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Approaches to the Management of Acute Kidney Injury in Children

Rajit K. Basu, MD and **Derek S. Wheeler, MD**
Division of Critical Care Medicine, Cincinnati Children's Hospital Medical Center

Department of Pediatrics, University of Cincinnati College of Medicine

The Kindervelt Laboratory for Critical Care Medicine Research, Cincinnati Children's Research Foundation

Abstract

Acute kidney injury (AKI) causes increased morbidity in critically ill children and damage to the kidney, a central mediator of homeostasis in the body, affects survival. The incidence of AKI in pediatrics is significant and despite alarming data, therapeutic interventions have failed to effect a meaningful difference in outcomes. In this review, we will discuss the epidemiology of AKI in pediatrics, treatment strategies attempted to date, experimental therapies targeting molecular patterns associated with AKI, and highlight the needed direction of AKI research and management. Prospective trials in pediatrics are needed to test the validity of diagnostic tools, to identify the point of most efficacious intervention, and to underscore the therapies that can be effective in the different downstream effects of AKI.

Keywords

acute kidney injury; children; intensive care; epidemiology; pathophysiology; management; renal replacement therapy

Introduction

Acute kidney injury (AKI), more commonly known as acute renal failure, is a common affliction in hospitalized patients. While many disease processes may cause AKI in children (Table 1) (1), most share mechanistic similarities such as impaired renal perfusion and direct renal tubular injury. The steep oxygen gradient from cortex to glomeruli places the renal tubular beds at significant risk of hypoxic and oxidative injury as well (2). Both ischemia and hypoxemia are hallmarks of the dysregulation that occur during the systemic inflammatory response syndrome (SIRS), the first stage of the sepsis syndrome (3). Sepsis is one of the leading causes of AKI in children, which may be secondary to inflammatory mediator effects on renal vascular endothelium and aberrations in the microvascular perfusion of the glomerulus from derangements in the coagulation system. Another leading cause of AKI in children is cardiopulmonary bypass. Several "combination syndromes", e.g. hepato-renal, pulmonary-renal, and cardiorenal syndromes link AKI to other visceral injury – with a likely commonality of impaired distal perfusion.

Address for correspondence Rajit K. Basu, M.D. Cincinnati Children's Hospital and Medical Center 3333 Burnet Avenue Division of Critical Care, ML 2005 Cincinnati, OH 45229 USA Tel: (513)-636-4529 Fax: (513)-636-4267 Rajit.basu@cchmc.org.

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The definitions of AKI are heterogeneous. Fold changes in serum creatinine or creatinine clearance, changes in fractional excretion of sodium (FE_{Na}), and progressive oliguria are some of the criteria that have been used in different patterns to diagnose AKI (Table 2). Many are highly variable secondary to age, sex, body mass, race, measurement technique, and diet (Table 3). Moreover, changes in serum creatinine values lag behind the degree of injury to the renal tubular epithelial cell. The degree of oliguria can be variable based on the time considered to be 'zero'. To amend this variability, international consensus panels standardized the definition of AKI in 2002 using the "RIFLE" criteria (4), which were later modified in 2007 using the "AKIN" criteria (5). Based on glomerular filtration rate (GFR), serum creatinine values, and urine output plotted against time of admission, RIFLE (Table 4) is a mnemonic for three levels of severity – Risk, Injury, and Failure, and two outcomes - Loss and End-stage kidney disease. RIFLE marks progressive degrees of injury in both critically ill and non-critically ill patients. In contrast, the AKIN criteria (Table 5) defines AKI based on time in relation to absolute creatinine increase, percentage increase, or documented oliguria, broadening the window for time of AKI diagnosis and creating an automatic "failure" designation for any patient placed on renal replacement therapy (5). Within RIFLE and AKIN, the incidence of AKI varies from 18-63% in all hospitalized adults and up to 67% for critically ill patients in the ICU. The RIFLE criteria were modified in pediatrics (pRIFLE) (Table 6) to incorporate creatinine clearance and have been used to stratify patients with AKI in several retrospective studies (6). The reported incidence of AKI in pediatric populations varies from 1-82%, with a recent study finding an incidence of 339/3396 (~10%) patients admitted to the pediatric intensive care unit (PICU) (7). Using pRIFLE, roughly 50% of pediatric patients studied developed some degree of kidney injury early in their hospital stay (mean time to pRIFLE stratum 3.3±3.1 days, 82% diagnosed within 7 days) (6).

AKI increases overall mortality, independent of disease severity. In some reports, adult mortality increases to nearly 80% (8-9), specifically in conjunction with sepsis, trauma, burns, transplant, and acute respiratory distress syndrome (ARDS). AKI is an independent risk factor for mortality, with odds ratios as high as 4.8, and independently increases hospital costs, length of stay, and ventilator days (10). AKI also leads to end stage renal disease in a significant proportion of adults (11). In a study of nearly 4000 critically ill children, AKI increased mortality and lengthened intensive care stay four-fold (7). AKI increases mortality with multi-organ failure, hematopoietic stem cell or solid organ transplant, extra-corporeal membrane oxygenation (ECMO), or ARDS anywhere from 10-57.1% (12-14). AKI carries a high risk of death independent of PRISM II (Pediatric Risk of Mortality II) scores in these patients (6). AKI affects between 2.7 and 28% of children following CPB and carries a notable increased morbidity risk, including longer duration of mechanical ventilation and hospital length of stay (15-16). For these children, even a small creatinine rise of ≥25% is a significant risk factor for AKI (17). Finally, at 3-5 year follow-up, 40-50% of pediatric patients who suffered AKI show signs of chronic renal insufficiency, indicating that sub-lethal injury permanently alters the renal bed (18).

Collectively, these studies strongly suggest that AKI represents a serious burden to the pediatric patient population (12). In this review, we will discuss existing paradigms and advancements in diagnosis, management, and prevention. We will also highlight the concepts of proximal injury during AKI and research investigating the global effects of isolated AKI.

AKI Diagnosis

Biomarkers

Timely identification of children with AKI may be critical to management; however current laboratory and clinical markers may be unreliable for acute injury. It is clear that while the RIFLE and AKIN strata are helpful for retrospective reviews and epidemiological study, they have limited utility to the clinician evaluating a child in real-time. Because of this, the search is on for real-time marker(s) of AKI which would allow for rapid and reliable diagnosis, theoretically providing a therapeutic advantage to intensivists akin to the use of troponins as a biomarker for acute myocardial infarction (19). Many candidate biomarkers of AKI have been identified (Table 7) (20-21) and tested retrospectively to diagnose established AKI, to predict AKI, and to estimate AKI severity.

Established AKI—Serum levels of cystatin C, an inhibitor of cysteine protease present on all nucleated cells, identified established AKI in 76% of adult patients versus only 20% for serum creatinine (22). Median urinary interleukin-18 (IL-18) levels were significantly greater in patients with acute tubular necrosis (644 pg/mg) and delayed graft function after cadaveric transplant (924 pg/mg) than in healthy controls (16 pg/mg) and prompt graft function after cadaveric transplant (171 pg/mg), respectively (23). In a number of baseline pediatric studies, serum cystatin C levels were diagnostically superior to serum creatinine and were independent of gender, body composition, or muscle mass (24).

Prediction of AKI—Neutrophil gelatinase-associated lipocalin (NGAL) is a bacteriostatic siderophore which was first identified as a consistently up-regulated gene product in experimental models of AKI. Urinary NGAL levels have been tested in a number of pediatric studies. Urinary NGAL (uNGAL) levels of ≥ 50 μg/L were 100% sensitive and 98% predictive in the 20/71 children post CPB who developed AKI (25). In a prospective cohort study, mean and peak uNGAL concentrations rose at least six-fold higher in children with AKI than control patients admitted to the PICU (26). Serum NGAL levels within 2 hours of CPB of ≥ 150 mg/L were 84% sensitive and 94% predictive in children who developed AKI within 3 days (27). Serum cystatin C levels increased with 82% sensitivity and 95% specificity 1.5 days earlier than serum creatinine in 44 patients who developed AKI (28). IL-18, liver type fatty acid binding protein (L-FABP), and kidney injury molecule-1 (KIM-1) have all been tested to predict AKI with promising results.

Prediction of AKI Severity—Using the outcomes of death or the need for renal replacement therapy, biomarkers have been tested for predictive efficacy. Serum cystatin C levels were 76% sensitive and 93% specific for renal replacement therapy (RRT) need 24 hours prior to initiation based on creatinine levels (28). In pediatrics, uNGAL levels demonstrated sharp increases to >5000 ng/mg within 2-4 hours in patients who would eventually require RRT (29).Additionally, the uNGAL area under the receiver operating curve for predicting worsening of AKI was 0.61.

Renal Angina—The utility of biomarkers is limited by the inability to identify the optimal time to test patients. An asymmetry with the previously mentioned troponin analogy is that unlike chest pain for myocardial injury, there usually is no physical symptom like pain associated with kidney injury. Thus, while troponin measurement has some standardization based on time of testing in relation to physical symptoms, the use of any biomarker for AKI has yet to gain such an advantage. Retrospective analysis suggests, though, that patients who develop AKI may share risk factors on presentation. Further analysis may be able to identify a constellation of risk factors and patient indicators that highlight a state of renal *angina*,

during which the collection of biomarkers would gain more power and offer a starting point for therapeutic maneuvers (30).

Diagnostic Adjuncts

Other real-time modalities are being tested for AKI diagnosis. Minute to minute variations in somatic near infrared spectroscopy (NIRS) numbers may be correlative with low perfusion states, including hypovolemic pediatric emergency room patients (31-32). Imaging modalities such as BOLD (blood oxygen level dependent) magnetic resonance imaging have been used in adults to determine changes in renal parenchymal oxygenation (33). BOLD uses deoxyhemoglobin as an endogenous contrast agent to identify areas of reduced oxygen tension within the kidneys – resulting in decreased intensity on T2-weighted MR images. Ultrasound and contrast enhanced ultrasound have been used to identify AKI manifest as changes in echogenicity and blood flow detectable by Doppler, however the dangers of contrast instillation have limited the utility of computed tomography in AKI diagnosis (34) Adult urine pO_2 levels, assumed to mirror changes in renal oxygenation, have been correlated to AKI (35). At present, imaging diagnostic adjuncts are still in validation studies and offer only anecdotal bedside support for the diagnosis of AKI.

Management

The wide-ranging medical management of AKI mirrors its historical variability in diagnosis. Though many different interventions have been attempted, few consistent efficacious therapies have been discovered. Recommendations were recently offered, but many of these are based on retrospective study and few prospective AKI therapies have proven to be effective (36). In many instances, AKI progresses unthwarted towards renal replacement therapy, end stage disease, and death. Interventions that attempt to reverse root causes of kidney injury hold promise, but often yield conflicting results in prospective study. A wide array of new targets are being tested for efficacy in combating AKI.

Impairment: Aberrant renal perfusion

Renal perfusion pressure—The use of renal vasodilators to increase renal perfusion has not been associated with improved outcomes. Adult studies of low-dose, or so-called “renal-dose”, dopamine have failed to show benefit and may actually be harmful (37-38). A meta-analysis of dopamine use in adults showed that in 24 studies, dopamine did not prevent mortality (relative risk, 0.9 [0.44-1.83]), the onset of acute kidney failure (relative risk, 0.81 [0.55-1.19]), or the need for dialysis (relative risk, 0.83 [0.55-1.24]) (39). In another meta-analysis of 61 trials, low dose dopamine increased urine output by 24% but resulted in no significant improvement in serum creatinine levels (40). Low dose dopamine in children has not been effective at improving outcomes either (1, 41). Further, low dose dopamine may increase the risk of tachyarrhythmias and ischemic injury to the myocardium by increasing myocardial oxygen consumption. Additionally, its natriuretic effects may worsen the effective hypovolemia seen in AKI. Fenoldopam, a selective dopamine agonist, increases renal blood flow and may reduce mortality and the need for renal replacement (RRT) in adults. Compared to low dose dopamine, fenoldopam dosed from 0.05 to 0.1 μg/kg/min was shown to improve serum creatinine values in 100 adults matched for severity of illness (42), but showed no difference in 80 patients undergoing cardiac surgery (43). Fenoldopam of 0.07 ± 0.08 mg/kg/min increased urine output in critically ill children with progressive oliguria (44), but did not affect overall outcome. Neither low-dose dopamine nor fenoldopam have been tested in a large prospective cohort pediatric study and cannot be recommended for prevention or management of AKI outside of the context of a clinical trial.

Preload Optimization—No consensus exists regarding the appropriate balance of fluids, diuresis, and dialysis for patients with AKI. In response to hypoperfusion, many patients may receive total fluid doses to reach central venous pressure and mean arterial pressure targets that result in total body water overload (45-46). Intravenous fluids are medicines, prescribed and administered like all other drugs, and warning signs of "overdose" should be heeded before every dose. A study of more than 3000 adult patients revealed a link between positive fluid balance and mortality in AKI (47). Additionally, the Fluid and Catheter Treatment Trial (FACCT) in adults demonstrated that in 244 surgical patients, the use of a conservative fluid management strategy resulted in more ventilator-free and ICU-free days in patients with acute lung injury (48). The Prospective Pediatric Continuous Renal Replacement Therapy Registry Group (ppCRRT), studying a sample of 116 children, retrospectively found increased fluid administration to be independently associated with mortality in children started on CRRT (49). The proper 'dose' of preload is patient specific, especially in the setting of volume responsive versus volume unresponsive AKI. Therefore, contextual clues must be used to determine the adequate amount of fluid appropriate to optimize renal preload.

Crystalloid vs Colloid resuscitation—In the adult population, studies have compared albumin to saline (SAFE study (50)) and hydroxyethyl starches to saline (SOAP study (51)) for resuscitation. Neither demonstrated clear benefit in colloid over crystalloid infusions. There was no survival difference in over 7000 patients between recipients of albumin or saline (SAFE). Conflicting correlations between AKI and the use of starches for resuscitation during sepsis have been reported (52). There have been no published studies relating type of fluid used in pediatric resuscitation and AKI incidence or outcomes. As such, there are no conclusive recommendations regarding which particular type of fluid resuscitation is better for critically ill children with or at risk of developing AKI.

Impairment: Fluid Overload

Diuretics—Reducing fluid overload with diuresis can limit the use of renal replacement therapy but has not been proven to improve outcomes from AKI. The use of diuretics in adults with AKI has been associated with an increased risk of death (odds ratio, 1.77 [1.14-2.76]) and has shown no benefit in recovery of kidney function (53-54). While robust evidence indicates that hypoxia figures prominently into ischemic kidney injury, the theoretic benefit of loop diuretics limiting energy consumption by inhibiting sodium-potassium ATPases have not been shown to be clinically significant (55-57). There is also no evidence of a mortality benefit in using diuretics to convert oliguric AKI into non-oliguric AKI. In a limited adult study of 61 patients after CPB with >50% increase in serum creatinine, an infusion of 50 ng/kg/min of atrial natriuretic peptide demonstrated hazard ratios of 0.28 [0.1-0.73] and 0.35 [0.14-0.82] for eventual dialysis or death (58). Data regarding augmentation of urine output in pediatric AKI using diuretics is limited to BMT and post bypass patients (59-60). The use of natriuretic peptides has been attempted in patients with AKI and cardiorenal syndrome (61). Brain natriuretic peptide (nesiritide), described in children with decompensated heart failure, increases diuresis, but its effect on isolated AKI is not known (62). There have been no prospective studies on the use of diuretics in pediatric AKI.

Continuous Renal Replacement Therapy (CRRT)—Other than emergent dialytic therapy for electrolyte disturbance or ingested toxins, controversies abound with regard to the proper timing of initiation, dose, route, and duration of CRRT in AKI. Prospective adult data based on blood urea nitrogen value cutoffs is heterogeneous for timing of initiation and outcome. The mortality for adults started on CRRT is nearly 60% in some studies (63-65).

In pediatrics, the percent fluid overload (%FO) has been used as an initiating trigger and is calculated as:

$$\text{FLUID OVERLOAD} = \left[\left(\Sigma \text{Fluid}_{\text{IN}} - \Sigma \text{Fluid}_{\text{OUT}} \right) / \text{Admission weight} \right] * 100$$

Retrospective study of 21 children receiving CRRT for AKI suggested that the degree of FO at time of CRRT initiation was significantly lower in survivors than in non-survivors (16.4% vs. 34%) (66). In a larger study of 113 children with multi organ dysfunction syndrome (MODS) started on CRRT, median % FO was significantly lower in survivors compared to non-survivors (7.8% vs. 15.1%), independent of severity of illness (67). Even more recently, in 297 patients, % FO was again significantly lower in survivors versus non-survivors (12.5% vs. 23.0%) (68). DiCarlo initiated CRRT for ten children with ARDS after BMT regardless of presence of AKI in a prospective observational study with an 80% survival rate (69). The mortality for children started on CRRT is 10-57.1%. While ppCRRT data suggests that 10-15% FO is the signal for CRRT or peritoneal dialysis (PD) initiation, this has yet to be prospectively proven. Further, it has yet to be demonstrated that children placed on CRRT for AKI have better outcomes than those without such therapy.

RRT Dose and Modality—A large recent study with meticulous documentation of actual doses received, demonstrated no improvement in kidney function or mortality outcome in adults receiving high intensity CRRT (35 ml/kg/hr) versus low intensity CRRT (20 ml/kg/hr) or intermittent hemodialysis (64). The few outcomes studies performed in pediatrics investigating the effects of RRT dosage and modality are retrospective. The ppCRRT in 2007 demonstrated no difference in overall outcomes based on modality or dose of CRRT used (70). While another study showed some improvement in outcome using convective CRRT modes for bone marrow transplant patients, many centers only offer one mode of CRRT delivery and thus study applicability is limited.

Peritoneal dialysis—Peritoneal dialysis (PD) can be efficacious in FO and offers advantages for smaller children including: simplicity, less invasiveness, and improved hemodynamic tolerance (71). PD is generally safe and effective in children post CPB, with some investigators utilizing it as a prophylactic therapy as well (72).

In summary, little prospectively validated data exists regarding the effect of CRRT on outcomes. While some data suggest that early and aggressive CRRT initiation may be beneficial in children with fluid overload, the questions that need to be objectively addressed are the definitions of “early” and “aggressive.”

Impairment: Direct Cellular Injury

Cell based therapy—Tubular cell death from acute tubular necrosis is commonly viewed as a central cog in the AKI machinery and is implicated in the progression of disease. Several novel therapies attempt to reconstitute tubular cell volume and function. A renal assist device (RAD) which contains animal or human renal tubule cells integrates tubular cell function with the filtration of dialysis for a “complete” renal replacement therapy (73). Selective cytopheretic inhibitory devices are synthetic membranes on extracorporeal devices which bind circulating leukocytes theoretically reducing microvascular damage promoted by activated leukocytes in AKI and SIRS (73). Mesenchymal stem cells (MSC) home to sites of renal injury and act in paracrine fashion to aid with glomerular growth, post-glomerular circulation, reduce local inflammation, and enhance filtration (74-79). Serum amyloid A protein (SAA) is an acute phase response protein which promotes tubulogenesis and when

programmed into transformed cells accelerates renal recovery in multiple animal models of renal failure (80).

Impairment: Oxidative and Inflammatory Injury

CRRT for immunomodulation—CRRT has been used in septic adults with the intention of altering levels of circulating cytokines and inflammatory mediators (81-82). Modifications of CRRT have not improved outcomes for such patients. To date, literature does not support the routine use of CRRT for sepsis without AKI.

Oxidative Injury—The kidney suffers derangements in oxygen homeostasis during AKI. Though prospective study of CPB patients demonstrated that anemia is independently associated with AKI, the risks of increased volume and blood viscosity must be balanced against the presumed benefit of increased oxygen carrying capacity. Studies of N-acetylcysteine and dexamethasone therapies to limit oxidative and inflammatory damage in AKI post CPB showed conflicting results (83-86). Pro-inflammatory signaling pathways are targets of experimental therapy for AKI. The anti-inflammatory effects of the tryphostins, tyrosine kinase inhibitors, ameliorate acute kidney injury (87). Heat shock proteins are molecular chaperones that attenuate inflammatory damage in cellular stress. Of note, HSP-70 induction by geranylgeranylacetone (GGA) improves AKI *in vitro* (88) and HSP-90 inhibition by radicolol, which increases HSP-70 expression, also lessens the severity of AKI (89). Reducing the formation of peroxynitrite in the glomerulus by inducible nitric oxide synthase (iNOS) has been shown to improve experimental AKI (90). Oxidative balance in the kidney is regulated on multiple levels by the transcription factor, hypoxia-inducible-factor-1 (HIF-1) (91-92). Prevention of HIF-1 degradation by selective inhibition of prolyl-hydroxylase enzymes lessens *in vitro* AKI severity (93). Finally, sepsis-associated AKI (SA-AKI) has drawn considerable interest due to its high clinical preponderance. Several targets of sepsis mediated injury have been investigated as targets of SA-AKI. Ethyl pyruvate, a potent anti-oxidant and free radical scavenger, leads to more renoprotection in rodent models of SA-AKI (94). Chloroquine, a commonly available anti-inflammatory drug, inhibits toll-like receptor 9 mediated renal damage during SA-AKI (95). Anti-inflammatory agents such as 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors and IL-10 modulate cytokine responses to sepsis and have both been shown to decrease kidney dysfunction in animal sepsis models (96-97). Finally, microthrombosis and disruption of the coagulation cascade, briefly discussed earlier as culpable etiologies of damage in SA-AKI, are targets of therapy. Activated protein C (APC), used in adult sepsis therapy, is an anticoagulant that reduces kidney injury in animal sepsis models (98-99). A summary of novel therapies for AKI is shown in Table 8.

Drugs that impair renal perfusion or intra-renal hemodynamics such as non-steroidal anti-inflammatory drugs (NSAIDS), angiotensin-converting enzyme inhibitors (ACE), and calcineurin inhibitors must be used with caution in patients with AKI (100). The use of direct nephrotoxins such as aminoglycoside antimicrobials, radiocontrast media, antifungal agents, and immunosuppressive drugs are associated with high rates of AKI and must be diligently constrained (101).

Impairment: Malnutrition

Nutrition in adult AKI is important and minding macro and micro nutrient requirements is vital to outcome (13). Optimizing nutrition in pediatric AKI patients can be challenging and Bunchman recommends using a metabolic cart to determine the amount of nutrition necessary (102). CRRT may reduce fluid concerns when optimal nutrition, using reno-protective and anabolic formulas, is desired. Recent large prospective randomized control trials suggest that tight glucose control increases overall mortality, also showing no

difference in the number of adult patients requiring RRT based on glycemic control strategy (103). A prospective pediatric study demonstrated morbidity improvements in children receiving intensive insulin therapy, but no effects on outcomes with AKI or dialysis were seen (104).

Impairment: Distal Targets of Kidney Injury

Abundant clinical evidence suggests that kidney injury worsens the progression of inpatient and outpatient disease (105-106). The inability to detect early and subtle kidney injury has likely hampered the ability to observe the possible concurrent deleterious effects of AKI on the lung, heart, or brain. Experimental evidence suggests that ischemic AKI alters host immune reponse (107), blood-brain permeability and astrocyte function (108), and left ventricular systolic function (109). Experimental AKI leads to aberrant lung water balance and lung function (110-112). Clinical evidence indicates that patients with ARDS or ventilator-induced lung injury (VILI) with concurrent AKI have increased ventilator needs and duration (113). Taken together, early kidney injury may have a role in dysregulation of systemic homeostasis before the manifestations of oliguria, high serum creatinine, or overt 'kidney failure'. It is unknown how early kidney injury, which may phenotypically be *renal angina*, affects host responses to subsequent injury or multi-organ disease.

Future Directions

Management of acute kidney injury, a clear burden to critically ill adults and children, is complex and challenging. Our understanding and ability to detect renal distress and its possible autocrine and endocrine effects is in its infancy. To date, therapy of AKI revolves around optimizing renal perfusion pressure and oxygenation, through a combination of judicious fluid prescription, inotropy, and renal replacement therapy while attending to proper nutrition and avoidance of additional nephrotoxins. However, practitioners have limited consensus or best practice parameters to follow as little prospective evidence is available. Kidney injury is likely incremental, more temporally proximal than fluid overload and anuric failure, and likely causes more significant distal harm than previously appreciated. It is fair to state that despite advances in diagnosis, stratification, pharmacotherapy, and extra-corporeal techniques, little progress has been made to improve outcomes. The successful management of AKI depends on several things.

Renal Angina and Biomarkers

Identification of patients at risk of kidney injury is critical if therapies are to be initiated that can reverse on-going injury. The epidemiologic strata based on creatinine and urine output are useful, but not for real-time management. Analysis of patients who develop AKI will hopefully identify a renal angina phenotype which would parallel chest pain for heart disease. Along these lines, biomarker study will be needed to isolate a marker(s) that would have high sensitivity and specificity for prediction of disease, diagnosis of established disease, and prediction of severity of disease.

Molecular targets of AKI

The cellular machinery that is activated in acute kidney injury requires elucidation. Evidence suggests involvement of molecular chaperone proteins, transcription factors responsive to regional hypoxia, and inflammatory cytokines. Renal assist devices, which reconstitute 'normal' tubular function may offer more complete renal replacement therapy. Drugs such as the tryphostins, HMG-CoA reductase inhibitors, iNOS inhibitors, and modulators of HSP-70 may help in abrogating the development of a milieu of progressive injury in the renal parenchymal bed.

The Endocrine Kidney

The central role of the kidney in host homeostasis is underscored by the findings of increased morbidity and mortality with AKI. The findings of distal organ injury during isolated experimental AKI may hold clinical relevance. Further research may lead to the elucidation of a pattern of kidney mediated danger signals or injury activators that lead to the clinical findings of worsened respiratory mechanics, heart function, and neurologic function.

Prospective Study

Prospective study of AKI in adults and children is needed if any supportable therapy can be found. Management of diseases such as ARDS, stroke, and myocardial infarction advanced and gained consensus because of prospective trials and validation. No consensus exists regarding the utility of early diagnosis, early intervention, the use of pharmacotherapy, the initiation or use of renal replacement therapy, or adjunctive therapies in AKI. Epidemiologic study shows that many critically ill patients, adults and children have some degree of kidney dysfunction. Thus, *now* is the time for prospective studies.

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Table 1

Etiologies of Pediatric Acute Kidney Injury

Pre-renal / Hypoperfusion	Renal / Intrinsic	Post-renal / Obstruction
↓ Intravascular volume	Glomerular	Urethral obstruction
Hemorrhage post surgical, trauma	Acute Glomerulonephritis	Posterior urethral valves
Severe dehydration	Immune mediated nephropathy	
3rd-space loss – sepsis, capillary leak		
↓Effective Circulating Volume	Vascular	Obstruction of solitary kidney tract
Cardiac dysfunction	Hemolytic-uremic syndrome	
Acute Liver failure	Malignant hypertension	
Sepsis-associated vasodilation	Lupus nephritis	
↓Renal Blood Flow	Interstitial	Ureteral Obstruction
Renal artery occlusion or stenosis	Acute interstitial nephritis – drug related	Nephrolithiasis
ACE inhibitors	Pyelonephritis	
	Tubular	
	Acute tubular necrosis: ischemia-reperfusion	
	Toxin/poison mediated	

Table 2

Previous Markers of AKI

Index	Pre-renal AKI	Intrinsic or Renal AKI
Urine color	Dark Yellow	Yellow
Urine specific gravity	High (>1.020)	Low (<1.020)
Urine sodium	Low (<10 mmol/L)	High (>20 mmol/L)
Urine sediment	Normal	Epithelial casts
FE_{NA}	<1%	>1%
FE_{Urea}	<35%	>35%
Urine osmolality	High (>500 mOsm/kg H_2O)	Close to serum (<300 mOsm/kg H_2O)
Urine/Plasma osmolality	> 1.5	1 – 1.5
Urine/plasma creatinine ratio	High (>40)	Low (<10)
BUN/creatinine ratio	High	Normal
Urine sodium/potassium ratio	Low (<1/4)	High
RFI (Renal Failure Index)	< 1	>2

Note: FENA-fractional excretion of sodium, FEUrea – fractional excretion of urea, mOSM- milliosmoles, mmol - millimole

Table 3

Reported factors that impact the accuracy of commonly used markers of acute kidney injury (AKI) in the clinical setting.

Serum Marker	Factor	
Creatinine	Increase S_{CR}	Decrease S_{CR}
	Younger age	Older age
	Male gender	Female gender
	Large lean muscle mass	Small lean muscle mass
	High protein diet (meat)	Vegetarian diet
	Strenuous exercise	Neuromuscular disease
	Rhabdomyolysis	Malnutrition
	Drugs (e.g., cimetidine, trimethoprim)	Amputation
		Jaffe reaction (e.g. DKA)
Urea	Increase BUN	Decrease BUN
	Dehydration	Overhydration
	High protein diet	Vegetarian diet
	Critical illness	Pregnancy
	Gastrointestinal bleeding	Liver disease
	Drugs (e.g., corticosteroids)	
Cystatin C	Increase Cystatin C	Decrease Cystatin C
	Older age	Younger age
	Male gender	Female gender
	Large lean muscle mass	Small lean muscle mass
	Inflammation	Immunosuppression
	Hyperthyroidism	Hypothyroidism
	Smoking	

Note: S_{Cr} -serum creatinine concentration, DKA – diabetic ketoacidosis

Table 4

RIFLE Criteria (Acute Dialysis Quality Initiative)

Stage	Serum Creatinine Criteria	GFR Criteria	Urine Output Criteria
R = Risk for renal dysfunction	Increase in serum creatinine ≥ 1.5× baseline	Decrease in GFR ≥ 25%	< 0.5 mL/kg/hr for 6 h
I = Injury to the kidney	Increase in serum creatinine ≥ 2.0 × baseline	Decrease in GFR ≥ 50%	< 0.5 mL/kg/hr for 12h
F = Failure of kidney function	Increase in serum creatinine ≥ 3.0× baseline OR serum creatinine ≥ 4.0 mg/dL in the setting of an acute rise ≥ 0.5 mg/dL	Decrease in GFR ≥ 75%	< 0.3 mL/kg/hr for 24 hr or anuria for 12 hr
L = Loss of kidney function	Persistent failure > 4 weeks		
E = End-stage renal disease (ESRD)	Persistent failure > 3 months		

Note: GFR – glomerular filtration rate, mg/dl – milligrams/deciliter, and the urine output criteria are the same for both RIFLE and AKIN.

Table 5

Comparison of the ADQI RIFLE Criteria with the AKIN Staging Criteria

RIFLE Stage	RIFLE criteria	AKIN Stage	AKIN Criteria
R	≥150% increase in serum creatinine, or >25% GFR decrease	**I**	≥150% or ≥0.3 mg/dL increase in serum creatinine
I	≥200% increase in serum creatinine, or >50% GFR decrease	**II**	>200% increase in serum creatinine
F	≥300% increase in serum creatinine, or serum creatinine of ≥ 4.0 mg/dL in setting of increase≥ 0.5 mg/dL, or >75% GFR decrease	**III**	>300% increase in serum creatinine, or serum creatinine of ≥ 4.0 mg/dL in setting of increase≥ 0.5 mg/dL

Note: GFR – glomerular filtration rate, mg/dl – milligrams/deciliter, and the urine output criteria are the same for both RIFLE and AKIN.

Table 6

The modified pediatric version of the RIFLE Criteria (pRIFLE)

Stage	Estimated Creatinine Clearance (eCCL)	Urine Output
R = Risk for renal dysfunction	eCCl decrease by 25%	< 0.5 mL/kg/hr for 8 h
I = Injury to the kidney	eCCl decrease by 50%	< 0.5 mL/kg/hr for 16 h
F = Failure of kidney function	eCCl decrease by 75% or eCCl < 35 mL/min/1.73m^2	< 0.3 mL/kg/hr for 24 hr or anuria for 12 hr
L = Loss of kidney function	Persistent failure > 4 weeks	
E = End-stage renal disease (ESRD)	Persistent failure > 3 months	

Note: Estimated Creatinine clearance is estimated by the Schwartz formula (114)is: eCCl = CL_{CR} = (k × Ht) / Scr, where Ht height (length) in cm, SCr is the serum creatinine, k is a constant (k = 0.43) and BSA is body surface area.

Table 7

Biomarkers Currently Under Study for AKI[115]

Time Frame	Established AKI	Early Detection	Prognosis	Death
Serum	NGAL, Cystatin C, Carb-Hb	NGAL Cystatin C Pro-ANP Neutrophil-CD11b	NGAL ,RRT, Cystatin C	IL-6, IL-8, IL-10
Urine	NGAL, IL-18 GST, NAG α-1 microglobulin KIM-1, NHE-ɜ MMP-9	NGAL, IL-18, KIM-1, GST, γ-GT, π-GST, α-GST, AP, NAG, LDH MMP-9	NGAL, RRT, Cystatin C, α-1-microglobulin, β-2-microglobulin, NAG, α-GST, GGT, LDH, KIM-1	NGAL, IL-18, NAG, KIM-1

Note: Carb-Hb = carbamino hemoglobin, NGAL=neutrophil gelatinase associated lipocalin, IL-interleukin, KIM-1=kidney injury molecule-1, NAG = N-acetyl-β-d-glucosamide, RRT = renal replacement therapy, a-GST = a-glutathione-s-transferase, GGT = g-glutamyltransferase, LDH = lactate dehydrogenase, MMP-9=matrix metalloproteinase 9, AP = alkaline phosphatase, NHE3 = sodium hydrogen exchanger 1, ANP = atrial natriuretic peptide

Table 8

Novel Molecular Therapies for AKI[74, 116-117]

Modulators of Ischemia-Reperfusion	Anti-inflammatory Agents	Inhibitors of Apoptosis	Modulation of Endothelium and Coagulation	Cell-based therapies
Ethyl pyruvate M2AA Bezafibrate iNOS inhibitors HIF modulators Chloroquine GGA Radiculol	HMG-CoA Reductase inhibitors AP-214 Anti-CD147 antibody IL-10 Ghrelin	Caspase-3 inhibitor Sphingosine-1-phosphate analog A2A analog Theophylline	Activated Protein C sTM EPO	MSC SAA RAD Selective cytopheretic inhibition

Note - agent (target): M2AA – methyl-2-acetamidoacrylate(modulators of inflammatory response) , bezafibrate (peroxisome proliferating receptor alpha), iNOS – inducible nitric oxide synthase (peroxynitrite formation), HIF – hypoxia inducible factor, GGA – geranylgeranylacetone (heat-shock protein), HMG-CoA – hydroxymethylglutarate coenzyme A, AP214 – a-melanocyte stimulating hormone analog(cyclophilin receptor), IL – interleukin, A2A – adenosine receptor 2A subtype, sTM – soluble thrombomodulin, EPO – erythropoietin, MSC – mesenchymal stem cells, SAA – serum amyloid A protein, RAD – renal assist device