Pediatric RESEARCH

REVIEW ARTICLE

Advances in pediatric acute kidney injury

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The objective of this study was to inform the pediatric nephrologists of recent advances in acute kidney injury (AKI) epidemiology, pathophysiology, novel biomarkers, diagnostic tools, and management modalities. Studies were identified from PubMed, EMBASE, and Google Scholar for topics relevant to AKI. The bibliographies of relevant studies were also reviewed for potential articles. Pediatric (0–18 years) articles from 2000 to May 2020 in the English language were included. For epidemiological outcomes analysis, a meta-analysis on data regarding AKI incidence, mortality, and proportion of kidney replacement therapy was performed and an overall pooled estimate was calculated using the random-effects model. Other sections were created highlighting pathophysiology, novel biomarkers, changing definitions of AKI, evolving tools for AKI diagnosis, and various management modalities. AKI is a common condition seen in hospitalized children and the diagnosis and management have shown to be quite a challenge. However, new standardized definitions, advancements in diagnostic tools, and the development of novel management modalities have led to increased survival benefits in children with AKI.

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IMPACT:

- This review highlights the recent innovations in the field of AKI, especially in regard to epidemiology, pathophysiology, novel biomarkers, diagnostic tools, and management modalities.

INTRODUCTION

Acute kidney injury (AKI) is a condition commonly seen in hospitalized children throughout the world. Within the past two decades, the epidemiology of pediatric AKI has expanded due to standardized AKI definitions, recent advances in AKI-defining biomarkers, and increased global awareness.[1] In addition, evolution of kidney replacement therapy (KRT) modalities has illustrated beneficial outcomes in terms of reduced mortality and length of hospital stay. Therefore, we here summarize the various advances in AKI pathophysiology, the fruition of novel biomarkers and diagnostic tools, the evolution of current modalities, and the emergence of novel KRT machines for pediatric AKI patients.

Methodology

An electronic literature search was conducted in PubMed, EMBASE, and Google Scholar by two reviewers (R.C., R.R.). The search strategy included the Medical subject headings (MeSHs): "acute kidney injury," acute renal failure," acute tubular necrosis," renal ischemia," "pediatrics," "epidemiology," and "kidney replacement therapy." Pediatric (0–18 years) articles from 2000 to May 2020 in the English language were included. Additional articles were incorporated after examination of the reference list of included literature. For analysis of epidemiological outcomes, a meta-analysis on data regarding AKI incidence, mortality, and proportion of KRT was performed. An overall pooled estimate was calculated utilizing the random-effects model and a test for heterogeneity was applied using I^2 statistics. The random-effects model was chosen to take into account heterogeneity between the included studies. Forest plots were created to visualize these outcomes and combine estimated outcomes with 95% confidence intervals (CIs) reported for each study. Publication bias was assessed using funnel plots and $p \le 0.05$ was considered for statistical significance. A summary of all included studies has been reported in Table 1. All statistical analyses were performed with R software version 3.1.0.

Global epidemiology of pediatric AKI

The global epidemiology of pediatric AKI has increased due to the standardized AKI definitions, reliable AKI-defining biomarkers, the formation of national registries, and multinational studies. The AWARE (Assessment of Worldwide Acute Kidney Injury, Renal Angina, and Epidemiology) study, an observational study of 4683 children, was the first multinational study on pediatric AKI patients.[2] The investigators reported an AKI incidence of 26.9%, with 11.6% developing severe AKI (Kidney Disease Improving Global Outcomes (KDIGO) stage 2 or 3) and a higher 28-day mortality in patients with severe AKI vs. those without (11% vs. 2.5%, respectively).[2] In addition, various other worldwide studies have reported data on AKI incidence and mortality. In our meta-analysis, 12 publications included critically ill or high-risk AKI population from pediatric intensive care unit (PICU) or neonatal intensive care unit (NICU) or with baseline and follow-up creatinine level, while two publications (Sutherland et al.[3] and Cao et al.[4]) had pediatric inpatient population. The total incidence of pediatric AKI was 18.7% (95% CI: 14.3–23.5%; $I^2 = 99.96\%$; $p < 0.0001$) across all 14 publications (Table 2 and Fig. 1)[2–15] and

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Table 1. Included studies with data on AKI incidence, mortality, and kidney replacement therapy among pediatric patients.

Study	Study details	AKI criteria
Jetton et al.[15]	• Study type: retrospective • Country: Australia, Canada, India, USA • Multicenter • Neonates admitted to 24 NICUs and received IV fluids for at least 48 h ($n = 2022$)	KDIGO
Kaddourah et al.[2]	• Study type: prospective • Country: Asia, Australia, Europe, and North America • Multicenter • 3 months and 25 years old admitted to 32 PICUs ($n = 4984$)	KDIGO
Rustagi et al.[10]	• Study type: prospective • Country: India • Single center • 2 months to 18 years admitted to the PICU ($n = 380$)	pRIFLE
Tresa et al.[18]	• Study type: prospective • Country: Pakistan • Single center • Patient between 1 month and 15 years old with AKI ($n = 116$)	pRIFLE
Volpon et al.[9]	• Study type: prospective • Country: Brazil • Single center • ≤20 years admitted to the PICU ($n = 160$)	KDIGO, pRIFLE
Sanchez-Pinto et al.[7]	• Study type: Retrospective • Country: USA • Single center • 1 month to 21 years admitted to PICU ($n = 7731$)	KDIGO
Sutherland et al.[8]	• Study type: retrospective • Country: USA • Single center • <18 years admitted to hospital with baseline creatinine, and follow-up creatinine values ($n = 14,795$)	pRIFLE, AKIN, KDIGO
Carmody et al.[14]	• Study type: retrospective • Country: USA • Single center • Low birth weight infants (≤1500 g) admitted to NICU surviving >48 h after admission ($n = 455$)	KDIGO
Bresolin et al.[6]	• Study type: prospective • Country: Brazil • Single center • 28 days to 15 years admitted to the PICU ($n = 84$)	pRIFLE
Cao et al.[4]	• Study type: prospective • Country: China • Multicenter • 15 days to 18 years admitted in 27 hospitals (14 children's and 13 general hospitals) ($n = 3,88,763$)	AKIN
Selewski et al.[13]	• Study type: retrospective • Country: USA • Single center • Neonates treated with therapeutic hypothermia for perinatal asphyxia in NICU ($n = 96$)	AKIN
Sutherland et al.[3]	• Study type: retrospective • Country: USA • KID database • ≤18 years in the 2009 Kids' Inpatient Database (KID) database ($n = 26,44,263$)	ICD-9-CM codes
Viswanathan et al.[12]	• Study type: retrospective • Country: USA • Single center • Extremely low birth weight infants admitted to the NICU ($n = 472$)	Oliguria of <1 ml/kg/h of urine output that developed 24 h after birth and persisted for at least 24 h and/or a raising of the serum creatinine level >1.5 mg/dl for 72 h after birth in the presence of normal maternal creatinine levels
Koralkar et al.[11]	• Study type: prospective • Country: USA	AKIN

Table 1. continued

Study	Study details	AKI criteria
	• Single center • Very low birth weight infants (≤1500 g) admitted to the NICU surviving >48 h after admission ($n = 229$)	
Schneider et al.[5]	• Study type: retrospective • Country: USA • Single center • 31 days to 21 years admitted to the PICU ($n = 3202$)	pRIFLE
Ball and Kara[85]	• Study type: retrospective • Country: New Zealand • Single center • ≤15 years old admitted with AKI who require KRT ($n = 226$)	N/A
Vachvanichsanong et al.[17]	• Study type: retrospective • Country: Thailand • Single center • Patients between 1 month and 17 years old ($n = 311$)	N/A
Olowu and Adelusola[16]	• Study type: prospective • Country: Nigeria • Single center • ≤15 years old admitted with AKI ($n = 123$)	N/A

AKIN acute kidney injury network, *ICD-9-CM* International Classification of Diseases, Ninth Revision, Clinical Modification, *IV* intravenous fluids, *KDIGO* Kidney Disease Improving Global Outcomes, *KRT* kidney replacement therapy, *N/A* not available, *NICU* neonatal intensive care unit, *pRIFLE* pediatric risk, injury, failure, loss, end-stage renal disease.

24.4% (95% CI: 14.2–36.4%; $I^2 = 99.79\%$; $p < 0.0001$) across 12 publications including critically ill or high-risk AKI patients. Visual inspection of the funnel plot for 14 publications reporting AKI incidence showed a significant asymmetry indicating publication bias or heterogeneity. Figure 1b shows the funnel plot for 12 publications (excluding those two publications with a different population to minimize clinical heterogeneity). Pediatric AKI patients had eight times higher odds of mortality in comparison to those without AKI odds ratio: 8.03 (95% CI: 3.59–17.93); $I^2 = 98.7\%$; $p < 0.0001$ across 13 publications (Table 2 and Fig. 1)[2,3,5–15] and seven times higher odds of mortality in comparison to those without AKI [odds ratio: 7.11 (95% CI: 4.00–12.65); $I^2 = 94.2\%$; $p < 0.001$] across 12 publications including critically ill or high-risk AKI patients. Figure 1d shows the funnel plot for 12 publications reporting mortality among pediatric patients (excluding Sutherland et al.[3]).

In addition, the incidence of KRT during AKI has increased the overall pooled incidence of 13.2% (95% CI: 8.9–18.2%; $I^2 = 97.4\%$; $p < 0.001$; $n = 13$) (Table 2 and Fig. 1)[2–5,9,10,13–18]. Figure 1f shows the funnel plot for publications reporting incidence of KRT. More specifically, continuous KRT (CKRT) and hemodialysis (HD) were reported to be most widely utilized modality. According to a survey by Raina et al.,[19] the use of HD (85.1%) was reported as the predominant KRT modality in developed countries, while peritoneal dialysis (PD) (68.5%) was preferred in developing countries, which was the most effective and economical option[19]. Regardless of modality choice, the increase in KRT incidence has improved survival outcomes among pediatric AKI patients.

Pathophysiology

The pathogenesis of AKI is multifaceted and involves apoptotic, inflammatory, and immune pathways, most commonly seen in ischemic or toxic injury.[20] The pathophysiology may be split into microvascular and tubular mechanisms (Fig. 2). The microvascular mechanism includes enhanced vasoconstriction, reduced vasodilation, vascular smooth muscle and endothelial impairment, and elevated leukocyte–endothelial adhesion, resulting in vascular obstruction and inflammation.[21] In contrast, tubular injury induces cytoskeletal breakdown and loss of polarity that leads to apoptosis and necrosis. The resulting inflammatory vasoactive mediators enhance vascular compromise leading to a positive feedback mechanism, where reduction in oxygen delivery to the tubules activates the microvascular mechanisms.[21] This involvement of multiple pathophysiological pathways attributes to the complexity of AKI and advancements through research have led to the development of novel therapeutic strategies.

Newer therapeutics have emerged and are directed at these pathways (Fig. 3). For instance, the reduction/absence of proapoptotic factors, such as Fas receptors and tumor necrosis factor (TNF) alpha receptor 1, and inhibition of the apoptotic pathway using caspase inhibitors have shown to be associated with decreased kidney injury.[22,23] In addition, peroxisome proliferator-activated receptors have been found to be protective against AKI.[24] Emerging pharmacological treatments, such as p53-siRNA, deferiprone (an iron chelator),[25] α-melanocyte-stimulating hormone (α-MSH) analog, mesenchymal stem cells, and alkaline phosphatase, have shown to be effective in manipulating the above mechanisms in experimental models (Table 3).[26–30] Deficiency in C5, a critical component of the complement system, has been shown to lead to a significant reduction in neutrophil infiltration into the kidney, tubular cell apoptosis, and loss of kidney function in mice.[31] However, further developments and clinical trials are needed to elucidate the true clinical effectiveness of these treatments.

Moreover, advancement in the understanding of AKI pathophysiology has led to targeted studies of genetic polymorphisms associated with AKI. Few candidate polymorphisms include genes of TNF-α, interleukin-6 (IL-6), IL-10, and apolipoprotein E (APO-E).[32–36] It has been postulated that increased prevalence of TNF-α and IL-6, and reduction of IL-10, leads to increased prevalence of AKI in neonates.[32–34] Stafford-Smith et al.[35] reported that the combination of two IL-6 alleles, 572C and angiotensinogen

Table 2. Meta-analysis of global AKI incidence, mortality in patients with/without AKI, and incidence of kidney replacement therapy.

Acute kidney injury incidence

Study	Eligible population	% Incidence (95% CI)	Weight (%) (random)
Jetton et al.[15]	2022	29.92 (27.93–31.97)	7.45
Kaddourah et al.[2]	4984	31.34 (30.05–32.65)	7.5
Rustagi et al.[10]	380	13.95 (10.63–17.84)	7.15
Volpon et al.[9]	160	48.13 (40.17–56.15)	6.68
Sanchez-Pinto et al.[7]	7731	5.76 (5.25–6.30)	7.51
Sutherland et al.[8]	14,795	42.9 (42.10–43.70)	7.52
Carmody et al.[14]	455	39.78 (35.25–44.44)	7.21
Bresolin et al.[6]	84	19.05 (11.30–29.08)	6.07
Cao et al.[4]	3,88,763	0.32 (0.31–0.34)	7.53
Selewski et al.[13]	96	37.5 (27.82–47.97)	6.22
Sutherland et al.[3]	26,44,263	0.39 (0.38–0.40)	7.53
Viswanathan et al.[12]	472	12.5 (9.65–15.83)	7.22
Koralkar et al.[11]	229	17.9 (13.17–23.50)	6.92
Schneider et al.[5]	3202	10.59 (9.54–11.71)	7.48
Total (random effects)	30,67,636	18.66 (14.25–23.52)	100

Acute kidney injury mortality

Study	AKI (died/total)	Non-AKI (died/total)	Odds ratio (95% CI)	Weight (%) (random)
Jetton et al. [15]	59/605	20/1417	7.55 (4.50–12.65)	8.12
Kaddourah et al.[2]	86/1562	83/3422	2.34 (1.72–3.19)	8.3
Rustagi et al.[10]	19/53	27/327	6.21 (3.13–12.33)	7.92
Volpon et al.[9]	9/79	2/81	5.08 (1.06–24.30)	6.37
Sanchez-Pinto et al.[7]	246/974	197/7286	12.16 (9.93–14.89)	8.36
Sutherland et al.[8]	157/6347	80/8448	2.65 (2.02–3.48)	8.32
Carmody et al.[14]	26/181	9/274	4.94 (2.26–10.81)	7.78
Bresolin et al.[6]	21/58	3/68	12.3 (3.44–44.02)	6.94
Selewski et al.[13]	5/36	2/60	4.68 (0.86–25.52)	6.11
Sutherland et al.[3]	1579/10,322	15,804/2,633,941	29.92 (28.29–31.64)	8.4
Viswanathan et al.[12]	33/46	10/46	9.14 (3.53–23.63)	7.52
Koralkar et al.[11]	17/41	9/188	14.09 (5.65–35.12)	7.58
Schneider et al.[5]	166/533	52/2863	24.45 (17.58–34.01)	8.28
Total (random effects)	2423/20,837	16,298/2,658,421	8.03 (3.59–17.93)	100

Incidence of kidney replacement therapy

Study	Pediatric patients with AKI	% Proportion (95% CI)	Weight (%) (random)
Jetton et al.[15]	605	4.13 (2.69–6.04)	8.48
Kaddourah et al.[2]	1562	4.67 (3.68–5.84)	8.62
Rustagi et al.[10]	53	18.87 (9.44–31.97)	6.6
Tresa et al.[18]	116	53.45 (43.95–62.76)	7.59
Volpon et al.[9]	77	11.69 (5.49–21.03)	7.13
Carmody et al.[14]	181	0.55 (0.014–3.04)	7.96
Cao et al.[4]	1257	15.12 (13.18–17.22)	8.6
Selewski et al.[13]	36	8.33 (1.75–22.47)	5.94
Sutherland et al.[3]	10,322	8 (7.49–8.54)	8.7
Koralkar et al.[11]	41	0 (0.00–8.60)	6.17
Schneider et al.[5]	339	11.8 (8.57–15.72)	8.29
Vachvanichsanong et al.[17]	318	17.3 (13.30–21.91)	8.27
Olowu et al.[16]	123	53.66 (44.45–62.69)	7.65
Total (random effects)	15,030	13.18 (8.85–18.22)	100

Overall (pooled) estimate was calculated with random-effects model.

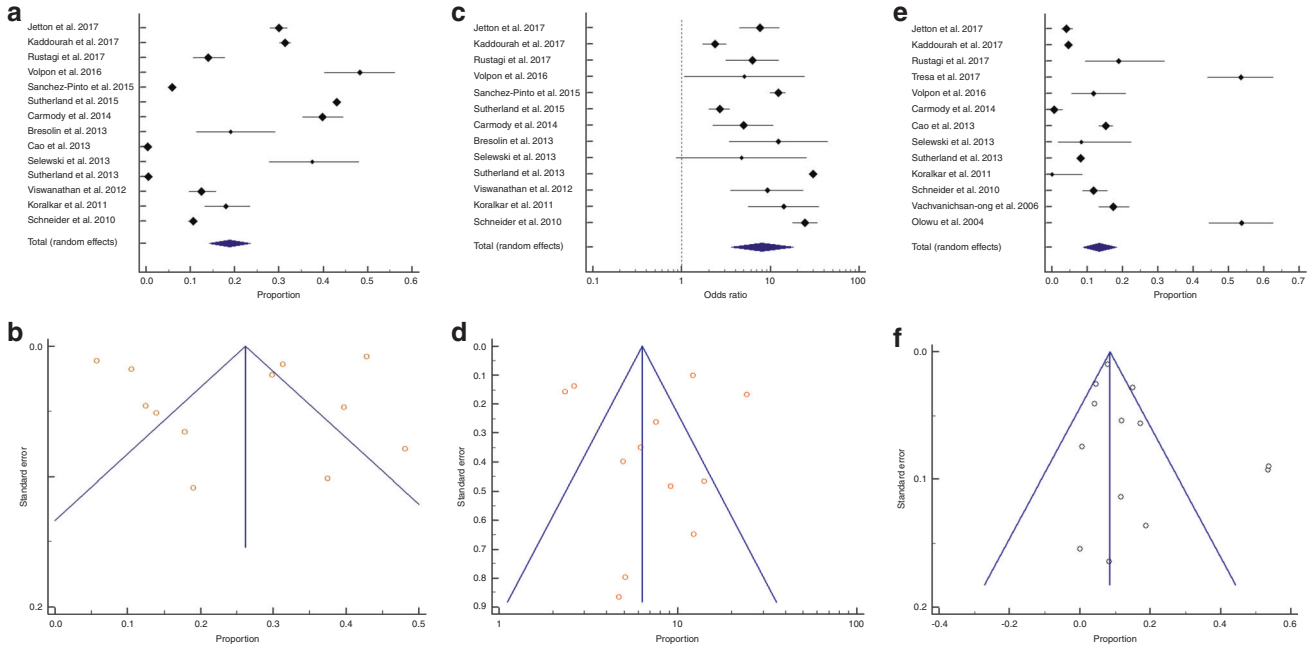


Fig. 1 Meta-analysis of studies regarding AKI epidemiology among pediatric patients. Overall (pooled) estimate was calculated with random-effects model and a test for heterogeneity was applied using the I^2 statistics. Forest plots were used to visualize the outcomes from each study and illustrate the combined estimated outcomes with 95% confidence intervals. The lower diamond in the graph represents the pooled estimate. Publication bias was assessed graphically using funnel plots. A p value ≤ 0.05 was considered for statistical significance. **a** Forest plot of AKI incidence in different studies. **b** Funnel plot for studies reporting AKI incidence. **c** Forest plot for mortality among patients with or without AKI in different studies. **d** Funnel plot for studies reporting mortality among pediatric patients. **e** Forest plot of KRT incidence in AKI patients among different studies. **f** Funnel plots for studies reporting incidence of KRT.

842C, showed a stronger association with AKI. Similarly, APO-E ε4 has been shown to provide protection against postoperative AKI in patients undergoing cardiac surgery.[36] Chew et al.[36] reported reduced peak serum creatinine (SCr), especially with the APO-E ε4 in comparison to APO-E ε2 and APO-E ε3 alleles. However, there is currently limited evidence regarding these genetic candidates and the results of currently ongoing studies are awaited to find conclusive evidence.

Biomarkers

Biomarkers are crucial tools for the diagnosis of a patient and elevation in levels has shown association with mortality, increased length of stay in ICU, and need for KRT.[37] Currently, SCr and urine output (UO) are the most common AKI biomarkers.[37–39] However, both have significant limitations in children and can lead to misleading conclusions. SCr is only detectable hours or days after kidney injury and can be influenced by total muscle mass, fluid balance, and medications, while UO can be affected by the hydration status and use of diuretics.[40,41] Thus, the focus has shifted on the discovery of novel biomarkers (Fig. 4). Currently, the main urinary and serum AKI biomarkers include neutrophil gelatinase-associated lipocalin (NGAL), cystatin C (Cys-C), kidney injury molecule-1 (KIM-1), IL-18, liver-type fatty acid-binding protein (L-FABP), and TIMP-2/IGFBP-7 (tissue inhibitor of metallo-proteinase-2/insulin-like growth factor-binding protein 7) (Table 4).[40–45] NGAL has been studied most extensively and shown to be the superior biomarker as it is protease-resistant, can be rapidly analyzed, and is sensitive (83%) and specific (89%) to tubular injury.[41] In addition, a recent study by Krawczeski et al.[46] of children undergoing cardiac surgery reported that urine NGAL levels increased within 2 h, IL-18 and L-FAB levels were elevated within 6 h, and KIM-1 within 12 h. Lastly, TIMP-2/IGFBP-7 (NephroCheck®) has recently been identified as a novel biomarker to predict AKI and renal recovery. A study of 50 patients at high risk for AKI reported an area under the receiver-operating characteristic curve (AUC) of 0.84 (sensitivity: 92% and specificity: 81%).[45] In addition, this study suggests that the use of multiple biomarkers may be more useful in the diagnosis of AKI. Various new biomarkers based on animal studies are illustrated in Fig. 4.

Changing definitions of AKI

Various advancements in standardized definitions of AKI have been vital for our increased understanding of AKI epidemiology (Fig. 5). The first staged definition was the RIFLE criteria created by the Acute Dialysis Quality Initiative group, which defined AKI based on both SCr and UO.[47] Modifications to this definition were made to include various patient populations. The first modification was by the AKI Network (AKIN), where the definition was expanded to include patients with a ≥0.3 mg/increase in Sc within 48 h.[48] In addition, a pediatric modification was made to the adult RIFLE criteria to create the pediatric RIFLE (pRIFLE) criteria.[49] This definition utilized the change in estimated creatinine clearance rather than SCr, as SCr can be inaccurate due to childhood growth and development.[49] Furthermore, the KDIGO in 2012 standardized the RIFLE, AKIN, and pRIFLE definitions to create the KDIGO classification system.[50] This definition is applicable for both adult and pediatric populations and provides a unified definition. Lastly, Xu et al.[51] developed a creatinine-based AKI diagnostic tool known as the pediatric reference change value optimized criterion (pROCK) for AKI in children. This new criteria allow for the consideration of individuals with low and highly variable SCr levels. It defined pediatric AKI as a SCr increase of 20 µmol/L (0.23 µg/dL) and a 30% increase over baseline; AKI stage 2 as a SCr increase of 40 µmol/L and a 60% increase over baseline and AKI stage 3 as a SCr increase of 80 µmol/L and a 120% increase over baseline.[51] pROCK may be useful in preventing overdiagnosis of AKI stage 1, as it considers the normal SCr variability that may be

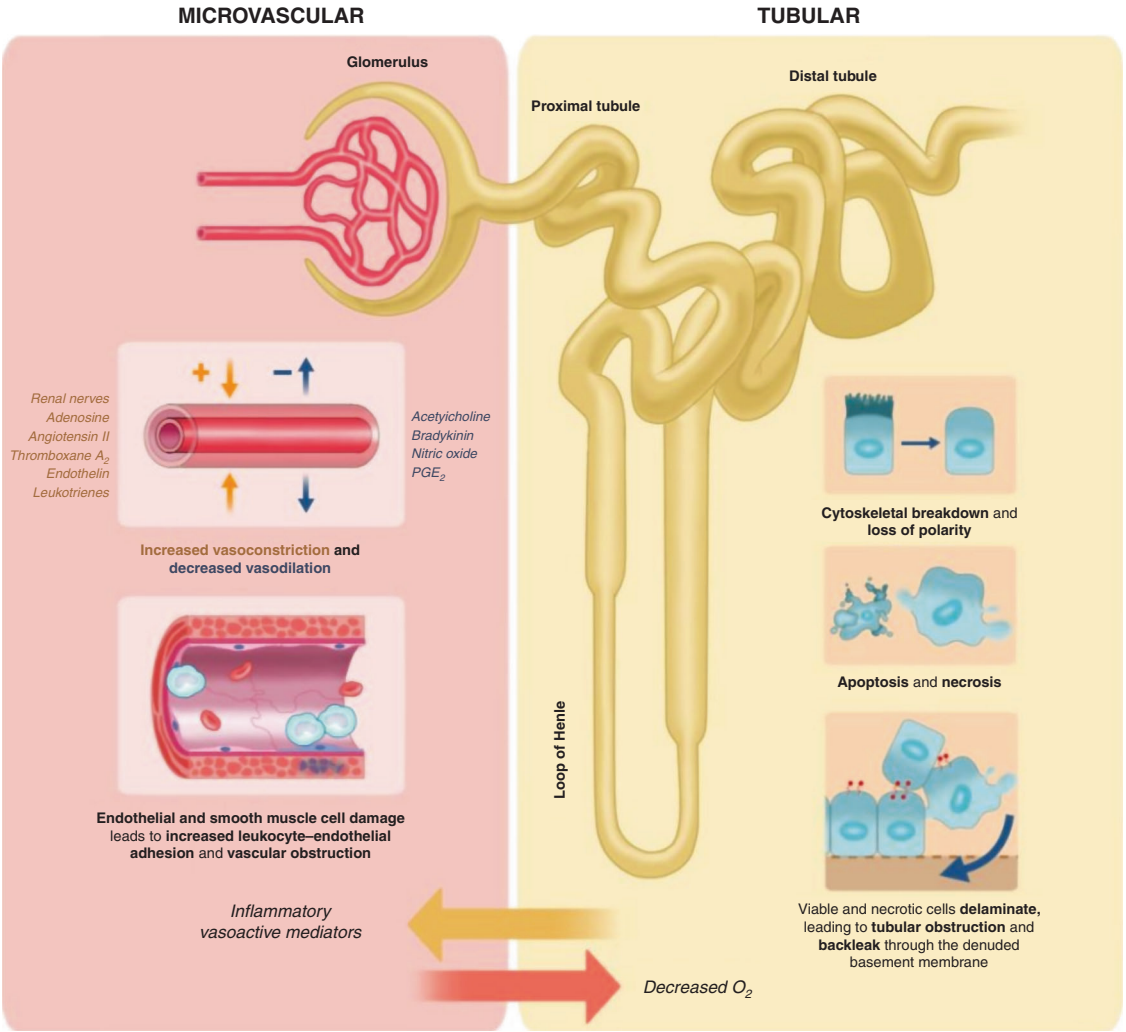


Fig. 2 Pathophysiology of acute kidney injury. The pathophysiology can be classified into the microvascular and tubular aspect. In the microvascular aspect, there is an increase in vasoconstriction, reduction in vasodilation, vascular smooth muscle and endothelial damage, and elevation in leukocyte–endothelial adhesion. Tubular injury leads to cytoskeletal breakdown and loss of polarity that progresses to apoptosis and necrosis. This process results in inflammatory mediators, which cause a positive feedback mechanism where reduced oxygen delivery to the tubules causes the activation of the microvascular mechanisms. O_2 oxygen, PGE_2 prostaglandin.

flagged as AKI by the KDIGO/pRIFLE criteria (5.3% vs. 10.2/15.2%, respectively).[51] These results indicate that utilization of the pROCK criteria may be the best choice for children. Overall, each classification system comes with its own set of risks and benefits, with potential for excessive use of tests and misdiagnosis, and thus should be used based on each unique situation.

Evolving tools for AKI diagnosis

Within the past few years, there have been advancements in predictive and preventive tools for AKI. The Renal Angina Index (RAI) was proposed for the prediction of critically ill patients at high risk of developing severe AKI and was validated in 2014 as a functional risk stratification tool.[52] This model combines the markers of kidney dysfunction and patient characteristics to determine RAI. Various studies have reported that an RAI of ≥8 within the first 12 h of admission has very high sensitivity and negative predictive value for AKI development.[52–54] This model also provides context to biomarker measurement and significantly improves AKI prediction, parallel to the cardiac angina–troponin relationship.[52–54] In addition, an RAI > 8 was shown to be associated with an increased need for KRT, prolonged mechanical ventilation, and a higher risk of mortality when compared to children with an RAI < 8.[52] Overall, RAI is a great tool to differentiate patients at risk for severe AKI.

A different and often utilized tool is the renal functional reserve (RFR) test, which evaluates the difference between maximum glomerular filtration rate (max GFR) of the kidney and baseline GFR and is known as the RFR-glomerular (RFR-G).[55] This tool measures the capacity of the kidney to elevate GFR following certain stimulations such as acute protein load (1–1.2 g/kg) with normal patients displaying a significant increase after 1–2 h.[55,56] In a study by Husain-Syed et al.[57] ($n = 110$), preoperative RFR predicted the development of AKI (AUC: 0.83). Patients with AKI had a lower RFR value (15.57 ml/min)in comparison to those without (27.067 ml/min). In addition, in patients with preoperative RFR < 15 ml/min/1.73 m^2, the risk of AKI development increased by 11.8-fold ($p < 0.001$).[57] Overall, RFR testing can identify individuals at risk for AKI development; however, larger prospective studies are essential for validation.

Similar to RFR, the furosemide stress test (FST) uses an intravenous administration of furosemide (1.0–1.5 mg/kg) to identify patients at risk of progression to stage 3 AKI. Furosemide is utilized to induce an increase in UO, which allows for the assessment of tubular function.[58] In a study by Chawla et al.,[59]

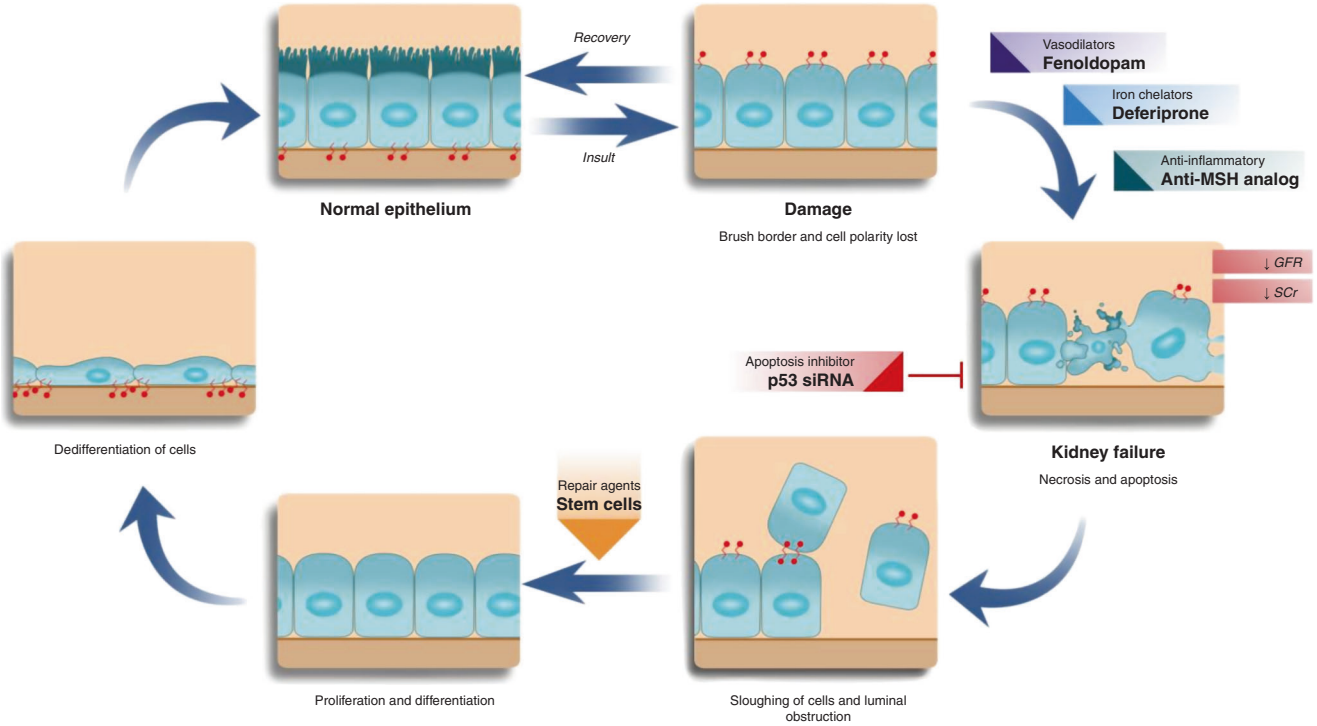


Fig. 3 AKI morphology and emerging pharmacotherapies. Newer and more advanced pharmacotherapies have emerged that can directly target the pathophysiology of acute kidney injury. GFR glomerular filtration rate, MSH melanocyte-stimulating hormone, p53 tumor protein, SCr serum creatinine.

Table 3. Emerging therapeutics for AKI.

Treatment	Biological role	Intended effect	Current efficacy/adverse effects
P53-siRNA[86,87]	Apoptosis inhibitor via inhibition of p53	Lower serum creatinine levels and rate of necrosis	Animal studies have shown promising beneficial results; however, inhibition of p53 can result in excessive proliferation-mutated cells
Deferiprone (iron chelator)[88]	Iron chelator; inhibits the production of reactive oxidant species and lower excess levels of iron	Aids in treatment of thalassemia patients and prevention of AKI development and progression	Promising animal studies but human trials have been found to cause neutropenia, agranulocytosis, hypotension, and progressive hepatic fibrosis
α-MSH analog[89,90]	Anti-inflammatory and antiapoptotic cytokine; decreases pro-inflammatory cytokines (TNF-α, IL-10), neutrophil adhesion molecules, and nitric oxide production	Protection from AKI due to ischemia–reperfusion, nephrotoxins, and sepsis causes	α-MSH analog treatment did not lower AKI incidence using AKIN criteria, influence the elevations of novel biomarkers, or change 90-day outcomes in patients after cardiac surgery. Further studies are needed
MSCs[91]	Multipotent stem cells found in bone marrow that are important for making and repairing skeletal tissues, such as cartilage, bone, and the fat found in bone marrow	Ameliorates damage done AKI by exerting paracrine renoprotective effects and by stimulating tissue repair. Both angiogenic and antiapoptotic	MSC capacity to treat AKI demonstrated very positive results, with patients requiring a shorter hospital stay, decreased chance of readmission, and prevention of further renal damage. Ethical issues can arise from the collection of cell, either through invasive bone marrow removal or through fetal membrane
ALP[92,93]	A ubiquitous membrane-bound glycoprotein that catalyzes the hydrolysis of proteins	Dephosphorylation of endotoxins and pro-inflammatory ATP	ALP treatment increased endogenous creatine clearance and favorably modulated the immune response by reducing systemic and urinary markers (C-reactive protein, IL-6, KIM-1, and IL-18)

α-MSH alpha-melanocyte-stimulating hormone, *MSCs* mesenchymal stem cells, *ALP* alkaline phosphatase, *AKI* acute kidney injury, *AKIN* acute kidney injury network, *ATP* adenosine triphosphate, *IL* interleukin, *KIM-1* kidney injury molecule-1, *TNF-α* tumor necrosis factor-alpha.

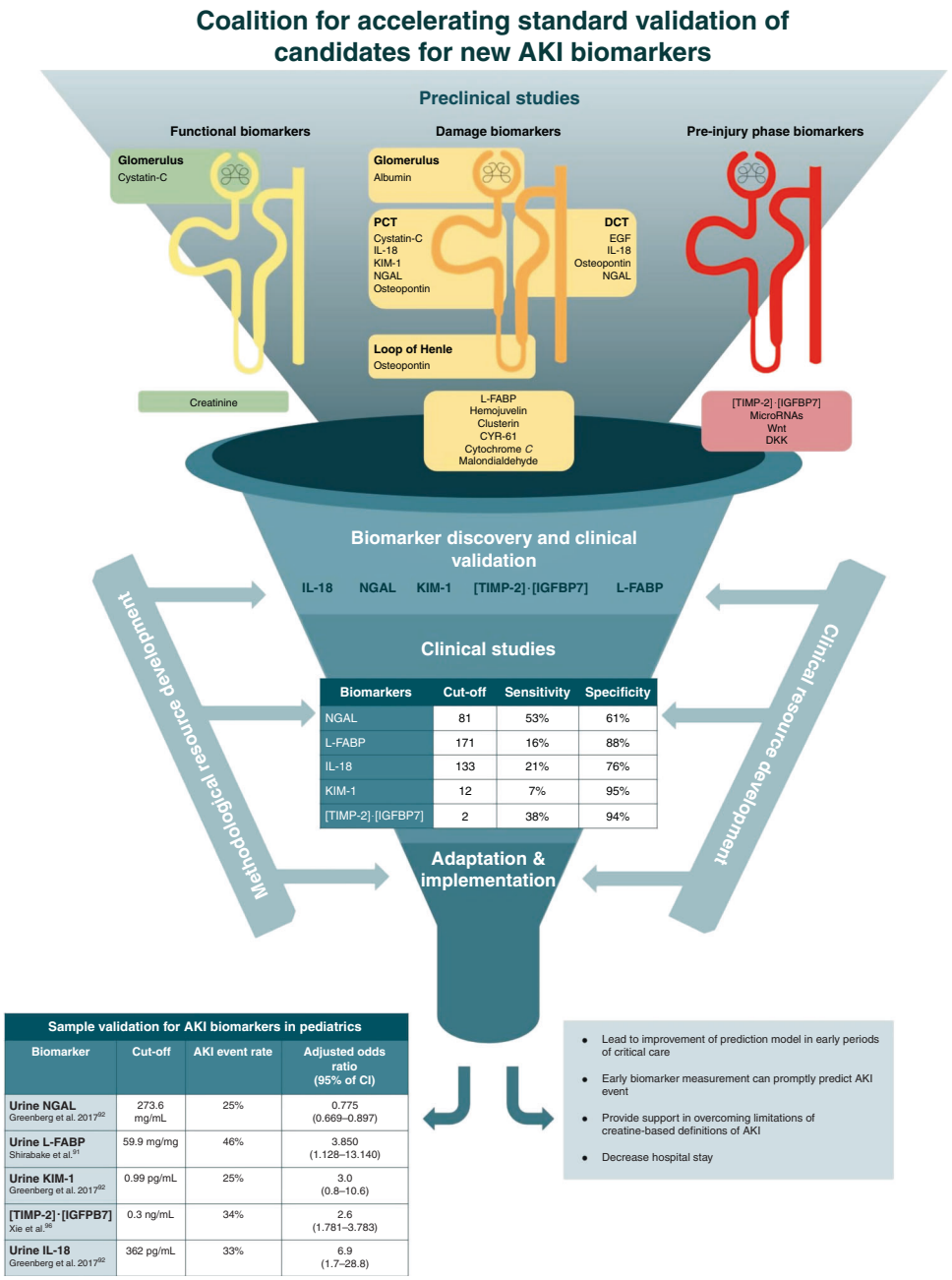


Fig. 4 The process of AKI biomarker discovery and validation. DT distal tubule, IGFBP-7 insulin-like growth factor-binding protein 7, IL interleukin, KIM-1 kidney injury molecule-1, L-FABP liver-type fatty acid-binding protein, NGAL neutrophil gelatinase-associated lipocalin, PT proximal tubule, TIMP-2 tissue inhibitor of metalloproteinases-2.

critically ill patients with KDIGO stage I/stage II AKI were subjected to FST and showed that the 2-h UO effectively predicted progression to stage III AKI within 14 days (AUC: 0.87) with sensitivity and specificity of 87.1 and 84.1%, respectively. In a different study by Kakajiwala et al.,[60] infants undergoing cardiac surgery were retrospectively analyzed after an FST and the resulting decrease in UO predicted AKI within 2 and 6 h with AUC of 0.74 and 0.77, respectively. Overall, FST has shown to be a simple tool and crucial predictor of individuals with high risk of severe AKI.

Management of AKI

The management of pediatric AKI should treat the underlying cause of AKI and focus on preserving tissue perfusion, increased therapeutic monitoring, minimization of nephrotoxic medications (Nephrotoxic Injury Negated by Just-in-time Action), and prevention of other complications.[61] Non-dialytic management of AKI via fluid therapy has shown to be effective in the management of pediatric AKI. Initial management with isotonic crystalloids (instead of colloids such as albumin) is common for volume depletion and has been recommended by the KDIGO guidelines.[61,62] In addition, the Crystalloid vs. Hydroxyethyl Starch Trial (CHEST) reported a higher risk of AKI or requirement for KRT in patients receiving colloids (hydroxyethyl starch) in comparison to crystalloids.[62] However, bolus fluids may be harmful in certain patients. For example, the Fluid Expansion as Supportive Therapy study reported that administration of saline/albumin led to increased mortality in African children with severe sepsis in

Table 4. Novel biomarkers for AKI.

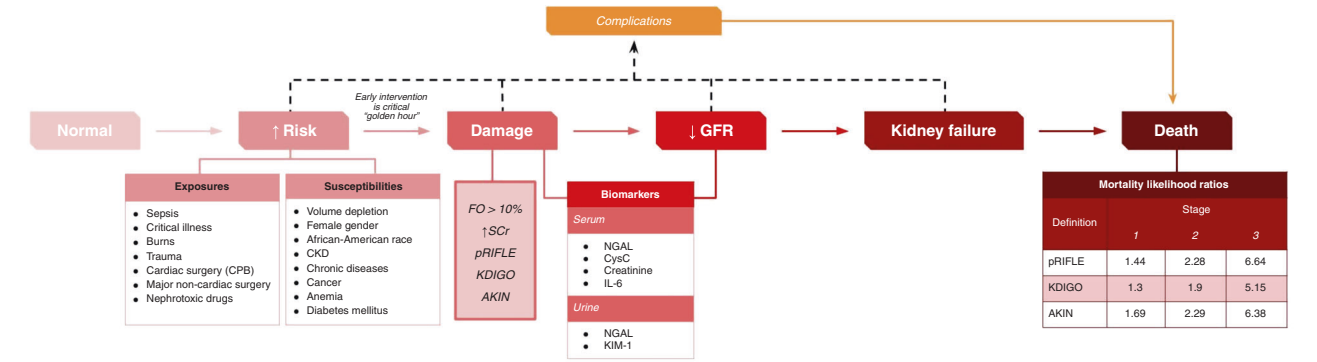
Biomarker	Type	Description/function	AUC-ROC	Specificity (%)	Sensitivity (%)
NGAL	Serum or urine	A 25-kDa protein released from injured kidney epithelial cells; chelates iron complexes released from damaged tubules, prevents the formation of hydroxy radicals, and upregulates hemeoxygenase-1	0.93	89	83
Cys-C	Urine or serum	A 13-kDa protein (cysteine protein inhibitor) created in all nucleated cells; high levels indicate renal inefficiency and urinary marker exhibits urinary dysfunction	0.85	83	78
IL-18	Urine	A pro-inflammatory cytokine excreted by the proximal tubule following injury; helps control the induction of the acute-phase response and mediates immunoglobulin class switching	0.70	75	58
L-FABP	Serum and urine	A 14 kDa protein that binds long-chain fatty acids; suppresses tubule-interstitial damage	0.93	90	83
KIM-1	Urine	A type-1 membrane glycoprotein excreted from the proximal tubule cells following injury; activates immune cells, promotes apoptotic and necrotic cell clearance, and remodeling of injured epithelia	0.86	86	74
[TIMP-2]* [IGFBP-7]	Urine	A 21- and 29-kDa protein; TIMP-2 stimulates p27 expression while IGFBP-7 increases the expression of p53 and p21 and blocks cyclin-dependent protein kinase complexes on cell cycle promotion	0.84	81	92

AUR-ROC area under, *Cys-C* cystatin C, *IL-18* interleukin-18, *L-FABP* liver-type fatty acid-binding protein, *KIM-1* kidney injury molecule-1.
An asterisk symbol suggests the combination of the two markers.

comparison to patients with no boluses ($P = 0.003$).[63] Moreover, the administration of adenosine receptor antagonists (ARAs), such as theophylline, have been suggested for asphyxia neonates, who are at a high risk of AKI.[64,65] The use of ARAs can reduce feedback-mediated vasoconstriction, increase renal blood flow, and restore GFR in AKI patients.[65] Vasopressor therapy has also shown benefits in hypotensive vasodilated patient with AKI as it can improve renal perfusion and function; however, this still remains the subject of debate.[66] In addition, nutritional support is crucial for the management of AKI as up to 42% of patients with AKI are malnourished and inadequate nutrition may lead to increased urea, nitrogen, and azotemia production.[67] Adequate calorie intake (20–30 kcal/kg/day) via the enteral route without increasing fluid volumes has been recommended by the KDIGO guidelines.[62] Lastly, furosemide as a potential treatment has shown to be beneficial in maintaining fluid balance by improving UO and reducing the severity of hyperkalemia, acidosis, and FO in AKI patients.[68] In the management of septic AKI, fluid resuscitation avoiding FO, terlipressin, hydrocortisone, and intensive insulin therapy may be helpful but further studies are required.

For instances of AKI where non-dialytic management is suboptimal, dialytic strategies, such as PD, HD, CKRT, and sustained low efficiency dialysis (SLED), may be required. The various advances in utilization of current KRT modalities, development of novel KRT machines for infants, and measures to protect pulmonary and cardiac organ systems have led to better outcomes.[69] Modifications to PD including biocompatible solutions (neutral pH, low glucose degradation product solutions), and improved ultrafiltration methods (such as high-volume PD, tidal PD, and continuous flow PD) have improved patient outcomes.[70] The introduction of high flow CKRT has shown increased clearance of metabolic waste products (i.e., leucine), leading to survival benefit in hemodynamically unstable patients.[71] Increased awareness of the association between FO and adverse outcomes has led to earlier initiation of CKRT to alleviate the onset and severity of AKI. In a retrospective cohort study, Modem et al.[72] reported that the earlier initiation (≤5 days) of CKRT was associated with lower mortality than late initiators (>5 days) with a hazard ratio of 1.56. In addition, advancements in membrane adsorbers, such as CytoSorb (CytoSorbents Corporation, NJ), and oXiris (Baxter, IL), have shown clinical improvements in some studies. The CytoSorb device is a single-use device with adsorbent polystyrene divinylbenzene polymer beads specifically designed to remove cytokines from the blood via hydrophobic interactions.[73,74] In a study by Zuccari et al.,[74] septic patients undergoing KRT with CytoSorb showed reduction in IL-8 but not of other cytokines. Similarly, the oXiris filter set consists of an AN69 membrane coated with polyethyleneimine and unfractionated heparin to adsorb endotoxins and cytokines.[75] In a retrospective study, the use of oXiris via CKRT for management of septic AKI showed a greater reduction in Sequential Organ Failure Assessment scores after 48 h in comparison to controls (37% vs. 3%).[75] Although these results show possible benefits, more studies are needed for further justification.

Various advancements have also been made with hybrid modalities. The use of sustained low-efficiency daily dialysis-filtration (SLEDD-f) has recently shown to optimize clearance of small solutes with higher blood and dialysate flow along with increased convective clearance and lesser requirements for anticoagulation.[76] SLEDD-F can be performed in underweight patients requiring inotropic support and its low cost and relative ease of use show promise to be a standardized treatment in low-income areas.[76] Furthermore, the development of a new generation of dialyzers that utilize both convection and diffusion, and can produce ultrapure fluids during dialysis, have led to greater clearance rates. Currently, machines such as the HF20™ CKRT circuit (Baxter Healthcare, McGaw Park, IL), CARPEDIEM™ (Cardio-renal Pediatric Emergency Machine; Medtronic Inc., Mirandola,



pRIFLE

Category	SCr	Δ UO
Risk (R)	↓ by 25%	<0.5 mL/kg/h (8 h)
Injury (I)	↓ by 50%	<0.5 mL/kg/h (16 h)
Failure (F)	↓ by 75% OR 35 mL/min/1.73 m^2	<0.3 mL/kg/h (24 h) OR anuric (12 h)
Loss (L)	Loss of renal function >4 weeks	
End stage	End stage renal disease >3 months	

KDIGO

AKI stage	SCr	Δ UO
1	1.5–1.9 × baseline OR > 0.3 mg/dL increase	<0.5 mL/kg/h for 6–12 h
2	2.0–2.9 × baseline	<0.5 mL/kg/h for ≥ 12 h
3	3.0 × baseline OR ↑ SCr > 4.0 mg/DL OR initiation of RRT OR ↓ GFR < 35 mL/min/1.73 m^2	<0.3 mL/kg/h for ≥ 24 h OR anuria for ≥ 12 h

AKIN

AKI stage	SCr	Δ UO
1	↑ 0.3 mg/dL OR 150–200% × baseline increase	<0.5 mL/kg/h for 6 h
2	200–300% × baseline increase	<0.5 mL/kg/h for 12 h
3	≥300% × baseline increase OR SCr ≥4 mg/dL (with acute rise of ≥0.5 mg/dL)	<0.3 mL/kg/h for ≥ 24 h OR anuria for ≥ 12 h

pROCK

AKI stage	SCr
1	↑ ≥20 µmol/ L and ≥30% increase
2	↑ ≥40 µmol/ L and ≥60% increase
3	↑ ≥80 µmol/ L and ≥1200% increase

Fig. 5 Clinical continuum of AKI. AKI acute kidney injury, AKIN acute kidney injury network, CPB cardiopulmonary bypass, FO fluid overload, GFR glomerular filtration rate, SCr serum creatinine, UO urine output.

Italy), NIDUS (Newcastle Infant Dialysis and Ultrafiltration system), and Aquadex™ (Baxter Corporation, Minneapolis, MN) allow for both acute and chronic KRT in small infants.[77–81] These new machines utilize slow motion pumps, highly sensitive scales, and miniaturized tubing and filtration systems (extracorporeal volume <20 mL) to provide effective KRT with minimal complications.[77–81] In addition, the Selective Cytopheretic Device (Seastar Inc., San Diego, CA), which is utilized in combination with CKRT, has shown improved outcomes in adult AKI patients and is currently being evaluated in the pediatric cohort (NCT02820350, R01FD005092).[81] Overall, these various advancements in extracorporeal therapies have led to beneficial outcomes, although additional studies are needed within the pediatric population. The ultimate choice of KRT modality should be based on the availability of resources, expertise and preference of the physician, and the relative cost of the modality.

CONCLUSION

Diagnosis and management of AKI have been quite challenging in the pediatric population.[82–84] However, the introduction of new standardized definitions, advancements in diagnostic tools and KRT modalities, and the development of novel extracorporeal therapies have led to increased survival benefits in children with AKI.

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R.R., R.C., S.K.S. and T.B. contributed to the conception and design of this review. R.R., R.C., S.K.S., A.T. and T.B. were involved in the data analysis and interpretation of the data and R.R., R.C., S.K.S. and T.B. drafted the article and revised it critically for important intellectual content. All authors have approved the final version of this manuscript.

ADDITIONAL INFORMATION

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