

Acute kidney injury in children – not just for the nephrologist

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Abstract

Acute kidney injury (AKI) is a condition that is characterised by an abrupt reduction in kidney function, and is not limited to acute renal failure. However, it is potentially treatable. Failure to do so may result in death or progression to chronic kidney disease (CKD). AKI requires urgent management in order to ensure a better clinical outcome. Traditionally, AKI is classified according to aetiology, i.e. pre-renal, intrinsic renal and post-renal AKI. Clinical features depend on the age of the patient, the cause and related complications. Symptoms and signs may be non-specific, e.g. poor feeding and vomiting, or more specific, e.g. oedema, macroscopic haematuria and oliguria. The staging of AKI is based on the estimated glomerular filtration rate and urine output. AKI from any cause increases the risk of CKD developing, and vice versa. There are absolute indications for renal replacement therapy, e.g. anuria, whereas other patients can be managed successfully conservatively.

Keywords: acute kidney injury, AKI, children, fluid management, pRIFLE, renal replacement therapy

Introduction

The phrase “acute renal failure” has given way to the term “acute kidney injury” (AKI) in order for definitions to be standardised.¹ This term includes the full spectrum of, and mechanisms underlying, renal dysfunction.¹ The Kidney Disease: Improving Global Outcomes (KDIGO) guideline defines AKI as “an abrupt reduction in kidney function that includes, but is not limited to, acute renal failure”.² AKI is further defined as an increase in serum creatinine of 0.3 mg/dl ($\geq 26.5 \mu\text{mol/l}$) within 48 hours, or an increase in serum creatinine ≥ 1.5 times the baseline, if known; or urine volume $< 0.5 \text{ ml/kg/hour}$ for six hours.² The natural history of AKI is one of full recovery in kidney function or progression to chronic kidney disease (CKD), which can eventually evolve into end-stage kidney disease.³ The prompt diagnosis and stratification of AKI risk allows treatment to be instituted early in order to prevent progression of the disease.⁴

Epidemiology of acute kidney injury in children

Globally, AKI in children is under-reported owing to limited medical personnel, an inability to recognise the condition, cultural disparities in seeking medical assistance and seasonal variations in presentation.³ AKI occurs in roughly 8–30% of the children in paediatric intensive care, and in 5–10% of patients in neonatal intensive care units.⁵ The number of affected children with AKI in a study from Thailand rose from 4.6 to 9.9 cases per 1 000 paediatric admissions,⁶ and from 2.0–11.7% of paediatric admissions in India.³ Survival depends on the cause and available treatment. Seventy-three per cent of children

survived in the USA where post cardiac surgery was a major risk factor of AKI.⁷ Mortality was 50% in children in whom three organ systems were involved.⁷

Pathogenesis

The primary renal insult is a critical decrease in the blood supply, which results in the desquamation of tubular cells, tubular cast formation, intraluminal tubular obstruction and back leakage of the glomerular filtrate. Consequently, retention of nitrogenous waste products, an increase in the serum creatinine and derangement of the fluid and electrolyte homeostasis occurs. Structural damage ensues, and neutrophils adhere to the injured ischaemic endothelium in the kidney, releasing substances which promote inflammation.

Aetiology

Traditionally, the causes of AKI are divided into:^{5,8}

- Pre-renal, owing to the reduction in intravascular volume.
- Intrinsic renal, such as vasomotor nephropathy, glomerulonephritides, interstitial nephritis and nephrotoxicity secondary to toxins and drugs.
- Post-renal, owing to obstructive uropathies.

The frequency with which each type occurs differs by age group.⁸ Hypoxic-ischaemic kidney injury or nephrotoxic drug exposure, e.g. aminoglycosides and nonsteroidal anti-inflammatory drugs (NSAIDs), renal vascular events (renal artery and renal vein thrombosis, and coarctation of the aorta), and prematurity

and congenital heart disease are common in neonates.^{9,10} Even correctly dosed NSAIDs increase disease severity in young children.¹¹ The list of common causes has shifted in developed countries from primary glomerular disorders to hospital-acquired causes,⁶ while common causes in developing countries include acute tubular necrosis secondary to dehydration or sepsis, haemolytic uraemic syndrome and acute glomerulonephritis.⁶ The three most common causes of AKI in older children in South Africa were haemolytic uraemic syndrome (35%), acute tubular necrosis (31%) and acute glomerulonephritis (16%).¹² Acute glomerulonephritis and nephrotic syndrome accounted for 39% of causes of AKI, and sepsis and malaria for 26% and 11%, respectively, in Nigeria.^{12,13} The clinical presentation depends upon aetiology and related complications, and patients may present with poor feeding, vomiting, diarrhoea and dehydration, oliguria, anuria, hypotension or hypertension, fluid overload, haematuria, proteinuria, skin lesions or a rash and/or encephalopathy.

Acute kidney injury severity criteria

Staging of AKI is best performed by using the serum creatinine value and the urine output to assess severity (Table 1).

Table 1: Staging of acute kidney injury²

Stage	Serum creatinine	Urine output
1	1.5–1.9 x baseline, or ≥ 26.5 μmol/l (≥ 0.3 mg/dl) increase	< 0.5 ml/kg/hour for 6–12 hours
2	2.0–2.9 x baseline	< 0.5 ml/kg/hour for ≥ 12 hours
3	3 x baseline, or serum creatinine ≥ 353.6 μmol/l (4.0 mg/dl), or Initiation of renal replacement therapy, or If < 18 years old, eGFR* < 35 ml/minute/1.73m ²	< 0.3 ml/kg/hour for ≥ 24 hours, or anuria for ≥ 12 hours

eGFR: estimated glomerular filtration rate

* Estimated glomerular filtration rate using the Schwartz formula:¹⁴ eGFR = 40 x height (cm)/serum creatinine (μmol/l)

Serum creatinine is not the ideal marker of renal functional impairment because it is influenced by nonrenal factors, such as gender, lean muscle mass, metabolism and hydration status.⁵ However, it is still used in clinical practice. Serum creatinine takes several days to reach a steady state, and may not change significantly until approximately 50% of kidney function has been lost.⁵

The “RIFLE” criteria (risk, injury, failure, loss and end-stage renal disease) were proposed by the Acute Dialysis Quality Initiative for AKI in adults.¹⁵ Ackan-Arikan et al. have modified these criteria into a paediatric version – paediatric modified RIFLE criteria (pRIFLE), based on the decrease in the estimated creatinine clearance and the urine output (measured as ml/kg body weight).¹⁶ Three levels of kidney injury (risk, injury and failure) and two outcomes (loss of kidney function and end-stage renal disease) have been graded according to the pRIFLE criteria⁶ (Table 2). The Acute Kidney Injury Network (AKIN) has based its

revision on acute alterations in serum creatinine or urine output¹⁵ because smaller changes in the serum creatinine are associated with worse outcomes.⁸ AKI standardised definitions, used widely with respect to children, are based largely on pRIFLE, AKIN and KDIGO classifications.⁶ The measurement of urine output in the first 24 hours is an absolute requirement in the diagnosis of AKI. Oliguria is defined as urine output < 500 ml in 24 hours,⁸ or < 0.5 ml/kg/hour in an older child and < 1 ml/kg/hour in infants. Anuria is a urine output of < 50 ml/day or 1 ml/kg/day.⁵ Oliguria or anuria is commonly associated with intrinsic kidney disorders, such as haemolytic uraemic syndrome, glomerulonephritis and hypoxic or ischaemia kidney injury, while nonoliguric kidney injury is more commonly associated with nephrotoxic drugs (aminoglycosides), contrast nephropathy and acute interstitial nephritis.⁸

Table 2: Paediatric modified risk, injury, failure, loss and end-stage renal disease criteria¹⁶

	eCCL	Urine output
Risk	↓ eCCL by 25%	< 0.5 ml/kg/hour for 8 hours
Injury	↓ eCCL by 50%	< 0.5 ml/kg/hour for > 16 hours
Failure	↓ eCCL by 75%	< 0.3 ml/kg/hour for > 24 hours, or anuria for 12 hours
Loss	Persistent failure > 4 weeks	
End-stage disease criteria	End-stage renal disease (persistent failure > 3 months)	

↓ decreasing

* eCCL: estimated creatinine clearance (estimated glomerular filtration rate)

Biomarkers of acute kidney injury

Biomarkers of AKI are proteins which appear early in the plasma and urine of patients with AKI in response to renal tubular cell injury. This permits the early recognition and initiation of treatment of AKI to prevent ongoing renal damage.^{4,17,18} The most important biomarkers are plasma neutrophil gelatinase-associated lipocalin (NGAL) and cystatin C levels, urine NGAL, interleukin-18 and kidney injury molecule-1.^{17,18} Plasma and urinary NGAL levels increase within hours in post-cardiac surgery patients who develop AKI, compared to the delayed rise of serum creatinine, which only occurs much later.¹³ Plasma NGAL is a non-specific predictor of AKI in critically ill children with septic shock.¹⁹ Liver fatty acid-binding protein is an early predictor of AKI in children specifically after cardiac surgery.¹⁸ None of these biomarkers are commercially available in South Africa.

The management of acute kidney injury

Fluids and electrolytes

Saline 0.9% is the standard of care for intravascular volume expansion.²⁰ Four per cent albumin and 0.9% saline were equally safe for resuscitation, and there was no difference in the need for or duration of renal replacement therapy in a randomised controlled trial [Saline versus Albumin Fluid Evaluation (SAFE) study].²¹ There was no evidence of difference in the risk of death in trauma, burn or postoperative patients following resuscitation with colloids or crystalloids in a Cochrane review.²²

A meta-analysis demonstrated that hyperoncotic albumin was renoprotective, while hyperoncotic starch was nephrotoxic.²³ Colloids, e.g. albumin, have been shown to be superior to crystalloids with respect to resuscitation in conditions with chronic hypoalbuminaemia.²⁰

Appropriate crystalloids are required for electrolyte imbalances. Large volumes of 0.9% saline cause hyperchloraemic metabolic acidosis.²⁴ However, buffered solutions produce less acid base disturbances. It is not known whether or not they lead to a better clinical outcome.²⁰

Shocked patients should receive a fluid bolus of 20 ml/kg intravenously *stat*. If the response is unsatisfactory, a second bolus of 20 ml/kg intravenously should be given. Once resolved, the volume used is guided by the fluid status of the patient, urine output and extra renal fluid losses.

There are three differentiating scenarios:

- The fluid volume required for a well hydrated patient with no excessive losses is total urine output over the past 24 hours, plus insensible losses. The calculation for insensible losses is 30–40 ml/kg/24 hours in term neonates and young children, and 20–25 ml/kg/24 hours in older children.
- Fluid is replaced according to the severity of dehydration in a volume-depleted but not shocked patient with increased extra renal fluid losses, plus maintenance fluid requirements (Table 3). Dehydration can be severe, moderate or mild, i.e. requiring 100ml/kg/24 hours, 50 ml/kg/24 hours and 20 ml/kg/24 hours, respectively. Body weight is used as an indicator of hydration status and should be measured twice a day.
- Fluid is restricted to insensible losses only in an anuric, volume-overloaded patient. In the event of fluid overload and pulmonary oedema, intubation and ventilation, intravenous furosemide, the restriction of salt and fluids to insensible losses only, the initiation of dialysis, and the treatment of hypertension, if present, are all required.

Table 3: Maintenance fluids in children²⁵

Child maintenance fluid requirement volumes

- 120 ml/kg/24 hours for children aged ≤ 1 year old

The sum of the following in children aged ≥ 1 year old:

- 100 ml/kg/24 hours for each kilogram of body weight up to 10 kg
- 50 ml/kg/24 hours for each additional kilogram of body weight more than 10 kg
- 20 ml/kg/24 hours for each additional kilogram of body weight more than 20 kg

Vasopressor and vasodilator therapy

Avni et al. demonstrated that compared to dopamine, norepinephrine was associated with improved central venous pressure, increased urine output, a reduction in blood lactate levels and reduced risk in all-cause mortality, major adverse events and cardiac arrhythmias.²⁶ Dopamine is not recommended in AKI.²⁰

Diuretics and other therapies

The use of diuretics in volume-overloaded patients with AKI does not prevent the development, nor change the outcome, of renal failure.²⁰ Perinatal asphyxia leads to AKI in 60% of term neonates,²⁷ and a single dose of theophylline given in the first hour of birth improves the outcome.²⁸⁻³⁰

Nephrotoxic drugs, including antibiotics (at normal or inappropriately high doses), contrast media and others should be avoided. Therapeutic drug monitoring, where available, assists in drug dosing when the use of nephrotoxic drugs is inevitable. Topical formulations, e.g. aerosolised tobramycin, are recommended.²⁰

Nutrition and glycaemic control

Enteral nutrition is preferred in AKI, and the recommended energy and protein intake is 20.0–30.0 kcal/kg/day and 0.8–1.7 g/kg/day, respectively.²⁰ Blood glucose should be maintained between 6.1 mmol/l and 8.3 mmol/l.²⁰

Prognosis

Volume overload and a high pRIFLE score have a negative impact on outcome, while the early initiation of dialysis and the aggressive use of diuretics has been demonstrated to improve outcome.^{31,32} Children with non-oliguric AKI have a better survival rate than those with oliguric-anuric AKI.¹¹ A low predialysis serum albumin concentration is a co-predictor of mortality in patients with AKI.⁷

Recommended indications for renal replacement therapy are listed in Table 4.

Table 4: Indications for renal replacement therapy

Absolute indications	Relative indications
<ul style="list-style-type: none"> • Anuria • Fluid overload • Pulmonary oedema • Convulsions or coma • Uraemic pericarditis • Bleeding diathesis 	<ul style="list-style-type: none"> • Persistent hyperkalaemia and/or hyponatraemia • Persistent metabolic acidosis (pH < 7.1 or serum HCO₃ < 10 mmol/l) • Uncontrollable hypertension • Severe hyperphosphataemia and/or hypercalcaemia

HCO₃: bicarbonate

AKI from any cause is a risk factor for the development of CKD, especially if AKI occurs before the kidneys have attained adult function.⁵ AKI and CKD are interconnected, and underlying CKD is a risk factor for the development of AKI.³³ They lead to the development of cardiovascular disease,³³ and are associated with an increased risk of morbidity and mortality. A high index of suspicion must be exercised by clinicians in order to reduce the burden of disease in the long term.

Conflict of interest

The authors did not declare a conflict of interest.

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