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Sub-phenotypes of AKI in Children

Katja M. Gist, DO, MSc[1], **Dana Fuhrman, DO, MS**[2], **Natalja Stanski, MD**[1], **Shina Menon, MD**[3], **Danielle E. Soranno, MD**[4]

[1]Department of Pediatrics, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati OH.

[2]Department of Pediatrics, Children's Hospital of Pittsburgh, University of Pittsburgh School of Medicine, Pittsburgh PA.

[3]Department of Pediatrics, Seattle Children's Hospital, University of Washington School of Medicine, Seattle WA.

[4]Department of Pediatrics, Riley Hospital for Children, Indiana University School of Medicine, Indianapolis IN.

Abstract

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

Recent Findings: AKI is a heterogenous disease that imposes significant morbidity and mortality on critically ill and non-critically 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 sub-phenotypes that vary by etiology 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 sub-phenotypes of AKI that may not be otherwise readily apparent.

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

Keywords

Pediatrics; Acute Kidney Injury; Hospital acquired AKI; Precision biomarkers

Introduction:

Acute Kidney Injury (AKI) is a heterogenous disease that imposes significant morbidity and mortality on critically ill and non-critically ill patients across the age spectrum. Epidemiologic studies among neonates and children report varying risk factors for AKI development and associated outcomes[1–3]. In each of the 3 major epidemiology studies, AKI was associated with increased mortality, and in some settings, increased hospital resource

Corresponding author Danielle E. Soranno, MD, DSoranno@IU.edu.

utilization characterized by longer duration of ventilation and longer time in the intensive care unit (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 sub-phenotypes that vary by etiology 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 sub-phenotypes 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 sub-phenotypes of pediatric hospital acquired AKI. Importantly, the role of prognostic and predictive enrichment in defining AKI phenotypes will be discussed.

Hospital Acquired AKI

Nephrotoxic Medication Associated AKI

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 ≥ 3 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 sub-phenotype includes several mechanisms of injury calling for further characterization (Figure 1). Nephrotoxicity from medications most commonly presents as 3 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 5,686 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 (Figure 1) [15,16].

Early recognition of patients at risk for NTMx-AKI is paramount. Programs directed nephrotoxic medication surveillance have 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 sub-phenotype, with a 37% reduction in AKI rates per exposure and 24% reduction in AKI prevalence rates[17].

Cardiac Surgery Associated AKI

An extremely large proportion of children undergoing congenital heart surgery experience AKI in the postoperative period. There appears to be substantial variation in the rate of AKI that is affected by patient age, the degree of heterogeneity in the population studied, center differences in intra- and post-operative 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 2 studies[18]. Adjudication of AKI was also dissimilar across studies[18]. The heterogeneity in AKI rates was reported in a recent report from the multicenter Neonatal and Pediatric Heart and Renal Outcomes Network, including 2240 neonates undergoing cardiac surgery with or without cardiopulmonary bypass[19]. AKI rates across centers ranged from 27–86%, of which 0–31% were quantified as severe (KDIGO ≥2). The vast majority of AKI was diagnosed by urine output and occurred early in the postoperative course. In this study, only stage 3 AKI was associated with mortality. Another example of discrepant AKI rates across centers was reported by Blinder *et al.*, in a secondary analysis of the Safe Pediatric Euglycemia after Cardiac Surgery trial[20]. The difference in AKI rates between the 2 centers was 51%. While there was an overall association of longer duration of AKI with longer time spent on the ventilator and time in the ICU, when the variables were compared between centers, the median duration of ventilation and length of stay at the center with the highest AKI rate was significantly shorter ventilation duration and length of stay. Both studies have reinforced the notion that not all creatinine elevation, or decrements in urine output are because of tubular dysfunction. Indeed, creatinine elevation may be affected by significant hemoconcentration resulting from intra-operative ultrafiltration.

These studies have prompted investigators to evaluate the contribution of AKI duration for delineation of sub-phenotypes and the associations with outcomes as recommended by the 16th Acute Disease Quality Initiative (ADQI) [4]. Gist and colleagues compared the association of transient (≤ 48 hours) and persistent (>48 hours) in a 2-center study of children with hypoplastic left heart syndrome[21]. Mortality was four times higher (41% vs. 12%) in those with persistent AKI, although this association was not significant on multivariable analysis. However, severe persistent AKI was associated with a 59% increase in the expected duration of ventilation. Lobasso and colleagues classified a heterogenous cohort of 3620 children in groups by recovery. The overall AKI rate was 19%, only 3.4% were characterized as persistent (3–7 days) or acute kidney disease (>7 days). In this study, there was a graded increase in the odds of mortality with transient, persistent, and acute kidney disease (AKD) phenotypes as compared to no AKI[22].

There are hundreds of studies describing novel urinary AKI biomarkers for early detection of AKI after cardiac surgery that are beyond the scope of this review. Unfortunately, few have made it to the clinical space, and thus integration into clinical care has not occurred. The 23rd ADQI consensus conference recommended integration of biomarkers into the AKI definition to delineate sub-AKI phenotypes in which patients can either be creatinine/urine output positive or negative with or without biomarker elevation (Figure 2)

[23]. Among a cohort of critically ill children without cardiac disease, patients with both creatinine and biomarker elevation had the highest odds for predicting day 3 severe AKI compared to only elevation of one of the parameters. Furthermore, the need for kidney replacement therapy (KRT) and mortality were highest among patients with both creatinine and biomarker positivity[24]. There are no studies evaluating this in children following cardiac disease. Demonstrating differences in AKI prediction and associations with outcomes by delineating AKI sub-phenotypes by creatinine/urine output and biomarker elevation following congenital heart surgery has the potential to enhance prognostic and predictive enrichment, and even stratify patients into specific care pathways.

Sepsis-Associated Acute Kidney Injury (S-AKI):

S-AKI is a unique sub-phenotype of AKI with heterogeneous underlying pathobiology that is in large part driven by the host dysregulated immune response to infection[25,26]. While 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 macro- 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 sub-phenotypes of S-AKI by incorporating demographic, clinical and biomarker data and using cluster analysis and/or machine learning methodologies[28–30]. These unique sub-phenotypes 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 sub-grouped by AKI severity and duration, with those with severe (≥ KDIGO Stage 2) and/or persistent (present for ≥ 48 hours) AKI suffering higher rates of mortality and fewer ICU-free days compared to 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]. While none of these sub-phenotyping 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.

Onco-Nephrology

There has been significant advancement in the diagnosis and treatment of children with oncologic diseases. The survival rates for childhood cancers has substantially increased in recent years with over 80% of children and adolescents diagnosed with cancer surviving ≥ 5 years between 2008–2014[33]. The reported incidence of AKI in children with cancer is 11–84%[34,35]. In a prospective study of 1,047 children admitted to the ICU, the most common admission diagnoses in AKI cases were hemolytic uremic syndrome and oncologic pathologies[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 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 multi-center study of children hospitalized with cancer the administration of purine analogues carried the highest rate of AKI when compared to 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, while 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 to adults, the future study of AKI prevention and treatment requires a focus on the unique sub-phenotype of AKI in pediatric oncology patients.

Neonatal AKI

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 etiology 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 epinephrine, 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 oligo- 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 pathophysiologies, 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 Figure 3.

Prognostic Enrichment in AKI- What to Predict and Why?

Before prognostic enrichment strategies can be identified, one must first answer two questions: (1) what is a clinical outcome of interest worth predicting, and (2) 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, when 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 to 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 AKI- 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 clinically 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[54–56]. 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 (1) patients with AKI had higher serum renin levels and (2) those with AKI *and* elevated serum

renin levels who received angiotensin II had increased rates of renal recovery compared to placebo[57–59]. 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[57]. 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 AKI sub-phenotypes

Traditionally, AKI was considered a self-resolving condition with no long-term implications. There is now better understanding of kidney recovery after AKI, and how it depends on AKI severity, etiology, 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[60]. 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[61]. 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.

Conclusions:

Pediatric hospital-acquired AKI sub-phenotypes 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, portends significance throughout the patient's lifespan.

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*Special Interest

**Outstanding Interest

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Key Points

- Acute kidney injury in children is common and is associated with significant morbidity and mortality
- Multiple sub-phenotypes of AKI in children exist that may have prognostic and therapeutic implications
- Sub-phenotypes of AKI may be disease specific but may also vary but onset, duration and severity
- Precision biomarkers may further clarify and refine AKI specific sub-phenotype

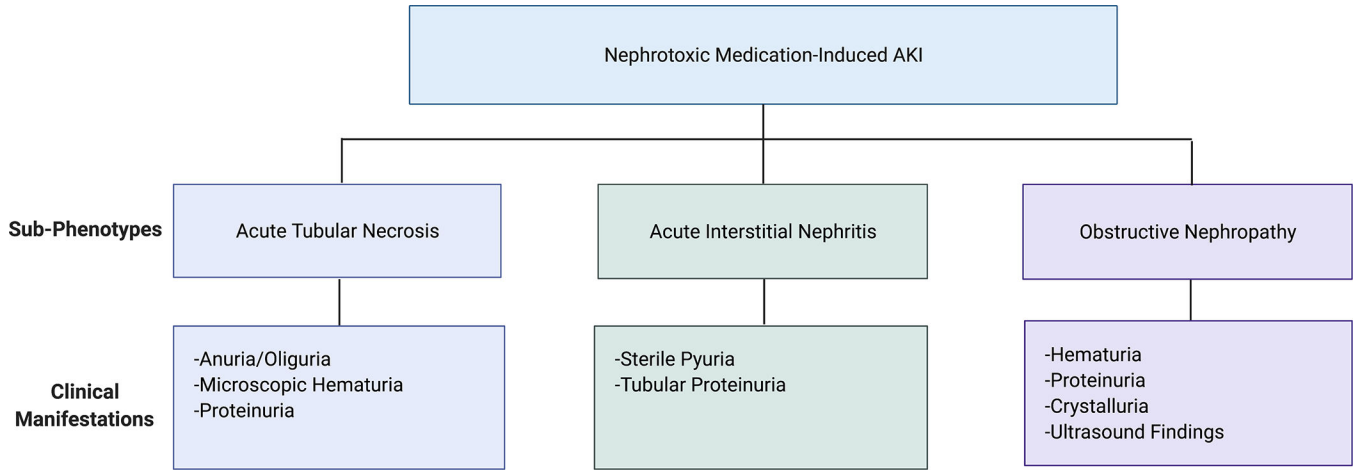

Figure 1.
Phenotypes of Nephrotoxic Medication Associated AKI

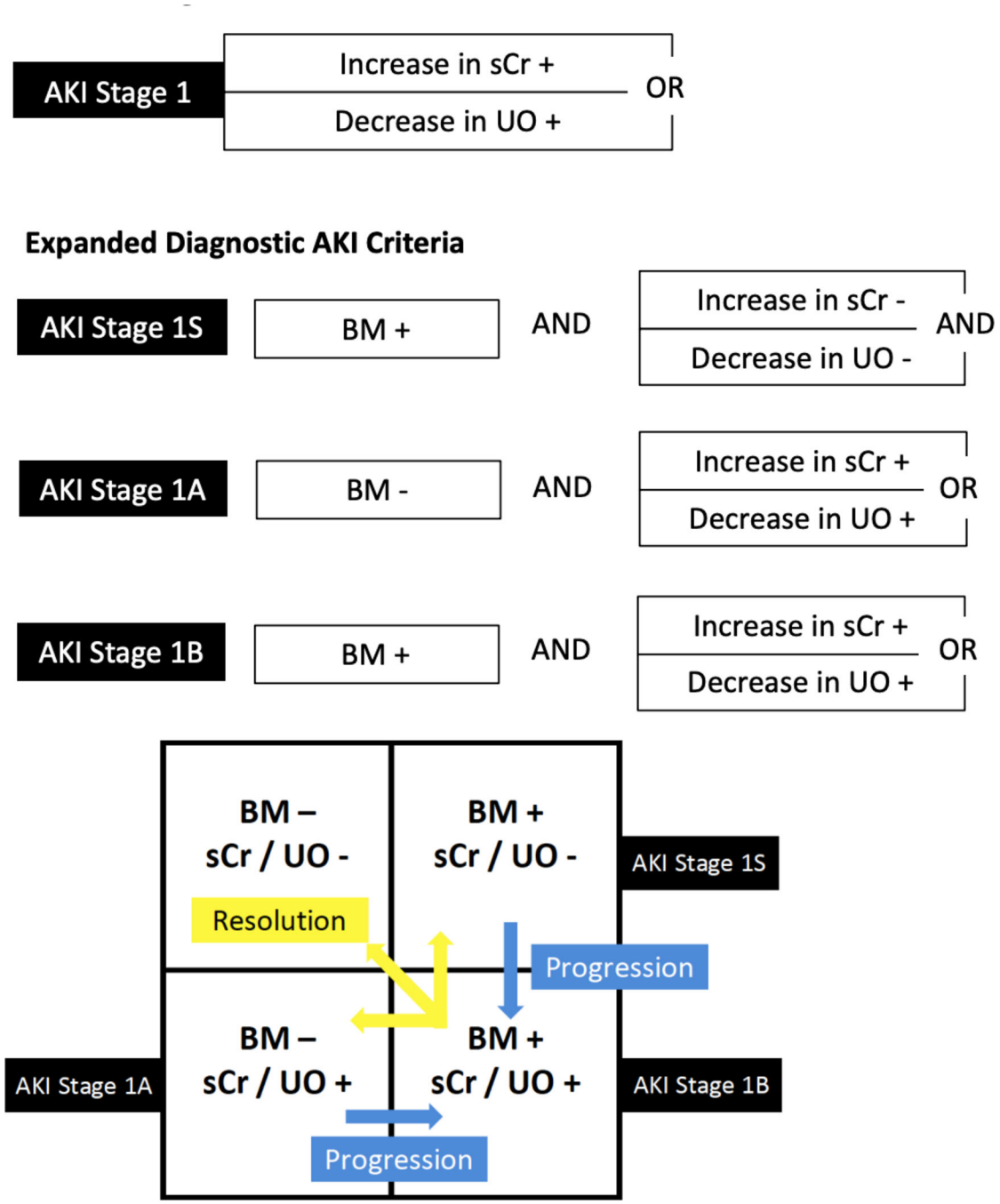

Figure 2. Acute kidney injury phenotypes.

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. sCr = serum creatinine; UO =

urine output; BM = biomarker. Reprinted from Acute Disease Quality Initiative 23 (https://www.ADQI.org), used with permission.

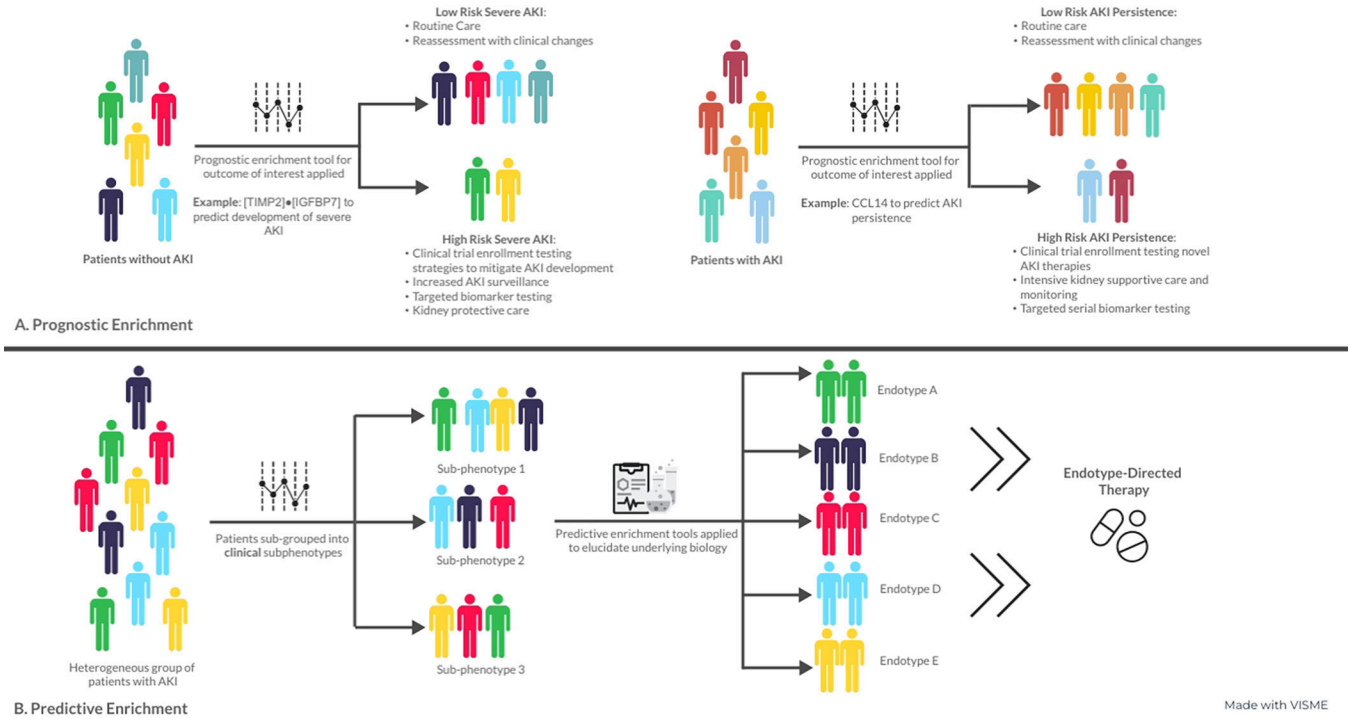

Figure 3.
Prognostic and Predictive Enrichment in AKI

Table 1:

Proposed outcomes of interest for prognostic enrichment, their potential utility, and some existing examples in patients with and without AKI.

	Outcomes of Interest	Proposed Use	Examples
Patient without AKI	Development of *any* AKI	• Increased surveillance for AKI • Consideration of alternatives to nephrotoxic medications or procedures • Closer monitoring of drug levels (i.e. vancomycin), when applicable • Patient/family education • Targeted novel biomarker testing	• Various machine learning algorithms, including EHR-embedded[51,62,63]
	Development of *severe* and/or *persistent* AKI	*In addition to above:* Clinical trial enrichment for studies examining standardized AKI prevention strategies	• The Renal Angina Index *[64–67] • [TIMP2]•[IGFBP7] [55]
Patient with AKI	Development of *severe* and/or *persistent* AKI	• Clinical trial enrichment for studies examining novel therapies for AKI • Intensive kidney supportive care (i.e. strict urine output monitoring, frequent laboratory monitoring) • Patient/family counseling • Targeted *serial* novel biomarker testing	• The Renal Angina Index *[64–70] • CCL14[54,71] • Furosemide stress test *[68–70]
	Need for KRT	• Clinical trial enrichment for studies examining timing of KRT initiation • Inform clinical decision making • Patient/family counseling	• Furosemide stress test *[68–70]
	Development of CKD	• Clinical trial enrichment for studies examining therapies to prevent AKI/AKD to CKD transition • Identify patients appropriate for outpatient nephrology follow-up • Patient/family counseling	• No validated tools available

Abbreviations: AKI- acute kidney injury; KRT- kidney replacement therapy; AKD- acute kidney disease; CKD- chronic kidney disease; [TIMP2]•[IGFBP7]- the product of tissue inhibitor of metalloproteinases-2 and insulin-like growth factor-binding protein 7; CCL14- C-C motif chemokine ligand 14

* Indicates tools that are well studied in children