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RENAL (R PAREKH, SECTION EDITOR)

Acute Kidney Injury (AKI): Current Thoughts and Controversies in Pediatrics

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Abstract AKI is a common syndrome that is independently associated with increased mortality. This review hopes to address recent advances in scoring systems as they have advanced and become paediatric specific. Causes of AKI are widespread but specifically sepsis with relevance of molecular mechanisms will be reviewed. Prevention of AKI is important and needs attention to nephrotoxic drugs specifically. Fluid management in AKI following resuscitation can be specifically challenging requiring removal if fluid overloaded and use of continuous renal replacement therapy if available. Biomarkers remain very topical but their use in practical clinical practice has been a distinct challenge. For this reason, practical attempts to identify a Renal Troponin I and resultant renal Angina score are very helpful. Neonatal AKI has its own specific challenges, and scoring systems may need to be redefined. Finally, a global initiative called '0 by 2025' to eliminate preventable deaths by the ISN is a challenging global initiative with potential widespread impact.

Keywords Acute kidney injury (AKI) · Creatinine clearance · Urine output

Introduction

Acute kidney injury is a common syndrome that is well described as independently associated with increased morbidity and mortality in paediatric and neonatal practice. The term AKI has largely replaced the term of acute renal failure or renal impairment in an attempt to simplify terminology, standardise the diagnosis and make it 'more user friendly' especially for non-medical people.

Scoring Systems for Assessment of AKI

In the last few years, there have been a large number of varying scoring systems to try and add objectivity to monitoring this condition and providing consistency worldwide with impact on clinical care and research [1••].

Rifle

Scoring systems started in the adult world with RIFLE criteria for acute renal dysfunction with RIFLE representing five stages of Risk, Injury, Failure, Loss and End-stage kidney disease. The two main criteria that are focused on include the renal function in the form of a rising creatinine >50 % of baseline and/or fall in glomerular filtration rate (GFR) by >25 % and/or decrease in the urine output <0.5 ml/kg/h for 6 h or more [2•].

AKIN

The AKI Network (AKIN), a study group looking at adult AKI then merged this into three stages Risk, Injury and Failure with a specific rise in creatinine of >0.3 mg/dl within 48 h included in stage 1 and GFR being removed.

It was emphasised that adequate fluid resuscitation should be performed and urinary obstruction excluded [3].

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KDIGO

More recently, the International Kidney Disease Improving Global Outcomes (KDIGOs) merged RIFLE and AKIN to form more controversial guidelines. In addition to including the two main components of creatinine rise and urine output decrease, new terms were introduced. These included 'Acute Kidney Disease' (AKD) for kidney damage less than 3 months as compared to Chronic Kidney Disease (CKD) as well as 'Acute on Chronic Kidney Disease' (ACKD). Controversy included biological variability, unresolved issues of AKI and ACKD with particular reference to baseline renal function and renal parenchymal measurements, imaging and biopsies [4].

pRIFLE

Paediatric patients need a more specific scoring system, and thus, a Paediatric rifle (pRifle) was introduced, which has only three criteria and focuses more on the AKI component. This scoring system also consisted of two parts including estimated creatinine clearance (eCCL) and Urine Output. The eCCL was reduced by 25, 50 and 75 % and urine output observed over 8, 16 and 24 h.

In practice, creatinine is used but the AKI may be underestimated but practically urine output is useful in assessing onset of AKI even for non-nephrologists [5].

NICE Review

A recent NICE review including RIFLE, AKIN, KDIGO and pRIFLE looked at two factors specifically the diagnosis with staging of AKI and then the prediction of future outcomes. In comparison, most of the databases were those based on critical care databases—thus not entirely representative of all patient groups and definitions were often applied differently. The conclusions were that large studies with robust definition use and longer term follow-up are required [6].

Updated Schwartz Formula

The Schwartz formula for estimation of kidney function with correction for body surface area has been used in practice for CKD in children for many years [7].

More recently, an updated version has been published which has also been validated in a 'non-CKD' population [8•, 9] (Fig. 1).

Causes of AKI

In well-resourced countries, causes of AKI may include sepsis, postoperative cardiac cases, and nephrotoxins including aminoglycoside as well as specific population groups including premature neonates as well as solid organ transplants.

On the whole, critically ill children either develop AKI due to hypotensive episodes or multiple nephrotoxic insults; both are usually associated with sepsis.

AKI in Africa and Asia is relatively common and can be due to similar causes to developed countries. However, there are some extra factors that also play a role in less well-developed countries, and these commonly include diarrhoea and vomiting (gastroenteritis), septicaemia, pneumonia and malaria as common factors.

Haemolytic syndrome (HUS) associated with diarrhoea depending on the region may not as commonly be caused by *E. coli* with increased cases reported of Shigella. Atypical HUS is not as prevalent as elsewhere in view of diagnosis and treating facilities.

A very large study of 2,055 children in Uganda hospitalised with primary diagnosis of acute gastroenteritis, malaria or pneumonia was enrolled with a total of 278 (13.5 %) of children having AKI on admission with 114/278 (41 %) of those with renal failure having serum creatinine over threefold upper limit of age. AKI prevalence is particularly high in gastroenteritis (28.6 %) and underweight children with associated hypoalbuminemia (20.7 %). Twenty-five percent of

An example of pediatric AKI in a 7-year-old child with length (height) of 120 cm

Premorbid (baseline)			AKI		Change
Height	120 cm		Height	120 cm	
Cr	50 μmol/l (0.57 mg/dl)	→	Cr	67 μmol/l (0.76 mg/dl)	33% Rise
eGFR*	88 ml/min per 1.73 m^2		eGFR	65 ml/min per 1.73 m^2	25% Fall

Abbreviations: AKI, acute kidney injury; Cr, creatinine; eGFR, estimated glomerular filtration rate.

eGFR is calculated using the revised or Bedside Schwartz equation,[118,122,123] which adjusts the estimated GFR to a standard (adult) body size of 1.73 m^2. Note, the reduction in eGFR with AKI is 25%–that is, pRIFLE stage R, while the increase in creatinine (Cr) is 133%—that is, less than the required increase in Cr to be classified as pRIFLE stage R. Thus, the change in kidney function in one child may be classified differently, if either GFR or creatinine alone is used.[125] This is inherent with the use of both creatinine and GFR changes within the same definition (that is, within RIFLE or pRIFLE).

The original Schwartz equation[119,120] (using a modified Jaffe reaction to measure creatinine):

$$\mathrm{GFR\,(ml/min\ per\ 1.73\,m^2)} = \frac{0.55\times(\text{length or height})(\mathrm{cm})}{\mathrm{Creatinine\ (mg/dl)}} \quad \text{or}$$

$$\frac{48.6\times(\text{length or height})(\mathrm{cm})}{\mathrm{Creatinine\ (\mu mol/l)}}$$

The revised or 'Bedside' Schwartz equation[118,121–123] (using an enzymatic assay of creatinine—traceable to an isotope-dilution mass spectrometry reference):

$$\mathrm{GFR\,(ml/min\ per\ 1.73\,m^2)} = \frac{0.413\times(\text{length or height})(\mathrm{cm})}{\mathrm{Creatinine\ (mg/dl)}} \quad \text{or}$$

$$\frac{36.5\times(\text{length or height})(\mathrm{cm})}{\mathrm{Creatinine\ (\mu mol/l)}}$$

To convert creatinine in mg/dl to μmol/l, multiply by 88.4.

Fig. 1 Schwartz formula calculation [1••]

children with AKI died during hospitalisation, compared to 9.9 % with no AKI. Thus, AKI in children admitted with gastroenteritis, malaria or pneumonia was common and associated with high in-hospital mortality [10].

A specific study of 378 Congolese children in comparison with severe malaria showed that 89 children (23.6 %) had AKI of which Blackwater fever was the leading cause of renal failure. Overall in both groups, many of the children had hypoperfusion-induced AKI in the face of infection-associated changes in renal blood flow. Scoring systems such as RIFLE criteria would be recommended when designing future studies. The only problem here is that it can be difficult in some centres to get serial electrolyte results with creatinine levels even as a single measurement value not being routinely available due to lack of tests or cost implications [11].

In addition to infective causes, some AKI may be caused or exacerbated by administration of drugs (e.g. aspirin or non-steroidal anti-inflammatories) or toxins which are sometimes inadvertently administered by traditional healers who are frequently consulted as part of local health care providers. Further unusual causes of AKI have even included hair dyes poisoning as described in Sudan [12].

Sepsis

This is reported as the commonest cause of AKI, and a unified theory for septic AKI combining inflammation, microcirculatory dysfunction, bioenergetics and tubular adaptation to injury has been proposed [13]. The relationship between tubular cell injury and loss of GFR is poorly understood but a tubuloglomerular feedback (TGF) has been suggested leading to afferent arteriolar vasoconstriction, decreased hydrostatic pressure in the glomerulus and subsequent decrease in GFR [14].

More recent studies have shown that AKI often occurs independently of hypoperfusion. AKI is thus mediated by concomitant pro- and anti-inflammatory state activated in response to various pathogen-associated molecular patterns such as endotoxins. These molecular patterns are recognised by Toll-like receptors (TLRs) found in the kidney and effecting downstream inflammatory pathways together with apoptosis [15]. Targeted therapies to date have failed but research is needed to identify where on the immunological spectrum the patient with AKI lies, in order to target therapies at inflammatory cascade, TLRs and apoptosis.

Fluid Management in AKI

There has been much debate recently about early goal directed therapy (EGDT) in septic shock as originally described by Rivers where early and aggressive fluid resuscitation is advocated as part of a protocol-driven fluid algorithm using crystalloid or colloid [16].

De Oliviera study took this further in combining fluid resuscitation with mixed venous saturations in attempts to achieve certain end points [17].

Despite these studies being criticised in terms of study size and patient selection, nonetheless, both the Surviving Sepsis Campaign and the American College of Critical Care Medicine–Paediatric Advanced Life Support (ACCM–PALS) Guidelines have recommended in cases of septic shock, giving boluses of 20 ml/kg fluid boluses up to 60 ml/kg over 15 min as their mainstay to improve perfusion before proceeding to inotropes and ventilator support. These guidelines and teaching principles are followed extensively worldwide in both developed and underdeveloped countries [18, 19].

It was thus a significant concern when a significant and well-thought out study of more than 3000 shocked paediatric patients out of East Africa showing adverse effects of fluid boluses was published by Maitland et al. in the NEJM in 2011 [20••]. The FEAST (Fluid expansion as supportive therapy) trial showed an increased proportion of children who died after receiving boluses either with Saline or Albumin compared to those who were not given any fluid boluses. The cause of death was not identified as no post-mortems were performed, and ideas postulated included cardiac, respiratory or neurological causes even by the authors themselves [21, 22]. Equal amounts of children had malaria and were anaemic in both groups.

This has led to local recommendations about fluid boluses to be given with caution in areas where no supportive facilities are in place.

In well-resourced countries, paediatric-specific intensive care facilities are available for full support including inotropes, ventilator and dialysis support. In poorly resourced areas, such as those in the FEAST trial, fluid boluses are harmful for non-diarrhoeal shock, and if given, careful consideration should be given to route, speed and type of fluid. In comparison with ‘middle-resourced’ countries, e.g. parts of South Africa, there is consideration after 40 ml/kg of fluid boluses, to institute the use of ‘Bubble CPAP’ and peripheral infusions of inotropes even where formal PICUs are not available.

The World Health Organisation is at time of going to press reviewing their policy on fluid boluses as it is so region and disease specific, e.g. fluid boluses are the treatment of choice in diarrhoeal disease or Dengue fever, whereas clearly in East Africa with non-diarrhoeal shock, fluid boluses are deleterious.

Extensive commentary regarding this fluid bolus controversy by Bellomo in particular, is worth reviewing, with starches and possibly saline being avoided in the first

instance in AKI. Subsequently 3 recently completed worldwide but adult-based trials including ARISE, PROMISE and PROCESS have added interesting discussion to EGDT [23, 24].

ARISE (Australian resuscitation of sepsis evaluation) was a multicentre trial of 51 centres with 1,600 patients enrolled of which 796 were assigned to EGDT and 804 to 'usual-care' group. The EGDT group of patients who received larger volumes of intravenous fluid in the first 6 h was more likely to receive vasopressor infusions including dobutamine and red cell transfusions.

However, the conclusion was that in critically ill patients presenting to the emergency department with early septic shock, EGDT did not reduce all-cause mortality at 90 days [25•]. The findings suggest that the value of incorporating EGDT into international guidelines as a standard of care is questionable.

The ProCESS trial which enrolled 1,341 patients with 439 protocol-based EGDT, 446 protocol-based standard therapy and 456 'usual care' similarly showed no significant differences in 90 days mortality, 1-year mortality or the need for organ support [26•].

Finally, a recent meta-analysis suggests that EGDT significantly reduces overall mortality in patients with sepsis, especially when initiated early. The pre-specified primary outcome was overall mortality with the results included in a total of 13 trials involving 2,525 adult patients. However, due to the variable quality of the studies, strong and definitive recommendations cannot be made [27].

In response to both of these trials, an editorial blog by Ryan Radecki from University of Texas Houston, USA (www.emlitefnote.com/2014/10/arise-and-cast-off-shackles-of-egdt.html) entitled *ARISE and cast off the shackles of EGDT* suggested that EGDT receives credit for making us aware of the impact of early identification and intervention on mortality. The suggestion was made that it is time to leave behind EGDT and identify new resuscitation targets and sensible strategies for achieving them.

Phases of Fluid Management in AKI

Clinically, there is a conflict between the desire to achieve adequate resuscitation of shock and the need to mitigate the harmful effects of fluid overload [28] (Fig. 2).

For this reason, it is refreshing to adopt the sensible approach as suggested by Goldstein in J Intensive Care Med 2014 with three phases:

1. Fluid resuscitation—restoring end organ perfusion and achieving physiological end points
2. Maintenance of fluid balance homeostasis and/or prevention of worsening fluid overload—including assessing all needs for fluid including medication, nutrition and all blood products as well as patient's ability to maintain fluid balance(Urine, stool and drain losses)
3. Fluid removal—ideally not as an emergency, allowing weaning off ventilation and to prevent further ischaemic events).

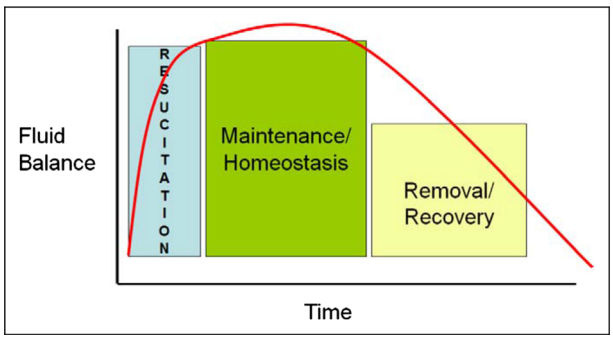

Fig. 2 The acute kidney injury fluid epidemiology paradigm. Permission from [29••]

Clinical problems arise when the patient with AKI cannot tolerate the required fluid volumes without developing fluid overload. At this point, intervention may be required in a step-wise approach to maintain fluid homeostasis and prevent negative effects of worsening fluid overload, but also according to what is available in the clinical setting.

The recommended approach adopted by most clinicians but described eloquently by Goldstein includes [29••]:

1. Fluid restriction
2. Diuretic administration
3. Renal Replacement therapy

Fluid restriction has its own problems in that it may limit nutrition, appropriate medication and blood products especially in areas such as Africa and Asia where malaria plays a significant role in sepsis (*personal communication Elizabeth Molyneux)*

Diuretics are widely used in patients with oliguric AKI—both in adult, paediatric and neonatal practice. This is despite studies showing that diuretics neither prevent AKI nor improve long-term outcomes in AKI. However, in clinical practice, specifically where infants may be too small or sick to perform RRT easily or where facilities for RRT may not be available, polyuric AKI may be easier to manage clinically following administration of diuretics. Furosemide is the commonest diuretic in use as it can be used intravenously as a stat dose or as an infusion [30]. Controversially, the diuretic effects of Aminophylline are also used in combination with Furosemide especially in neonates [31].

The ideal situation would be to avoid a state of fluid overload in the first place.

Fluid Removal

Admission weight and percentage fluid overload are very useful practical markers in patient care as fluid overload can impede organ oxygenation and adversely affect patient morbidity.

A simple definition is used as follows [32]:Fluid overload percentage (FO%) = [Fluid input -fluid output in litres]/Patient admission weight in kg $\times 100$ Studies have shown that percentage fluid overload at the time of RRT initiation in children with AKI is associated independently with mortality and in cases of >20 % fluid overload, mortality being as high as 40–60 %. The general consensus at present is that CRRT rather than intermittent Haemodialysis should be started as soon as possible [33, 34]. Timing of renal replacement therapy has been shown to be crucial to the clinical outcomes in critically ill patients with severe AKI [35–37].

Alternatives to Conventional CRRT

The challenge in many less-resourced countries is the lack of dialysis facilities of any nature and specifically not the CVVHD/F which is considered when CRRT is discussed.

In many parts of the world, peritoneal dialysis (PD) is seen as CRRT, and this is performed as either Continuous Automated PD (CAPD) via cycling machines but more commonly as manual PD.

This can even be with 'make-shift' equipment using chest drains or central lines as acute PD catheters with home-made dialysis fluid (Ringer's lactate with dextrose added) when commercial equipment is not easily available.

In recent years, there has been a combined effort by numerous organisations to provide availability of peritoneal dialysis catheters and fluid for areas in particularly Africa and Asia where these are not available.

A new organisation concentrating only on Acute PD for AKI only, called Saving Young Lives (SYL) in Africa and Asia, has been established with the help of International Society of Nephrology (ISN), International Society of Peritoneal Dialysis (ISPD), Sustainable Kidney Care Foundation (SKCF) and International Paediatric Nephrology Association (IPNA) to mention just a few organisations [38]. This group has identified areas of need and drawn up memoranda of understanding with local facilities to be funded initially by SYL(for PD catheters and dialysis fluid) and then commit to ensure local sustainability as well as partnering these areas with mentors from facilities elsewhere. Many of these paediatric nephrology doctors have done basic nephrology training elsewhere in Africa funded by ISN/ISPD/IPNA. (Personal communication McCulloch, Gajjar, Nourse, Sinclair, Du Buisson—Red Cross War Memorial Children's Hospital, Cape Town). This has included training in the insertion of 'bedside PD' catheters by non-surgical doctors and nurses. The main aim is to provide acute dialysis for children with AKI [39, 40].

There have been recent PD guidelines for AKI published including a paediatric component which addresses PD at all levels including those from well-resourced as well as poorly resourced regions. This is in an attempt to ensure that any child with AKI can have access to acute PD in the first instance [41••].

Prevention of AKI

In addition to preventing fluid overload in AKI by excessive administration of fluid, there are other nephrotoxic factors at play. These frequently include drugs such as Non-steroidal inflammatory agents (NSAIDS) as well as anti-microbial agents including aminoglycosides and anti-fungal agents such as Amphotericin (especially non-liposomal variety).

Preventing Contrast-induced Nephropathy or AKI has also been a much debated topic with the following interventions being studied [42]:

- Adequate hydration with a fluid choice of both sodium bicarbonate or Isotonic Saline being fairly standard practice
- NAC (N Acetyl Cysteine) infusion with Saline as a free radical scavenger
- Low-volume non-ionic low-osmolar or iso-osmolar contrast preparations—all different?
- Angiotensin Converting Enzyme Inhibitors (ACEI)/ Angiotensin Receptor Blockers (ARBS) given peri-procedurally
- Peri-procedural Haemofiltration
- Fenoldopam or Theophylline if available
- Most recently, high dose vs low dose statins [43]

Biomarkers

Over the last decade, a lot of research has gone into developing a urinary kidney marker panel which allows early detection of kidney disease whilst distinguishing between various types of kidney diseases. The hope would be that this would result in a more cost-effective means of

managing kidney injury. For many years, the serum creatinine has been the 'gold standard' but is in fact a late marker of injury and has been suggested by some groups as being the 'bronze standard' [44].

Ideally such an AKI biomarker should be accurate, reliable, reproducible and easy to measure with a standard assay whilst being specific and sensitive [45].

The urinary panel that is best known so far and is site specific includes [46]

Glomerulus

- Cystatin C is probably currently the most used in clinical practice specifically in cardiac surgery and is produced by all nucleated cells. It is a functional marker of GFR but not a direct marker of tissue injury. It is not affected by sex, race or muscle mass and is better for early detection—preceding rises in creatinine by 5.8 ± 13 h.
- B2-microglobulin also originates from the glomerulus and the proximal tubule and is also used in clinical practice.

Proximal Tubules

- NGAL (neutrophil gelatinase-associated lipocalin) which is expressed by neutrophils and epithelial cells allows diagnosis of AKI up to 48 h prior to RIFLE criteria with stronger evidence in children.
- Interleukin IL-18 is a pro-inflammatory cytokine and important in sepsis. It has been shown to mediate ischaemic ATN in mice but is inconsistent and also seen in systemic inflammation, sepsis and heart failure which all co-exist or result in AKI.
- KIM-1 (kidney injury molecule − 1) is seen after ischaemic/toxic injury and not detectable in normal tissue and useful in established AKI

The Loop of Henle produces Osteopontin and NHE-3, *Distal tubules* produce Osteopontin, and Clusterin and H-FABP and *Collecting Ducts* produce Calbindin D28 with numerous more being discovered as this field expands.

Currently, **NGAL** is used most commonly in a variety of clinical settings including fluid resuscitation, burns, cardiac and emergency settings. Quicker testing by Point of care (POC) devices will be instrumental in patient management as well as triage decision-making [47].

How to Use Biomarkers in Practice

Despite the intense interest in the discovery and validation of biomarkers, the kidney-specific biomarkers have seen very limited clinical application. For this reason, a working group recently met to review four areas for utilisation of biomarkers including [48•]

1. Risk assessment, diagnosis and staging
2. Differential diagnosis
3. Prognosis and management
4. Novel physiological techniques including imaging

A proposal has been made to combine functional and damage biomarkers to better understand AKI. Together with use of imaging techniques (e.g. Contrast ultrasound and MRI) and other physiologic markers (e.g. real-time GFR), the clinicians ability to understand the relationship between damage and function will be expanded.

Renal Angina and Need for Renal Troponin

Following on from the above, nephrologists and Intensivists must define a 'renal angina syndrome'. In the same way, as troponin I is accepted in management of chest pain, there is a search for 'renal troponin I' to realise the full potential of biomarkers [49•].

The empiric clinical model of renal angina is used to identify which critically ill patients would be at greatest risk of AKI. The renal angina construct includes three risk groups from PICU population (tranches)—very high risk (intubated with inotropes), high risk (solid organ or bone marrow transplant) and moderate risk (ICU admission) to fulfil renal angina. The renal angina index scoring system has devised tiered AKI risk strata assigned point values for risk and signs of injury. A resultant renal angina index score was developed ranging from 1 to 40 with a score of $\geq$8 used for renal angina [50].

A further study reviewed severe AKI at 72 h (Day-3 AKI) as indicative of the extent of AKI burden in the PICU. Risk stratification of a patient with AKI using both renal angina scoring with AKI biomarkers to reliably differentiate which patients are responsive to restorative therapy compared to those progressing to severe subsequent AKI [51].

In conclusion, these studies show that incorporation of AKI biomarkers into the RAI improves discrimination for severe AKI [49•] (Fig. 3).

Most recently, there is a recognition that AKI is associated with subsequent development of chronic kidney disease and end-stage renal disease. This is either as a progression of an underlying CKD or as de novo CKD following AKI episode. Advanced age is an independent risk factor but multiple AKI episodes are also potential risk factors. In conclusion, then, our clinical focus at present should be avoidance of subsequent AKI in the critically ill.

Biomarkers are finding their way into practice as evidenced by a paper using Urine neutrophil gelatinase-

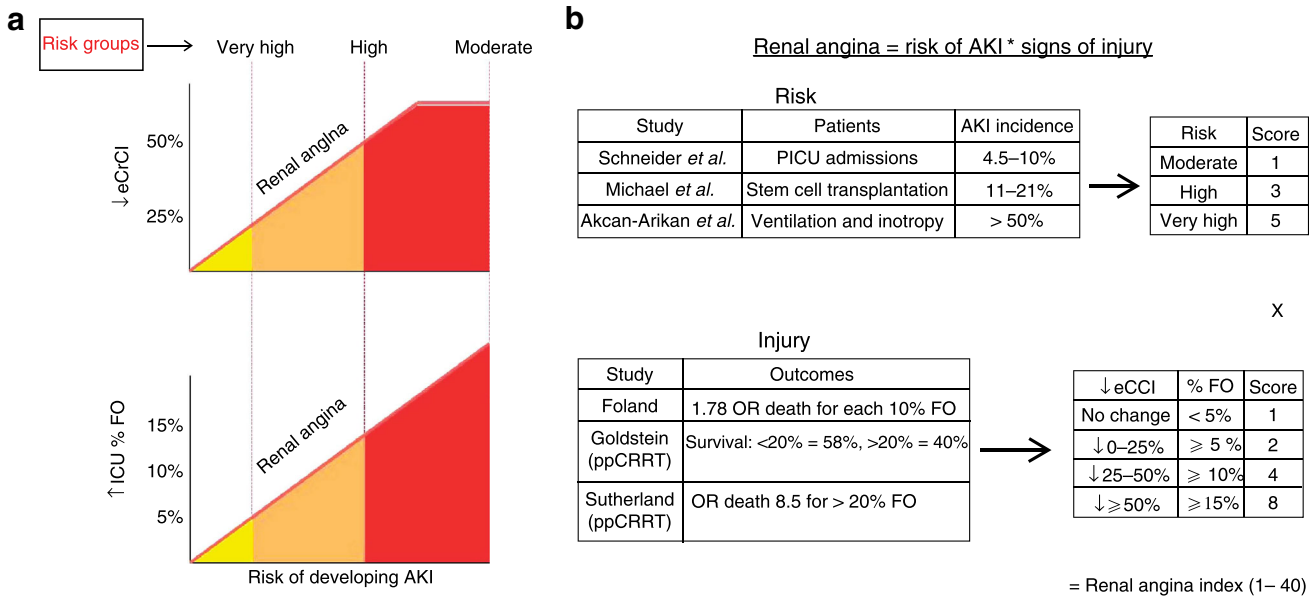

Fig. 3 Renal Angina [51]

associated lipocalin (NGAL) in 108 asphyxiated neonates from Nairobi, Kenya [52].

AKI in Neonates

Critically ill neonates are at high risk for AKI due to a combination of several potential exposures including nephrotoxic drugs, sepsis, hypotension and adverse perinatal events including asphyxia [53•].

AKI has been well documented as an independent risk factor for poor outcomes; thus, close attention is needed to at-risk patients and early changes in kidney function. There are particular groups of new-borns who are particularly at risk including premature/or very low birth weight infants, congenital cardiac patients particularly needing bypass or ECMO, septic new-borns and those with congenital kidney abnormalities.

The scoring systems including pRIFLE and KDIGO have also been used in neonates; however, there are concerns that the standard Serum Creatinine (SCr) increase of 0.3 mg/dL (KDIGO AKI Stage 1) is not sufficient to trigger concern. Recent modifications to the KDIGO definition have suggested that as SCr normally declines in first week of life, each SCr be compared with the previous value. Also that a SCr of 2.5 mg/dL cutoff defines AKI stage 3(as this value represents a GFR < 10 ml/min/1.73 m^2). This has not been validated in large numbers but agreed at a NIH Neonatal workshop 2013 as being the current best definition [54].

The traditional anatomical classification of causes of AKI of pre-renal, intrinsic and post-renal is still used as a simple bedside evaluation.

Long-term outcomes between prematurity, low birth weight and CKD progression are a concern as preterm delivery disrupts nephrogenesis which is usually not complete until 34–36 weeks gestation [55]. Nephrogenesis following premature delivery is then halted early with remaining nephrons hypertrophying to compensate with resultant hyperfiltration and associated sodium retention, systemic hypertension, proteinuria and progressive CKD (Brenner hypothesis).

Renal replacement therapy in neonates has been peritoneal dialysis preferentially in view of ease of use and practicality especially in less-resourced areas.

Newer technologies even for neonates have been developed allowing CVVH and ECMO even in the smallest of infants. Most recently, the Cardio-Renal, Paediatric Dialysis Emergency Machine (CARPEDIEM) has been developed for the treatment of neonates as little as 2 kg [56].

Of concern are increasing studies showing that AKI survivors are at risk of CKD, and thus, this has implications on long-term follow-up for these infants [57]. Neonatal AKI research is required by neonatologists and nephrologists to develop better AKI definitions using novel biomarkers for specific clinical end points.

Future

The hope would be early identification of AKI using clinical markers such as SCr and urine output together with biomarkers which have robust clinical end points to ensure renal recovery after AKI [58, 59]. Standardised Scoring systems such as KDIGO help define this condition in

combination with renal troponin equivalent and renal angina scores.

Preventing repeat episodes of AKI in sick children is also important as there is growing evidence that CKD and ESRD can develop subsequently.

Prevention of clinical fluid overload with more conservative use of intravenous fluid as part of fluid maintenance aiming for percentage fluid overload of less than 20 percent (FO % <20 %) and early commencement of CRRT which is appropriate to setting and facilities. Newer technology such as renal tubular assists devices and CARPEDIEM for infants and potentially stem cell advances [60].

International initiatives in the Field of AKI

The burden of AKI has been identified as a world-wide problem, and as a result, increasing studies have been done taking 'snapshots' of the incidence of AKI on specific days or over a certain number of months [61••].

The International Nephrology Society (ISN) has a new project called the "0 by 25" Initiative which has as its aim that nobody should die of preventable and treatable Acute Kidney Injury (AKI) by 2025.

The Mission: Eliminate Preventable Deaths from Acute Kidney Injury (AKI) Worldwide by 2025

(http://www.theisn.org/isn-information/0-by-25-initiative).

The basis of this initiative is that AKI is preventable and treatable but challenges reside in emerging countries where it is difficult to catching the disease early and a lack of data means that patients in these regions cannot get care before it is too late.

Dr Ravindra Mehta, the 0 by 25 Project Leader and Giuseppe Remuzzi, ISN President 2013-2015, is leading this exciting initiative as one of the many ways to make a difference and advance nephrology globally.

The ISN Programmes and the Saving Young Lives Programmes have already made substantial steps to improve awareness, training and gather data. Teaching doctors about the basics of peritoneal dialysis is key to developing a short-term solution, and making treatment more affordable. We believe that with our experience in training doctors and raising awareness about the different issues within nephrology, we can start making this statement a reality.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. •• Thomas ME, Blaine C, Dawnay A, Devonald MA, Ftouh S, Laing C, Latchem S, Lewington A, Milford DV, Ostermann M. The definition of acute kidney injury and its use in practice. Kidney Int. 2014;R1–12. *Important clinical paper with clinical definitons and guidelines for adult and paediatric patients.*
2. • Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P; Acute Dialysis Quality Initiative workgroup. Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care. 2004;8(4):R204–12. *International consensus group guidelines.*
3. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11(2):R31.
4. Kidney Disease: Improving Global Outcomes(KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guidelines for acute kidney injury. Kidney Int Suppl 2012;2:1–138.
5. Akcan-Arikan A, Zappitelli M, Loftis LL, Washburn KK, Jefferson LS, Goldstein SL. Modified RIFLE criteria in critically ill children with acute kidney injury. Kidney Int. 2007;71(10):1028–35.
6. National Clinical Guideline Centre. Detecting AKI, section H.3. In: Acute Kidney Injury. Clinical guideline CG169, appendices(A-M).National Institute for Health and Care Excellence, UK, pp 338– 346. Available at http://guidance.nice.org.uk/CG169/Guidance/Appendices/pdf/English. Accessed 26 Oct 2014.
7. Schwartz GJ, Haycock GB, Edelmann CM Jr, Spitzer A. A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. Pediatrics. 1976;58(2):259–63.
8. • Schwartz GJ, Muñoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, Furth SL. New equations to estimate GFR in children with CKD. J Am Soc Nephrol. 2009;20(3):629–37. *New GFR guidelines for pediatrics.*
9. Staples A, LeBlond R, Watkins S, Wong C, Brandt J. Validation of the revised Schwartz estimating equation in a predominantly non-CKD population. Pediatr Nephrol. 2010;25(11):2321–6.
10. Imani PD, Odiit A, Hingorani SR, Weiss NS, Eddy AS. Acute kidney injury and its association with in-hospital mortality among children with acute infections. Pediatr Nephrol. 2013;28(11):2199–206.
11. Kunuanunua TS, Nsibu CN, Gini-Ehungu, Bodi JM, Ekulu PM, Situakibanza H, Nseka NM, Magoga K, Aloni MN. Insuffisance rénale aiguë dans les forms graves du paludisme chez les enfants vivant à Kinshasa. Nephrol Thérapeutique 2013;9:160–165.
12. Abdelraheem MB, EL-Tigani MAA, Hassan EG, Ali MAM, Mohamed IA, Nazik AE. Acute renal failure owing to paraphenylene diamine hair dye poisoning in Sudanese children. Ann Trop Paediatr. 2009;29:191–6.
13. Gomez H, Ince C, De Backer D, Pickkers P, Payen D, Hotchkiss J, Kellum JA. A unified theory of sepsis-induced acute kidney injury: inflammation, microcirculatory dysfunction, bioenergetics, and the tubular cell adaptation to injury. Shock. 2014;41(1):3–11.

14. Pettilä V, Bellomo R. Understanding acute kidney injury in sepsis. Intensive Care Med. 2014;40(7):1018–20.
15. Morrell ED, Kellum JA, Pastor-Soler NM, Hallows KR. Septic acute kidney injury: molecular mechanisms and the importance of stratification and targeting therapy. Crit Care. 2014;18:501.
16. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M, Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001; 345(19):1368–77.
17. de Oliveira CF, de Oliveira DS, Gottschald AF, Moura JD, Costa GA, Ventura AC, Fernandes JC, Vaz FA, Carcillo JA, Rivers EP, Troster EJ. ACCM/PALS haemodynamic support guidelines for paediatric septic shock: an outcomes comparison with and without monitoring central venous oxygen saturation. Intensive Care Med. 2008;34(6):1065–75.
18. Brierley J, Carcillo JA, Choong K, Cornell T, Decaen A, Deymann A, Doctor A, Davis A, Duff J, Dugas MA, Duncan A, Evans B, Feldman J, Felmet K, Fisher G, Frankel L, Jeffries H, Greenwald B, Gutierrez J, Hall M, Han YY, Hanson J, Hazelzet J, Hernan L, Kiff J, Kissoon N, Kon A, Irazuzta J, Lin J, Lorts A, Mariscalco M, Mehta R, Nadel S, Nguyen T, Nicholson C, Peters M, Okhuysen-Cawley R, Poulton T, Relves M, Rodriguez A, Rozenfeld R, Schnitzler E, Shanley T, Kache S, Skippen P, Torres A, von Dessauer B, Weingarten J, Yeh T, Zaritsky A, Stojadinovic B, Zimmerman J, Zuckerberg A. Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. Crit Care Med. 2009;37(2):666–88.
19. Levy MM, Rhodes A, Phillips GS, Townsend SR, Schorr CA, Beale R, Osborn T, Lemeshow S, Chiche JD, Artigas A, Dellinger RP. Surviving sepsis campaign: association between performance metrics and outcomes in a 7.5-year study. Crit Care Med. 2014. [Epub ahead of print].
20. •• Maitland K, Kiguli S, Opoka RO, Engoru C, Olupot-Olupot P, Akech SO, Nyeko R, Mtove G, Reyburn H, Lang T, Brent B, Evans JA, Tibenderana JK, Crawley J, Russell EC, Levin M, Babiker AG, Gibb DM; FEAST Trial Group. Mortality after fluid bolus in African children with severe infection. N Engl J Med. 2011;364(26):2483–95. *Important findings in large paediatric trial regarding fluidmanagement.*
21. Maitland K, George EC, Evans JA, Kiguli S, Olupot-Olupot P, Akech SO, Opoka RO, Engoru C, Nyeko R, Mtove G, Reyburn H, Brent B, Nteziyaremye J, Mpoya A, Prevatt N, Dambisya CM, Semakula D, Ddungu A, Okuuny V, Wokulira R, Timbwa M, Otii B, Levin M, Crawley J, Babiker AG, Gibb DM, FEAST trial group. Exploring mechanisms of excess mortality with early fluid resuscitation: insights from the FEAST trial. BMC Med. 2013; 14(11):68.
22. Todd J, Heyderman RS, Musoke P, Peto T. When enough is enough: how the decision was made to stop the FEAST trial: data and safety monitoring in an African trial of Fluid Expansion As Supportive Therapy (FEAST) for critically ill children. Trials. 2013;26(14):85.
23. Schneider AG, Bellomo R. Acute kidney injury in 2012: type of resuscitation fluid-it does matter! Nat Rev Nephrol. 2013;9(2): 72–3.
24. Prowle JR, Bellomo R. Fluid administration and the kidney. Curr Opin Crit Care. 2013;19(4):308–14.
25. • ARISE Investigators; ANZICS Clinical Trials Group, Peake SL, Delaney A, Bailey M, Bellomo R, Cameron PA, Cooper DJ, Higgins AM, Holdgate A, Howe BD, Webb SA, Williams P. Goal-directed resuscitation for patients with early septic shock. N Engl J Med. 2014;371(16):1496–506. *Recent large adult trial which does not support EGDT.*
26. • ProCESS Investigators, Yealy DM, Kellum JA, Huang DT, Barnato AE, Weissfeld LA, Pike F, Terndrup T, Wang HE, Hou PC, LoVecchio F, Filbin MR, Shapiro NI, Angus DC. A randomized trial of protocol-based care for early septic shock. N Engl J Med. 2014;370(18):1683–93. *Recent large adult trial which does not support EGDT.*
27. Gu WJ, Wang F, Bakker J, Tang L, Liu JC. The effect of goal-directed therapy on mortality in patients with sepsis—earlier is better: a meta-analysis of randomized controlled trials. Crit Care. 2014;18(5):570.
28. Prowle JR, Kirwan CJ, Bellomo R. Fluid management for the prevention and attenuation of acute kidney injury. Nat Rev Nephrol. 2014;10(1):37–47.
29. •• Goldstein SL. Fluid management in acute kidney injury. J Intensive Care Med. 2012;29(4):183–189. *Good review with practical guidelines.*
30. Bagshaw SM, Bellomo R, Kellum JA. Oliguria, volume overload, and loop diuretics. Crit Care Med. 2008;36(4 Suppl):S172–8.
31. Tamburro RF, Thomas NJ, Ceneviva GD, Dettorre MD, Brummel GL, Lucking SE. A prospective assessment of the effect of aminophylline therapy on urine output and inflammation in critically ill children. Front Pediatr. 2014;12(2):59.
32. Arikan AA, Zappitelli M, Goldstein SL, Naipaul A, Jefferson LS, Loftis LL. Fluid overload is associated with impaired oxygenation and morbidity in critically ill children. Pediatr Crit Care Med. 2012;13(3):253–8.
33. Hayes LW, Oster RA, Tofil NM, Tolwani AJ. Outcomes of critically ill children requiring continuous renal replacement therapy. J Crit Care. 2009;24(3):394–400.
34. Sutherland SM, Zappitelli M, Alexander SR, Chua AN, Brophy PD, Bunchman TE, Hackbarth R, Somers MJ, Baum M, Symons JM, Flores FX, Benfield M, Askenazi D, Chand D, Fortenberry JD, Mahan JD, McBryde K, Blowey D, Goldstein SL. Fluid overload and mortality in children receiving continuous renal replacement therapy: the prospective pediatric continuous renal replacement therapy registry. Am J Kidney Dis. 2010;55(2):316–25.
35. Bagshaw SM, Uchino S, Kellum JA, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A, Oudemans-van Straaten HM, Ronco C, Bellomo R; Beginning and Ending Supportive Therapy for the Kidney (B.E.S.T. Kidney) Investigators. Association between renal replacement therapy in critically ill patients with severe acute kidney injury and mortality J Crit Care. 2013;28(6):1011–8.
36. Bagshaw SM, Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A. Oudemans-van Straaten HM, Ronco C, Kellum JA; Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) Investigators. Septic acute kidney injury in critically ill patients: clinical characteristics and outcomes. Clin J Am Soc Nephrol. 2007;2(3):431–9.
37. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A, Ronco C, Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) Investigators. Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA. 2005;294(7):813–8.
38. Finkelstein FO, Smoyer WE, Carter M, Brusselmans A, Feehally J. Peritoneal dialysis, acute kidney injury, and the Saving Young Lives program. Perit Dial Int. 2014;34(5):478–80.
39. Esezobor CI, Ladapo TA, Lesi FE. Peritoneal dialysis for children with acute kidney injury in Lagos, Nigeria: experience with adaptations. Perit Dial Int. 2014;34(5):534–8.
40. Abdelraheem M, Ali el-T, Osman R, Ellidir R, Bushara A, Hussein R, Elgailany S, Bakhit Y, Karrar M, Watson A, Abu-Aisha H. Outcome of acute kidney injury in Sudanese children—

an experience from a sub-Saharan African unit. Perit Dial Int. 2014;34(5):526–33.
41. •• Cullis B, Abdelraheem M, Abrahams G, Balbi A, Cruz DN, Frishberg Y, Koch V, McCulloch M, Numanoglu A, Nourse P, Pecoits-Filho R, Ponce D, Warady B, Yeates K, Finkelstein FO. Peritoneal dialysis for acute kidney injury. Perit Dial Int. 2014;34(5):494–517. *New guidelines for acute peritoneal dialysis applicable to a variety of clinical settings.*
42. Yang K, Liu W, Ren W, Lv S. Different interventions in preventing contrast-induced nephropathy after percutaneous coronary intervention. Int Urol Nephrol. 2014;46(9):1801–7.
43. Wu H, Li D, Fang M, Han H, Wang H. Meta-analysis of short-term high versus low doses of atorvastatin preventing contrast-induced acute kidney injury in patients undergoing coronary angiography/percutaneous coronary intervention. J Clin Pharmacol. 2014.
44. Goldstein SL. Acute kidney injury biomarkers: renal angina and the need for a renal troponin I. BMC Med. 2011;9:135.
45. Nguyen MT, Devarajan P. Biomarkers for the early detection of acute kidney injury. Pediatr Nephrol. 2008;23(12):2151–7.
46. Krawczeski CD, Goldstein SL, Woo JG, Wang Y, Piyaphanee N, Ma Q, Bennett M, Devarajan P. Temporal relationship and predictive value of urinary acute kidney injury biomarkers after pediatric cardiopulmonary bypass. J Am Coll Cardiol. 2011; 58(22):2301–9.
47. Ronco C, Legrand M, Goldstein SL, Hur M, Tran N, Howell EC, Cantaluppi V, Cruz DN, Damman K, Bagshaw SM, Di Somma S, Lewington A. Neutrophil gelatinase-associated lipocalin: ready for routine clinical use? An international perspective. Blood Purif. 2014;37(4):271–85.
48. • Murray PT, Mehta RL, Shaw A, Ronco C, Endre Z, Kellum JA, Chawla LS, Cruz D, Ince C, Okusa MD; ADQI 10 workgroup. Potential use of biomarkers in acute kidney injury: report and summary of recommendations from the 10th Acute Dialysis Quality Initiative consensus conference. Kidney Int. 2014;85(3): 513–21. *Recommendations for the clinical use of biomarkers.*
49. • Basu RK, Wang Y, Wong HR, Chawla LS, Wheeler DS, Goldstein SL. Incorporation of biomarkers with the renal angina index for prediction of severe AKI in critically ill children. Clin J Am Soc Nephrol. 2014;9(4):654–62. *Expansion of Renal angina index concept in a clinical setting.*
50. Goldstein SL, Chawla LS. Renal angina. Clin J Am Soc Nephrol. 2010;5(5):943–9.
51. Basu RK, Zappitelli M, Brunner L, Wang Y, Wong HR, Chawla LS, Wheeler DS, Goldstein SL. Derivation and validation of the renal angina index to improve the prediction of acute kidney injury in critically ill children. Kidney Int. 2014;85(3):659–67.
52. Essajee F, Were F, Admani B. Urine neutrophil gelatinase associated lipocalin in asphyxiated neonates: A prospective cohort study in two large hospitals in Kenya. 2014. Currently under review.
53. • Jetton JG, Askenazi DJ. Acute kidney injury in the neonate. Clin Perinatol. 2014;41(3):487–502. *Clinical review of neonatal AKI.*
54. Palevsky PM, Liu KD, Brophy PD, Chawla LS, Parikh CR, Thakar CV, Tolwani AJ, Waikar SS, Weisbord SD. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for acute kidney injury. Am J Kidney Dis. 2013;61(5):649–72.
55. Jetton JG, Askenazi DJ. Update on acute kidney injury in the neonate. Curr Opin Pediatr. 2012;24(2):191–6.
56. Carmody JB, Charlton JR. Short-term gestation, long-term risk: prematurity and chronic kidney disease. Pediatrics. 2013;131(6): 1168–79.
57. Kaddourah A, Goldstein SL. Renal replacement therapy in neonates. Clin Perinatol. 2014;41(3):517–27.
58. Mammen C, Al Abbas A, Skippen P, Nadel H, Levine D, Collet JP, Matsell DG. Long-term risk of CKD in children surviving episodes of acute kidney injury in the intensive care unit: a prospective cohort study. Am J Kidney Dis. 2012;59(4):523–30.
59. Goldstein SL, Chawla L, Ronco C, Kellum JA. Renal recovery. Crit Care. 2014;18(1):301.
60. Dong X, Chen J, He Q, Yang Y, Zhang W. Construction of bioartificial renal tubule assist device in vitro and its function of transporting sodium and glucose. J Huazhong Univ Sci Technolog Med Sci. 2009;29(4):517–21.
61. •• Koyner JL, Cerdá J, Goldstein SL, Jaber BL, Liu KD, Shea JA, Faubel S; Acute Kidney Injury Advisory Group of the American Society of Nephrology. The daily burden of acute kidney injury: a survey of U.S. nephrologists on world kidney day. Am J Kidney Dis. 2014;64(3):394–401. *Important survey of AKI world wide.*