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EDITORIAL

When Healing Hurts: Preventing Nephrotoxic Acute Kidney Injury in Children

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Acute kidney injury (AKI) is a significant contributor to morbidity and mortality among hospitalized children. Retrospective studies report incidences in pediatric intensive care units (ICUs) ranging from 8% to 30%, with approximately 16% of these cases being attributable to nephrotoxic medications.[1] A recent meta-analysis encompassing nearly 196,000 pediatric patients estimated the overall incidence of drug-induced kidney injury at 18.2%, with critically ill children at higher risk (19.6% vs 16.1%).[2] These alarming numbers are particularly disconcerting because, unlike other causes of AKI, drug-induced nephrotoxicity is often predictable and preventable.

The systemic consequences of nephrotoxic AKI extend well beyond the kidney itself. In the short term, patients experience delayed recovery, greater susceptibility to infection, fluid overload, and prolonged hospitalization. AKI triggers a cascade of multi-organ disturbances. Cardiovascular complications include volume overload and arrhythmias precipitated by hyperkalemia, pulmonary injury may arise from fluid accumulation and microvascular damage caused by renal cell-derived debris., and accumulation of uremic toxins and inflammatory mediators can lead to encephalopathy. In addition, hepatic dysfunction can result from systemic inflammation and fluid overload, bone-marrow suppression and immune dysregulation may lead to cytopenias and acquired immunodeficiency, and intestinal ischemia, acidosis, and congestion disrupt the gut barrier and alter the microbiome, thus promoting bacterial translocation.[3] In the longer run, the affected children bear an elevated risk of developing chronic kidney disease, hypertension, proteinuria and, in some cases, of progressing to end-stage kidney disease – a trajectory well documented in follow-up studies.[4]

Vulnerability to nephrotoxic insults is multifactorial. Neonates, especially those born preterm, and children younger than five years are particularly susceptible due to immature renal physiology.[1] Comorbid conditions such as sepsis, hypoalbuminemia, pre-existing kidney disease, liver or heart failure, malignancies, and acid-base imbalances further amplify this risk. Drug-related factors, including intrinsic nephrotoxicity, cumulative dosing, therapy duration, and especially polypharmacy with multiple nephrotoxins, exponentially elevate the risk. Notably, nephrotoxicity must be considered even when another cause for AKI exists, as coexisting insults often act synergistically.

Historically, recognition of nephrotoxic AKI has been reactive, with diagnoses frequently made only after detection of a rise in serum creatinine, by which point kidney damage is already underway. However, evidence-based prevention strategies exist: baseline assessment of renal function upon hospital admission in children receiving potential nephrotoxins; daily creatinine monitoring in high-risk populations, as recommended by organizations such as the Canadian Paediatric Society;[5] dose adjustments based on estimated glomerular filtration rate (eGFR); and therapeutic drug monitoring for agents with narrow therapeutic indices. The interpretation of drug levels must be context-sensitive, especially regarding dosing regimens such as extended-interval and intermittent-dose aminoglycoside therapy. Concurrently, clinicians should be proactive in discontinuing non-essential nephrotoxic agents and in choosing safer alternatives whenever feasible.

Serum creatinine, while it is still the current gold standard for diagnosing and monitoring AKI, has major limitations. Its concentration typically rises only after more than 50% of functional renal mass has been lost, making it a late marker of both injury and recovery. Levels may remain elevated even once renal function has begun to improve, complicating assessment of recovery. In critically ill children, aggressive fluid

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resuscitation can dilute serum creatinine, masking the severity of injury, whereas prolonged illness and reduced muscle mass can lower creatinine production, falsely reassuring clinicians. These factors also render eGFR unreliable during acute episodes. To overcome these shortcomings, a new generation of early and more specific biomarkers, including neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), cystatin C, and interleukin-18 (IL-18), can be detected in serum or urine within hours of tubular injury. Incorporating such markers into diagnostic panels enables earlier AKI detection, improved risk stratification, and more timely adjustments of nephrotoxic therapies, with the potential to significantly improve outcomes in at-risk children.[6]

The *Nephrotoxic Injury Negated by Just-in-time Action (NINJA)* initiative provides compelling real-world evidence that structured prevention can dramatically reduce nephrotoxic AKI.[7] Implemented among hospitalized children outside ICUs, NINJA involved daily serum creatinine surveillance and systematic identification of nephrotoxic exposures. In its first year, while 25% of at-risk children still developed AKI, there was a 42% reduction in AKI days per 100 days of nephrotoxic exposure. Over three years, nephrotoxic exposures dropped by 38%, and AKI incidence fell by 64%.[8] Similar interventions in neonatal ICUs ("Baby NINJA") proved equally effective, cutting high-nephrotoxic drug exposures from 16.4 to 9.6 per 1,000 patient-days (P = 0.03), lowering the proportion of nephrotoxin-associated AKI from 30.9% to 11.0% (P < 0.001), and decreasing AKI intensity from 9.1 to 2.9 per 100 susceptible patient-days (P <0.001). Over the 18-month sustainability period, these measures averted an estimated 100 episodes of AKI.[9]

The 2012 and 2024 KDIGO Clinical Practice Guidelines for the Evaluation and Management of Chronic Kidney Disease emphasized early detection, prevention, and risk stratification in pediatric AKI.[10,11] System-level interventions such as electronic alerts for nephrotoxic drug combinations, standardized monitoring protocols, and stewardship programs are necessary to reinforce clinician vigilance.

When prevention fails and nephrotoxicity occurs, withdrawal of the offending agent, whenever clinically justifiable, remains the primary intervention. Though challenging, especially in children who need such drugs for life-threatening conditions, early substitution with less nephrotoxic alternatives must be prioritized. Adequate supportive care, including fluid and electrolyte management and careful monitoring of urine output, is indispensable. Renal replacement therapy may become necessary in severe cases but does not replace prompt cessation of nephrotoxic exposure.

In sum, drug-induced AKI is a common, clearly identifiable, and largely preventable cause of kidney injury in children. The evidence is compelling: structured surveillance programs and timely intervention can cut its incidence dramatically. To translate this knowledge into routine practice, a stronger and more sustained investment in the education of all healthcare professionals who prescribe or monitor nephrotoxic agents is essential. Training should emphasize early risk recognition, individualized dosing, and prompt response to subtle changes in renal function. Pediatric nephrologists, together with pediatricians, must champion a culture of anticipation rather than reaction, shifting clinical care from passive recognition to proactive prevention. At the institutional level, hospitals should commit resources to electronic prescribing safeguards, standardized monitoring protocols, and true multidisciplinary collaboration—including doctors, pharmacists, nurses, and other healthcare professionals—to ensure that safe prescribing and vigilant follow-up become embedded in everyday care. Moreover, the incorporation of more sensitive and specific biomarkers into routine clinical practice is imperative, while sustained scientific research should be strategically directed toward the discovery, validation, and clinical translation of novel biomarkers to advance both diagnostic precision and therapeutic effectiveness.

In an era where precision medicine and patient safety are paramount, preventable kidney injury from therapeutic agents must be regarded as unacceptable. Nephrotoxic AKI in children represents not merely a complication of hospitalization but a clarion call to vigilance, stewardship, and unwavering preventative efforts.

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