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From acute kidney injury to chronic kidney disease in children: maladaptive repair and the need for long-term surveillance - a literature review

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Abstract

Pediatric Acute Kidney Injury (AKI) is an increasingly prevalent global health concern that extends far beyond a transient clinical event, posing a significant risk for long-term kidney dysfunction. This review consolidates current knowledge on the pathophysiological transition from pediatric AKI to Chronic Kidney Disease (CKD), critically evaluating the mechanisms of maladaptive repair, the utility of biomarkers, and the state of long-term surveillance strategies. The progression to CKD is driven by maladaptive repair, a process where the kidney's healing mechanisms become dysregulated following a severe or prolonged insult. This pathological cascade involves persistent inflammation, endothelial dysfunction, tubular epithelial cell cycle arrest, and the activation of myofibroblasts, culminating in irreversible interstitial fibrosis and nephron loss. The kidneys of preterm infants and neonates are particularly vulnerable; preterm infants may have incomplete nephrogenesis, leading to a reduced nephron endowment, while neonates exhibit functional immaturity. An AKI during these critical early periods can have a disproportionately large impact, amplifying the lifetime risk for hypertension and accelerated CKD. Evidence confirms that pediatric AKI survivors face a substantially increased risk of incident CKD, hypertension, and proteinuria, even when serum creatinine levels return to baseline. Current diagnostic tools, reliant on creatinine, are insensitive and lag behind the actual injury, hindering timely intervention. While novel biomarkers show promise for early AKI detection, their ability to predict the transition to CKD remains an area of active investigation. Major conclusions from this review highlight that pediatric AKI must be reframed as a sentinel event that necessitates a long-term approach to kidney health. However, care is often fragmented, a challenge compounded by a lack of pediatric-specific, evidence-based follow-up guidelines. Future progress depends on dedicated research into the unique aspects of maladaptive repair in developing kidneys, the validation of predictive biomarkers, and the development of targeted, age-appropriate therapies.

Clinical trial number

Not applicable.

Keywords Pediatrics, AKI, CKD, Fibrosis, Biomarkers, Surveillance

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Background

Pediatric Acute Kidney Injury (AKI) is a global health concern with significant morbidity and mortality [1]. Beyond its immediate impact, AKI is now recognized as a potent catalyst for long-term kidney dysfunction, fundamentally shifting the clinical paradigm [1]. It is no longer viewed as a transient event but as an injury capable of inflicting permanent nephron loss, thereby initiating a potential progression toward Chronic Kidney Disease (CKD) [2].

This process is especially concerning in the context of the developing kidney. Preterm infants are born with structural immaturity, as nephrogenesis may be incomplete, leading to a lifelong deficit in nephron number [3]. Neonates exhibit functional immaturity, with ongoing renal maturation in the early postnatal period. An acute insult during these specific windows of vulnerability can easily lead to maladaptive repair, with lifelong consequences.

The escalating incidence of pediatric AKI is not merely an artifact of enhanced surveillance. Improved survival rates for children with complex congenital and acquired diseases have, paradoxically, expanded the population at risk for AKI due to exposure to aggressive, yet necessary, therapies such as major cardiac surgeries and nephrotoxic medications [1]. This expanding cohort of vulnerable young survivors amplifies the AKI burden, demanding a strategic pivot from reactive treatment to proactive prevention and meticulous management.

At the heart of the ominous transition from AKI to CKD lies the concept of "maladaptive repair"—a process where the kidney's inherent healing mechanisms go awry, fostering scarring and a relentless erosion of function instead of restoring normal architecture [4]. When maladaptive repair processes—such as persistent inflammation and unchecked fibrosis—are superimposed upon this developing organ, the consequences can be profound, consuming a proportionally larger segment of the functional renal parenchyma and charting a course for an accelerated decline in kidney function over a lifetime.

This review dissects the intricate pathophysiology fueling the AKI-to-CKD transition in children. We will critically analyze the molecular and cellular mechanisms of maladaptive renal repair, evaluate the current landscape of biomarkers for early detection and prognostication, and scrutinize prevailing long-term surveillance strategies. By identifying crucial knowledge gaps and charting future research directions, we aim to galvanize a deeper, more nuanced understanding of this critical issue and inspire concerted efforts to safeguard the long-term outcomes for these vulnerable young patients.

The evolving landscape of pediatric acute kidney injury

A startling scale and a critical blind spot

The sheer scale of pediatric AKI is startling. In high-risk settings, such as following cardiac surgery, its incidence can affect 30–50% of infants and children [1]. Within pediatric intensive care units (PICUs), it affects approximately 10–35% of young patients [1]. The landmark Assessment of Worldwide Acute Kidney Injury, Renal Angina and Epidemiology (AWARE) study, a global snapshot of 4,683 critically ill children, found that 26.9% developed AKI within one week of ICU admission, with severe injury (KDIGO Stage 2 or 3) directly linked to a stepwise escalation in mortality [1]. The challenge begins at birth. The Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates (AWAKEN) study documented AKI in 30% of newborns, with the most vulnerable—those born before 29 weeks' gestation—experiencing a staggering incidence of 47.9% [5]. Even among general hospital admissions, AKI is estimated to occur in 1–7% of children [6].

Yet, a gap often exists between this research data and clinical practice. When an AKI episode goes unrecognized, the critical window for intervention closes, increasing the odds of maladaptive repair and progression to CKD [7]. A radical improvement in recognition is needed, driven by provider education and systemic safeguards like electronic alerts.

Shifting etiologies and a window for prevention

The etiological landscape of pediatric AKI is diverse. In developing countries, community-acquired insults such as severe dehydration from gastroenteritis, overwhelming sepsis, and hemolytic uremic syndrome (HUS) remain predominant causes [1]. In developed nations, while these conditions are still significant contributors, there has been a shift toward a greater proportion of hospital-acquired AKI [1]. Common causes in all settings include sepsis from infections like pneumonia or bronchiolitis, and severe dehydration [8–10].

A substantial portion of hospital-acquired cases are iatrogenic or, at the very least, predictable. Key contributors include complications of critical illness, major surgeries (particularly cardiac procedures), and exposure to a wide range of nephrotoxic medications [1]. This predictability presents a profound opportunity. Initiatives like the Nephrotoxic Injury Negated by Just-in-time Action (NINJA) program have successfully reduced medication-associated AKI [11]. This foresight permits robust risk stratification and the deployment of preemptive countermeasures: aggressive hydration, scrupulous dosing of nephrotoxins, and intensified monitoring. A comprehensive classification of etiologies is in Table 1.

Table 1 Common etiologies of pediatric AKI

Category	Sub-Category	Specific Examples
Pre-renal Injury	Decreased True Intravascular Volume	Dehydration (vomiting, diarrhea), hemorrhage, burns, poor fluid intake [6]
	Decreased Effective Intravascular Volume	Sepsis, shock, heart failure (cardiorenal syndrome), nephrotic syndrome, liver disease (hepatorenal syndrome), capillary leak [3]
Intrinsic Renal Disease	Acute Tubular Necrosis (ATN)	Hypoxic/ischemic insults (e.g., prolonged shock, asphyxia, cardiac arrest), sepsis-associated ATN [3]
	Nephrotoxin-Induced ATN	*Drugs*: Aminoglycosides, amphotericin B, cisplatin, ifosfamide, NSAIDs, ACE inhibitors, ARBs, vancomycin, acyclovir, contrast media [1]
		Endogenous Toxins: Hemoglobin (hemolysis), myoglobin (rhabdomyolysis), uric acid (tumor lysis syndrome), light chains [3]
		Exogenous Toxins: Ethylene glycol, methanol, heavy metals [3]
	Glomerulonephritis	Post-streptococcal glomerulonephritis, IgA nephropathy, lupus nephritis, ANCA-associated vasculitis, anti-GBM disease (Rapidly Progressive GN) [3]
	Acute Interstitial Nephritis (AIN)	*Drug-induced*: Penicillins, cephalosporins, sulfonamides, NSAIDs, proton pump inhibitors, rifampin [3]
		Infection-related: Bacterial, viral, fungal [3]
		Idiopathic/Systemic Disease: Sarcoidosis, TINU syndrome [3]
	Vascular Lesions	Renal artery thrombosis/stenosis, renal vein thrombosis, HUS, thrombotic thrombocytopenic purpura (TTP), cortical necrosis, vasculitis [3]
	Other Intrinsic	Hypoplasia/dysplasia with or without obstructive uropathy, exposure to nephrotoxic drugs *in utero* [6]
Post-renal (Obstructive Uropathy)	Upper Urinary Tract Obstruction	Bilateral ureteral obstruction (e.g., stones, clots, tumors, retroperitoneal fibrosis), obstruction in a solitary kidney, ureteropelvic junction obstruction [3]
	Lower Urinary Tract Obstruction	Posterior urethral valves, urethral stricture, neurogenic bladder, bladder outlet obstruction (e.g., stones, tumors) [3]

The Double-Edged sword of standardized definitions

The effort to standardize the definition of AKI was a watershed moment for the field of pediatric nephrology, rescuing it from an era of over 35 different definitions [1]. The evolution from pediatric RIFLE (pRIFLE) to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria has brought much-needed order, defining AKI via changes in serum creatinine (SCr) and urine output (UO) [1, 12, 13].

Despite this progress, debate rages over the limitations of these definitions (Table 2). The reliance on SCr is a primary contention. SCr is a flawed, lagging indicator influenced by non-renal factors like age, muscle mass, and hydration, making its interpretation in children complex [1]. It often remains normal until up to 50% of glomerular filtration is lost [1]. The very concept of a "baseline" SCr is frequently an illusion in acutely ill children with no recent measurements [1]. This is further complicated in conditions like diabetic ketoacidosis, where acetoacetate can interfere with certain creatinine assays, leading to falsely elevated levels [14]. In such cases, estimating baseline SCr using validated height-based equations is a commonly employed and recommended strategy, including in specific scenarios like T1DM onset [15–17]. These challenges are magnified in neonates, whose SCr initially reflects their mother's. UO, while an earlier signal, is easily confounded by fluid management and diuretic use [18]. This fundamental dissatisfaction with our current diagnostic toolkit is the principal engine driving the intensive search for novel biomarkers to detect injury earlier and more accurately.

The enduring scar: evidence, risks, and consequences

From acute insult to chronic impairment

The connection between pediatric AKI and subsequent CKD is now an incontrovertible link [2]. Even a single episode of mild AKI can double the long-term risk of CKD [19]. Children who survive an episode of AKI, even those not requiring acute kidney replacement therapy (KRT), face a significantly higher risk of long-term major adverse kidney events (MAKE) [20]. One large study found that over a median of 10 years, AKI survivors faced a 7.9-fold increased hazard of developing incident CKD compared to matched hospitalized children without AKI [21]. This evidence demolishes the misconception of pediatric AKI as a uniformly recoverable condition.

The adverse legacy of pediatric AKI extends beyond a formal CKD diagnosis to include hypertension and proteinuria (Table 3). Survivors have a 2.3-fold greater risk of developing hypertension, a potent accelerant of kidney disease progression [21]. The presence of proteinuria post-AKI is a powerful harbinger of future decline [22]. Furthermore, a child who survives one AKI episode has a 3.7-fold higher risk of subsequent AKI episodes, suggesting that even when SCr normalizes, the kidney is left with a scar of subclinical damage that erodes its functional reserve [21]. This grim cycle underscores

Table 2 Definitions and staging criteria for pediatric AKI and associated controversies

Definition System & Staging	Key Criteria	Key Controversies/Limitations
KDIGO (Kidney Disease: Improving Global Outcomes) [1]	**AKI Definition**: - Increase in SCr by ≥ 0.3 mg/dL (≥ 26.5 µmol/L) within 48 h, OR - Increase in SCr to ≥ 1.5 times baseline (known or presumed within 7d), OR - UO < 0.5 mL/kg/h for ≥ 6 h **Staging**: **Stage 1**: SCr 1.5 – 1.9 x baseline OR ≥ 0.3 mg/dL increase; UO < 0.5 mL/kg/h for 6–12 h **Stage 2**: SCr 2.0 – 2.9 x baseline; UO < 0.5 mL/kg/h for ≥ 12 h **Stage 3**: SCr ≥ 3.0 x baseline OR SCr ≥ 4.0 mg/dL (≥ 353.6 µmol/L) OR initiation of KRT OR (in children < 18y) eGFR < 35 mL/min/1.73m2; UO < 0.3 mL/kg/h for ≥ 24 h OR anuria for ≥ 12 h	- Reliance on SCr (late marker, influenced by muscle mass, age, and hydration). - Difficulty in defining baseline SCr. - UO criteria affected by fluid status/diuretics. - Neonatal application requires modification (e.g., AWAKEN adaptation with SCr ≥ 2.5 mg/dL for Stage 3). - Ongoing debate about revising or discarding the current staging.
pRIFLE (pediatric Risk, Injury, Failure, Loss, End-stage) [1]	Based on % change in estimated creatinine clearance (eCCl) or UO criteria. **Risk**: eCCl decrease by 25%; UO < 0.5 mL/kg/h for 8 h **Injury**: eCCl decrease by 50%; UO < 0.5 mL/kg/h for 16 h **Failure**: eCCl decrease by 75% OR eCCl < 35 mL/min/1.73m2; UO < 0.3 mL/kg/h for 24 h OR anuria for 12 h **Loss**: Persistent Failure > 4 weeks **ESRD**: Persistent Failure > 3 months	- Requires estimation of baseline eCCl (can be problematic). - SCr-based pRIFLE also exists. - Similar SCr limitations as KDIGO.
AKIN (Acute Kidney Injury Network) [1]	Based on absolute or relative SCr increase or UO. **Stage 1**: SCr increase ≥ 0.3 mg/dL OR 1.5 – 2.0 x baseline; UO < 0.5 mL/kg/h for > 6 h **Stage 2**: SCr increase > 2.0 – 3.0 x baseline; UO < 0.5 mL/kg/h for > 12 h **Stage 3**: SCr increase > 3.0 x baseline OR SCr ≥ 4.0 mg/dL with acute rise of ≥ 0.5 mg/dL OR KRT initiation; UO < 0.3 mL/kg/h for > 24 h OR anuria for 12 h	- More restrictive diagnostic timeframe for SCr change (≥ 0.3 mg/dL within 48 h). - Eliminates the need to estimate creatinine clearance but retains SCr limitations.
General Controversies [1]	- Optimal definition for neonates and infants with low muscle mass. - Impact of fluid overload on SCr and UO criteria. - Lack of incorporation of novel kidney damage biomarkers. - Need for definitions that better predict long-term outcomes like CKD.	- Calls to revise KDIGO staging or develop new systems incorporating biomarkers.

that surveillance must not only screen for CKD but also champion strategies to prevent recurrent AKI.

Identifying the vulnerable: risk factors for progression

The trajectory from AKI to CKD is modulated by a confluence of factors.

The nature of the injury The severity (higher KDIGO stage, need for KRT), duration, and frequency of AKI episodes are paramount [12]. The etiology is also critical; insults like severe ischemic ATN or HUS, known for causing extensive structural damage, carry a higher propensity for inducing irreversible fibrosis [3].

The developing host Age at injury is a uniquely critical determinant. Neonates, and especially premature infants, are an exceptionally vulnerable population. While traditionally it was thought that nephrogenesis continues until 34–36 weeks' gestation, recent evidence suggests this process may conclude much earlier, possibly by 40 days after birth, even in preterm infants [23]. An AKI occurring before the completion of nephrogenesis can permanently truncate the number of nephrons, resulting in a lifelong deficit [1]. Low birth weight is an independent risk factor for CKD [24]. Pre-existing conditions like congenital anomalies of the kidney and urinary tract (CAKUT), congenital heart disease, or malignancies also heighten susceptibility [6].

Early warning signs Persistent hypertension or proteinuria after an AKI episode is a significant predictor of future CKD [3, 22].

An insult to a growing organ: the impact of AKI on development

When AKI strikes a developing kidney, it can inflict permanent damage. Arresting nephron formation leads to a reduced nephron count, forcing the remaining nephrons into a state of compensatory hyperfiltration—a well-established driver of progressive glomerulosclerosis [24]. Thus, even a neonatal AKI that appears to resolve clinically can sow the seeds for kidney disease that manifests years or decades later [3].

Furthermore, the process of maladaptive repair unfolds within a growing organ. A volume of fibrotic scar tissue that might be relatively small in an adult kidney could compromise a much larger fraction of the total functional renal mass in an infant, leading to a more significant and

Table 3 Long-Term adverse outcomes following pediatric AKI

Outcome	Reported Risk/Incidence	Key Contributing Factors/Populations
Incident CKD [20]	– 16% in AKI survivors vs. 2% in comparators (HR 7.9) over ~ 10 years (non-KRT AKI) – 13.1% in dialysis-treated AKI survivors over ~ 9.6 years (HR 8.7 vs. comparators) – 28% with eGFR < 90 mL/min/1.73m2 at 6.5 years post-AKI	AKI severity, etiology, age (neonates, prematurity), recurrent AKI
Hypertension [21]	– 17% in AKI survivors vs. 8% in comparators (HR 2.3) over ~ 10 years (non-KRT AKI) – 12.1% in dialysis-treated AKI survivors over ~ 9.6 years (HR 3.35 vs. comparators) - Common in children with post-AKI CKD	AKI itself, development of CKD, and potential endothelial dysfunction
Proteinuria/ Albuminuria [40]	- Subnephrotic proteinuria at discharge/3 months post-AKI significantly associated with CKD at 1 year - Higher urine protein levels indicate an increased risk of CKD progression	Persistent tubular/glomerular damage
Subsequent AKI Episodes [21]	– 6% in AKI survivors vs. 2% in comparators (HR 3.7) during later hospitalizations (non-KRT AKI) – 14.0% in dialysis-treated AKI survivors	Residual kidney damage, reduced renal reserve, "sensitized" kidney
Cardiovascular Disease (CVD) [20]	- Increased risk in adulthood linked to AKI (less defined in children directly, but hypertension is a major CVD risk factor)	Hypertension, CKD development, chronic inflammation, endothelial dysfunction
Long-term KRT (Dialysis/ Transplant) [21]	– 2% in AKI survivors vs. < 1% in comparators (HR 11.7) over ~ 10 years (non-KRT AKI) – 2.6% of dialysis-treated AKI survivors developed kidney failure requiring chronic KRT	Severe initial AKI, progression to ESRD
Mortality [21]	- No significant difference in all-cause mortality for non-KRT AKI survivors in one large study - Increased risk of kidney failure or death (HR 2.96) for dialysis-treated AKI survivors	Severity of initial AKI, comorbidities, progression to ESRD
Impaired Growth [25]	- Lower length and weight z-scores post-AKI, especially in infants	Nutritional disturbances, chronic inflammation, metabolic acidosis, CKD development

earlier decline in function [3]. Beyond the kidney itself, AKI has been linked to impaired somatic growth, with studies showing lower length and weight z-scores in children post-AKI, an effect most pronounced in infants [25].

The biology of a scar: unraveling maladaptive repair

When healing fails: the switch to maladaptive repair

Following an acute insult, the kidney mobilizes a repair program. In an ideal outcome, this adaptive repair is a model of efficiency: cellular debris is cleared, surviving tubular epithelial cells (TECs) dedifferentiate and proliferate to repopulate the damaged scaffolding, and then redifferentiate into a fully functional epithelium, allowing the kidney to heal [4].

When this fragile process is disrupted by an injury that is too severe or prolonged, it veers into maladaptive repair, a pathological cascade of persistent inflammation and fibrosis that culminates in irreversible nephron loss—the definition of CKD [4]. Recent single-nucleus multiomics have revealed that "maladaptive" proximal tubule cells, with an aberrant epigenetic signature, can persist for months post-AKI [4]. This suggests a "cellular memory" of injury, encoded by lasting epigenetic modifications [26] or the presence of senescent cells [27], that serves as a critical checkpoint. This discovery suggests a profound therapeutic implication: the window for intervention may extend far beyond the acute phase. Therapies aimed at 'resetting' these persistent cellular aberrations could potentially halt the progression to CKD.

The cellular mechanisms of maladaptive repair

Multiple interconnected cellular processes contribute to the maladaptive repair cascade:

Persistent inflammation Failure of acute inflammation to resolve is a primary driver. A delayed switch of macrophages from a pro-inflammatory (M1) to a pro-reparative (M2) phenotype contributes to fibrosis [26].

Endothelial dysfunction and microvascular rarefaction Injury to peritubular capillaries leads to local hypoxia, a potent stimulus for fibrosis. The progressive loss of these capillaries, or rarefaction, is a cardinal feature of the AKI-to-CKD transition [26].

Tubular epithelial cell failure Severely injured TECs can become arrested in the G2/M phase of the cell cycle, adopting a pathogenic phenotype that secretes profibrotic factors [26]. Failure to fully redifferentiate also fuels the fibrotic process [4].

Myofibroblast activation and matrix deposition Myofibroblasts are the architects of the renal scar. They originate primarily from resident renal pericytes and interstitial fibroblasts and are responsible for the excessive deposition of extracellular matrix (ECM) [26].

Mitochondrial dysfunction and oxidative stress The proximal tubule is rich in mitochondria to fuel its high metabolic activity [28]. During AKI, mitochondrial damage leads to energy depletion and the production of reactive oxygen species (ROS) [29]. Persistent mitochondrial dysfunction and oxidative stress post-AKI can drive chronic inflammation, cellular senescence, and fibrosis, representing a key mechanism in the transition to CKD [30].

The molecular orchestra of fibrosis

A complex web of molecular signals orchestrates fibrosis (Table 4). Transforming Growth Factor-β (TGF-β) is the master regulator [3]. Developmental pathways like Wnt/β-catenin and Notch signaling are aberrantly reactivated, where their sustained activation promotes fibrosis [31–33]. Cellular senescence leads to a pro-inflammatory senescence-associated secretory phenotype (SASP) that drives fibrosis [27]. Epigenetic modifications can lock in a pro-fibrotic gene program [26]. Autophagy, while protective acutely, may become detrimental if persistently activated [34].

These pathophysiological mechanisms must be viewed through the lens of the developing pediatric kidney, which introduces specific vulnerabilities [3]. The most critical is the impact on nephron endowment. Since nephrogenesis continues until approximately 34–36 weeks of gestation (or potentially earlier, as recent evidence suggests), an AKI in a preterm infant can permanently arrest nephron formation, resulting in a congenitally low nephron number [3, 23]. This lifelong deficit predisposes the child to hypertension and CKD [24]. Furthermore, fibrotic scarring may have a disproportionately greater functional impact on a smaller, still-growing kidney.

The role of KRT in renal injury

For patients with severe AKI, KRT is a life-saving intervention. However, the therapy itself can contribute to further kidney injury and potentially influence the transition to CKD [35]. KRT-associated hypotension can cause ischemic insults to the recovering kidney. Furthermore, exposure of blood to extracorporeal circuits can trigger inflammatory and complement activation pathways, potentially exacerbating the existing inflammatory milieu within the kidney [36, 37]. While the choice of KRT modality and its operational parameters may have a significant impact on renal recovery, the optimal strategy to preserve long-term kidney function remains unknown. There is a notable lack of data from randomized controlled trials in children comparing outcomes such as long-term renal recovery between different modalities like continuous KRT (CKRT) and intermittent hemodialysis (IHD) [38]. Patients who experience AKI severe enough to require KRT (AKI-D) represent a particularly high-risk group for subsequent CKD, not only due to the

Table 4 Key cellular and molecular mechanisms implicated in maladaptive kidney repair Post-AKI

Mechanism	Key Cellular Players/Mediators	Pathophysiological Consequence (leading to fibrosis/CKD)
Persistent Inflammation [26]	Macrophages (M1, pro-fibrotic M2), Neutrophils, Lymphocytes, Pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), Chemokines (MCP-1/CCL2)	Chronic immune cell infiltration, sustained production of damaging mediators, promotion of fibroblast activation
Tubular Epithelial Cell Dysfunction [4]	Injured TECs	G2/M cell-cycle arrest with pro-fibrotic phenotype, failed redifferentiation, apoptosis, necrosis, persistent expression of injury markers (KIM-1)
Myofibroblast Activation & ECM Deposition [26]	Renal Pericytes, Resident Fibroblasts, (potentially Fibrocytes)	Differentiation into α-SMA + myofibroblasts, excessive production and deposition of ECM (collagens, fibronectin), tissue stiffening, organ dysfunction
Endothelial Dysfunction & Microvascular Rarefaction [26]	Peritubular capillary endothelial cells, Pericytes	Impaired blood flow, hypoxia, loss of capillaries, vascular instability, reduced delivery of oxygen/nutrients, promotion of fibrosis
TGF-β Signaling Dysregulation [3]	TGF-β1, Smad2/3, TECs, Macrophages, Myofibroblasts	Potent induction of myofibroblast differentiation, stimulation of ECM synthesis, inhibition of ECM degradation, promotion of epithelial cell changes
Wnt/β-catenin Signaling Dysregulation [31]	Wnt ligands, β-catenin, Frizzled receptors, TECs, Fibroblasts	Sustained activation promotes fibroblast proliferation and activation, ECM production; (beneficial in acute TEC repair)
Notch Signaling Dysregulation [32]	Notch receptors (1–4), Ligands (Jagged, Dll), Hes1	Prolonged/aberrant activation promotes tubular injury, dedifferentiation, fibrosis, impaired repair (especially in aging)
Cellular Senescence & SASP [26]	Senescent TECs, SASP components (IL-6, IL-1α, MCP-1, TGF-β)	Irreversible cell cycle arrest, secretion of pro-inflammatory/pro-fibrotic factors, paracrine senescence induction, chronic inflammation, fibrosis
Epigenetic Modifications [26]	DNA methylation changes, Histone modifications (acetylation, methylation)	Altered gene expression favoring sustained pro-inflammatory/pro-fibrotic states, "epigenetic memory" of injury
Dysregulated Autophagy [34]	Autophagosomes, Lysosomes, TECs	Persistent high levels in chronic phase may promote tubular degeneration and pro-fibrotic phenotype; (protective in acute phase)
Mitochondrial Dysfunction & Oxidative Stress [30]	Mitochondria, Reactive Oxygen Species	Energy depletion, persistent oxidative stress, promotion of inflammation, senescence, and fibrosis

severity of their initial injury but also due to these potential secondary insults from the therapy itself [39].

Beyond creatinine: the quest for biomarkers to illuminate the path to CKD

The failing light of traditional markers

Clinicians have long used the dim light of SCr and UO, which provide a delayed and clouded view of renal injury [1, 40]. This reliance on flawed metrics has fueled the quest for novel biomarkers. A key conceptual advance driven by this research is the move to differentiate between functional AKI (a physiological response with a drop in GFR but no cellular damage, previously termed 'pre-renal') and structural AKI (evidence of true parenchymal injury) [41, 42]. Biomarkers of damage, like NGAL or KIM-1, can identify structural injury even when SCr is normal, while a rise in SCr without elevated damage markers may represent functional AKI [43, 44]. This distinction is critical for prognosis and management [39].

A new dawn: the promise of novel injury biomarkers

An emerging panel of candidates holds promise for pediatric AKI (Table 5).

Early messengers of tubular injury Neutrophil Gelatinase-Associated Lipocalin and Kidney Injury Molecule-1 are released from damaged TECs hours before SCr rises [6, 45, 46].

A superior filtration marker Serum Cystatin C has emerged as a more reliable indicator of GFR than SCr [47]. Produced by all nucleated cells at a constant rate and freely filtered by the glomerulus, its levels are far less dependent on muscle mass, age, or sex, making it particularly valuable in the pediatric setting [6, 40, 48]. Studies in children have shown it can detect changes in GFR earlier than SCr and has utility in predicting AKI development and severity, though its performance can be influenced by factors like inflammation and corticosteroid use [49, 50].

Indicators of cellular stress and inflammation The urinary product of Tissue Inhibitor of Metalloproteinases-2 (TIMP-2) and Insulin-like Growth Factor-Binding Protein 7 (IGFBP7) signals G1 cell cycle arrest and serves as a powerful early warning system [6].

The great unmet challenge: from detection to prediction

While many biomarkers excel at early detection, their utility in predicting the AKI-to-CKD transition in children is less established [13]. Significant challenges hinder their translation, including variability in performance depending on the pediatric clinical setting (e.g., cardiac surgery vs. sepsis), a lack of standardized pediatric-specific assays and cutoff values, and confounding factors like UTIs [45, 51–53].

For a biomarker to be transformative, it must provide actionable information that improves outcomes, a high bar yet to be cleared [45]. An emerging approach suggests the trajectory of a biomarker over time may hold more prognostic power than a single measurement [25]. The future likely lies with an intelligently selected panel of biomarkers [54].

Table 5 Promising biomarkers for predicting AKI-to-CKD transition in children: utility, limitations, and controversies

Biomarker	Source	Proposed Utility	Advantages	Limitations/Controversies
Neutrophil Gelatinase-Associated Lipocalin (NGAL) [6]	Urine, Plasma	Early AKI detection (esp. post-cardiac surgery, CIN); Prediction of AKI severity; Potential for predicting AKI-CKD transition (dynamic changes)	Very early rise post-injury; Relatively stable	Elevated in UTI, sepsis, malignancies without AKI; Variable cutoffs; Role in CKD prediction needs more validation
Kidney Injury Molecule-1 (KIM-1) [6]	Urine	Early detection of proximal tubular injury; AKI diagnosis and severity assessment; Potential marker of maladaptive repair	Specific for proximal tubular injury; Stable in urine	Primarily reflects tubular injury, not GFR; Validation for CKD prediction ongoing
Cystatin C [6]	Serum, Urine	Early detection of GFR changes; AKI diagnosis, especially where SCr is unreliable (e.g., low muscle mass)	Less influenced by muscle mass than SCr; Reflects GFR	Influenced by thyroid function, inflammation, corticosteroids; Urinary Cystatin C less established; Cost
Interleukin-18 (IL-18) [6]	Urine	Marker of acute tubular inflammation and injury	Reflects inflammatory component of AKI	Not specific to kidney (produced by other cells); Short half-life; Variable performance
Cell Cycle Arrest Markers [6]	Urine	Early risk assessment for moderate-severe AKI (cell cycle arrest)	Predicts AKI development within 12–24 h; Reflects cellular stress	Performance may vary by AKI etiology; Less data on CKD prediction in children
Liver-type Fatty Acid-Binding Protein (L-FABP) [6]	Urine	Early marker of tubular stress/injury (ischemic/oxidative)	Reflects tubular response to hypoxia/oxidative stress	Limited pediatric data compared to NGAL/KIM-1; Specificity concerns
Panel/Multiple Biomarkers [54]	Urine, Plasma	Improved diagnostic/prognostic accuracy by reflecting diverse injury pathways	More comprehensive assessment of kidney status	Complexity of interpretation; Cost; Need for validated algorithms

Long-Term surveillance: rationale and challenges

Rationale for surveillance

The established link between pediatric acute kidney injury and subsequent chronic kidney disease creates a clear imperative for long-term surveillance [20]. This vigilance allows for the timely implementation of renoprotective strategies, such as blood pressure and proteinuria management, to slow disease progression [55].

Guidelines and Follow-up models

Despite this imperative, specific evidence-based guidelines for the long-term follow-up of all pediatric AKI survivors are lacking [56]. However, consensus statements and expert recommendations are emerging for specific high-risk populations, such as graduates of the neonatal ICU [57]. Clinicians currently rely on a mosaic of recommendations, many extrapolated from adult data. For instance, UK guidelines recommend specialist referral for severe AKI or persistent abnormalities [58], while some institutions utilize risk-stratified models based on nephrotoxic exposures, similar to those used in post-cancer care [59]. The optimal frequency and duration of follow-up remain unsettled. While some data suggest risk diminishes after one year in stable patients, other studies report CKD manifestation more than five years post-AKI [25, 56], underscoring the need for improved risk stratification.

A major challenge is the gap between recommendation and practice. One study found that while only 18% of pediatric ICU survivors with AKI saw a nephrologist, 95% had contact with a primary care provider (PCP) within a year [60]. This highlights the potential of empowering PCPs with clear protocols. Multidisciplinary post-AKI clinics offer a promising, comprehensive model, but implementation can be challenging. Evidence from adult populations suggests that resource-intensive follow-up does not always improve outcomes, necessitating efficient, risk-based approaches [61, 62]. A summary of selected recommendations is in Table 6.

Therapeutic strategies to prevent the AKI-to-CKD transition

Barriers to translation

Translating preclinical discoveries into effective therapies for preventing the AKI-to-CKD transition has proven challenging [63]. Key barriers include the clinical heterogeneity of AKI syndrome, where targeting a single pathway may be insufficient, and the limitations of preclinical animal models, which often fail to replicate the chronicity and complexity of human disease [63]. This is particularly true for pediatrics, as standard preclinical animal models do not account for the unique physiology of the developing kidney. The lack of validated biomarkers to track disease progression further complicates clinical trial design [63].

Table 6 Summary of selected Long-Term surveillance recommendations for pediatric AKI survivors

Guideline Source/Group	Target Population	Recommended Follow-up Timing (Initial & Ongoing)	Key Monitoring Parameters	Referral Criteria to Nephrology
British Association of Paediatric Nephrology (BAPN) / UK Renal Association [58]	Children post-AKI	Initial assessment ~ 3 months post-AKI. Duration/frequency depends on risk.	SCr (for eGFR), urine for proteinuria, and blood pressure.	AKI requiring dialysis; Persistent proteinuria or eGFR < 90 mL/min/1.73m2 at 3 months.
Children's Mercy Hospital (Institutional Example)	Children post-AKI	Within 3 weeks if AKI unresolved at discharge; within 3 months if AKI resolved. Frequency thereafter based on risk/findings.	SCr (for eGFR - CKiD U25 equation), blood pressure (age/height percentiles), and random urine protein. Counseling on nephrotoxins and hydration.	Hypertension; Proteinuria ≥ 1+; eGFR < 90% of baseline/normal.
International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) [59]	Childhood, adolescent, young adult cancer survivors with nephrotoxic exposures (e.g., ifosfamide, cisplatin, RTx)	Glomerular dysfunction: Every 2–5 years. Tubular dysfunction: Once at entry to LFU, then as clinically indicated.	eGFR (SCr, consider Cystatin C), urinalysis, electrolytes (for tubular dysfunction).	Based on findings (e.g., significantly reduced eGFR, persistent proteinuria).
American Society of Nephrology (ASN) - AKI-D Guidance Focus	Patients (incl. pediatric) with dialysis-requiring AKI (AKI-D) in outpatient setting	Focus on monitoring for recovery during AKI-D phase. Weekly assessment of endogenous kidney function, 12–24 h urine collections.	SCr, UO, electrolytes, volume status, BP, medication review.	Primarily for management during AKI-D; transition to CKD care if no recovery.
General Principles from Literature [56]	All pediatric AKI survivors, risk-stratified	Initial follow-up within 1–3 months. Duration and frequency highly debated (e.g., 1 year if stable vs. >5 years for high risk).	Blood pressure, urinalysis (proteinuria/albuminuria), eGFR, growth (infants).	Persistent abnormalities in BP, proteinuria, and eGFR.

Table 7 Key research gaps and future research priorities in pediatric AKI-to-CKD transition

Research Area	Specific Gap/Question	Potential Research Approach/Priority
Pediatric-Specific Pathophysiology [2]	How do maladaptive repair mechanisms (fibrosis, senescence, inflammation, epigenetics) differ in the developing vs. mature kidney? Are there unique pediatric pathways?	Develop and utilize age-appropriate pediatric animal models of AKI-CKD; Comparative -omics studies (pediatric vs. adult); Studies on the impact of AKI on nephrogenesis and kidney growth.
Risk Stratification [56]	How to accurately identify children at highest risk for CKD progression post-AKI? Beyond AKI severity, what are the key predictors?	Develop and validate pediatric-specific risk scores incorporating clinical data (AKI etiology/severity, age, comorbidities), novel biomarkers, genetic markers, and early recovery trajectory.
Biomarker Validation & Implementation [13]	Which novel biomarkers (or panels) reliably predict AKI-to-CKD transition in diverse pediatric AKI populations? How can they be integrated into clinical practice to guide management?	Large-scale, prospective, multicenter validation studies of biomarkers for long-term prognostication; Studies assessing clinical utility (impact on decisions/outcomes); Standardization of assays.
Targeted Therapeutics [63]	What are effective and safe therapies to interrupt maladaptive repair and prevent/slow AKI-to-CKD progression in children?	Preclinical testing of agents targeting fibrosis, senescence, epigenetic changes, specific signaling pathways (TGF-β, Wnt, Notch, AP-1, JNK) in pediatric models; Phase I/II clinical trials in high-risk children.
Optimizing Surveillance Strategies [21]	What is the optimal frequency, duration, and panel of monitoring parameters for long-term surveillance of different risk groups of pediatric AKI survivors? Cost-effectiveness?	Prospective, randomized controlled trials comparing different surveillance strategies; Cost-effectiveness analyses; Studies incorporating patient/family-reported outcomes and preferences.
Neonatal AKI Long-Term Impact [1]	What are the very long-term (into adulthood) renal, cardiovascular, and overall health consequences of neonatal AKI, especially in preterm infants with altered nephron endowment?	Long-term cohort studies following neonatal AKI survivors into adulthood; Mechanistic studies on how early life AKI programs later disease.
Understanding Developmental Differences in Repair [3]	How do immature renal cells respond differently to injury signals compared to adult cells? How does this impact the trajectory of repair and susceptibility to maladaptation?	In vitro studies using pediatric kidney cells/organoids; Comparative studies in neonatal vs. juvenile vs. adult animal models.
Interventional Trials for Prevention [63]	Can specific interventions (pharmacological, care bundles, nutritional support) during or immediately after AKI reduce the risk of subsequent CKD in high-risk pediatric populations?	Randomized controlled trials of preventative strategies in children at high risk for AKI or for AKI-to-CKD progression.
Role of Primary Care in Surveillance	How can primary care providers be effectively engaged and supported in the long-term surveillance of pediatric AKI survivors?	Development and evaluation of PCP-friendly guidelines, educational tools, and shared-care models with specialist centers.

Emerging therapeutic targets

Despite these challenges, research is exploring several strategies targeting maladaptive repair pathways. These include anti-fibrotic agents that inhibit key regulators like TGF-β; senolytics to clear senescent tubular epithelial cells and their pro-inflammatory secretome, though their use in growing children requires rigorous safety evaluation [26]; epigenetic modulators, such as DNA methyltransferase (DNMT) and histone deacetylase (HDAC) inhibitors, to reverse pro-fibrotic cellular memory [26, 64]; and inhibitors of specific signaling pathways, like c-Jun N-terminal kinase (JNK) or Activator Protein-1 (AP-1), that are persistently activated after injury [26, 63].

Pediatric research imperatives

Currently, no therapies are approved to prevent the AKI-to-CKD transition in any population [63]. A significant hurdle is the dual role of many signaling pathways, where an ill-timed intervention could disrupt beneficial acute repair processes [34, 63]. Critically, most mechanistic knowledge is extrapolated from adult models, which may not be applicable to the developing kidney [2]. A dedicated research agenda for pediatric AKI is therefore essential. Future priorities (summarized in Table 7) include developing pediatric-specific preclinical models, validating biomarkers to predict CKD transition, designing targeted therapies for high-risk children, and defining optimal long-term surveillance strategies for this growing population of survivors [1, 13, 21, 56, 63].

Conclusions

Pediatric AKI can no longer be regarded as a transient, self-resolving condition. It must be recognized as a formidable global health issue, a sentinel event that casts a long shadow over the future of a child's health. The evidence is now unequivocal: an episode of AKI in childhood, regardless of whether serum creatinine returns to a seemingly normal baseline, fundamentally increases the risk for the subsequent development of CKD, hypertension, and a host of adverse renal and cardiovascular outcomes. This review has charted the profound paradigm shift in our understanding of pediatric AKI, recasting it as a critical juncture that can initiate an inexorable trajectory towards lifelong kidney impairment, with particularly severe consequences for the vulnerable neonatal and preterm infant populations.

The transition from acute injury to chronic disease is propelled by a complex and pernicious process of maladaptive renal repair. The kidney's healing response becomes derailed, caught in a self-perpetuating cycle of persistent inflammation, endothelial dysfunction, and aberrant tubular epithelial cell behavior, including G2/M cell-cycle arrest and the damaging secretions of senescent cells. This cellular pathology is orchestrated by dysregulated molecular signals—including TGF-β, Wnt, and Notch—and locked in by lasting epigenetic modifications that create a pro-fibrotic memory of the initial injury. When these processes unfold within the delicate and dynamic environment of a developing pediatric kidney where nephrogenesis may still be incomplete, the consequences are particularly devastating, culminating in progressive interstitial fibrosis and permanent nephron loss.

This new understanding creates an urgent and currently unmet need for robust, evidence-based, and intelligently risk-stratified long-term surveillance programs for every child who survives an AKI episode. Such programs represent our best opportunity to detect the early signs of CKD and deploy interventions that can slow its progression. Yet, the implementation of such essential care is crippled by significant barriers, most notably alarmingly low rates of specialist follow-up and the lack of universally accepted, pediatric-specific guidelines.

The overarching theme that emerges is the need for a fundamental shift in the clinical mindset. This requires a concerted effort to enhance education for the full spectrum of healthcare providers—from intensive care specialists to primary care physicians—who manage the long-term health of these children. It also demands systemic improvements to our healthcare infrastructure to ensure that AKI survivors are tracked and receive appropriate, individualized follow-up care.

To secure a better future for these vulnerable patients, a collaborative and focused research effort is paramount. This research must prioritize pediatric-specific investigations into the mechanisms of maladaptive repair, the validation of biomarkers that can accurately predict the transition to CKD, the development of targeted therapies specifically designed to be safe and effective in the developing kidney, and the optimization of sustainable and effective long-term surveillance strategies. By dedicating ourselves to these critical tasks, the medical and scientific community can aspire to meaningfully improve the renal and overall health outcomes for the growing number of children scarred by acute kidney injury.

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Y.H.D. contributed to the Writing – original draft, funding acquisition, investigation, and methodology. Q.L. contributed to the Writing – review and editing. X.Q.L. contributed to the supervision. All authors have read and approved the final manuscript.

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No datasets were generated or analysed during the current study.

Declarations

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References

1. Sethi SK, Bunchman T, Chakraborty R, Raina R. Pediatric acute kidney injury: new advances in the last decade. Kidney Res Clin Pract. 2021;40:40–51. https://doi.org/10.23876/j.krcp.20.074.
2. Goldstein SL, Devarajan P. Acute kidney injury in childhood: should we be worried about progression to CKD? Pediatr Nephrol. 2011;26:509–22. https://doi.org/10.1007/s00467-010-1653-4.
3. Andreoli SP. Acute kidney injury in children. Pediatr Nephrol. 2009;24:253–63. https://doi.org/10.1007/s00467-008-1074-9.
4. Gerhardt LMS, Koppitch K, Van Gestel J, Guo J, Cho S, Wu H, et al. Lineage tracing and single-nucleus multiomics reveal novel features of adaptive and maladaptive repair after acute kidney injury. JASN. 2023;34:554–71. https://doi.org/10.1681/ASN.0000000000000057.
5. Jetton JG, Boohaker LJ, Sethi SK, Wazir S, Rohatgi S, Soranno DE, et al. Incidence and outcomes of neonatal acute kidney injury (AWAKEN): A multicentre, multinational, observational cohort study. Lancet Child Adolesc Health. 2017;1:184–94. https://doi.org/10.1016/S2352-4642(17)30069-X.
6. Rivetti G, Gizzone P, Petrone D, Di Sessa A, Miraglia Del Giudice E, Guarino S, et al. Acute kidney injury in children: A focus for the general pediatrician. Child (Basel). 2024;11:1004. https://doi.org/10.3390/children11081004.
7. Chisavu F, Gafencu M, Stroescu R, Motofelea A, Chisavu L, Schiller A. Acute kidney injury in children: incidence, awareness and outcome-a retrospective cohort study. Sci Rep. 2023;13:15778. https://doi.org/10.1038/s41598-023-43098-7.
8. Marzuillo P, Coppola C, Caiazzo R, Macchini G, Di Sessa A, Guarino S, et al. Acute kidney injury in children with acute appendicitis. Children. 2022;9:620. https://doi.org/10.3390/children9050620.
9. Marzuillo P, Di Sessa A, Golino R, Tirelli P, De Lucia M, Rivetti G, et al. Acute kidney injury in infants hospitalized for viral bronchiolitis. Eur J Pediatr. 2023;182:3569–76. https://doi.org/10.1007/s00431-023-05029-6.
10. Marzuillo P, Guarino S, Alfiero S, Annicchiarico Petruzzelli L, Arenella M, Baccelli F, et al. Acute kidney injury in children hospitalised for febrile urinary tract infection. Acta Paediatr. 2024;113:1711–9. https://doi.org/10.1111/apa.17247.
11. Stoops C, Stone S, Evans E, Dill L, Henderson T, Griffin R, et al. Baby NINJA (nephrotoxic injury negated by just-in-time action): reduction of nephrotoxic medication-associated acute kidney injury in the neonatal intensive care unit. J Pediatr. 2019;215:223–e2286. https://doi.org/10.1016/j.jpeds.2019.08.046.
12. Ciccia E, Devarajan P. Pediatric acute kidney injury: prevalence, impact and management challenges. Int J Nephrol Renovasc Dis. 2017;10:77–84. https://doi.org/10.2147/IJNRD.S103785.
13. Wang F, Ding J. Pediatric acute kidney injury to the subsequent CKD transition. Kidney Dis (Basel). 2021;7:10–3. https://doi.org/10.1159/000509935.
14. Kemperman FA, Weber JA, Gorgels J, van Zanten AP, Krediet RT, Arisz L. The influence of ketoacids on plasma creatinine assays in diabetic ketoacidosis. J Intern Med. 2000;248:511–7. https://doi.org/10.1046/j.1365-2796.2000.00768.x.

15. Feldman-Kiss D, Li D, Cleve R, Sinclair G, Dubland JA, Wang L. Interference of ketone bodies on laboratory creatinine measurement in children with DKA: A call for change in testing practices. Pediatr Nephrol. 2022;37:1347–53. https://doi.org/10.1007/s00467-021-05324-0.
16. Guarino S, Rivetti G, Di Sessa A, De Lucia M, Palma PL, Miraglia del Giudice E, et al. Diagnostic performance of height-estimated baseline creatinine in diagnosing acute kidney injury in children with type 1 diabetes mellitus onset. Child (Basel). 2022;9:899. https://doi.org/10.3390/children9060899.
17. Schwartz GJ, Muñoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol. 2009;20:629–37. https://doi.org/10.1681/ASN.2008030287.
18. Ostermann M, Bellomo R, Burdmann EA, Doi K, Endre ZH, Goldstein SL et al. Controversies in acute kidney injury: conclusions from a kidney disease: improving global outcomes (KDIGO) conference. Kidney Int. 2020;98:294–309. https://doi.org/10.1016/j.kint.2020.04.020
19. Doyle JF, Forni LG. Acute kidney injury: Short-term and long-term effects. Crit Care. 2016;20:188. https://doi.org/10.1186/s13054-016-1353-y.
20. Schuermans A, Van den Eynde J, Mekahli D, Vlasselaers D. Long-term outcomes of acute kidney injury in children. Curr Opin Pediatr. 2023;35:259–67. https://doi.org/10.1097/MOP.0000000000001202.
21. Robinson CH, Jeyakumar N, Luo B, Askenazi D, Deep A, Garg AX, et al. Long-term kidney outcomes after pediatric acute kidney injury. J Am Soc Nephrol. 2024;35:1520–32. https://doi.org/10.1681/ASN.0000000000000445.
22. Jan M, Ashraf M, Baba RA, Bhat SA. Risk factors and occurrence of chronic kidney disease following acute kidney injury in children. Ann Afr Med. 2022;21:366–70. https://doi.org/10.4103/aam.aam_103_21.
23. Perl AJ, Schuh MP, Kopan R. Regulation of nephron progenitor cell lifespan and nephron endowment. Nat Rev Nephrol. 2022;18:683–95. https://doi.org/10.1038/s41581-022-00620-w.
24. Primack W, Kleeman S, Boineau F, Jernigan S. Are my pediatric patients at increased risk of developing chronic kidney disease? Clin Pediatr (Phila). 2020;59:801–8. https://doi.org/10.1177/0009922820920015.
25. Ceschia G, Claes DJ, Krallman KA, Collins M, Goldstein SL. Long-term follow-up strategies for children after severe acute kidney injury. Pediatr Res. 2025. https://doi.org/10.1038/s41390-025-03965-7.
26. Ferenbach DA, Bonventre JV. Mechanisms of maladaptive repair after AKI leading to accelerated kidney ageing and CKD. Nat Rev Nephrol. 2015;11:264–76. https://doi.org/10.1038/nrneph.2015.3.
27. Lin X, Jin H, Chai Y, Shou S. Cellular senescence and acute kidney injury. Pediatr Nephrol. 2022;37:3009–18. https://doi.org/10.1007/s00467-022-05532-2.
28. Forst A-L, Reichold M, Kleta R, Warth R. Distinct mitochondrial pathologies caused by mutations of the proximal tubular enzymes EHHADH and GATM. Front Physiol. 2021;12:715485. https://doi.org/10.3389/fphys.2021.715485.
29. Cao M, Zhao X, Xia F, Shi M, Zhao D, Li L, et al. Mitochondrial dysfunction and metabolic reprogramming in acute kidney injury: mechanisms, therapeutic advances, and clinical challenges. Front Physiol. 2025;16:1623500. https://doi.org/10.3389/fphys.2025.1623500.
30. Fontecha-Barriuso M, Lopez-Diaz AM, Guerrero-Mauvecin J, Miguel V, Ramos AM, Sanchez-Niño MD, et al. Tubular mitochondrial dysfunction, oxidative stress, and progression of chronic kidney disease. Antioxid (Basel). 2022;11:1356. https://doi.org/10.3390/antiox11071356.
31. Huffstater T, Merryman WD, Gewin LS. Wnt/β-catenin in acute kidney injury and progression to chronic kidney disease. Semin Nephrol. 2020;40:126–37. https://doi.org/10.1016/j.semnephrol.2020.01.004.
32. Mukherjee M, Fogarty E, Janga M, Surendran K. Notch signaling in kidney development, maintenance, and disease. Biomolecules. 2019;9:692. https://doi.org/10.3390/biom9110692.
33. Sörensen-Zender I, Rong S, Susnik N, Zender S, Pennekamp P, Melk A, et al. Renal tubular Notch signaling triggers a prosenescent state after acute kidney injury. Am J Physiology-Renal Physiol. 2014;306:F907–15. https://doi.org/10.1152/ajprenal.00030.2014.
34. Xiang Y, Fu Y, Wu W, Tang C, Dong Z. Autophagy in acute kidney injury and maladaptive kidney repair. Burns Trauma. 2023;11:tkac059. https://doi.org/10.1093/burnst/tkac059.
35. Levine Z, Vijayan A. Prolonged intermittent kidney replacement therapy. Clin J Am Soc Nephrol. 2023;18:383–91. https://doi.org/10.2215/CJN.04310422.
36. Franzin R, Stasi A, Fiorentino M, Stallone G, Cantaluppi V, Gesualdo L, et al. Inflammaging and complement system: A link between acute kidney injury and chronic graft damage. Front Immunol. 2020;11:734. https://doi.org/10.3389/fimmu.2020.00734.
37. Ekdahl KN, Fromell K, Mannes M, Grinnemo K, Huber-Lang M, Teramura Y, et al. Therapeutic regulation of complement activation in extracorporeal circuits and intravascular treatments with special reference to the alternative pathway amplification loop. Immunol Rev. 2023;313:91–103. https://doi.org/10.1111/imr.13148.
38. Huang JX, Williams JAJ, Hsu RK. Continuous kidney replacement therapy in pediatric intensive care unit: little people, big gaps. Am J Kidney Dis. 2024;84:393–6. https://doi.org/10.1053/j.ajkd.2024.06.010.
39. Kellum JA, Romagnani P, Ashuntantang G, Ronco C, Zarbock A, Anders H-J. Acute kidney injury. Nat Rev Dis Primers. 2021;7:52. https://doi.org/10.1038/s41572-021-00284-z.
40. Kopač M. Acute kidney injury in children: classification, recognition and treatment principles. Child (Basel). 2024;11:1308. https://doi.org/10.3390/children11111308.
41. Kellum JA, Lameire N, KDIGO AKI Guideline Work Group. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (part 1). Crit Care. 2013;17:204. https://doi.org/10.1186/cc11454.
42. John JS, Deepthi RV, Rebekah G, Prabhu SB, Ajitkumar P, Mathew G, et al. Usefulness of urinary calprotectin as a novel marker differentiating functional from structural acute kidney injury in the critical care setting. J Nephrol. 2023;36:695–704. https://doi.org/10.1007/s40620-022-01534-3.
43. Verbrugge FH, Dupont M, Shao Z, Shrestha K, Singh D, Finucan M, et al. Novel urinary biomarkers in detecting acute kidney injury, persistent renal impairment and all-cause mortality following decongestive therapy in acute decompensated heart failure. J Card Fail. 2013;19:621–8. https://doi.org/10.1016/j.cardfail.2013.07.004.
44. Ostermann M, Legrand M, Meersch M, Srisawat N, Zarbock A, Kellum JA. Biomarkers in acute kidney injury. Ann Intensive Care. 2024;14:145. https://doi.org/10.1186/s13613-024-01360-9.
45. Bazargani B, Moghtaderi M. New biomarkers in early diagnosis of acute kidney injury in children. Avicenna J Med Biotechnol. 2022;14:264–9.
46. Han W. Biomarkers for early detection of acute kidney injury. CBF. 2012;77. https://doi.org/10.2147/CBF.S27898.
47. Shlipak MG, Matsushita K, Ärnlöv J, Inker LA, Katz R, Polkinghorne KR, et al. Cystatin C versus creatinine in determining risk based on kidney function. N Engl J Med. 2013;369:932–43. https://doi.org/10.1056/NEJMoa1214234.
48. Zaffanello M, Franchini M, Fanos V. Is serum cystatin-C a suitable marker of renal function in children? Ann Clin Lab Sci. 2007;37:233–40.
49. Skidmore M, Spencer S, Desborough R, Kent D, Bhandari S. Cystatin C as a marker of kidney function in children. Biomolecules. 2024;14:938. https://doi.org/10.3390/biom14080938.
50. Filler G, Huang S-HS, Yasin A. The usefulness of Cystatin C and related formulae in pediatrics. Clin Chem Lab Med. 2012;50:2081–91. https://doi.org/10.1515/cclm-2012-0257.
51. Abbas Q, Laghari P, Jurair H, Nafis J, Saeed B, Qazi MF, et al. Neutrophil gelatinase-associated Lipocalin as a predictor of acute kidney injury in children with shock: A prospective study. Cureus. 2023;15:e34407. https://doi.org/10.7759/cureus.34407.
52. Greenberg JH, Zappitelli M, Jia Y, Thiessen-Philbrook HR, de Fontnouvelle CA, Wilson FP, et al. Biomarkers of AKI progression after pediatric cardiac surgery. J Am Soc Nephrol. 2018;29:1549–56. https://doi.org/10.1681/ASN.2017090989.
53. Meena J, Thomas CC, Kumar J, Mathew G, Bagga A. Biomarkers for prediction of acute kidney injury in pediatric patients: A systematic review and meta-analysis of diagnostic test accuracy studies. Pediatr Nephrol. 2023;38:3241–51. https://doi.org/10.1007/s00467-023-05891-4.
54. Yang H, Chen Y, He J, Li Y, Feng Y. Advances in the diagnosis of early biomarkers for acute kidney injury: A literature review. BMC Nephrol. 2025;26:115. https://doi.org/10.1186/s12882-025-04040-3.
55. Elendu C, Elendu RC, Enyong JM, Ibhiedu JO, Ishola IV, Egbunu EO, et al. Comprehensive review of current management guidelines of chronic kidney disease. Med (Baltim). 2023;102:e33984. https://doi.org/10.1097/MD.0000000000033984.
56. Robinson CH, Jeyakumar N, Luo B, Wald R, Garg AX, Nash DM, et al. Long-term kidney outcomes following dialysis-treated childhood acute kidney injury: A population-based cohort study. J Am Soc Nephrol. 2021;32:2005–19. https://doi.org/10.1681/ASN.2020111665.
57. Kamel H, Longstreth WT, Tirschwell DL, Kronmal RA, Marshall RS, Broderick JP, et al. Apixaban to prevent recurrence after cryptogenic stroke in patients with atrial cardiopathy. JAMA. 2024;331:573–81. https://doi.org/10.1001/jama.2023.27188.

58. Kanagasundaram S, Ashley C, Bhojani S, Caldwell A, Ellam T, Kaur A, et al. Clinical practice guideline acute kidney injury (AKI). UKKA. 2019;8:217–24. https://doi.org/10.22141/2307-1257.8.4.2019.185121.
59. Kooijmans ECM, Mulder RL, Marks SD, Pavasovic V, Motwani SS, Walwyn T, et al. Nephrotoxicity surveillance for childhood and young adult survivors of cancer: recommendations from the international late effects of childhood cancer guideline harmonization group. JCO. 2025. https://doi.org/10.1200/JCO-24-02534. ;:JCO-24-02534.
60. Robinson C, Hessey E, Nunes S, Dorais M, Chanchlani R, Lacroix J, et al. Acute kidney injury in the pediatric intensive care unit: outpatient follow-up. Pediatr Res. 2022;91:209–17. https://doi.org/10.1038/s41390-021-01414-9.
61. Ortiz-Soriano V, Singh G, Chang A, Ruiz EF, Wald R, Silver SA, et al. Processes of care in survivors of acute kidney injury followed in specialized postdischarge clinics. Clin J Am Soc Nephrol. 2022;17:1669–72. https://doi.org/10.2215/CJN.00160122.
62. Silver SA, Adhikari NK, Bell CM, Chan CT, Harel Z, Kitchlu A, et al. Nephrologist follow-up versus usual care after an acute kidney injury hospitalization (FUSION): A randomized controlled trial. Clin J Am Soc Nephrol. 2021;16:1005–14. https://doi.org/10.2215/CJN.17331120.
63. Zhang T, Widdop RE, Ricardo SD. Transition from acute kidney injury to chronic kidney disease: mechanisms, models, and biomarkers. Am J Physiology-Renal Physiol. 2024;327:F788–805. https://doi.org/10.1152/ajprenal.00184.2024.
64. Zheng X, Guo X, Chen Y, Zhuang K, Gong N, Fu Y, et al. Integration of DNA methylome and transcriptome analysis to identify novel epigenetic targets in the acute kidney injury–chronic kidney disease transition. Biomolecules. 2025;15:498. https://doi.org/10.3390/biom15040498.

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