10 Diagnosis and Management of Acute Kidney Injury in Critical Illness

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AKI in Critical Illness: A Pediatric Epidemic

Case Scenario

A 10-year-old, 40 kg, Hispanic female presented to the ED with a history of cough, fever, and decompensated shock. She was found to have pneumonia and bacteremia. At presentation, she had mixed respiratory and metabolic acidosis, serum creatinine was 0.9 mg/dL, and BUN was 14 mg/dL. She received 40 mL/kg of normal saline and was intubated, started on a dopamine infusion, and admitted to the PICU. Over the next 12 h, she received an additional 2 L of fluid including 1 L of blood products and was started on a norepinephrine drip.

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The importance of early recognition and proper management of AKI is now at the forefront of critical care medicine. In those who are critically or acutely ill, AKI is exceptionally common and is associated with negative outcomes independent of severity of illness [1–3]. In an effort to better define the global incidence of AKI, a worldwide meta-analysis of over 300 adult and pediatric retrospective and prospective cohort studies was performed [4]. The incidence of AKI was approximately 34% in children based upon KDIGO-defined AKI criteria. Higher rates of AKI were found in those who were critically ill, including those in the ICU and post-cardiac surgery. The occurrence and outcomes of KDIGO-defined AKI in a worldwide ICU population was investigated in the adult population in the Acute Kidney Injury-Epidemiologic Prospective Investigation (AKI-EPI) [5]. This was the first multinational, cross-sectional study on the epidemiology of AKI in a worldwide ICU population. AKI occurred in over half of the ICU patients with an independent association between AKI severity and mortality. On various continents, the rate and mortality of those with AKI were very similar.

In children, a recent cross-sectional analysis of over two million pediatric hospital admissions in the United States identified risk factors for AKI [6]. The incidence of AKI was found to be higher in African Americans, in teenagers aged 15–18 years of age, and in neonates admitted to

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the pediatric ICU. Neonates, and those requiring renal replacement therapy, had the highest mortality rates. In addition to this cross-sectional study, our understanding of AKI in the pediatric ICU has greatly expanded with the recent multinational, multicenter prospective study entitled AWARE (Assessment of Worldwide Acute Kidney Injury, Renal Angina and Epidemiology in Critically Ill Children) [7].

The AWARE study examined pediatric and young adult patients admitted to the pediatric ICU and children admitted to the pediatric cardiac ICU (but not after surgery for congenital heart disease). This study provides the most comprehensive analysis of the epidemiology of AKI with recruitment from over 30 pediatric ICUs from four continents. Findings revealed that during the first 7 days of ICU admission, AKI occurred in approximately one-fourth of the patients and severe AKI occurred in approximately 12%. Even after controlling for multiple potential confounders and severity of illness scores, severe AKI and receipt of renal replacement therapy (RRT) were significant predictors of death by 28 days of admission. Severe AKI was also associated with increased use of mechanical ventilation, RRT, and longer ICU length of stay. These findings correlate with aforementioned adult data, specifically with AKI-EPI.

Defining AKI in the neonatal population is challenging due to confounders including the presence of maternal serum creatinine (sCr) and immaturity of the proximal tubules. For these reasons, investigations are ongoing to identify biomarkers to assist with AKI diagnosis in neonates. A 24 center, multinational study was recently performed: the AWAKEN (Assessment of Worldwide Acute Kidney injury Epidemiology in Neonates) study [8]. Of the over 2000 infants studied, 30% (605) of the patients were found to have AKI with the majority of those being less than 29 weeks gestation followed by those greater than 36 weeks gestation. AKI was defined by the neonatal modified KDIGO criteria [9]. Like the AKI-EPI and the AWARE studies, even after adjusting for multiple potential confounders, those with AKI had longer length of hospital stay and higher mortality.

Children who undergo surgery to correct congenital heart lesions commonly develop cardiac surgery-associated AKI (CS-AKI), with an incidence of up to 50% postoperatively and with an even higher incidence in neonates [10, 11]. Emerging data now reveals that factors such as prolonged cardiopulmonary bypass (CPB) time, young age, and higher RACHS-1 (Risk Adjusted classification for Congenital Heart Surgery) category are less likely to be independently associated with CS-AKI. The increase in CS-AKI is likely attributed to the increased complexity of heart surgeries that are performed along with increased survival of patients with congenital heart lesions. CS-AKI is also associated with increased length of ICU hospital stay and mortality [11, 12].

Outcomes Ascribed to AKI

AKI is common in adults, children, and neonates admitted to intensive care units [1, 7, 13]. Even after controlling for numerous potential confounders, those with AKI have higher mortality, prolonged mechanical ventilation, and increased ICU length of stay. In addition, growing evidence suggests that AKI is not only associated with short-term but also long-term consequences such as chronic kidney disease (CKD) and end-stage renal disease (ESRD) [14, 15]. Even if an AKI episode seems to resolve and the sCr returns to baseline, there is evidence that these patients may have "subclinical CKD" and are at higher risk to progress to CKD [16]. In a prospective study, the association between children with AKI in the pediatric and cardiac ICU and the incidence of CKD at 1–3 years after AKI was evaluated, and it was found that 10% developed CKD (eGFR <60 mL/min/1.73m^2) and an additional 50% were at risk for development of CKD (measured GFR 60–90 mL/min/1.73 m^2, hypertension, or hyperfiltration) [15]. In the kidney transplant population, those who develop AKI within 3 years of kidney transplantation are at an increased risk for development of CKD and graft failure [17]. Unfortunately, although guidelines for care suggest that all patients should have kidney

follow-up within 3 months of hospital discharge, very few programs have a systematic method to follow these patients, and in some reports, only 40% of those who develop AKI may actually follow up with a nephrologist [18].

Recognition: Does It Matter?

Current AKI criteria include both sCr and urine output for diagnosis; however, until recently, many studies on AKI in the pediatric ICU did not include oliguria. The importance of inclusion of both for diagnosis remains in question. There are quite a few studies that suggest omitting oliguria fails to identify a significant number of individuals with AKI.

Serum Creatinine as a Metric for AKI

Serum creatinine currently remains the gold standard for AKI diagnosis as it is often readily available and inexpensive. Importantly, sCr changes act as a biomarker of kidney function, not injury. Serum creatinine changes are often seen days after the initial injury, thus delaying diagnosis and early management. Serum creatinine is not the ideal biomarker in the detection of AKI as it is affected by many other nonrenal factors such as gender, muscle mass, and fluid balance. It is extremely important to be mindful of those patients who are fluid overloaded and its effects on the measurement of sCr, likely masking the severity of AKI. Prior studies have demonstrated that failure to correct sCr for fluid balance underestimates the prevalence of AKI, therefore suggesting that in some cases, oliguria may be a better indicator of AKI [19, 20].

Urine Output as a Metric for AKI

There is limited independent data on inclusion of urine output as criteria for AKI diagnosis, and its use is somewhat controversial. Using oliguria in the definition for AKI must be done in the context of additional clinical criteria including hydration status, use of diuretics, and urinary tract obstructions. The AWARE study demonstrated that not including oliguria as a criterion for AKI failed to identify a significant number of patients with AKI and oliguria in of itself was associated with an increased risk of mortality [7]. Unfortunately, obtaining both urine and sCr can be difficult in children in the critical care setting. If an indwelling bladder catheter is not in place, the clinician then must depend on reports of number of voids or weighing of diapers and not having a true hourly urine flow rate. Of course, risks and benefits must be considered in the decision of maintaining an indwelling bladder catheter with concerns of increased risk of infection.

More individuals are diagnosed with AKI by incorporating urine output criteria than by using sCr alone [21–24]. In a prospective observational study of over 300 critically ill patients, the authors demonstrated that the diagnosis of AKI occurred earlier in patients with oliguria in comparison to those without [24]. In another prospective observational study in critically ill adults, the RIFLE (risk, injury, failure, loss of kidney function, and end-stage kidney disease) criteria with sCr alone was compared to sCr plus urine output. Using the RIFLE criteria with sCr alone failed to recognize as many patients with AKI, failed to identify the maximum AKI severity, and led to delays in AKI diagnosis. Incorporation of urine output into the definition was associated with higher mortality [23]. The added value of urine output was also recently explored in a retrospective analysis of over 30,000 hospital admissions over 8 years. In this cohort, approximately 75% of the patients developed AKI. Individuals who met both sCr and urine output criteria for AKI had worse outcomes than those who met only one criterion [25]. Collectively, these studies strongly support the need for both sCr and urine output in defining AKI in the ICU population.

Definitions

There are several definitions of AKI in the published literature which were initially based upon absolute changes in sCr. In 2005, a consensus categorical definition was proposed entitled the

Table 10.1 RIFLE classification of AKI

RIFLE classification criteria		
Class	Serum creatinine or GFR	Urine output
Risk	Increase in serum creatinine × 1.5 or GFR decrease >25%	Less than 0.5 mL/kg/h for more than 6 h
Injury	Increase in serum creatinine × 2 or GFR decrease >50%	Less than 0.5 mL/kg/h for more than 12 h
Failure	Increase in serum creatinine × 3 or serum creatinine >4 mg/dL with an acute rise >0.5 mg/dL or GFR decrease >75%	Less than 0.3 mL/kg/h for 24 h or anuria for 12 h
Loss	Persistent acute renal failure (complete loss of kidney function >4 weeks)	
End-stage kidney disease	End-stage renal disease >3 months	

Table 10.2 AKIN classification of AKI

AKIN classification criteria		
Stage	Serum creatinine	Urine output
1.	Increase in serum creatinine of ≥0.3 mg/dL or increase ≥150–200% (1.5–2-fold) from baseline	Less than 0.5 mL/kg/h for more than 6 h
2.	Increase in serum creatinine >200–300% (>2–3-fold) from baseline	Less than 0.5 mL/kg/h for more than 12 h
3.	Increase in serum creatinine >300% (>3-fold) from baseline or ≥ to 4 mg/dL with an acute increase of at least 0.5 mg/dL or on renal replacement therapy	Less than 0.3 mL/kg/h for 24 h or anuria for 12 h

Table 10.3 KDIGO classification of AKI

KDIGO classification criteria		
Stage	Serum creatinine	Urine output
1	1.5–1.9 × baseline or ≥ 0.3 mg/dL increase	Less than 0.5 mL/kg/h for 6–12 h
2	2–2.9 × baseline	Less than 0.5 mL/kg/h for ≥12 h
3	3 × baseline or increase in serum creatinine ≥4 mg/dL or initiation of renal replacement therapy or, in patients <18 years, decrease in eGFR to <35 mL/min/1.73 m^2	Less than 0.3 mL/kg/h for ≥24 h or anuria for ≥12 h

RIFLE criteria (Table 10.1). A modified version of the RIFLE criteria, pRIFLE, was developed for the pediatric population in 2007 [26]. In 2008, modifications to RIFLE culminated in the Acute Kidney Injury Network (AKIN) classification (Table 10.2). Subsequently, additional modifications defining AKI were made by Kidney Disease: Improving Global Outcomes (KDIGO) (Table 10.3). The KDIGO AKI definition includes a combination of the RIFLE, pRIFLE, and AKIN definitions and encompasses both adult and pediatric criteria [27].

A recent study in pediatrics compared the incidence of AKI in both the ICU and non-ICU settings between pRIFLE, AKIN, and KDIGO according to creatinine changes [28]. This retrospective study revealed that both AKI incidence and staging varied among all three definitions. By detecting the most stage 1 cases, pRIFLE generated the largest AKI cohort. In reference to AKI diagnosis, AKIN and KDIGO were the two that corresponded most accurately. These findings demonstrate that while these definitions are similar, there are differences significant enough to cause variation in AKI staging. There should be a constant pursuit to find methods to improve the ability to predict meaningful outcomes. It is possible that incorporation of fluid overload and biomarkers may improve our ability to properly detect AKI. For now, KDIGO-defined AKI should be the standardized criteria used for AKI diagnosis.

Biomarkers

Novel biomarkers are continually being examined to obtain an earlier, accurate diagnosis of AKI. The nature of current biomarkers such as sCr and oliguria leads to delayed AKI diagnosis. If novel biomarkers are validated as early markers of AKI, they can be incorporated with other markers of kidney injury or combined with risk

factors to better guide appropriate management. Based upon their specific physiological characteristics, biomarkers can be divided into categories of markers of tubular injury, glomerular filtration rate (GFR), inflammation, and cell cycle arrest [29]. Some of the common biomarkers investigated include neutrophil gelatinase-associated lipocalin (NGAL), cystatin C (CysC), kidney injury molecule-1 (KIM-1), IL-18, liver-type fatty acid-binding protein (L-FABP), tissue inhibitor of metalloproteinase-2 (TIMP-2), and insulin-like growth factor-binding protein 7 (IGFBP7). While these biomarkers are promising for AKI diagnosis, reference ranges for pediatrics and widespread availability continue to be a challenge and require more investigation.

NGAL is a marker of tubular injury and is one of the most extensively studied AKI biomarkers with over 200 studies in the medical literature. Both serum and urine NGAL (uNGAL) are upregulated following nephrotoxic and ischemic injury such as ischemia-reperfusion injury, drug toxicity, hypoxia, and bacterial infections [30–32]. In both the neonatal and pediatric population requiring CPB, NGAL measured within 2 h after initiating CPB was found to be an excellent early predictor of AKI [33]. In a single-center, case-control study of pediatric patients, the utility of multiple urinary biomarkers of AKI after CPB was evaluated. Urine NGAL was the only biomarker elevated at 2 h post initiation of CPB with an area under the operating curve (AUC) of >0.9 for AKI predictive ability. It was not until 12 h that the combination of NGAL with other biomarkers improved the AUC for the prediction of AKI [34]. While NGAL has been extensively studied and its utilization continues to increase, there are still some ongoing concerns such as confounders in which NGAL is affected including sepsis [35] and urinary tract infections [36]. Furthermore, determining the cutoff values for uNGAL in varying age groups such as adult vs pediatric vs neonatal population remains an ongoing issue. The impact of uNGAL over a variety of hospitalized patients with ages ranging from 4 months to 25 years, with various diagnoses including nephrotic syndrome, cancer, and hypoplastic left heart syndrome, was evaluated in a single-center study. Specified cutoff values for interpretation of AKI risk were used based upon cutoff values generated by their clinical laboratory. The trend of serial uNGAL values provided both predictive and prognostic value and served as a means of support for clinical decision-making in their population [37].

Cystatin C is a marker of GFR. It is an endogenous cysteine protease inhibitor that is produced in all nucleated cells and is not affected by gender or muscle mass [38]. CysC has a relatively short half-life of 2 h and responds rapidly to changes in GFR. A recent meta-analysis of 13 studies evaluated the ability of CysC to predict AKI. Of the 13 studies, most were adult studies and involved individuals post-cardiac surgery. Serum CysC had an AUC of 0.96 for predicting AKI. However, subgroup analysis revealed that only when measured within 24 hour of renal injury or ICU admission was serum CysC of diagnostic value [39]. A multicenter prospective study of almost 300 children undergoing cardiac surgery evaluated whether measuring pre- and postoperative serum CysC improved the prediction of AKI in comparison to sCr. Postoperative serum CysC measured within 6 h of CPB strongly predicted the development of AKI with an AUC of 0.89 (AKI was defined by sCr AKI). Postoperative serum CysC also predicted longer ICU length of stay and longer duration of ventilation [40]. There is apprehension about utilizing CysC alone in detecting AKI because it is affected by multiple factors including corticosteroids, thyroid function, and CRP levels. These elements make its value questionable in accurately detecting AKI. Serum CysC in combination with urine NGAL was investigated in a retrospective analysis of 345 pediatric patients who underwent CPB. Combining both serum CysC and urine NGAL at 2 h post-CPB was superior to sCr alone in predicting both AKI severity and duration [41].

KIM-1 is also a marker of tubular injury [42]. KIM-1 was evaluated in 40 pediatric patients after CPB and was found to be elevated at 12 h post-CPB with an AUC of 0.83 in the individu-

als who developed AKI [42]. Another study set out to characterize the patterns of KIM-1 and uNGAL in the pediatric ICU and assess their properties in identifying those at risk for the development of AKI. KIM-1 was not found to be as reliable in identifying those at risk for AKI development and peaked between 12 and 24 h post-ICU admission with an AUC of 0.74. The patients with sepsis had higher levels of both uNGAL and KIM-1, irrespective of development of AKI [43]. As demonstrated, these studies yield conflicting results for the accuracy of KIM-1 in predicting AKI.

IL-18 is a pro-inflammatory cytokine that is a mediator of ischemic renal injury [44]. By systemic review and meta-analysis, the utility of biomarkers in predicting the need for RRT in critically ill patients was evaluated. IL-18 had an AUC of 0.66 in predicting the need for RRT [45]. In a prospective, multicenter cohort study of children with congenital cardiac lesions, it was found that IL-18 peaked at 6 h post-cardiac surgery. IL-18 along with uNGAL improved risk prediction for severe AKI including the need for dialysis, mechanical ventilation, and length of hospitalization; however, it was only moderately accurate in diagnosing severe AKI with an AUC of 0.72 [46]. Another analysis demonstrated that in non-septic critically ill children, IL-18 increased before sCr and predicted the severity of AKI as well as mortality [47].

L-FABP is induced in the proximal tubule early after AKI. In a single-center study of pediatric patients post-CPB, L-FABP was found to increase 6 h post-CPB with an AUC of 0.77 in predicting AKI [48]. In contrast, a prospective multicenter study consisting of children and adults undergoing CPB found that L-FABP was not associated with AKI development [49].

IGFBP7 and TIMP-2 are markers of cell cycle arrest [29]. There are limited pediatric studies on the use of [TIMP-2]*[IGFBP7] for the prediction of AKI. In a case-control study evaluating 50 patients at high risk for AKI development post-CPB, it was found that [TIMP-2]*[IGFBP7] was significantly increased at 4 h post-CPB with an AUC of 0.81 [50].

While there continues to be ongoing investigation of biomarkers for early AKI detection, incorporating their use into routine clinical practice remains a challenge. Expecting a single biomarker to replace sCr and urine output for investigating renal function is not realistic. The combination of novel biomarker(s) with current standards of assessing renal function will likely prove more effective. For example, combining sCr, CysC, and uNGAL can help delineate glomerular from structural tubular damage. Aside from CysC, uNGAL is the most studied and readily available biomarker but does not yet have widespread availability. Its use is advantageous in comparison to other biomarkers as uNGAL has been shown to be elevated within 2 h of injury and is not removed by dialysis, so it can also be used as a measure of renal recovery even in those patients receiving dialysis and appears to be closer to validation in the pediatric population.

Furosemide Stress Test

While not labeled as a biomarker, furosemide has been examined as a means to determine renal tubular function. Furosemide is a highly protein-bound loop diuretic that is not filtered at the glomerulus and is actively transported to the tubular lumen. Its use results in natriuresis by inhibiting active chloride transport in the thick ascending limb of the loop of Henle. Therefore, the urinary response to furosemide provides a functional assessment of renal tubular function. There are an increasing number of adult studies that have examined the kidney's response to furosemide as a marker of renal functional reserve in AKI in what is known as the furosemide stress test (FST). What makes this test ideal is that often in the setting of oliguric AKI, many are "challenged" with a dose of furosemide in order to determine if the patient will have a urinary response. In many cases, multiple doses are

given to no avail thus delaying the initiation of RRT. Standardization of the FST in the pediatric ICU population will assist in predicting those who will likely have progression of AKI thus allowing earlier intervention such as timely initiation of RRT.

In an adult study, it was hypothesized that the FST could predict which patients would have progression of AKI. This was done by measuring urine volume and flow after the administration of 1–1.5 mg/kg of furosemide. The sum of the urine volume at the first 2 h after receiving furosemide had the best predictive ability for progression to AKIN stage 3 within 14 days of performing the FST. Urine volume of less than 200 mL at 2 h offered the best sensitivity and specificity for predicting AKI progression [51]. The FST was combined with other AKI biomarkers in the previous study cohort. The combination of the FST with uNGAL increased the prediction of progression to AKIN stage 3, receipt of RRT during admission, and inpatient death [52]. These findings suggest that in combination with uNGAL, the FST may improve risk stratification in early AKI.

The FST was evaluated in neonates at risk for CS-AKI. Neonates and infants less than 90 days of age who received furosemide within 24 h of CPB were included in a single-center, retrospective study [53]. Hourly and cumulative urine output for 6 h after the initial postoperative furosemide dose was evaluated. The maximum urine output occurred in the first hour with almost half of the cumulative urine output in the first 2 h with an average urine output of 1.6 mL/kg/h. Cumulative urine output was lower in patients with CS-AKI. Furosemide response had significant areas under the curve predictive of CS-AKI, prolonged peritoneal dialysis, prolonged mechanical ventilation, and peak fluid overload greater than 15%. Unlike the adult data, a specified cutoff point for cumulative urine output after furosemide was unable to be determined for CS-AKI prediction. While prospective studies will be needed for validation of furosemide stress testing in this population, current data suggests combining the FST with novel AKI biomarkers may aid early assessment of renal function and serve as a guide for clinical decision-making.

Risk Stratification

The concept of renal angina was devised to apply objectivity in the assessment of AKI risk analogous to the components for angina pectoris [54]. While there are no specific symptoms of AKI such as chest pain for angina pectoris, clinical signs such as oliguria and fluid overload were utilized. Renal angina therefore identifies those at higher risk of AKI and guides the use of additional diagnostic evaluation for those who will benefit from additional biomarker assays. From this idea, the renal angina index (RAI) was derived, which is a product of AKI risk and signs of injury, with a value of >/=8 as fulfillment of renal angina (Fig. 10.1). This model was found to be useful in the pediatric critical care population of detecting likelihood of severe AKI development 3 days post-ICU admission [55]. Additionally, urinary biomarkers combined with RAI improved AKI prediction [56]. The authors illustrate that these findings provide a potential model for AKI risk stratification upon early ICU admission (Fig. 10.2).

Management Options

Understanding the etiology of AKI allows for the elimination of offending agents and reversible etiologic factors which include low oncotic pressure, low hydrostatic pressure, abdominal compartment syndrome, bladder obstruction, and nephrotoxic medications. To date, there are no medications or therapies that prevent or treat AKI, and management is largely based upon early detection, removal or mitigation of the offending agent and supportive therapy. Modifications that can improve outcomes in those with AKI include prevention of worsening kidney injury, nutrition optimization, minimization of fluid overload, and optimization of acid/base and electrolyte balance.

AKI Risk Tranche

Risk Factor	Risk Tranche	Risk Score
ICU Admission	Medium	1
History of Transplantation (Solid Organ or Bone Marrow)	High	3
Vasoactive Support & Mechanical Ventilation	Very High	5

X **= Renal Angina Index (Range 1-40)**

AKI Injury Tranche

Change in Creatinine	Fluid Overload %	Injury Score
<0	<0 – 5%	1
1.0 – 1.49x	5 – 9.99%	2
1.5 – 1.99x	10 – 14.99%	4
>2x	≥15%	8

Fig. 10.1 Renal angina index (RAI). (Copyright permission obtained and adapted from Basu et al. [55])
Renal angina index (RAI) – Based on existing pediatric AKI literature, tiered AKI risk strata were assigned point values for "risk" and "signs" of injury. The worse parameter between change in estimated creatinine clearance from baseline and % fluid overload was used to yield an injury score. The RAI index score can range from 1 to 40. A cutoff value of >/= 8 is used to determine fulfillment of renal angina (from Basu et al. [55] with permission)

Fluid Overload

Case Scenario Continued

After 24 h, her total intake since admission was 4.2 L and she had voided 200 mL. Her BUN was 30 mg/dL, and her sCr was 1.7 mg/dL. After 48 h, she had a total volume intake of 5.4 L with 400 mL of urine output. She was on 70% Fi02 with a progressive increase in ventilator settings. She had not received any nephrotoxic medications. A renal ultrasound revealed normal-sized hyperechoic kidneys with a decompressed bladder with an indwelling bladder catheter in place. Her calculated fluid overload was 12.5%. Urine NGAL was 247 ng/mL and serum albumin was 1.9 mg/dL. She was given 1 g/kg of 25% albumin over 4 h followed by a 1 mg/kg dose of furosemide intravenously. If medical therapy did not achieve the goal of net negative fluid balance over the next 12 h, RRT would be initiated.

Fluid overload, as a consequence or perhaps a biomarker of AKI, is significant because it is the most common indication for continuous renal replacement therapy (CRRT) in critically ill children [57]. It has been demonstrated in the critically ill pediatric population that those who were initiated on CRRT at greater than 20% fluid overload had significantly higher mortality rates than those who were initiated at 10–20% fluid overload even after controlling for severity of illness and numerous potential confounders [57].

A three-phase fluid management model has been proposed in an effort to assist with proper resuscitation and attempt to prevent fluid overload [58]. Based upon clinical status, management approaches of critically ill individuals with AKI or those individuals at risk for AKI development are divided into the following three phases: (1) fluid resuscitation, (2) maintenance of fluid balance, and (3) fluid recovery/removal (Fig. 10.3). While aggressive fluid resuscitation may be essential in the resuscitation phase, overly aggressive resuscitation that

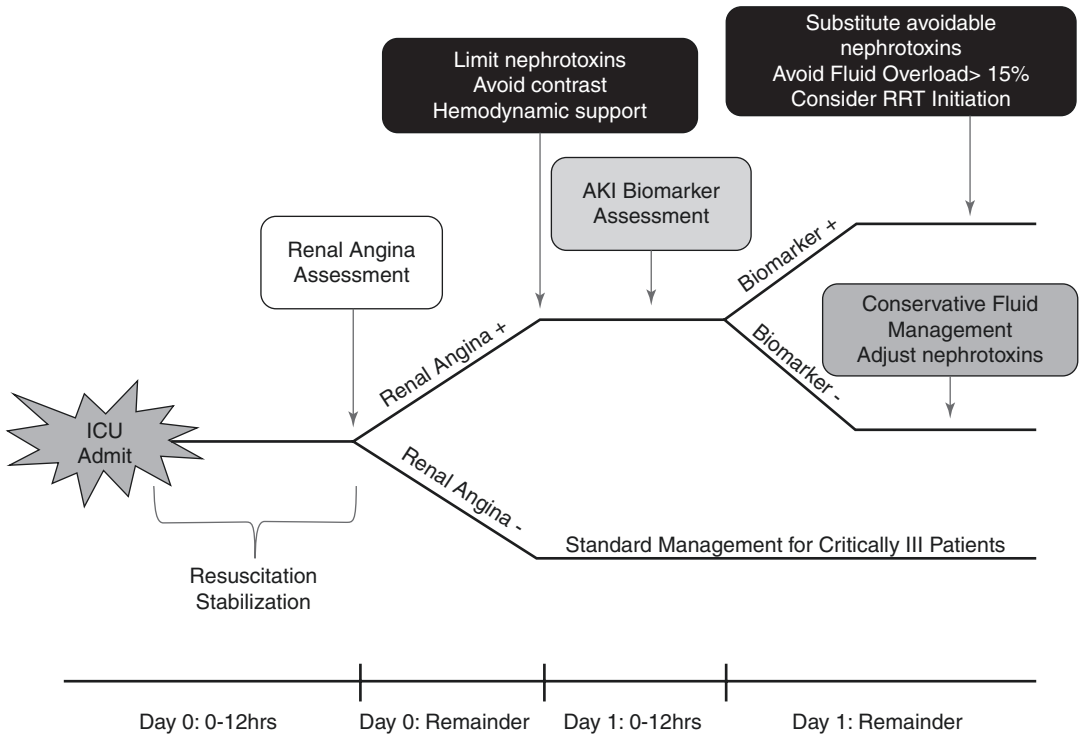

Fig. 10.2 Schema of use of RAI for AKI stratification after ICU admission. (Copyright permission obtained and adapted from Menon et al. [56])
Represented is a potential trial of prospective evaluation on outcome based on the use of the RAI for AKI risk stratification after ICU admission (from Menon et al. [56] with permission)

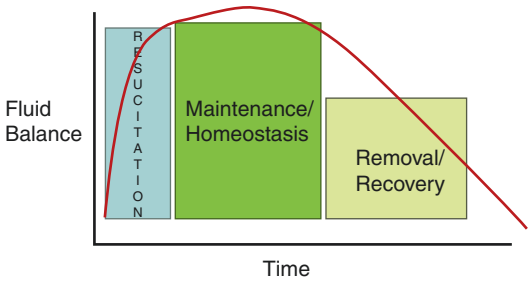

Fig. 10.3 The AKI fluid paradigm. (Copyright permission obtained and adapted from Goldstein [58])
AKI fluid epidemiology paradigm and proposed fluid accumulation three-phase conceptual model for the patient with AKI (from Goldstein [58] with permission)

continues into the maintenance phase is what usually leads to the need for fluid removal via CRRT or aggressive diuresis with resultant electrolyte imbalances in the recovery phase. During fluid resuscitation, the goal is to restore end-organ perfusion; however, in the setting of AKI, attention must be paid to the physiological response to fluids to avoid propagation of fluid overload. During the maintenance phase, fluid needs are assessed, including nutrition, ongoing hydration, and potential blood products and are balanced against output. It is during this phase that the physician must determine if the individual is able to maintain a safe balance between required intake and output. To assist with this decision, the percent cumulative fluid overload should be calculated (**% fluid overload = ((fluid input (L) – fluid output (L)) / (patient ICU admission weight (kg)) × 100**) and tracked to avoid worsening fluid overload and kidney function as well as identify an increased risk of mortality. Options during this time are to either limit volume intake, initiate diuretics, or initiate renal replacement therapy. Limiting volume risks inadequate nutrition in

an individual that may already be in a catabolic state. While diuretics are potentially another option for volume control, close attention must be paid to the kidney's response without delaying what may be ultimately required, which is RRT. In theory, the fluid removal phase should not be aggressive or urgent if the first two phases were appropriately managed [58].

Preventive Therapies

Employing preventive therapies requires knowledge of the timing of renal injury. While the exact timing of injury can be difficult to identify, in certain settings such as patients following CPB, it is known. The pathophysiology of the injury is very complex, but this is one area in which utilization of biomarkers has been progressing to provide earlier diagnosis.

Various medications have also been examined in the setting of CS-AKI prevention including fenoldopam and theophylline/aminophylline in efforts of AKI prevention. However, multiple studies have not demonstrated their effectiveness in decreasing the incidence of AKI. A randomized trial of children receiving prophylactic aminophylline post-CPB did not demonstrate AKI prevention [59]. A single-center trial examined the effects of implementing a "KDIGO bundle" that used a multifactorial approach in prevention of CS-AKI in high-risk populations. This bundle consisted of multiple components including nephrotoxin avoidance, hyperglycemia prevention, and optimization of fluid status [60]. While the occurrence and severity of AKI were reduced, there was no impact on secondary outcomes of need for RRT during hospitalization or length of stay. Utilization of a type of "KDIGO bundle" for CS-AKI can be beneficial in the neonatal and pediatric population as well. Once early diagnosis of CS-AKI is obtained, we should be "proactive" by attempting to mitigate worsening outcomes associated with AKI progression as opposed to "reactive" later as AKI progresses.

Renal Replacement Therapy

Case Scenario Continued

The urine output did not significantly improve over the next 12 h, uNGAL increased to 310 ng/mL, and calculated fluid overload increased to 14%, and she was placed on CRRT. Three days after CRRT initiation, urine output improved, uNGAL trended down to 100 ng/mL, and CRRT was discontinued. The patient's kidney function steadily improved over the next 2 weeks, uNGAL trended down to less than 50 ng/mL, and she was transferred to the floor in stable condition. She was scheduled for a follow-up visit with pediatric nephrology to evaluate for long-term renal sequelae after AKI.

There continues to be an ongoing debate regarding the best time for RRT initiation. As addressed above, those with significant fluid overload at the time of RRT initiation, particularly in those with greater than 20% fluid overload, have been shown to have worse outcomes. The timing of RRT has been evaluated in two adult randomized trials: a single-center study known as the ELAIN (the Early Versus Late Initiation of Renal Replacement Therapy in Critically Ill Patients with Acute Kidney Injury) trial and a multicenter trial known as the AKIKI (Artificial Kidney Initiation in Kidney Injury) trial. ELAIN was a single-center study that randomized critically ill patients with KDIGO stage 2 AKI and elevated uNGAL [61] to early vs delayed RRT. Early intervention was RRT initiation within 8 h of AKI diagnosis and delayed defined as RRT initiation within 12 h of KDIGO stage 3 AKI or no initiation of RRT. Patients randomized to early initiation of RRT had a reduced 90-day mortality, earlier recovery of renal function by day 90, decreased duration of RRT, and decreased length of stay in comparison to late initiation.

In contrast, the AKIKI trial had very different findings. Patients with severe AKI, defined as KDIGO stage 3, were randomized to either the early strategy or delayed strategy. Those in the early strategy initiated RRT immediately after randomization and those in the delayed strategy initiated RRT if very specific clinical criteria such as hyperkalemia and pulmonary edema were met [62]. There was no difference in mortality between the two groups. While these discrepant findings are concerning and somewhat discouraging, care must be taken when evaluating the differences in these two trials including the inclusion criteria and sample size.

Early intervention of RRT was evaluated in the CS-AKI population in an effort to determine if peritoneal dialysis (PD) catheter placement in infants undergoing CPB at high risk for AKI improved outcomes [63]. Early initiation of PD resulted in better fluid balance and improved clinical outcomes including shorter time to negative fluid balance, decrease in ventilator time, and fewer electrolyte abnormalities. This was further confirmed in a single-center randomized trial in PD versus furosemide for fluid overload prevention in infants after cardiac surgery [64]. There was no difference in negative fluid balance between the two groups on postoperative day 1; however, those randomized to receive furosemide were more likely to develop 10% fluid overload and have longer duration of mechanical ventilation, longer requirement for inotropes, and more electrolyte abnormalities.

Fluid overload is one clinical situation in which RRT is often delayed. While there is no definitive data on specific criteria for initiating RRT, there is strong evidence that suggests that an individual who is at least 20% fluid overloaded has worse outcomes. Having a framework for early, multidisciplinary decision-making regarding identification and management of fluid overload allows the medical team to be "proactive" as opposed to "reactive." This can prevent worsening fluid overload or identify the possible need for RRT prior to reaching 20% fluid overload.

Case Scenario Conclusion

The clinical scenario presented throughout the chapter provides the opportunity to not only understand the importance of initiation of RRT prior to significant fluid overload but also demonstrates the usefulness of the RAI for AKI risk stratification upon ICU admission (Fig. 10.2). *The initiation of this predictive model should be within 12 h of ICU admission. Upon presentation to the ICU, the patient required ongoing fluid resuscitation and vasoactive support for stabilization. Based on her AKI risk tranche value of 5 for mechanical ventilation and vasoactive support and her AKI injury tranche value of 4 based upon her change in serum creatinine as well as fluid status, her RAI would be calculated as 20 which fulfils criteria for renal angina, and the decision for standard ICU management should not be pursued. Proactive decisions would be made to limit nephrotoxin exposure and to closely follow drug levels of required nephrotoxins. Biomarker assessment in this patient revealed an elevated uNGAL, which continued to rise and is suggestive of moderate to high AKI risk. She also had worsening fluid overload at which time the decision was made to initiate CRRT. It was beneficial to have nephrology involved in a multidisciplinary approach when the patient was approximately 10% fluid overloaded to begin the discussion on additional therapeutic options and the possible need for RRT. Trending uNGAL was also particularly helpful in predicting renal recovery and assisted with the daily decision on whether or not CRRT should be continued.*

What Lies Ahead

Advances in RRT

The ability to provide adequate RRT safely to neonates remains a challenge due to difficulties in vascular access as well as the relatively large extracorporeal volume (ECV) required by current machines. Currently, the smallest CRRT circuit available in the United States has an ECV of approximately 90 mL, which equals over half of the circulating blood volume of a 2 kg neonate. In an effort to provide safe RRT therapy in this population, the Aquadex™ machine has been adapted to provide continuous veno-venous hemofiltration (CVVH) via incorporation of prefilter replacement fluid [65]. Aquadex™ is FDA approved for use in adults with heart failure who require fluid removal. The circuit has an ECV of 33 mL therefore requiring blood priming for infants less than 4 kg. Because of the smaller circuit, the machine can operate at a slower blood flow that can be accommodated by smaller vascular catheters, widening the scope of infants who can benefit from this modality. A case series was performed in critically ill children documenting the use of Aquadex™ for fluid removal, with the smallest patient weighing 2.7 kg and the youngest age of 4 days old. RRT was safely performed, and there were no deaths associated with the use of CVVH. Ongoing utilization of Aquadex™ by a small subset of nephrologists continues to show promising results in the neonatal population. There are also new machines being used in Europe that have been designed explicitly for the neonatal and infant population; however, these are not yet available in the United States. One such machine is the CARPEDIEM™ (Cardio-Renal Pediatric Dialysis Emergency Machine) which has circuits available with ECV less than 30 mL [66], and the NIDUS (Newcastle Infant Device) which has an ECV of 10 mL and can be used with a single lumen 4 F catheter. There is optimism that the CARPEDIEM™ and NIDUS will soon be FDA approved for use in the United States potentially expanding the group of children who can safely benefit from RRT.

Electronic Medical Records

Advanced technology such as electronic medical records (EMR) and data warehouses should be leveraged to improve AKI identification and enhance management and healthcare quality. The idea of incorporating data technology to improve AKI management and research has been recently explored with the idea of increasing AKI quality improvement [67]. As suggested, AKI can potentially be diagnosed via EMR based upon KDIGO-defined AKI criteria. However, some significant challenges include lacking a baseline sCr for proper staging as well as tracking hourly urine output in patients without indwelling bladder catheters. EMR can be used to alert providers when their patient has developed or has had worsening AKI. There are trials that have published data on e-alerts for AKI with some documenting failure to show any improvement in clinical outcomes, while others have demonstrated their effectiveness [68–70]. As previously mentioned, long-term follow-up of individuals with AKI is suboptimal, and there is evidence of long-term sequelae including CKD and ESRD. Opportunities exist for EMR to make improvements in this area by tracking individuals and prompting appropriate follow-up for not only the patient but also alerting their primary physician.

Summary AKI remains extremely common and impacts outcomes for critically ill pediatric patients. AKI is no longer thought to be a transient event, but there is evidence of long-term sequelae including hypertension, proteinuria, CKD, and ESRD that should be monitored via long-term care. The standardization of an AKI definition via KDIGO has improved the ability to better evaluate AKI in the pediatric population including better understanding of the epidemiology. Urine output should be a part of AKI surveillance programs. The ongoing investigation of novel biomarkers and their proper incorporation into clinical decision making has made promising strides in AKI research with anticipation of providing earlier diagnosis, thus leading to timely therapy and better long-term outcomes. Fluid overload is common in AKI and is associated with poor outcomes, therefore ongoing evaluation and management of fluid balance is very important. Care must be taken to not become overly aggressive with fluid resuscitation in order to prevent the need for emer-

gent fluid removal later on. New technology has made significant advancements and promises to improve the safety of RRT in neonates or small infants who would have otherwise not been eligible for these therapies.

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