Subphenotypes of acute kidney injury in children

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Purpose of review
The purpose of this review is to describe acute kidney injury (AKI) phenotypes in children.

Recent findings
AKI is a heterogeneous disease that imposes significant morbidity and mortality on critically ill and noncritically ill patients across the age spectrum. As our understanding of AKI and its association with outcomes has improved, it is becoming increasingly apparent that there are distinct AKI subphenotypes that vary by cause or associated conditions. We have also learned that severity, duration, and repeated episodes of AKI impact outcomes, and that integration of novel urinary biomarkers of tubular injury can also reveal unique subphenotypes of AKI that may not be otherwise readily apparent.

Summary
Studies that further delineate these unique AKI subphenotypes are needed to better understand the impact of AKI in children. Further delineation of these phenotypes has both prognostic and therapeutic implications.

Keywords
acute kidney injury, hospital-acquired acute kidney injury, pediatrics, precision biomarkers

INTRODUCTION
Acute kidney injury (AKI) is a heterogeneous disease that imposes significant morbidity and mortality on critically ill and noncritically ill patients across the age spectrum. Epidemiologic studies among neonates and children report varying risk factors for AKI development and associated outcomes [1,2,3]. In each of the three major epidemiology studies, AKI was associated with increased mortality, and in some settings, increased hospital resource utilization characterized by longer duration of ventilation and longer time in the ICU and hospital.

As our understanding of AKI and its association with outcomes has improved, it is becoming increasingly apparent that there are distinct AKI subphenotypes that vary by cause or associated conditions. We have also learned that severity, duration, and repeated episodes of AKI impact outcomes, and that integration of novel urinary biomarkers of tubular injury can also reveal unique subphenotypes of AKI that may not be otherwise readily apparent [4]. Pediatric AKI incidence, severity, and outcomes are further complicated by variables such as patient age, nephron endowment, and kidney development.

The purpose of this review is to summarize the clinical subphenotypes of pediatric hospital-acquired AKI. Importantly, the role of prognostic and predictive enrichment in defining AKI phenotypes will be discussed.

HOSPITAL-ACQUIRED ACUTE KIDNEY INJURY

Nephrotoxic medication-associated acute kidney injury
Nephrotoxic medication-associated AKI (NTMx-AKI) is common in hospitalized children. Approximately 30% of children exposed to a nephrotoxic medication while hospitalized will develop AKI [5]. The risk is greater for children who receive at least three concomitant nephrotoxins or prolonged intravenous aminoglycoside antibiotics [5]. Particular patient
groups as described below frequently develop AKI where nephrotoxin exposure is a primary contributing factor [6–9].

The NTMx-AKI subphenotype includes several mechanisms of injury calling for further characterization (Fig. 1). Nephrotoxicity from medications most commonly presents as three subtypes, including acute tubular necrosis (ATN), acute interstitial nephritis (AIN), and/or obstructive nephropathy [10,11]. Drugs such as aminoglycosides, vancomycin, and amphotericin B are frequently implicated in causing a direct nephrotoxic effect leading to ATN [10]. Studies in children show a relatively low rate of AKI associated with vancomycin use alone, but an increased risk of AKI in patients receiving vancomycin concomitantly with other medications [5,12]. In a cohort of 5686 pediatric critically ill patients, it was piperacillin/tazobactam and not vancomycin that was independently associated with increased AKI risk [12]. Alternatively, exposure to a medication can result in an idiosyncratic effect as occurs with AIN [11]. Antiviral medications are commonly implicated in obstructive nephropathy, which can occur when medications crystallize in the urinary system [13,14]. The clinical manifestations of the different subtypes of NTMx-AKI phenotype can differ (Fig. 1) [15,16].

Early recognition of patients at risk for NTMx-AKI is paramount. Program-directed nephrotoxic medication surveillance has been shown to be impactful in decreasing the burden of AKI in children. An example of this is seen with the Nephrotoxic Injury Negated by Just-in-time Action (NINJA) collaborative through which an alert is delivered to a pharmacist who notifies a care team of nephrotoxin exposure [17]. The NINJA collaborative has demonstrated the impact of focusing attention on a single AKI subphenotype, with a 37% reduction in AKI rates per exposure and 24% reduction in AKI prevalence rates [17].

Cardiac surgery-associated acute kidney injury

An extremely large proportion of children undergoing congenital heart surgery experience AKI in the postoperative period. There appears to be a substantial variation in the rate of AKI that is affected by patient age, the degree of heterogeneity in the population studied, center differences in intraoperative and postoperative management strategies, timing of diagnosis, and which AKI definition is applied. This has made direct comparisons of multiple studies particularly challenging. Of the 20 studies included in a recent meta-analysis describing strategies to prevent AKI after cardiac surgery, the timing, severity, and duration of AKI were not similar between more than two studies [18]. Adjudication of AKI was also dissimilar across studies [18]. The heterogeneity in AKI rates was reported in a recent

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**KEY POINTS**

- Acute kidney injury in children is common and is associated with significant morbidity and mortality.
- Multiple subphenotypes of AKI in children exist that may have prognostic and therapeutic implications.
- Subphenotypes of AKI may be disease-specific but may also vary in onset, duration, and severity.
- Precision biomarkers may further clarify and refine AKI-specific subphenotype.
Sepsis-associated acute kidney injury

Sepsis-associated acute kidney injury (S-AKI) is a unique subphenotype of AKI with heterogeneous underlying pathobiology that is in large part driven by the host-dysregulated immune response to infection [25,26]. Although historically described as a consequence of renal hypoperfusion in the setting of shock, our current understanding leverages what we have learned about sepsis heterogeneity to recognize S-AKI as a complex, multifactorial disorder of altered macrocirculatory and microcirculatory blood flow, metabolic derangements, and disordered inflammation that is quite variable at the individual patient level [25–27]. Recognizing this variability, several groups have begun to identify unique subphenotypes of S-AKI by incorporating demographic, clinical, and biomarker data and using cluster analysis and/or machine-learning methodologies [28–30]. These unique subphenotypes have been shown to be associated with differences in inflammatory patterns, markers of endothelial dysfunction, response to therapy, and outcomes [28–30]. In children specifically, one group recently identified differences in outcomes for patients subgrouped by AKI severity and duration, with those with severe (≥KDIGO stage 2) and/or persistent (present for ≥48 h) AKI suffering higher rates of mortality and fewer ICU-free days compared with those with mild and/or transient AKI [31**]. Highlighting the importance of the septic inflammatory response in the development of S-AKI, another group recently demonstrated the association between validated biomarkers of the pediatric septic inflammatory response and the development of S-AKI and incidence of renal recovery [32]. Although none of these subphenotyping strategies have been widely applied to clinical practice at the bedside, this preliminary work has made it clear that
S-AKI is a heterogeneous disorder that requires improved diagnostic precision in order to identify effective therapies and improve outcomes.

**Onconephrology**

There has been significant advancement in the diagnosis and treatment of children with oncologic diseases. The survival rates for childhood cancers have substantially increased in recent years with over 80% of children and adolescents diagnosed with cancer surviving at least 5 years between 2008 and 2014 [33]. The reported incidence of AKI in children with cancer is 11–84% [34,35]. In a prospective study of 1047 children admitted to the ICU, the most common admission diagnoses in AKI cases were hemolytic uremic syndrome and oncologic diseases [6].

The direct infiltration of the urinary system by cancer cells or exposures encountered during cancer therapy are well known risk factors for AKI [36]. Notable exposures that increase the risk for AKI

**FIGURE 2.** Acute kidney injury phenotypes. Patients with a biomarker of injury positivity without elevation/decline in serum creatinine and not reaching urine output criteria should be classified as 1S. Reassessment should be performed according to patient clinical context and temporal trends. Patients reaching SCr/UO criteria, and no elevation on biomarker are defined as 1A, and those reaching SCr/UO criteria with elevated biomarker are reclassified as 1B. Biomarker positivity should be based on its mechanism and defined threshold. BM, biomarker; sCr, serum creatinine; UO, urine output. Reproduced with permission from Acute Disease Quality Initiative 23 (https://www.ADQI.org).
include a diagnosis of tumor lysis syndrome, use of contrast for computed tomography scans, chemotherapeutic agents and hematopoietic stem cell transplantation [36–38]. In a multicenter study of children hospitalized with cancer, the administration of purine analogs carried the highest rate of AKI when compared with other types of chemotherapy [39].

With the advent of newer therapies such as CD19-targeted chimeric antigen receptor T-cell therapy and vascular endothelial growth factor-targeted therapy, there is a need for increased attention to the study and prevention of AKI in children with cancer. Embryonal tumors of the hemopoietic system and the central nervous system are more common in children, whereas tumors occurring in solid organs are more common in adults [38]. Given that the types of cancer diagnoses and treatments differ substantially in children when compared with adults, the future study of AKI prevention and treatment requires a focus on the unique subphenotype of AKI in pediatric oncology patients.

**Neonatal acute kidney injury**

AKI is common in critically ill neonates and adversely impacts outcomes. Similar to other age groups, AKI in neonates is a heterogeneous syndrome consisting of distinct phenotypes based on unique neonatal factors like gestational age and postnatal age (early vs. late AKI) in addition to cause and underlying diseases [3,40–42]. The current diagnosis and staging of AKI severity in neonates uses the neonatal modified KDIGO definition, which is based on the rise in creatinine from a previous trough or decrements in urine output [43]. It is possible that future definitions of neonatal AKI may incorporate gestational age, varying creatinine thresholds, and other metrics like fluid balance and urinary biomarkers to enhance the definition, and better delineate these phenotypes [44,45].

AKI in extremely low-gestational-age neonates is often associated with nephrotoxin medication exposure. In term or near-term neonates, AKI is often multifactorial and may be related to other associated conditions like hypoxic–ischemic encephalopathy, congenital cardiac disease and/or surgery, and multiorgan dysfunction [3]. Early-onset neonatal AKI, defined as AKI diagnosed on postnatal days 2–7 is associated with resuscitation with ephinephrine, inborn errors of metabolism, or need for surgery at admission [40]. On the other hand, late AKI (occurring >7 days after birth) is associated with oligohydramnios and polyhydramnios, presence of congenital mild–moderate renal anomalies, diagnoses of congenital heart disease, necrotizing enterocolitis, and exposure to nephrotoxic medications [41]. Recognition of different phenotypes can improve AKI screening and lead to work to mitigate the consequences of AKI.

**PRECISION BIOMARKERS AS A WAY TO ELUCIDATE PATHOPHYSIOLOGY, TREATMENT, AND PROGNOSIS**

As outlined above, AKI is a heterogeneous disorder with multiple inciting etiologies and underlying pathophysiologicals, whose development is informed by unique patient-level susceptibilities. Because of this heterogeneity, a ‘one size fits all’ approach to its diagnosis and management is unlikely to be successful, as has been demonstrated by a number of failed clinical trials examining therapies and interventions for AKI [46–51]. As such, a precision medicine approach that leverages biomarkers (and other clinically available data) to identify strategies for both *prognostic* (i.e. identifying patients at high risk for an outcome of interest) and *predictive* (i.e. identifying patients with shared underlying biology more likely to respond to a specific therapy) enrichment is required to improve the care of children with AKI [27]. Furthermore, as biomarkers associated with different phenotypes of AKI are identified, it is important to consider their potential role in disease pathophysiology, as this could inform future development of novel therapeutics. A framework for a precision medicine approach to the study, diagnosis and management of pediatric AKI is outlined below and in Fig. 3.

**Prognostic enrichment in acute kidney injury: what to predict and why?**

Before prognostic enrichment strategies can be identified, one must first answer two questions: what is a clinical outcome of interest worth predicting, and how will predicting that outcome be useful? Table 1 outlines proposed relevant outcomes of interest for prognostic enrichment in AKI, potential use cases for such tools, and some existing examples, whenever applicable. Notably, there has been an appropriate focus on identifying tools to predict who will develop severe and/or persistent AKI, as there is a growing body of evidence suggesting an association between these outcomes and morbidity and mortality in both adults and children [1,4,21,31**]. Importantly, utilization of prognostic enrichment tools designed to predict these outcomes may facilitate enrichment of future clinical trials aimed at preventing AKI (as has been done successfully in some adult studies) [52,53], and testing novel therapeutics, reducing the number of patients needed to enroll,
and increasing the likelihood of seeing a benefit if one exists. The former is of particular importance in pediatrics, given the relatively small patient population compared with adults. Finally, additional work is needed to identify and validate prognostic enrichment tools to better predict who will need KRT, and which patients are at highest risk of developing chronic kidney disease (CKD) following an episode of AKI (Table 1). Having the ability to reliably identify these populations could inform care at the bedside (i.e., identify those who need nephrology follow-up after discharge), and similarly enrich future clinical trials in these patient populations.

**Predictive enrichment in acute kidney injury:**

**tying clinical phenotypes to biological endotypes**

As increasing numbers of clinically relevant AKI phenotypes are identified, it is important to characterize the biological underpinnings (i.e., endotypes) of these unique subsets of patients in order to identify novel treatment strategies. Currently, the most commonly available AKI biomarkers ([TIMP2]-[IGFBP7], CCL14, NGAL) are all markers of tubular stress and/or direct tubular injury – as opposed to modifiable targets in AKI pathogenesis – and therefore, have limited utility for predictive enrichment [64–66]. Thus, identification of biomarkers elucidating underlying patient biology is sorely needed to help develop novel therapeutics or identify subsets of patients who may respond to existing therapies. A recent and promising example of this concept can be found in serum renin levels. Recent post hoc analyses of the ATHOS-3 trial examining the use of the novel vasoactive medication angiotensin II in adults with vasoplegic shock demonstrated that patients with AKI had higher serum renin levels and those with AKI and elevated serum renin levels who received angiotensin II had increased rates of renal recovery compared with placebo [67–69]. Importantly, the investigators were also able to tie elevation in serum renin (an upstream molecule in the renin–angiotensin–aldosterone pathway that is easily measured in the serum) to increases in angiotensin I/angiotensin II ratios, suggesting a relative deficiency of angiotensin II in these patients and providing strong biological plausibility for their findings [67]. Similar work is needed in children with AKI to begin delivering the right therapy to the right patients to improve outcomes.

**THE ROLE OF DEVELOPMENT AS A BIOLOGICAL VARIABLE IN ACUTE KIDNEY INJURY SUBPHENOTYPES**

Traditionally, AKI was considered a self-resolving condition with no long-term implications. There is now better understanding of kidney recovery after

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**FIGURE 3.** Prognostic and predictive enrichment in acute kidney injury.
AKI, and how it depends on AKI severity, cause, duration, and baseline kidney function. Various phenotypes of recovery after AKI have been identified: early sustained AKI reversibility, late sustained AKI reversibility, relapse AKI and recovery, relapse AKI without recovery and never recovered AKI [70]. Each of these correlates differently with long-term outcomes. Despite increasing awareness of the link between AKI and chronic kidney disease (CKD), numerous knowledge gaps persist. The progression from AKI to CKD likely involves maladaptive regeneration after tubulointerstitial injury, fibrosis, and glomerulosclerosis [71]. More details on these mechanisms, and strategies to halt or reverse them are still being studied. Unique to pediatrics, the timing, duration, and severity of AKI and how it interacts with the patient’s nephron endowment and development, likely play a critical role in long-term outcomes. However, data supporting this hypothesis are lacking and future studies are warranted to investigate the interplay of development as a biological variable and pediatric AKI outcomes. Although we have ample evidence of the high rates of CKD and hypertension after pediatric AKI, there are no protocols or guidelines regarding follow-up of these patients. This stems from lack of clear data on which patients are most likely to develop complications, how long should children with AKI be followed post discharge, and what evaluation is needed during follow-up.

**CONCLUSION**

Pediatric hospital-acquired AKI subphenotypes are informed by numerous factors and are distinct from hospitalized adult patients. The risk of developing AKI as well as the chance for renal recovery and/or progression to CKD are also informed by the patient’s nephron endowment and renal development at the time of AKI. This concept of development as a biological variable is unique to pediatrics; however, it portends significance throughout the patient’s lifespan.

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Conflicts of interest
There are no conflicts of interest.

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"Papers of particular interest, published within the annual period of review, have been highlighted as:
 ■ of special interest
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