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Current trends in the management of acute kidney injury in children

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Abstract Acute Kidney Injury (AKI) previously known as acute renal failure (ARF) is a common problem in the paediatric emergency wards with infections like sepsis and malaria being the commonest causes in Nigeria.

It has been known by various nomenclatures with a lack of standardised definition. This has made comparison of data very difficult. In the last decade, attempts have been made to standardize the definition by developing a classification criterion termed “RIFLE”. This is in turn undergoing various modifications with the most recent classification system developed by the Kidney Disease: Improving Global Outcomes (KDIGO).

Despite these interesting developments, the basis of these classifications which is the use of serum creatinine measurements is

fraught with its own limitations. This has led to discovery of various urinary and serum biomarkers like the cystatin C and neutrophil gelatinase associated lipocalin (NGAL) which appear to have very promising advantages over the well known creatinine measurements.

Management of AKI continues to be anticipatory with appropriate fluid therapy and adequate treatment of infections. The benefits of furosemide and dopamine in management are still a constant source of debate. Treatment of life threatening complications like hyperkalaemia and hypertension as well as maintaining the kidney through the period of non-function can lead to remarkable recovery of renal homeostatic function.

Keywords: acute kidney injury, paediatrics, management

Introduction

Acute kidney injury (AKI) formerly known as acute renal failure (ARF) is a clinical syndrome that has been known by about twenty-five different nomenclature over the years. It evolved from the 18th century when it was first known as “ischuria renalis” (“ischuria” meaning suppression of urinary output) to the current terminology “acute kidney injury” in the 21st century.

Acute kidney injury has also been defined in over thirty-five different ways in the last few centuries. It is widely defined as a clinical syndrome characterised by a sudden deterioration in renal function resulting in an inability of the kidneys to maintain fluid and electrolyte homeostasis. It has also been defined as onset of reduced kidney function manifested by increased serum creatinine or a reduction in urine output.

Epidemiology

As a result of the deficiency of a standardized definition, epidemiological data have been widely varying and difficult to compare. AKI or ARF is said to be encountered in about 3% to 10% of all admissions to neonatal intensive care units with approximately 1% of ill children in the developed world having AKI at the time of admission.

In Nigeria, incidence rates have been stated as 6.6% in Zaria, 4.7% in Portharcourt, 7.1% in Enugu and 3.13% in Ife. Esezabor *et al*, in Lagos found a prevalence of 17.4 cases per 1000 children Mortality in acute kidney injury has been found to be high. Adedoyin *et al* reported 57.9% in Ilorin, Esezabor *et al* found 28.4% while Olowu *et al* reported 46.2% in Ife.

Anatomy and physiology of the Kidney

The kidney is a paired, retroperitoneal organ located between the transverse processes of T12- L3 vertebrae. Fig 1 shows the gross anatomy of the kidney with the microanatomy of the nephron. The kidneys receive 25%

of the cardiac output and the highly vascularised cortex takes over 90% of the renal supply. The kidney's control over homeostasis allows it to regulate extracellular fluid (ECF) volume, osmolality, and acid-base balance. The physiologic functions of the kidney are summarised in Fig 2.

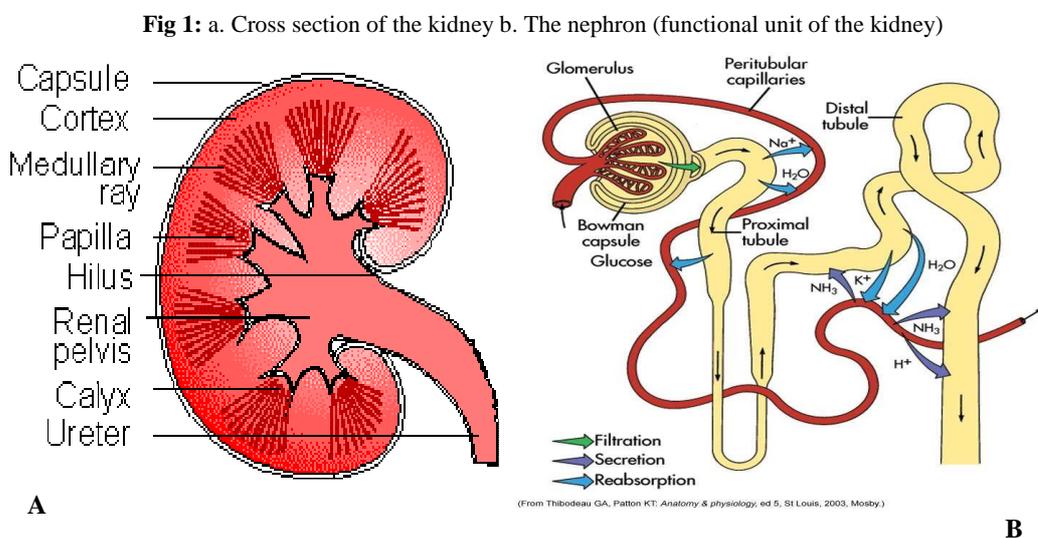
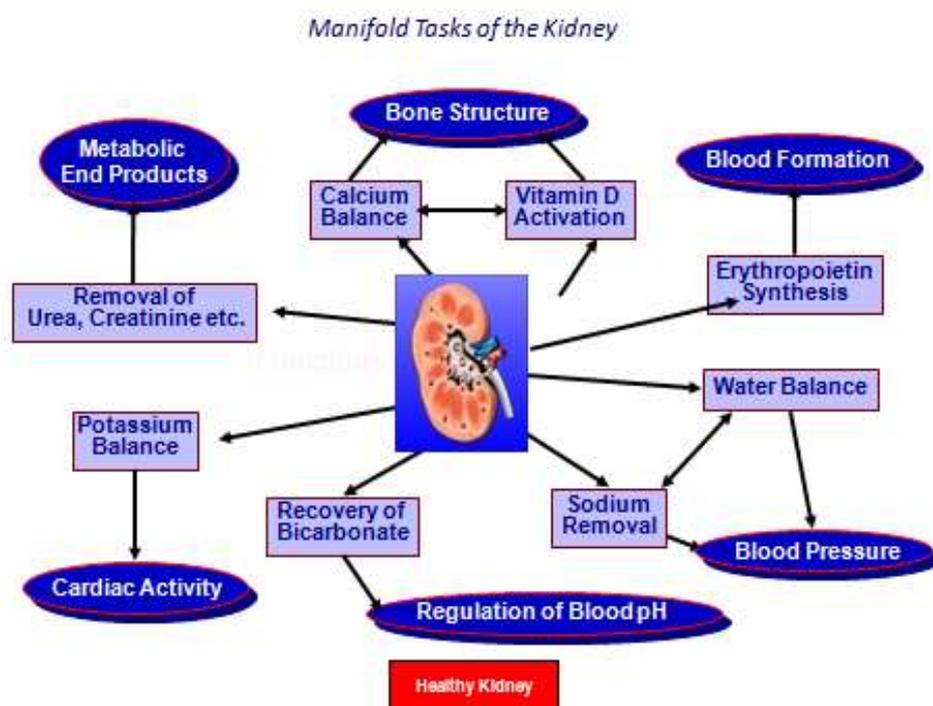


Fig 2: Summary of the physiologic functions of the skin



Causes and pathophysiology of acute kidney injury

The causes of acute kidney injury can be divided into three based on their pathophysiologic mechanisms. These are highlighted in Table 1

Prerenal injury

Prerenal injury occurs when there is diminished effective circulating arterial volume resulting in inadequate renal perfusion and a decreased glomerular filtration rate

(GFR). The kidneys are intrinsically normal with no evidence of renal parenchyma damage and prerenal injury is reversible once the blood volume and haemodynamic conditions have been restored to normal. The pathophysiology has been summarised in Fig 3.

Intrinsic renal disease

Renal injury results in damage to the renal parenchyma and it could result from prolonged renal hypoperfusion or from nephrotoxic renal insults. This form of AKI

could complicate diverse diseases of the renal parenchyma including diseases of the glomeruli, tubules, vascular and renal interstitial injury. The 3 phases of ischemic ARF can be seen in fig 3.

Table 1: Common causes of Acute Kidney Injury in children

Prerenal	Intrinsic renal	Postrenal
<p>Hypovolaemia</p> <p>Acute diarrhoea disease</p> <p>Excessive vomiting</p> <p>Diabetes ketoacidosis</p> <p>Severe hemorrhage</p> <p>Burns</p> <p>Toxic epidermal necrolysis</p> <p>Staphylococcal scalded skin syndrome (SSSS)</p> <p>Hypotension</p> <p>Sepsis</p> <p>Congestive cardiac failure</p> <p>severe anaphylaxis</p> <p>Drugs</p>	<p>Glomerulonephritis</p> <p>Poststreptococcal GN</p> <p>Rapidly progressive glomerulonephritis</p> <p>Henoch-scholein purpura</p> <p>HUS</p> <p>Acute tubular necrosis</p> <p>Ischaemia (prolonged hypovolaemia)</p> <p>Drugs (aminoglycosides, NSAIDs)</p> <p>Haemoglobinuria (excessive hemolysis)</p> <p>Myoglobinuria</p> <p>Ethylene glycol</p> <p>Heavy metals</p> <p>Contrast nephropathy</p> <p>Interstitial nephritis</p> <p>Penicillins,</p> <p>sulphonamide</p> <p>ciprofloxacin</p> <p>NSAIDs</p> <p>Infections</p> <p>Acute pyelonephritis</p> <p>HBV, EBV, HIV infections</p>	<p>Posterior urethral valves</p> <p>Ureteropelvic junction obstruction</p> <p>Ureterovesicular junction</p> <p>Ureterocele</p> <p>Tumor</p> <p>Urolithiasis</p> <p>Hemorrhagic cystitis</p> <p>Neurogenic bladder</p>

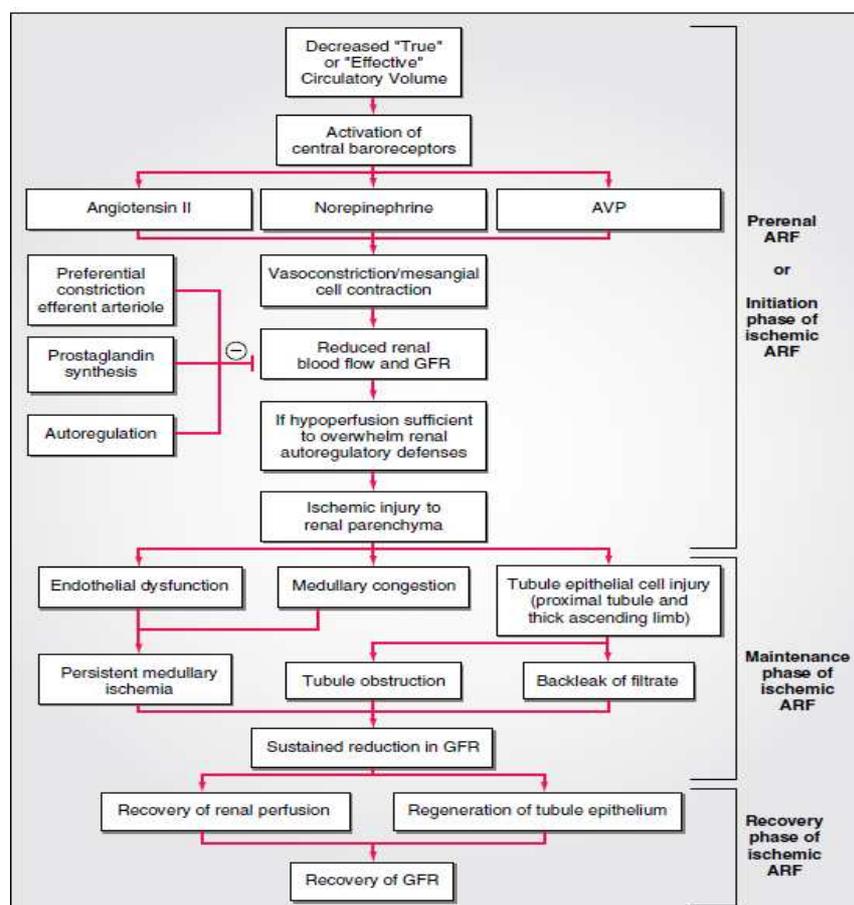


Fig 3: Pathophysiology of Prerenal and intrinsic renal failure (ischemic ARF)

FIGURE 260-1 Overview of the pathophysiology of prerenal ARF and ischemic intrinsic renal ARF: A spectrum of manifestations of renal hypoperfusion. ARF, acute renal failure; AVP, arginine vasopressin; GFR, glomerular filtration rate.

Post-renal causes

Includes a variety of disorders characterized by obstruction of various parts of the urinary tract. An increase in fluid pressure proximal to the obstruction leads to renal damage with decreased renal function from back pressure effect.

Epidemiologic variation in aetiology of AKI

Causes of AKI in industrialised countries have been found to be majorly due to intrinsic renal disease, postoperative septic shock (especially after open heart surgery) and organ/bone marrow transplantation. This is quite different from what obtains in developing nations like Nigeria.

Secondary causes of acute renal failure like severe malaria and sepsis were found to be the commonest aetiology in Ife. Anochie *et al*, in Port-Harcourt found gastroenteritis and malaria as the most common cause of ARF in older children while severe birth asphyxia and septicaemia were the prominent causes among neonates. Sepsis, acute diarrhoeal disease and haemoglobinuria were the leading causes of ARF in Ilorin.

Definitions of terminology

Oliguria: Reduction in urine output to less than 300ml/m² per day or <1ml/kg/hr

Anuria: Defined as urine <75ml/day in an adult or <1ml/kg/day in children

Polyuria: Urine output >4ml/kg/hr

Azotaemia: High nitrogenous waste as indicated by high urea.

Uraemia: Uraemia is the symptom complex reflecting organ dysfunction that occurs when kidneys fail to regulate body composition.

Clinical manifestations

A good history will aid identification of the cause of AKI. Vomiting, diarrhoea and fever suggest pre-renal azotemia from hypovolaemia or a septicemic illness. Antecedent skin or throat infection suggests intrinsic AKI from PSAGN. Drug history such as use of NSAIDs and aminoglycosides could be a pointer to acute tubular necrosis while flank masses may suggest obstruction as a cause of post renal AKI.

Common manifestations due to failure of kidney function include oliguria or anuria, polyuria, anaemia, oedema and hypertension.

Investigations

All suspected cases of AKI should at least have urine analysis, urine specimen for microscopy and culture and urinary biochemistry (Table 2). Serum electrolytes may show hyperkalemia, hyponatraemia and raised urea and creatinine levels. Full blood count, Chest X-ray, abdominal ultrasonography and roentgenograms, autoimmune screen, renal biopsy can be done to investigate the cause of the AKI.

Table 2: Urine chemistries and osmolality in Acute Kidney Injury

Urinary indices	Prerenal	Intrinsic Renal
Urine osmolality (mosmol/kg H ₂ O)	>500	<350
Urine SG	>1.020	<1.020
Urinary Na	< 20	>20
Fractional excretion of filtered Na (%) FENa	< 1	>1

$$FENa = \frac{U_{Na} \times P_{Cr}}{U_{Cr} \times P_{Na}}$$

Novel approaches to diagnosis

The varying definitions of AKI made comparisons between studies very difficult. In 2004, the Acute Dialysis Quality Initiative group (ADQI) standardised the definition of AKI using the RIFLE criteria which was based on GFR, serum creatinine values and urine output. The term ARF was also replaced with AKI as defined by this criteria such that it encompasses the entire spectrum of the syndrome and not just the aspect of failure. In 2007, the Acute Kidney Injury Network (AKIN) proposed some modifications to this criterion that was based on time in relation to the creatinine values or documented oliguria. Recently in 2012, Kidney Disease: Improving Global Outcomes (KDIGO) proposed another classification system which combines the RIFLE and AKIN criteria

RIFLE is a mnemonic for level of severity & outcome. There are 3 levels of severity; Risk, Injury and Failure and 2 outcomes measures; Loss of renal function and End-stage renal disease (ESRD). The pRIFLE a modified form for paediatric use can be seen in Table 3.

Table 3: The modified RIFLE criteria for paediatric patients (pRIFLE)

CLASS	Change in eCrCl (by Schwartz)	Urine Output
Risk	Decrease by 25 %	<0.5 ml/kg/hr X 8 hrs
Injury	Decrease by 50 %	<0.5 ml/kg/hr X 16 hrs
Failure	Decrease by 75 %, or < 35ml/min/1.73m ²	<0.3 ml/kg/hr X 24 hrs or ANURIA > 12 hrs
Loss	Failure > 4 weeks	
End Stage Renal Disease	Failure > 3 months	

Schwartz equation -K* Height (cm)/ SCr (mg/dl) where K is constant

The RIFLE and AKIN classifications use changes in serum creatinine to estimate loss in GFR. However, serum creatinine has many limitations. It differs with age, sex, dietary intake and muscle mass and doesn't reflect dynamic changes but only increases when there is substantial loss of renal function. It cannot be used as a monitoring tool after dialysis as it is easily dialysed and its secretion can be impaired by drugs like trimethoprim. This led to the discovery of newer biomarkers that can aid earlier detection of kidney injury (Table 4).

Neutrophil Gelatinase Associated Lipocalin (NGAL) is secreted by renal tubular epithelium and serum levels

rise markedly after epithelial damage following ischaemic or nephrotoxic injury. There is increase in urine levels of NGAL before rise in serum creatinine and has both diagnostic and prognostic value for AKI.

Table 4: Protein biomarkers for early detection of acute kidney injury

Biomarker	Associated Injury
Cystatin C	Proximal tubule injury
KIM-1	Ischemia and nephrotoxins
NGAL (lipocalin)	Ischemia and nephrotoxins
NHE3	Ischemia, pre-renal, post-renal AKI
Cytokines (IL-6, IL-8, IL-18)	Toxic, delayed graft function
Actin-actin depolymerizing F	Ischemia and delayed graft function
α -GST	Proximal T injury, acute rejection
π -GST	Distal tubule injury, acute rejection
L-FABP	Ischemia and nephrotoxins
Netrin-1	Ischemia and nephrotoxins, sepsis
Keratin-derived chemokine	Ischemia and delayed graft function

GST = glutathione S-transferase; IL = interleukin; KIM = kidney injury molecule; L-FABP = L-type fatty acid binding protein; NGAL = neutrophil gelatinase-associated lipocalin; NHE = sodium-hydrogen exchanger.

Cystatin C is a protein secreted by all nucleated cells. It is minimally influenced by weight, sex, race, age, muscle mass but mostly reflects a reduction in GFR rather than acting as a marker of renal tubular damage. It rises earlier than serum creatinine

Kidney Injury Molecule – 1 (KIM-1) is an epithelial cell adhesion molecule that is expressed at a low level in normal kidneys. It is highly up regulated in the proximal tubules after ischaemic or toxic AKI. Urinary KIM-1 is used to distinguish ischaemic AKI from pre-renal disease and chronic renal disease and can be used as a predictor of graft loss in kidney transplant patients.

Treatment of Acute Kidney Injury

Management is generally directed at treating any life threatening features, attempting to halt or reverse the decline in renal function and if unsuccessful providing support by renal replacement anticipating renal recovery. Provided the patient can be maintained through the period of non-function and no further insults accrue, the kidney is remarkable in its ability to recover its normal homeostatic role.

Fluid management

The major goal is to restore and maintain intravascular volume. AKI may manifest with hypovolemia, euvolemia or volume overload and an estimation of fluid status is a prerequisite for initial and ongoing therapy. Children with intravascular volume depletion require prompt and vigorous fluid resuscitation. Initial therapy includes normal saline or lactated Ringer's solution at 20 ml/kg over 30 minutes and may be repeated twice if necessary, after careful monitoring to avoid possible

fluid overload. If anuria persists after 3 fluid boluses, the possibility of an intrinsic or post renal failure should be entertained.

Fluid input and output records, daily weights, physical examination, and serum sodium concentration guide ongoing therapy. During the recovery phase, children develop significant polyuria and natriuresis and may become dehydrated if appropriate adjustments in fluid requirements are not made.

Oliguria in the presence of volume overload requires fluid restriction (previous day's output plus insensible water loss (300ml/m²/day) and possibly intravenous administration of furosemide, mannitol or both. Rationale for the use of loop diuretics in ARF is due to the inhibition of the Na⁺/K⁺/2Cl pump in the thick ascending limb of the loop of Henle with subsequent decrease in Na⁺/K⁺2ATPase activity, which reduces the oxygen requirements of these cells and thus their susceptibility to ischaemic damage. However, recent studies have not demonstrated any differences in outcome of patients with or without furosemide.

Dopamine

The use of low dose (1–3 µg/kg/min) dopamine had been long advocated to increase renal perfusion by causing vasodilatation in critically ill patients. However, recently there has been a lot of debate in the literature about its benefit.

Electrolytes and acid-base balance

Hyperkalaemia (>5.5mEq/L) can be managed by the use of diuretics, sodium bicarbonate therapy, insulin glucose infusions and dialysis. The primary treatment of hyponatremia is free water restriction and use of hypertonic saline (3%). Oral phosphate binders (eg calcium carbonate) can be used to treat both hyperphosphataemia and hypocalcemia. Moderate acidosis to severe acidosis should be treated with oral or intravenous sodium bicarbonate.

Hypertension resulting from hyperreninemia can be managed with salt and water restriction and diuretic administration; calcium channel blockers (amlodipine) or β blockers (propranolol; labetalol) can be used. Hypertensive urgency/emergency should be treated with continuous infusions of sodium nitroprusside, labetalol or esmolol

The anaemia of ARF is usually mild and may require transfusion of packed red blood cells if the hemoglobin level falls below seven g/dL. Avoidance of nephrotoxic drugs like aminoglycosides and dose adaptations should be taken for medications that are largely eliminated by the kidney.

Renal replacement therapy

Dialysis: This aims at removing endogenous and exogenous toxins and to maintain fluid, electrolyte and acid-base balance until renal function returns. It uses the principles of diffusion of molecules in solution across a

semi-permeable membrane along an electrochemical concentration gradient.

Dialysis can be in form of peritoneal dialysis (continuous or intermittent), haemodialysis, haemofiltration and haemodiafiltration.

Indications for dialysis include volume overload with evidence of hypertension and/or pulmonary oedema refractory to diuretic therapy; persistent hyperkalaemia; severe metabolic acidosis unresponsive to medical management; neurologic symptoms (altered mental status, seizures), blood urea nitrogen greater than 100–150 mg/dL (or lower if rapidly rising); calcium/phosphorus imbalance with hypocalcaemic tetany; poor nutrition leading to progressive loss of weight.

The choice between haemodialysis and peritoneal dialysis depends on the overall clinical condition, availability of technique, aetiology of the AKI, institutional preferences and specific indications or contraindications. In general, peritoneal dialysis is the preferred method in infants and younger children. Specific contraindications include abdominal wall defects, bowel distention, perforation or adhesions, and communications between the abdominal and chest cavities. Haemodialysis has the distinct advantage of rapid correction of fluid, electrolyte and acid-base imbalances and may be the treatment of choice in haemodynamically stable patients, especially older children. Disadvantages include the requirement for vascular access, large extracorporeal blood volume, heparinization, and skilled personnel.

Diet: Aggressive nutritional support is important. Adequate calories to account for maintenance requirements and supplements to combat excessive catabolism must be provided. Oral feeding is the preferred route of administration.

Surgical Care: Patients with AKI secondary to obstruction frequently require urologic care.

Renal treatment modalities for the future

Experimental treatments include anti-endothelin antibodies; oxygen free radical scavengers, inhibitors of

inducible nitric oxide synthetase, all designed to reduce renal damage occurring in the context of sepsis.

Infusions of atrial natriuretic peptide (ANP) or a synthetic analogue anaritide may improve renal perfusion.

Recombinant erythropoietin can reduce ischaemic renal injury. Therapeutic strategies in the more distant future may include bioartificial kidneys as a renal replacement modality and possible stem cell therapy to improve native kidney recovery.

Complications of AKI

Infections develop in 30–70% of patients with AKI due to impaired defenses from uraemia and excessive use of antibiotics. Other complications may be cardiovascular (hypertension, congestive heart failure and pulmonary oedema); gastrointestinal (anorexia, nausea, vomiting, ileus, bleeding); haematologic (anaemia, platelet dysfunction); neurologic (confusion, somnolence, seizures)

Prognosis

Recovery of renal function is likely after AKI resulting from prerenal causes, HUS, ATN, acute interstitial nephritis, or tumor lysis syndrome. Recovery of renal function is unusual when AKI results from most types of rapidly progressive glomerulonephritis, bilateral renal vein thrombosis, or bilateral cortical necrosis.

Conclusion

AKI is a significant cause of morbidity and mortality in children. The main focus of physicians should be to prevent its occurrence (by adequate rehydration of ill children) and when it does occur to intervene promptly and adequately.

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References

- Nattachai S, Kellum JA. Acute Kidney Injury—Definition and Classification. *US Nephrology* 2011;5:45-48.
- Rajasree S, Ellis DA. Acute Renal Failure. In: Kliegman RM, ed. Nelson textbook of paediatrics. 19th Edition. Elsevier, 2011.
- Chan JCM, Williams DM, Roth KS. Kidney Failure in Infants and Children. *Pediatrics in Review* 2002; 23(2):47-60
- Bellomo R, Kellum JA, Ronco C. Acute kidney injury. *Lancet* 2012; 380: 756–66
- Adedoyin OT, Adesiyun OA, Mark F, Adeniyi A. Childhood Renal Disorders in Ilorin, North Central Nigeria. *Niger Postgrad Med J.* 2012;19:88-91.
- Esezebor CI, Ladapo TA, Osinaike B, Lesi FE. *PLoS One.* 2012;7:e51229.
- Olowu WA, Adefehinti O, Bisiriyu AL. Hospital-acquired acute kidney injury in critically ill children and adolescents. *Saudi J Kidney Dis Transpl.* 2012;23:68-77.
- Brady HR, Brenner MB. Acute Renal Failure. In: Braunwald, Fauci, Kasper *et al*, ed. Harrison's principle of internal medicine 15th edition. New York, McGraw-Hill Companies Inc Publishers). 2001:1544.
- Anochie IC, Eke FU. Acute Renal Failure in Nigerian Children: Port-Harcourt experience. *Pediatr nephrology* 2005;20:1601-4.

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10. Olowu WA, Adelusola KA. Paediatric Acute Renal Failure in Southwest Nigeria. *Kidney Int.* 2004;66:1541-8
 11. Lum GM. Kidney and urinary tract. In: Hay VW, Levin MJ, Sondheimer JM, Deterding RR, eds. *Current Diagnosis & Treatment Paediatrics*. 19th edition. New York: McGraw Hill; 2009.
 12. Dilys AW, Richard NF. Acute Renal Failure in Children. *Pediatrics in Review.* 2008;29:299-307.
 13. Rinaldo B, John AK, Claudio R. Acute kidney injury; *Lancet.* 2012;380:756-66.
 14. The Kidney Disease Improving Global Outcomes (KDIGO) Working Group. Definition and classification of acute kidney injury. *Kidney Int.* 2012; suppl 2:19-36.
 15. Flynn JT. Causes, management approaches and outcome of acute renal failure in children. *Curr Opin Pediatr.* 1998;10:1894-189.
 16. Fry AC, Farrington K. Management of acute renal failure. *Postgrad Med J.* 2006;82:106-16.