and patients develop progressive loss of glomerular filtration if the obstruction is not relieved [3]. Patients who develop anuria typically have obstruction at the level of the bladder or downstream to it.

Early Detection of AKI

The lack of early markers for the detection of AKI in clinical practice leads to unacceptable delays in initiation of therapy. In present clinical practice, AKI is typically diagnosed by measuring serum creatinine levels. In children serum creatinine levels vary widely with age. Other factors such as gender, lean muscle mass, muscle metabolism, and hydration status influence the levels of serum creatinine. Also at low rates of glomerular filtration, the amount of tubular secretion of creatinine, results in over estimation of renal function. During acute changes in glomerular filtration, serum creatinine may take several days to reach steady-state equilibrium and therefore in the interim does not accurately depict kidney function. Lastly, severe creatinine levels may not change until about 50% of kidney function has already been lost [30, 31, 32].

Animal studies have shown that AKI can be prevented and/or treated by appropriate therapy if instituted early, well before there is a rise in serum creatinine. The lack of early biomarkers for the detection of AKI has seriously impeded the development of novel therapies in humans [33, 34].

Biomarkers of the detection of AKI are also needed for the following:

(a) Differentiation between pre-renal, intrinsic renal, or post renal AKI.
(b) Identification of AKI aetiologies e.g. sepsis, toxins, or a combination of these.

(c) Differentiating AKI from other forms of kidney disease (urinary treat infection, interstitial nephritis, and glomerulonephritis).
(d) Predicting AKI severity thus allowing for risk stratification for prognostication as well as to guide therapy.
(e) Monitoring the course of AKI.
(f) Assessing the impact of treatment.

Biomarkers used in clinical practice should have the following characteristics: [35].

(a) Non-invasive or minimally invasive and easy to perform using easily accessible samples such as blood and urine.
(b) Highly sensitive for the early detection of AKI and have a wide dynamic range and cut off values that allow for risk stratification.
(c) Easily measured with rapid turnaround times.
(d) Highly specific for AKI and enable the identification of AKI subtypes and aetiologies.

Table 7 shows the current status of promising AKI biomarkers in various clinical studies [35].

Of these markers neutrophil gelatinase-associated lipocalin (NGAL) has been identified as one of the easiest and most sensitive markers of AKI, and is easily detected in blood and urine soon after AKI [36-40]. Urine NGAL has been shown to predict the severity of AKI and dialysis requirements in a multicentre study of children with diarrhoea-associated haemolytic uremic syndrome [41]. However, although NGAL is proving to be a promising novel predictive biomarker of AKI, its measurement may be influenced by a number of co-existing variables, such as pre existing renal disease and systemic or urinary tract infections [42-44].

Cystatin C is a systemic protease inhibitor that is synthesized and released into the blood at a relatively constant rate by all nucleated cells. Blood levels of cystatin C are not significantly affected by age, gender, race or muscle mass and its secretion into the bloodstream by nucleated cells is at a fairly constant rate. Thus it is a better predictor of chronic kidney disease compared to serum creatinine [45]. A 50% increase in severe cystatin C levels predicts AKI one to two days prior to a corresponding rise in severe creatinine [46]. Compared to NGAL, cystatin C levels are elevated 12 hrs after that of NGAL. Nonetheless, both are independent predictors of AKI [35]. An advantage of cystatin C is that a standardized, immunonephelometric assay is commercially available and routine clinical storage conditions, freeze/thaw cycles, the presence of interfering substances and the aetiology of AKI does not affect its measurements [35].

Kidney injury molecule 1 (KIM-1) is a transmembrane protein that is highly over expressed in differentiated proximal tubule cells after ischemia or nephrotoxic AKI in animals [47,48]. A proteolytically processed domain is easily detected in urine [49]. An advantage of KIM-1 over NGAL is that KIM-1 appears to be more specific to nephrotoxic or ischemic AKI since patients with AKI induced by contrast do not show increased urinary KIM-1 excretion. [47]. Thus it is likely that NGAL and KIM-1 used in combination will not only aid in early detection of AKI but will help differentiate ischemic and nephrotoxic AKI from other causes of AKI.

Interleukin 18 (IL-18) is a proinflammatory cytokine that is induced and elevated in the proximal tubular and subsequently easily detected in the urine following AKI in animal models [50]. Human studies in children undergoing cardiac surgery have shown IL-18 and NGAL to be early, predictive, sequential biomarkers of AKI [51]. Urinary NGAL and IL-18 also predicts delayed graft function following kidney transplantation [52].

Multicentre studies in larger cohorts of patients will be required in the future to validate the sensitivity and specificity of these biomarkers panels for early detection of AKI, their ability to differentiating AKI from other forms of kidney disease, prognosticating outcome, and assessing the impact of interventions.

Management of AKI in children
Preventive Measure

In asphyxiated neonates, intravenous infusion of theophylline given within the first hour was associated with improved fluid balance, creatinine clearance and reduced serum creatinine levels in some studies. The potential mechanism that theophylline could protect from AKI in this setting may be by blocking of the adenosine receptor [53-55]. However additional studies are needed to determine the significance of these findings and the potential side effects of theophylline.

Diuretics and 'renal dose' dopamine are commonly used to prevent or limit AKI [56-63]. Although stimulation of urine output aids in improving fluid management in AKI, conversion of oliguric to non

Table 7: Current status of promising acute kidney injury (AKI) biomarkers in various clinical situations

Bio markers Name	Sample Source	Cardiac surgery	Contrast	Sepsis or ICU Nephro pathy	Kidney Transplant	Commercial Test
NGAL	Plasma	Early	Early	Early	Early	Boistea
Cystatin C	Plasma	Intermediate	Intermediate	Intermediate	Intermediate	Dade- Behring
NGAL	Urine	Early	Early	Early	Early	Abbot2
IL-18	Urine	Intermediate	Intermediate	Intermediate	Intermediate	None
KIM-1	Urine	Intermediate	Not tested	Not tested	Not tested	None

NGAL: neutrophil gelatinase-associated lipocalin, IL-18: interleukin 18, KIM-1: Kidney injury molecule 1a In development. Adapted with permission from reference [35]

oliguric AKI has not been shown to alter the cause of renal failure. Furosemide may decrease intra tubular obstruction by increasing urine flow rate. Also inhibition of Na+-K+-ATPase will limit oxygen consumption in already damaged tubules with a low oxygen supply [3]. Continuous infusion of furosemide may be associated with less toxicity than bolus administration [57]. 'Renal-dose' dopamine (0.5-5mcg/kg/min) may increase renal blood flow by promoting vasodilation and may improve urine output by promoting naturesis. However the use of dopamine has not been shown to decrease the need for dialysis or improve survival in patients with AKI. [59-63].

Fenoldopam is a potent, short-acting, selective, dopamine-1 receptor agonist that decreases vascular resistance while increasing renal blood flow [64] Several trials in adults have shown that the use of fenoldopam decreases the incidence of AKI, need for renal replacement therapy, length of hospital stay and the number of deaths from any cause [65]. Large scale paediatric studies are still outstanding.

All nephrotoxic agents should at best be avoided or used with extreme caution. Similarly, all medications cleared by renal excretion should be avoided or their doses should be adjusted appropriately.

A prophylactic therapy shown to decrease the incidence of contrast nephropathy is the intravenous administration of fluids. Normal saline or isotonic sodium bicarbonate given in a dose of 1ml/kg/hour 12 hours before and then 12 hours after the procedure is recommended.

N-acetylcysteine is another prophylactic agent used with varying success in high-risk patients and is given a day before a contrast study is performed and is continued on the day of the procedure [66].

Management of Acute Kidney Injury

Aggressive treatment should begin at the easiest indication of renal dysfunction. Recognising the presence of AKI and promptly initiating therapy is aimed at minimizing damage to the remaining functional renal mass. Reversing renal damage can only be accomplished by identifying the underlying cause and directing appropriate therapy.

Maintenance of volume homeostasis and correction of biochemical abnormalities remain the primary goals of treatment. Furosemide can be used to correct volume overload when patients are still responsive to it. Response to furosemide often portends a good progress. However furosemide plays no role in converting an oliguric AKI to a non oliguric AKI or to increase urine output when a patient is not hypervolemic.

The accompanying metabolic acidosis is corrected by bicarbonate administration. Hyperkalaemia can be life threatening and must be treated urgently. Treatment is aimed at decreasing the intake of potassium, delaying the absorption of potassium, exchanging potassium across the gut lumen using potassium-binding resins, controlling intracellular shifts and if these measures fail, by instituting dialysis.

Correcting haematological abnormalities (e.g. anaemia, platelet dysfunction) warrants appropriate measures, including blood transfusion and administration of desmopressin or oestrogens.

Dietary modulations to correct electrolytes imbalances particularly potassium and phosphate, and restricting fluids are crucial in the management of oliguric renal failure. During the recovery phase of AKI, patients are usually polyuric and may require dietary supplementation and increased intravenous fluids.

Future therapies in AKI

The future management of AKI may also include antioxidant; anti adhesion molecular therapy and the administration of vascular mediators or mesenchymal stem cells to prevent injury and/or promote recovery [67-70]. Despite promising animal models of intervention in AKI, clinical studies in humans have been largely disappointing, including studies that utilized anaritide (atrial natriuretic peptide) and 1GF-1 [71,72].

Prognosis of AKI

The progress of AKI is highly dependent on the underlying aetiology of the AKI. Progress is worse in children who developed AKI as a component of multisystem organ failure. Children with nephrotoxic AKI and hypoxic/ischemic AKI usually recover normal renal failure function. AKI is likely to be especially deleterious when the kidney has not yet grown to adult size and/or before the full complement of nephrons have developed [73].

Acknowledgements

I will like to thank Ms Slindile Phakati for her assistance in typing the manuscript, the authors and publishers to reproduce some of the published work that has been duly referenced.

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E-published : November 2009