THE CURRENT STATE OF THE ART IN PEDIATRIC ACUTE KIDNEY INJURY

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THE CURRENT STATE OF THE ART IN PEDIATRIC ACUTE KIDNEY INJURY

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Cardiopulmonary Bypass and AKI: AKI Is Bad, So Let's Get Beyond the Diagnosis

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It is now well-established that AKI is a serious and common complication following cardiopulmonary bypass (CPB) in both children and adults, adverse outcomes may occur in the short term as well as long term, with higher incidence of chronic kidney disease, increased healthcare utilization and higher frequency of cardiovascular events in patients who develop post-CPB AKI. Despite the advances in our understanding of the pathogenesis of the disease and the improvement in diagnostic tools, our therapeutic options have remained suboptimal. There are multiple challenges in designing a clinical therapeutic AKI trial, including a multi-factorial etiology, difficulties with accurate diagnosis of AKI, achievement of adequate study power, and determination of appropriate outcomes. We are often left with "supportive" care. Studies have shown some benefit to AKI bundles, but adherence to bundle guidelines may be suboptimal. Current best practices should include maintenance of adequate renal perfusion pressure and avoidance of fluid overload, with consideration of early renal replacement therapy. Finally, multi-center trials of AKI therapies are crucial to finding treatment for this devastating complication of CPB.

Keywords: acute kidney injury, cardiopulmonary bypass, pediatric, heart, kidney

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INTRODUCTION

It is now well-established that AKI is a serious and common complication following cardiopulmonary bypass (CPB) in both children and adults, leading to worse outcomes and higher mortality (1–3). While variable, most pediatric studies report an incidence of 30–50%, with higher rates in neonates, more complex surgeries, and longer cardiopulmonary bypass times (2–5). Perioperative AKI is not only associated with higher in-hospital mortality but also longer need for mechanical ventilation, longer intensive care and hospital lengths of stay, and worse ventricular function on discharge (2, 4–6). Adverse outcomes may also occur in the long term, with higher incidence of chronic kidney disease, increased healthcare utilization and higher frequency of cardiovascular events in patients who develop post-CPB AKI (7–10). Despite the advances in our understanding of the pathogenesis of the disease and the improvement in diagnostic tools, our therapeutic options for cardiac surgery-associated AKI have remained suboptimal. This manuscript will review the current status of clinical trials, the inherent problems with these trials, the use of supportive care bundles and potential promising therapies for AKI.

Before launching into potential AKI therapies, it is crucial to understand the pathogenesis of AKI after CPB, as doing so may allow the development of targeted treatment. The mechanism of

injury after CPB is multi-factorial, with variable contributions from each process affecting the ultimate AKI phenotype. Thus, AKI after CPB is not homogenous and treatment may not be one-size-fits-all. In addition to ischemia and reperfusion, CPB is associated with alterations in hemodynamics, vasoconstriction and loss of pulsatile blood flow. These factors may lead imbalances between oxygen supply and demand, leading to cellular injury. Activation of the systemic inflammatory response further potentiates cell damage via oxidative stress injury and coagulopathy. CPB also exposes blood cells to non-physiologic surfaces and shear forces, leading to cell lysis and release of plasma free hemoglobin into the circulation. This and other microemboli contribute to further tubular damage. On a cellular level, ischemic injury leads to profound ATP depletion and nitric oxide generation. A number of oxidative and cell death mechanisms are induced, including activation of caspase, increase in intracellular calcium, and generation of reactive oxygen molecules. During the extension phase, these pathways progress, resulting in apoptosis, cell membrane alterations, cytoskeletal degradation, and oxidant injury (11).

THERAPEUTIC TARGETS

A number of therapies with specific targets have been studied in clinical trials, including vasodilators, iron chelators, anti-inflammatory agents, anti-apoptotic agents, and diuretics. While some studies have shown modest improvement, no agent has seen universal success. Park et al. reviewed over 500 therapeutic AKI studies from 1950 to 2008 and noted several issues with these clinical trials (12). First and foremost is that most were single center trials and were underpowered to evaluate clinical outcomes. Secondly, the primary outcome in the majority of studies was laboratory based, rather than clinical, such as mortality or need for RRT. Lastly, the definition of AKI was highly variable over the studies, making comparisons difficult. While the latter has been addressed to some extent with the development of consistent AKI definitions such as KDIGO (13), clinical trials remain plagued by insufficient power. Faubel et al. noted this in a 2012 review of ongoing clinical trials in AKI (14). As an example of the difficulty in achieving adequate power, the authors reference the TRIBE-AKI multi-center AKI study (15), which had a 5% incidence of severe AKI, using AKIN (16) serum creatinine criteria. Using these data, to have an $\alpha = 0.05$, power of 0.9 and 30% effectiveness, almost 3,800 patients per arm would be needed in a randomized controlled study. Even with an enriched sample of high-risk patients, with a 20% incidence of AKI, over 800 patients would be needed in each arm of a study. While this sample number is difficult even in adult studies, it becomes nearly impossible in pediatric studies. Further, as with the earlier review by Park, the authors emphasize that, rather than laboratory based criteria, AKI trials need a clinically important endpoint, such as requirement for renal replacement therapy, quality of life measures, development of chronic kidney disease or mortality, and propose a national AKI clinical trials network to continue this important work.

As therapeutic options for AKI remain limited, the mantra around AKI management is "supportive care." This includes limiting fluid intake to avoid fluid overload, maintaining adequate cardiac output and blood pressure, avoiding high central venous pressure, augmenting fluid loss, avoiding nephrotoxins, and waiting for kidney recovery. While much of this seems intuitive, adherence to these recommendations often proves difficult. As an example, a 3 kg infant receiving total fluids at "2/3 maintenance" immediately after surgery has a fluid allotment of just 8 ml per hour. This amount would need to include any inotropic or vasoactive medications, antibiotics, pressure monitoring lines, sedation and analgesia, as well as dextrose. As one can easily imagine, fluid from these alone may be more than "maintenance," even without blood products or true nutrition. Fluid accumulation may be further exacerbated by oliguria, which is common after cardiac surgery. Nephrotoxin exposure is also common in the cardiac intensive care unit (ICU). In a retrospective study of cardiac surgical patients using the NINJA collaboration definition (17), Uber et al. found that 85% of cardiac ICU patients received at least 1 nephrotoxin and 21% received $\geq$3 nephrotoxins, demonstrating suboptimal adherence this recommendation as well (18). The most common nephrotoxin that was administered was non-steroidal anti-inflammatory agents (ketorolac and/or ibuprofen), which are used widely in post-operative pediatric cardiac patients and have been associated with subclinical kidney injury even in patients without AKI (19).

Impact of Hemodynamics

The role of blood pressure in avoiding or treating AKI is less clear. Significant hypotension during non-cardiac surgery has been associated with AKI, with higher rates of AKI in patients with mean arterial pressure <55 mmHg, even for short durations (20). While overt hypotension is clearly undesirable, "ideal" blood pressure to prevent AKI and the impact of minor hypotension are unknown. Studies of both healthy adults undergoing hip arthroplasty under controlled hypotension (21) and critically ill patients with sepsis (22) found no association between systemic blood pressure and AKI. However, the latter study demonstrated a significant association with central venous pressure, indicating that it is likely that adequate renal perfusion pressure, rather that systemic blood pressure alone, is key. Similar findings have been seen in pediatric studies of patients undergoing Fontan palliation, a physiology that is often associated with high CVP. A study by Algaze et al. found a significant association between higher post-operative CVP and the development of AKI in 158 patients after Fontan surgery (23). This finding has also been demonstrated in adult studies of patients with advanced decompensated heart failure. Mullens et al. found that worsening renal function (WRF) was associated with higher CVP on admission with a stepwise worsening in function with increasing CVP (24). Systolic blood pressure was not significantly different in patients with or without WRF and the development of WRF uncommon if CVP was <8 mmHg on admission. It should noted, however, that the elevated CVP and AKI are inter-related, since fluid overload from AKI may lead to increases in CVP, so determining cause and effect may be challenging at times.

Diuretics

Diuretic use to augment fluid loss, while used ubiquitously in the cardiac ICU, has not consistently been shown to improve outcomes and indeed, may be detrimental in some circumstances (25, 26). Lassnigg et al. noted in a single center study that continuous furosemide had no clinical benefit and was associated with increased incidence of AKI in 126 patients after cardiac surgery (27). In a meta-analysis of nine prospective randomized controlled trials, Ho and Sheridan found that furosemide was not associated with any clinical benefit, including decreased mortality, need for RRT, time to recovery of renal function or percent of patients with oliguria (28). One recent study demonstrated lower post-operative serum creatinine in patients receiving intra-operative and early post-operative furosemide but no difference in AKI incidence between study groups (29). Additionally, almost all diuretics must reach the tubular lumen by glomerular filtration or proximal tubular secretion to exert their action (30). If AKI causes a decrease in glomerular filtration, diuretic delivery is impeded and these medications are less effective.

With the thought that the detrimental effect of diuretics on outcomes may be related to intravascular depletion, investigators have looked at the impact of combined administration of diuretics and matched hydration which has been shown to have potential benefit in contrast-associated AKI (31). The impact of this management strategy in CPB-associated AKI is unknown, with an initial, small study of 10 at-risk adult patients demonstrating no AKI after CPB procedures (32). Further study of this management is warranted.

Supportive Care Bundles

The prevention of AKI using a supportive care "bundle" was evaluated in the PrevAKI trial (33). In this single center randomized controlled trial, 276 patients were randomized to a "KDIGO bundle" consisting of optimization of volume and hemodynamics, avoidance of nephrotoxins and prevention of hyperglycemia, or to standard care. The primary outcome was rate of AKI using KDIGO guidelines. The intervention group was found to have significantly less AKI and severe AKI. The intervention group received more dobutamine resulting in higher mean arterial pressure (and thus higher renal perfusion pressure), had less hyperglycemia, and received less angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers. There was no difference in need for renal replacement therapy or major adverse events between groups.

Fenoldopam

While supportive care is crucial, the development of AKI therapies remains a priority. Several therapies have shown some benefit in select populations and likely warrant further investigation in larger trials. Fenoldopam, a selective dopamine-1 receptor agonist, increases renal plasma flow, decreases renal vascular resistance, and inhibits tubular resorption of sodium. It was first evaluated in neonates after cardiac surgery who had insufficient response to conventional diuretics (34). In this single center study, neonates receiving fenoldopam had a significant increase in urine output. Ricci et al., in a randomized controlled trial of high-dose fenoldopam in children after cardiac surgery, found a decrease in post-operative neutrophil gelatinase-associated lipocalin and cystatin C levels and a trend toward less AKI, sooner extubation and shorter LOS in the treatment group (35). In a meta-analysis of 23 studies, fenoldopam treated patients had a significantly lower incidence of AKI, with an OR of 0.46 [0.27–0.79] but no difference was seen in mortality, rate of RRT or other clinical outcomes (36). This meta-analysis included both cardiac and non-cardiac surgical patients with differing durations of therapy so while promising, further multi-center studies are warranted.

Aminophylline

Aminophylline is a methylxanthine non-selective adenosine receptor antagonist and has been shown to decrease adenosine mediated vasoconstriction, inhibit phosphodiesterase, and increase urine output. One of the earliest single center double-blinded placebo controlled clinical trials in pediatric patients after CPB did not show significant differences in AKI incidence or difference in secondary clinical outcomes between treatment and control groups (37). Other studies however, have found variable effects, with several reporting improved clinical outcomes and lower incidence of AKI (38, 39).

Dexmedetomidine

Dexmedetomidine, an alpha-2 agonist, is used primarily for sedation. It is noted to have sympatholytic, cytoprotective and anti-inflammatory properties and has recently been evaluated in AKI studies. Kwiatkowski et al. noted significantly less AKI by KDIGO [adjusted OR 0.43 (0.27–0.98)] following congenital heart surgery but did not find differences in clinical outcomes (40). A prospective randomized trial in pediatric CPB patients also found a significant decrease in AKI in the treated group but also failed to show a difference in clinical outcomes (41).

Fluid Overload

The avoidance of fluid overload (FO) is perhaps the most important target for AKI intervention, as FO has independently been associated with worse outcomes including mortality in AKI (42). Early RRT has been associated with improvement in clinical outcome in both adult and pediatric patients and earlier institution of RRT has been associated with better survival (43). The concept of early, or "prophylactic" peritoneal dialysis has been around for decades (44–46) and its use is becoming more common (47). Several centers routinely place dialysis catheters intra-operatively at the time of cardiac surgery in high-risk patients, using a trans-diaphragm approach. Catheters are placed to passive drainage and if early signs of AKI occur, such as oliguria, peritoneal dialysis is begun with goal to avoid fluid overload, not necessarily to achieve net negative fluid balance. After a retrospective study of PD catheter placement after CPB in infants demonstrated improved clinical outcomes, including time to extubation and degree of FO (48), Kwiatkowski et al. embarked on a prospective randomized trial of PD vs. standard regimen of furosemide (47). This study found that PD patients were 3 times less likely to have 10% FO, achieved negative fluid balance one shift sooner, and had improved clinical outcomes

including less likelihood of prolonged ventilation, or prolonged ICU stay. Importantly, PD patients had no adverse events associated with catheter placement or use. Thus, it may be that prevention of FO with consideration of early RRT or PD is our current best "treatment."

CONCLUSION

While significant work has been done in the study of AKI and potential treatment, a single therapeutic strategy remains elusive. There are multiple challenges in designing a clinical therapeutic AKI trial, including a multi-factorial etiology, difficulties with accurate diagnosis of AKI, achievement of adequate study power, and determination of appropriate outcomes. We are often left with "supportive" care. Studies have shown some benefit to AKI bundles, but adherence to bundle guidelines may be suboptimal. Current best practices should include maintenance of adequate renal perfusion pressure and avoidance of fluid overload, with consideration of early renal replacement therapy. Finally, multi-center trials of AKI therapies are crucial to finding treatment for this devastating complication of CPB.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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Big Data and Pediatric Acute Kidney Injury: The Promise of Electronic Health Record Systems

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Over the last decade, our understanding of acute kidney injury (AKI) has evolved considerably. The development of a consensus definition standardized the approach to identifying and investigating AKI in children. As a result, pediatric AKI epidemiology has been refined and the consequences of renal injury are better established. Similarly, "big data" methodologies experienced a dramatic evolution and maturation, leading the critical care community to explore potential AKI/big data synergies. One such concept with tremendous potential is electronic health record (EHR) enabled informatics. Much of the promise surrounding these approaches is due to the unique position of the EHR which sits at the intersection of data accumulation and care delivery. EHR data is generated simply via the provision of routine clinical care and should be considered "big" from the standpoint of volume, variety, and velocity as a myriad of diverse elements accumulate rapidly in real time, spontaneously generating an immense dataset. This massive dataset interfaces directly with providers which creates tremendous opportunity. AKI can be diagnosed more accurately, AKI-related care can be optimized, and subsequent outcomes can be improved. Although applying big data concepts to the EHR has proven more challenging than originally thought, we have seen much success and continue to explore its potential. In this review article, we will discuss the EHR in the context of big data concepts, describe approaches applied to date, examine the challenges surrounding optimal application, and explore future directions.

Keywords: acute kidney injury (AKI), pediatrics, big data and analytics, electronic health record (EHR), outcomes

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INTRODUCTION

Acute kidney injury (AKI) has become a common complication amongst hospitalized children (1–3). Studies utilizing modern, consensus definitions report a prevalence of ∼5 and 25% in children receiving acute and critical care, respectively (3, 4). The frequency with which AKI occurs is of particular concern given its outcome implications. AKI has been associated with greater mortality, longer lengths of hospital and intensive care unit (ICU) stay, and the subsequent development of chronic kidney disease (CKD) (3, 5, 6). Recently, the critical care and nephrology communities have standardized the definition of AKI, culminating in the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines which identify AKI events based on increasing serum creatinine and/or decreasing urine output (UOP) (7). With this development, AKI can be identified consistently across practice environments, data sets, and health care platforms. In parallel, we have seen substantial growth in the adoption of electronic health records (EHRs) as well as

the development of innovative clinical informatics methods (8–10). While the establishment of a uniform approach to AKI identification and the evolution of healthcare informatics are not causally related, the temporal relationship has created unique opportunities for AKI research and care improvement.

Many of the aforementioned informatics techniques and methodologies have been categorized as "big data," a relatively novel concept to healthcare practitioners. Big data (or Big Data) is defined by the Oxford English Dictionary as, "data of a very large size, typically to the extent that its manipulation and management present significant logistical challenges; (also) the branch of computing involving such data (11)." Based on this definition, it is relatively easy to see the connection between big data and the EHR. The data contained within the EHR is "big" from the standpoint of volume (amount of data present), velocity (speed at which new data is generated), and variety (number of different types of data) (12–14). With regard to AKI, this means that the EHR contains all creatinine and UOP data for all patients affiliated with a particular organization, accrues new creatinine and UOP data in real time, and possesses a near-infinite number of AKI related data elements which are created and stored through the provision of routine patient care.

Thus, the EHR and its data create a unique opportunity (14, 15). The ability to accurately identify AKI events within a clinical platform allows AKI to be explored retrospectively, investigated prospectively, and studied for quality improvement or benchmarking purposes. Although the application of big data approaches to AKI research and care has proven more challenging than originally thought, we continue to explore refined, clinically applicable synergies. The goal of this manuscript is to consider the EHR in the context of big data concepts, appraise the approaches applied to date, examine the challenges surrounding optimal application, and explore future directions.

AKI IDENTIFICATION AND DIAGNOSIS

The cornerstone of EHR-enabled, big data AKI research and quality improvement is the ability to precisely diagnosis AKI events (14, 15). EHR data allows us, in a relatively straightforward manner, to identify AKI in real time by applying the KDIGO serum creatinine and/or UOP criteria (**Figure 1**) (7, 16, 17). For example, as creatinines become available, they may be compared to all prior creatinine values for that patient, and AKI may be diagnosed when the relative change threshold is met (**Figure 1A**). Serum creatinine results are discrete data which accumulate with an associated date and time; this, in turn, allows application of the full temporal components of the KDIGO definition. The same principles can be applied to the UOP criteria (**Figure 1B**). UOP is recorded hourly in milliliters (mL) and dividing this value by the

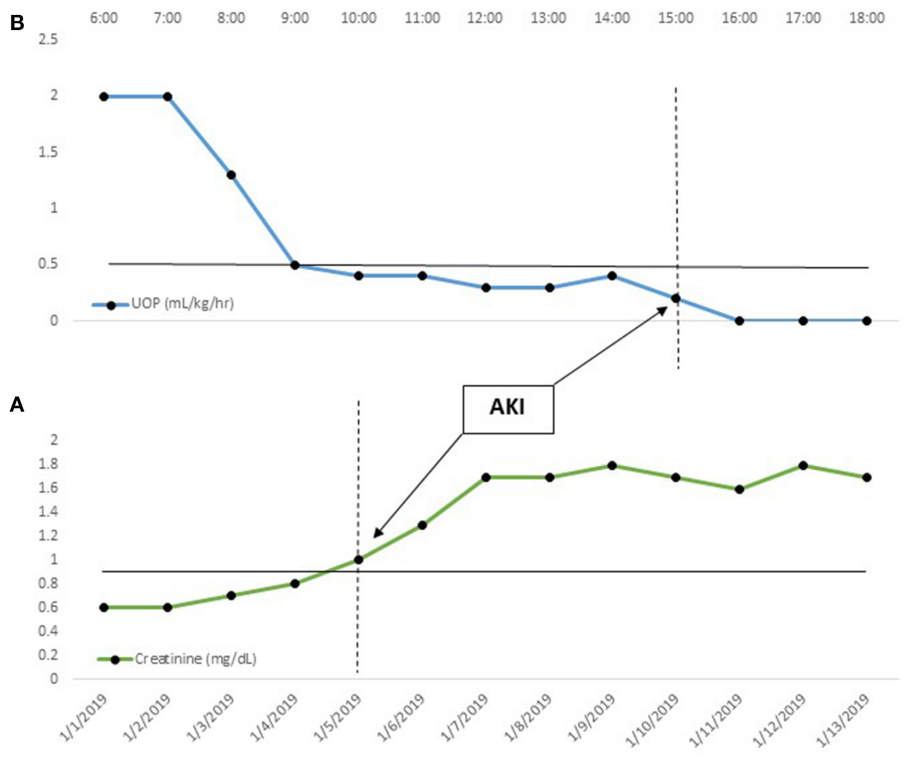

FIGURE 1 | Automated, Real-time AKI Identification. In this figure, temporal creatinine (daily) and urine output (hourly) trends are displayed. In **(A)**, the creatinine gradually increases from a baseline of 0.6 mg/dL, meeting AKI criteria (serum creatinine > 1.5× baseline) on 1/5/19. Likewise, in **(B)**, the patient develops progressive oliguria, meeting AKI criteria (UOP < 0.5 mL/kg/h for 6 h) at 15:00. In both cases, the ability to detect the threshold value upon documentation allows real-time diagnosis. This, in turn, opens up a myriad of big data AKI solutions.

patient's weight in kilograms (kg) generates a per-kg-per-unit-time rate (mL/kg/h).

Although automated, real-time AKI identification is technically feasible, aspects of the definition itself can be challenging to operationalize. One example is baseline creatinine determination. Setting each patient's baseline is important as it forms the basis for relative change determinations. Several approaches exist, each of which poses a different big data concern (16, 18–22). If available, a pre-admission creatinine may be used for the baseline. Many studies employing this approach have selected the lowest creatinine value available from the preceding 3–6 months. Outside of neonates and children under 3–6 months of age, creatinine is not likely to undergo a physiologic change in that timeframe. Unfortunately, prior creatinines are often unavailable within the EHR; this may be due to patients receiving ambulatory care in other health systems or it is possible, especially in pediatrics, that no prior creatinine has ever been obtained. When an actual value is not available, many have recommended using the admission creatinine as the baseline. This approach, while simple and effective from an informatics standpoint, will miss community acquired AKI which is manifest on admission; previously published studies suggest that this may underestimate the AKI burden by a third (20). Alternatively, a baseline creatinine can be estimated by back-calculating using a presumed creatinine clearance (CrCl). Studies in adults and children have tended to assume the CrCl to be 75 and 100–120 mL/min/1.73 m^2, respectively (18, 20, 21). This will capture community acquired AKI but misclassifies patients with chronic kidney disease (CKD) as having AKI. In adults, where CKD is highly prevalent, this approach can overestimate AKI incidence by AKI 50% (20). Technically, this method does requires a computation, adding complexity any automated AKI identification diagnostic tool. Furthermore, nearly all estimating equations require data which are unreliably available within the EHR (i.e., height and ethnicity). A final option for patients without a known baseline, is to apply an age-based normative creatinine value. In this scenario, a population-based serum creatinine is assigned to each patient based on their demographic characteristics (23, 24). Each of these potential solutions have been validated and, ultimately, the approach applied should reflect the goals of the diagnostic tool.

The UOP criteria also pose challenges, however, in this case the issues tend to be related to EHR limitations rather than definitional shortcomings. The most substantial issue is urine volumes are not obtained with the rigor or regularity of creatinine. Outside of the ICUs, very few children have indwelling urinary catheters capable of providing hourly data. As a result, these patients may not have urine data recorded for hours. In children, urine may be documented only as a void count, without giving a specific volume. Given the short temporal interval set by KDIGO, this could result in patients with normal renal function being inaccurately diagnosed with AKI. Secondly, EHRs tend to aggregate intake and output data at static 8–12 h intervals which coincide with nursing shifts. The UOP criteria, however, necessitate a dynamic approach which utilizes a rolling 6–24 h window. Processing a rolling calculation for each patient across an institution may pose resource, computational, and logistic challenges. Despite these potential issues, the ability to accurately diagnose AKI in real-time is technically feasible and this capacity unlocks numerous big-data approaches to AKI care. To fully realize its potential, however, a standardized solution and approach to the aforementioned problems must be adopted by the critical care nephrology community.

While no established approach yet exists, information is available to inform our approach. With regard to the creatinine criteria, most agree that a previously obtained creatinine should be used as the baseline value if it is available (3, 14, 15, 25). If computational resources are unlimited, one could determine and use the mean serum creatinine from the prior 12 months (25, 26). However, using the creatinine most proximal to the admission is a simpler solution which has demonstrated similar efficacy (26). If a creatinine is not available, given the relatively low incidence of CKD in children, using an imputed value as the baseline is a reasonable approach. Most studies to date have back calculated the imputed serum creatinine using an estimated creatinine clearance of 120 mL/min/1.73 m^2. However, using an age based normative value may be equally effective and will reduce computational requirements (3, 24); either approach should be considered valid. With regard to UOP, it is important to note that studies in adults and children demonstrate that some children meet only the UOP criteria for AKI; non-application of these KDIGO thresholds may underestimate AKI incidence (3, 27). Thus, if possible, the UOP criteria should be integrated into any diagnostic tool if possible. One reasonable compromise is to utilize the 12 h summative information in its static form to generate a volume-per-kg-per-hour rate. Although this is not as accurate as a dynamic window and will miss oliguria of $<$12 h duration, it is a simple way to implement the UOP criteria that will capture a larger portion of the true AKI population.

PREDICTING ACUTE KIDNEY INJURY EVENTS

Once AKI is accurately diagnosed in real-time, a number of EHR-enabled interventions become viable. One of the most exciting prospects is AKI prediction—detecting events before they occur. AKI events can be temporally anchored within the EHR which creates a pre-disease phase of care containing the data which accumulated prior to AKI. High-content, high-throughput techniques can be applied to this data to identify a pre-AKI signal which, in turn, can help discriminate between patients at low and high risk for AKI. The ability to predict AKI risk in this way may have dramatic impact as there are not currently treatments for AKI once it has developed (28–30). As patients at high risk are identified, care can be modified and preventative and harm avoidance strategies can be implemented (**Figure 2**) (31–36).

AKI prediction was the subject of the 15th Acute Dialysis Quality Initiative (ADQI) conference (13, 37–39). This conference highlighted several aspects related to AKI prediction and risk stratification which impact our ability to fully realize the potential of this big data approach. This consensus statement noted that at the time of publication, almost all AKI prediction models had employed a "supervised" approach, meaning that

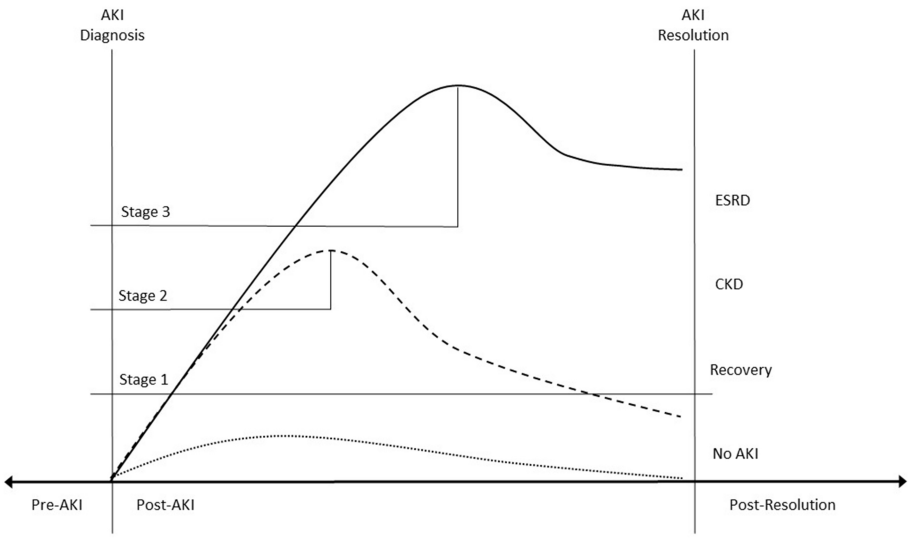

FIGURE 2 | Impact of Big-Data AKI Interventions. Real-time AKI diagnosis temporally separates EHR data into pre-illness and post-illness categories. The pre-AKI data can be used for predictive analytics. The ability to accurately identify patients at high AKI risk allows preventative strategies to be employed. An episode of Stage 2 AKI (dashed line) could be completely prevented, flattening the creatinine trajectory (dotted line). After AKI is diagnosed, real time notification allows providers to modify care with the goal of mitigating disease severity. Appropriate interventions might result in a patient developing Stage 2 (dashed line) rather than Stage 3 AKI (unbroken line). This, in turn, might improve long term (AKI resolution) outcomes. Regardless, once the AKI has resolved, the ability to identify these patients accurately, allows them to be "tagged" and followed whether they developed ESRD, CKD, or experienced full recovery.

potential predictors were chosen *a priori* based upon their association with AKI in prior studies (40–45). While certainly statistically sound, these approaches do not take full advantage of big data informatics methods. "Unsupervised" techniques identify predictors without oversight or prior prejudice. Although they represent a departure from more traditional model building approaches, the use of these innovative, dynamic techniques are necessary to completely optimize the use of EHR data (13).

Since the 15th ADQI conference, a number of studies examining AKI prediction models have been performed. An excellent systematic review of prognostic models was published in 2017 (46). Hodgson et al. identified 53 models designed to predict hospital acquired AKI, 11 of which met their inclusion criteria. Although the area under the receiver operative curve (AUROC) ranged from 0.71 to 0.8 in the model derivation populations, AUROC dropped significantly during the validation phase (0.66–0.8 and 0.65–0.71 in the internally and externally validated studies, respectively). The manuscript highlighted methodologic shortcomings and inadequate consideration of electronic automation as significant limitations to successful implementation. In 2019, a similarly styled review identified comparable issues with currently published predictive strategies (47). Interestingly, this study highlighted the fact that much AKI in adults is community acquired which cannot be addressed using most EHR-enabled prediction models. While this is true in adult populations, pediatric AKI tends to be hospital rather than community acquired (48, 49). Thus, it is possible that pediatric populations will benefit more substantially from predictive models.

To give you a better sense of how big data predictive techniques can be applied within the EHR, it may be helpful to discuss an exemplar in greater detail. Tomasev et al. applied deep learning techniques to a US Veteran's Affairs (VA) dataset (50). The dataset consisted of de-identified EHR data for all patients aged 18–90 years who were admitted to a VA hospital between October 2011 and September 2015. In total, the set comprised 703,782 patients and 6,352,945,637 clinical events (individual data elements). Unsupervised, deep learning modeling was applied to this dataset with the goal of predicting AKI. This approach predicted 56% of AKI events and 90% of dialysis-requiring AKI. 84% of Stage 3 AKI was predicted up to 48 h in advance of the event and only two false positive predictions were generated for each true positive. Although this may initially sound like a high false positive rate, responding to all alerts (positive and negative) would require attending to $<$1% of hospitalized patients. Although this population isn't representative of pediatric inpatients, the technique is certainly applicable and holds great promise. Future efforts should likely utilize similar machine learning methodologies and insure that any final models have the capacity for EHR integration.

ACUTE KIDNEY INJURY ALERTS

Accurately diagnosing AKI in real time also allows generation of automated notifications or alerts. Simply put, AKI alerts notify care providers as soon as a patient meets the diagnostic criteria for AKI. This information, in turn, allows practitioners to modify care in order to eliminate injurious agents or conditions,

prevent progression, and mitigate AKI sequelae (**Figure 2**). While AKI alerts seem straightforward and effective at first glance, in practice they have proven complex and challenging to implement effectively.

In 2017, Lachance et al. performed a systematic review of AKI alerting studies (51). Six studies comprised of 10,165 patients were included in the analysis. While some of the studies reported improvement in specific care processes, the pooled analysis did not demonstrate improved mortality or a reduced need for renal replacement therapy. Unlike many of the predictive studies described in the above section, the majority of the alerting systems were automated and fully integrated with the EHR. Perhaps the most telling aspect of the studies was the fact that most did not include a clinical decision support component. The studies performed to date are clear on this issue—real time AKI alerting in isolation is inadequate; any such alert must be accompanied by relevant care recommendations.

Since then, several additional alerting studies have been published. Al-Jaghbeer et al. studied 64,512 adult patients with AKI and found that an AKI alert combined with clinical decision support had a significant impact on patient outcomes (52). Although the effect was small, this intervention led to a sustained decreased in length of stay, need for RRT, and mortality. Park et al. studied an alerting mechanism in 3,193 adults (53). In this analysis, the AKI alert was accompanied by an automated nephrology consultation. While they did not find a significant reduction in mortality, they did find that AKI was accurately diagnosed more frequently, the risk for severe AKI was reduced, and AKI recovery was more common. Unfortunately, no outcome driven AKI alerting studies have been performed in children. Holmes et al. did prospectively implement an AKI diagnosis/alerting tool within the national Wales laboratory information management system, however, no intervention was included with the alert (54). As a result, it was not possible to assess the outcome impact of the alert, however, the authors did report a significantly increased incidence of AKI detected by this approach. It is clear that while alerting has great promise, we have not yet fully realized its potential. The combination of an alert with clinical decision support is a large part of the solution, but until better therapeutic options become available, AKI alerts may continue to have only an incremental impact.

LONGITUDINAL AKI CARE AND AKI TRACING: THE POST-DISEASE STATE

Traditionally, AKI was considered a self-limited disease. However, the long-term ramifications associated with renal injury have now been well-described. AKI has been linked with greater risk for new or progressive chronic kidney disease (CKD), hypertension, stroke, and cardiovascular disease (5, 55–58). Despite this, patients who experience AKI often do not receive adequate follow up care (59). Largely, this can be traced to a lack of awareness amongst patients and providers of both AKI and its consequent risks (60). This lack of recognition hampers our ability to track AKI survivors, especially across institutional boundaries and administrative datasets (60, 61).

One of the greatest potential benefits of applying big data concepts to AKI is the ability to overcome many of these barriers. Tracking patients with AKI hinges on our ability to apply an AKI identifier "tag" (61). The aforementioned EHR enabled identification technique described above allows such a tag to be reliably applied. While a myriad of potential identifiers could be used, something as simple as the International Classification of Diseases Ninth/Tenth Revision (ICD-9/10) AKI code might be adequate. Electronically applying the KDIGO AKI definition in an automated fashion within the EHR infrastructure will essentially eliminate the low sensitivity historically associated with ICD9/10 coding (62, 63). Regardless of the tag ultimately chosen, once applied, patients with AKI can be followed at the patient, institution, and population level.

At the patient level, children tagged as AKI survivors could be directed into the appropriate follow up clinic. For example, the AKI tag could, at discharge, automatically notify the primary provider of the diagnosis and place a nephrology referral (64). The discharge order could even generate outpatient orders for creatinine and albumin/creatinine ratios, which is consistent the recommendations of the KDIGO guidelines on AKI (7); currently patients who experience AKI should be assessed within 3 months of the event (7, 25). This is relevant as observational studies have suggested that ambulatory nephrology follow up care after AKI improves outcomes (65). Within an institution, this tag could increase awareness and support clinical decision making. Providers could be directed to avoid nephrotoxic medications or employ more frequent creatinine monitoring in tagged patients. Clearly, at the population and intuitional level, this will be most effective in a self-contained health care organization. Some degree of system integration will be required if follow up care will be provided outside of the institution which applies the tag (61). At the population level, accurate AKI diagnosis and tagging allows patients to be tracked over time. Patients could be assigned a unique identifier which would allow them to be followed between institutions and across administrative databases. The ability to trace patients in this manner would likely lead to a more comprehensive description of the healthcare burden generated by AKI. Administrative databases currently rely upon ICD9/10 codes to identify and track AKI events which is associated with underdiagnosis and a bias toward more severe episodes (60). As a result, the cost and morbidity data based upon analysis of these databases inaccurately reflects of the entire spectrum of disease. Additionally, at the population level, this approach could enable more efficient recruitment into clinical trials and registries which, in turn, creates greater opportunity for scientific advancement.

CONCLUSIONS

Over the past decade, the healthcare community has seen a surge in EHR adoption and the development of innovative informatics methods. Contemporaneously, the critical care and nephrology communities have created a standardized definition for AKI based upon relative chances in discrete data elements. This confluence of events has created unique opportunities for AKI research and care improvement. Integrating the definitional

criteria for AKI into the EHR can identify patients who develop AKI precisely at disease onset. This enables the application of predictive models, real time AKI alerting, and tracking of events and patients across institutions, registries, and databases. These interventions, in turn, allow us to better describe AKI epidemiology and improve outcomes at the patient and population level (**Figure 2**). The promise of EHR enabled big data approaches to AKI discovery and care improvement are substantial and the potential benefits warrant additional work to overcome existing challenges and barriers.

AUTHOR CONTRIBUTIONS

SS conceptualized and wrote the manuscript.

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REVIEW
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Urine Output Assessment in Acute Kidney Injury: The Cheapest and Most Impactful Biomarker

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Acute kidney injury (AKI) is independently associated with morbidity and mortality in critically ill neonates, children, adolescents, and young adults. AKI occurs commonly in this population, and the vast majority of published studies utilize only a serum creatinine based criteria for AKI diagnosis and staging. While urine output criteria have been a part of all AKI systematic and multidimensional AKI definitions for the past 15 years, oliguria based on these definitions is difficult to extract from the electronic health record. This manuscript reviews the published data regarding the impact of oliguria on patient outcomes, and the contribution of oliguria to % fluid overload and resultant changes in serum creatinine based epidemiology. The aim of this manuscript is to demonstrate that oliguria is an incredibly valuable biomarker for the management of patients with, or at-risk for, AKI.

Keywords: acute kidney injury, oliguria, children, fluid overload, epidemiology

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INTRODUCTION

Acute kidney injury (AKI) occurs commonly in patients admitted to intensive care units and is independently associated with morbidity and mortality across the entire spectrum of patient age, from neonates to elderly adults (1–3). While extensive efforts have been focused on identifying markers of structural kidney injury (4), our current diagnostic AKI criteria still rely on changes in kidney function markers, namely serum creatinine, and urine output (5). Most studies to date have utilized only serum creatinine, as it is a discrete data field in the electronic health record with a singular validated measured value, whereas urine output requires a dynamic assessment of change with a time based value in the denominator. Recent data, however, have demonstrated that oliguria may have a stronger association with patient outcomes, and neglecting the urine output definition leads to missing a substantial proportion of patients with AKI.

The aims of this manuscript are to review the published data regarding the impact of oliguria on patient outcomes, and the contribution of oliguria to fluid overload and resultant changes in serum creatinine based epidemiology. After this review, it will become clear that oliguria is an invaluable biomarker in the management of the patient with, or at-risk for AKI.

IMPACT OF OLIGURIA ON OUTCOMES IN THE CRITICALLY ILL PATIENT

Current diagnostic and staging criteria based on the recommendations of the Kidney Disease Improving Global Outcomes (KDIGO) Work Group for AKI are listed in **Table 1** (5). Kellum et al.

TABLE 1 | AKI staging by the kidney disease: improving global outcomes disease (KDIGO) guidelines (5).

AKI stage	Creatinine criteria	Urine output criteria
Stage 1	1.5–1.9 x baseline OR ≥ 0.3 mg/dL absolute increase*	<0.5 mL/kg/h for 6–12 h
Stage 2	2.0–2.9 × baseline	<0.5 mg/kg/h for ≥12h
Stage 3	≥3x baseline, OR Increase in creatinine to 4 mg/dL, OR Decrease in eGFR to <35 mL/min/1.73 m^2, OR Initiation of RRT**	<0.3 mL/kg/h for ≥24 h, OR Anuria for ≥12 h

While relative creatinine changes may occur over a 7 days period, this absolute change must occur over 48 h.

***Initiation of RRT was used as an outcome rather than a diagnostic criteria for this analysis.*

TABLE 2 | How do the KDIGO UOP AKI criteria impact fluid accumulation in a case of septic shock after 24 hours?

KDIGO stage	Metric	Duration	%FO
1	<0.5 ml/kg/h for 6–12 h	6 h (1,800 + 400 ml In−90 ml Out)	7.0
		12 h (1,800 + 800 ml In−180 ml Out)	8.1
2	<0.5 ml/kg/h ≥12 h	24 h (1,800 + 1,600 ml In−360 ml Out)	10.1
3	<0.3 ml/kg/h for 24 h	24 h (1,800 + 1,600 ml In−216 ml Out)	10.6
	OR	12 h (1,800 + 800 ml In−0 ml Out)	8.7
	Anuria	24 h (1,800 +1,600 ml In−0 ml Out)	11.3

Assumptions for calculations:

1) 30 kg patient (body surface area = 1.0 m^2) with septic shock.

2) 1,800 ml fluid resuscitation (60 ml/kg).

3) 1,600 ml/day standard fluid prescription (BSA metric).

4) Upper limit of KDIGO Urine Output criteria.

5) Insensible losses not factored into the calculation since critically ill patients are often intubated and have minimal insensible losses.

applied the serum creatinine and urine output AKI criteria in over 32,000 adults at their single center and assessed for associations with morbidity and mortality in patients who met the serum creatinine or urine output criteria alone and in combination (6). They observed a significant increase in hospital length of stay, renal replacement therapy provision and hospital, 30-, 90, and 1 year mortality in patients who experienced AKI by either criteria. Importantly, the occurrence of these poor outcomes nearly doubled in patients who developed AKI by both criteria vs. either criteria alone.

The multi-national prospective Assessment of Worldwide Acute kidney injury, Renal angina and Epidemiology (AWARE) study enrolled nearly 5,000 children to evaluate potential associations between KDIGO Stage 2 or 3 AKI and outcomes in critically ill children (2). Indeed, Stage 2 or 3 AKI was associated with a 1.77 increased risk of 28 days mortality, after controlling for 16 variables associated with mortality on univariable analysis. A recent study assessed the 3,318 patients in the AWARE cohort with sufficient serum creatinine and UOP data to compare outcomes based on AKI using either criterion alone, or in combination (7). Twenty-eight-day mortality was higher for patients Stage 2 or 3 AKI by creatinine criteria (6.7%) or UOP (7.8%) than patients with no AKI or Stage 1 AKI (2.9%). It is important to note that 18.1% of patients with Stage 2 or 3 AKI only met the UOP criteria, and would have been misclassified as not having severe AKI. While 28-day mortality did not differ between patients with Stage 2 or 3 AKI by creatinine alone vs. UOP alone, patients who met Stage 2 or 3 by both criteria experienced a 5-fold increased 28-day mortality rate (38.1%). Thus, taken together, these large adult and pediatric studies support routine assessment of both serum creatinine and UOP for AKI diagnosis in critically ill patients.

CONNECTION BETWEEN OLIGURIA AND RESULTANT FLUID OVERLOAD AND EFFECTS ON AKI EPIDEMIOLOGY

Multiple studies have demonstrated the association between ICU fluid accumulation and morbidity and mortality in children. These studies were the subject of a comprehensive systematic review and meta-analysis by Alobaidi et al. and an extensive review is beyond the scope of this paper (8). In general, however, fluid overload of >10–20% body weight was noted to be a threshold that demonstrated associations with prolonged mechanical ventilation, ICU length of stay and mortality, both in patients who received, or did not receive renal replacement therapy.

In the following case, we can assess the resultant fluid accumulation status based on a standard volume of fluid resuscitation, required daily intake, and oliguria based on KDIGO staging. The case involves a 30 kg (body surface area of 1 m^2) patient with septic shock. We will assume the patient receives 60 ml/kg of crystalloid (1,800 ml) for fluid resuscitation and then is put on a fixed rate of fluid of 1,600 ml/day (based on a standard rate of 1,600 ml/m^2 BSA for a patient with normal kidney and other homeostatic functions). **Table 2** details the percent fluid accumulation per unit time as defined by the upper limit of UOP for each of the three KDIGO AKI strata. These calculations demonstrate that the patient will achieve the 10% fluid overload threshold within 24 h by KDIGO Stage 2 or 3 criteria, and would be more than halfway to 10% fluid overload at 6–12 h with by Stage 1 criteria. Thus, it is extremely important to note the UOP rate and duration early in the ICU course, as the patient is at risk of developing significant fluid accumulation association with morbidity and mortality.

As noted in the previous section, nearly 20% children in the AWARE study who met the KDIGO UOP AKI criteria did not meet the serum creatinine criteria. Recent studies have demonstrated the impact of fluid accumulation on AKI ascertainment by serum creatinine criteria, with the concept that serum creatinine may be diluted in a fluid overloaded patient, thereby blunting the creatinine rise and leading to a false negative assessment for AKI. Liu et al. performed this assessment in the Fluid And Catheter Treatment Trial (FACTT), which randomized 1,000 adult patients to a liberal vs. conservative fluid provision strategy after resuscitation (9). They found a significant reclassification of AKI in the patients randomized to

TABLE 3 | How do the KDIGO UOP criteria affect serum creatinine based on a dilutional effect after 24 hours?

KDIGO stage	Metric	Duration	+FB (ml)	Corr [SCr]
1	<0.5 ml/kg/h for 6–12 h	6 h (1,800 + 400 ml In−90 ml Out)	2,100	0.90
		12 h (1,800 + 800 ml In−180 ml Out)	2,420	0.88
2	<0.5 ml/kg/h ≥ 12 h	24 h (1,800 + 1,600 ml In−360 ml Out)	3,040	0.86
3	<0.3 ml/kg/h for 24 h	24 h (1,800 +1,600 ml In−216 ml Out)	3,184	0.85
	OR	12 h (1,800 + 800 ml In−0 ml Out)	2,600	0.87
	Anuria	24 h (1,800 +1,600 ml In−0 ml Out)	3400	0.84

Assumptions for calculations:
1) 30 kg patient with septic shock.
2) 1,800 ml fluid resuscitation (60 ml/kg).
3) 1,600 ml/day standard fluid prescription (BSA metric).
4) Upper limit of KDIGO Urine Output.
5) Volume of distribution of water = 18,000 ml (600 ml/kg).
6) Corrected [SCr] = [(1 mg/dl) × 18,000 ml/(18,000 ml) + fluid balance (FB)].
7) Insensible losses not factored into the calculation since critically ill patients are often intubated and have minimal insensible losses.

the liberal fluid administration group, and a higher mortality rate in patients reclassified from not having AKI to having AKI based on creatinine correction for fluid overload, compared to patients who did not have AKI after creatinine correction. Basu et al. performed a similar exercise in a pediatric cohort undergoing the arterial switch operation for transposition of the great vessels (10). In this study, AKI was associated with poor outcomes including higher postoperative day 1 fluid balance, higher inotrope scores postoperative days 1 and 2, and longer: postoperative ICU length of stay, overall ICU length of stay, and postoperative hospital length of stay. All of these associations between AKI and morbidity strengthened after AKI status was reclassified based on serum creatinine correction for fluid overload. **Table 3** illustrates the impact of KDIGO UOP criteria on fluid balance and serum creatinine dilution applied to the case of the 30 kg patient with septic shock, assuming a measured serum creatinine of 1.0 mg/dl, after 12–24 h, the dilutional effect led to a 10–16% decrease in serum creatinine levels.

CONCLUSIONS

In summary, most published studies in the AKI field rely on serum creatinine based definitions, due to their ease of data extraction from the electronic health record as well as the technical challenges of urine collection in neonates, infants and toddlers without an indwelling bladder catheter (11). Yet, AKI defined by oliguria often portends a worse prognosis and the AKI diagnosis would be missed in a substantial proportion of patients where UOP is not assessed. While we don't yet understand the mechanisms for the worse outcomes with oliguria, all of these observations support the concept that assessment and recognition of oliguria, and its effect on patient fluid accumulation and serum creatinine based AKI diagnosis ascertainment, are crucial for management of critically ill patients at risk for AKI. It is important to note however, that early identification of patients at risk for severe AKI and adverse outcome can influence physician's decision-making, e.g., with regard to the implementation of the critical care bundle for AKI or with regard to the early insertion of catheters for subsequent initiation of renal replacement therapy. Hence, therapeutic management of AKI benefits from criteria that allow for an immediate diagnosis of AKI, integrating the information regarding the impact of UOP on AKI diagnosis presented in this article.

AUTHOR CONTRIBUTIONS

SG wrote the article and is responsible for all of the content.

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MINI REVIEW
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Dynamic Biomarker Assessment: A Diagnostic Paradigm to Match the AKI Syndrome

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Acute kidney injury (AKI) affects one in four neonates, children, and adults admitted to the intensive care unit (ICU). AKI-associated outcomes, including mortality, are significantly worsened. Several decades of research demonstrate evidence for a need to rethink the pathophysiology and drivers of injury as well as to reconsider the existing diagnostic framework. Novel urinary and serum biomarkers of injury have, however, not been readily integrated into practice—partially because of the limited scope to current testing. The predominant focus to date has been the adjudication of a single biomarker measured at a single point of time for the prediction of either AKI progression or disease-related mortality. This approach is pragmatically problematic. The imprecise, umbrella classification of AKI diagnosis coupled with the absence of a consistently effective set of therapies creates a difficult rubric for biomarkers to demonstrate value in the scope of practice. AKI is, however, not a binary process but more an ICU syndrome—with complex biology underpinning injury, interacting and disrupting other organ function, multidimensional in manifestation, and varying in severity over time. As such, a more appropriate diagnostic paradigm is needed. In this minireview, the status quo for AKI diagnosis and associated limitations will be discussed, and a novel, dynamic, and multidimensional paradigm will be presented. Appreciation of AKI as an ICU syndrome and creation of an appropriately matching and sophisticated diagnostic platform of injury assessment are possible and represent the next step in AKI management.

Keywords: AKI, biomarkers, pediatrics, critical care, syndrome, NGAL, TIMP2/IGFBP7, FST

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INTRODUCTION

Acute kidney injury (AKI) continues to be an epidemic in patients admitted to the intensive care unit (ICU) (1–4). Across age range (from neonates to adults), regardless of illness severity, and independent of socioeconomic factors, critically ill patients suffering AKI have increased hospital resource utilization (mechanical ventilation, length of stay), higher costs of care, and increased rate of death (1, 5). Significant academic effort has been placed into improved earlier recognition and prediction of disease, either through the tradition markers of serum creatinine (SCr) and/or urine output (UOP) or more novel biomarkers in the urine or serum. Despite nearly two decades of data, however, very few new assessment techniques have gained acceptance and integration into practice (6). Part of the reason may be a near monocular focus on biomarker prediction of AKI progression or AKI-related mortality—two outcomes which are confounded by myriad other factors. AKI

does not occur in isolation. The drivers of AKI and the end-organ effects of AKI, like other ICU syndromes such as sepsis and "ARDS," extend beyond the kidney itself, are multidimensional and change over time (7). Like sepsis and ARDS, management is supportive and aimed at preventing further injury if possible. Finally, there remain no consistently effective, definite therapy for AKI—as there are no true restorative or curative therapies for sepsis and ARDS. In sepsis and ARDS, a significant focus of attention is now placed on refining the phenotype of injury and identifying characteristic manifestations of the syndrome(s) amenable to intervention and trackable over time (8). This is possible for AKI as well. In this minireview, a contemporary approach to biomarker characterization will be discussed. A dynamic and multidimensional approach to AKI, using an AKI biomarker composite (ABC) panel over time, will be presented as a versatile theoretic construct usable to characterize and phenotype AKI itself, refining the precision of diagnosis and making possible the ability to track different aspects of the injury as they change over time. The dynamic assessment would facilitate a focus on the *process* of management, similar to how sepsis and ARDS are assessed and managed. Shifting the focus in this way would potentially increase the opportunities for AKI biomarkers to demonstrate importance in clinical management. Given the increasing broader recognition of both AKI and associated complications, a contemporary and renewed approach to the injury syndrome is warranted.

ONE POINT AND ONE OUTCOME: THE LIMITATIONS OF STATIC ASSESSMENT

Over two decades of research in biomarker research has failed to result in a consensus opinion on the value of incorporating novel diagnostics into routine practice (6, 9). Meta-analyses of biomarker data yield information with limited individual-specific clinical applicability (9, 10). A majority of the studies included in such analyses investigate a single biomarker measured at a single timepoint using the metric of predictive discrimination [area under curve–receiver operating characteristics (AUC-ROC)] to evaluate predictive performance for AKI progression, use of renal replacement therapy, and/or mortality. The AUC-ROC data available, however, identify very few biomarkers with consistently excellent performance (AUC-ROC $>$ 0.85–0.90) for prediction of the three separate outcomes or any individual outcome across multiple populations. Problematically, the comparisons between biomarkers are used to identify the "best" biomarker, with the implication that the best marker would be not only broadly applicable but also the parallel of troponin for acute coronary syndrome—sensitive to injury, responsive to degree of damage, and specific for type of injury (11). There are strengths and weaknesses with this approach. Numerous models of experimental or clinical AKI have identified a number of putative biomarkers, both in the urine and serum (12). Using a consistent outcome(s) leads to a generalizable understanding of the performance of a biomarker vs. other biomarkers (i.e., frame of reference). In addition, picking consistent outcome(s) allows adjudication of the performance of that biomarker across different populations of interest. Unfortunately, there are significant limitations to the current approach. The biomarkers themselves have been mapped to reflect different locations of injury or mechanisms of injury within the kidney, but the predicted outcomes do not reflect this etiologic or "geographic" heterogeneity (13, 14). The individual biomarkers demonstrate marked variation in kinetic profile in relation to injury—rate of rise, magnitude of elevation in relation to purported injury, and rate of decay of detectable biomarker concentration (7, 15, 16). However, using a single point in time does not consider how these biomarkers change over time. Available data would suggest, however, that the change in biomarker concentration can be correlated with phase of AKI (onset, progression, resolution). Together, biomarkers have not been commonly used to subtype or phenotype AKI (thereby refining the precision of diagnosis) but to predict AKI diagnosed by changes in SCr or UOP. Meanwhile, consensus expert opinion has explicitly delineated the importance of improving the precision of AKI diagnosis and, conversely, moving beyond the imprecision of using SCr or UOP alone for delineating functional vs. tubular damage associated AKI (17). In addition, comparison of biomarker AUC-ROC values between studies often does not typically involve statistical tests for superiority (i.e., which test is "better"). Finally, the conclusion of many individual studies and meta-analyses highlighting the biomarker(s) demonstrating the highest predictive performance stops short of offering suggestions of how management itself can change. The implementation is for diagnosis or prognosis only, rarely to guide therapy, or even predict response to therapy (theragnosis). Amidst the numerous meta-analyses, summary statements, and reviews on AKI biomarkers, over 200 biomarkers have been studied in some capacity in human populations—ranging across age and illness. The proportion of these data are notable—for the predominance of a small subset of the discovered markers ($\sim$ 10/200) and focus on certain populations of interest (**Supplementary Figure 1**).

The lack of proven therapeutic options and reliance on supportive management, an inherently reactive strategy, is partially a result of the limited diagnostic tools used in practice. Although stratification systems such as RIFLE, AKIN, and KDIGO have made possible the identification of AKI epidemiology and outcomes, there remains considerable skepticism about what AKI actually is Devarajan (18). Meaning, what injury is actually being predicted by the stratification system-based scores, by changes in creatinine concentration? Just as sepsis and ARDS syndromes are complex and unlikely to be completely described (either predicted or characterized) by a single marker such as fever, white blood cell count, or oxygen saturation, it would be illogical to presume that the complex biology of AKI could be comprehensively ascertained by a single biomarker. Yet, the diagnosis and monitoring of AKI, has largely been dependent on two determinants [change in serum creatinine (SCr) from baseline and then from day to day or tiered amounts of urine output] (**Supplementary Table 1**). The importance of urine output assessment has only recently been

highlighted (19, 20). These markers carry known limitations—including only affording the ability to identify AKI broadly and without precision to type of injury (12).

Taken together, the existing diagnostic paradigm is imprecise, poorly applicable to a complex and changing disease process akin to a syndrome, and not capable of helping guide management. Novel diagnostics have, unfortunately, been tested in the exact system as existing diagnostics, which has hindered identification of their potential for prognosis, diagnosis, and theragnosis.

PRECISION IN AKI: COMBINATIONS AND SEQUENTIAL BIOMARKERS

The management of critically ill patients is improved by diagnostics specific for the type of injury and the ability to rely on these tests to mirror the recovery or progression of injury. Problematically, the concordance of SCr change with renal injury, the mainstay of alerting a provider to the presence or development of kidney insult, is fraught with limitation, particularly in younger and smaller patients. Reliance on a substandard diagnostic has propagated misclassification of AKI into broad, outdated, and imprecise umbrella categories of "pre-renal" or "intrinsic" AKI. For example, "pre-renal" theoretically defines, in one term, severity, timing, duration, and reversibility of injury while simultaneously underscoring the recommended therapy (i.e., fluid administration). A patient with congestive heart failure, however, would be diagnosed as having pre-renal AKI but violates the aforementioned descriptions of injury and could be significantly harmed by such a one-size-fits-all approach. Furthermore, the pathobiology of pre-renal AKI, often attributed to volume depletion or ischemic AKI, demonstrates marked heterogeneity in acute gene dysregulation and adaptive or maladaptive protein expression in the kidney (18). There is also limited histological evidence supporting the dogma equating intrinsic AKI to acute tubular necrosis (21).

The diagnosis of AKI is being refined. The Acute Dialysis and Quality Initiative (ADQI) international consensus panels have been instrumental in shifting the current paradigm. The 10th ADQI advocated improving the precision of AKI nomenclature using more pathophysiological terms such functional or tubular damage-associated AKI (13) and using a combination of biomarkers to refine the biology related to damage. The combination of a functional marker (SCr) with a tubular damage biomarker such as urinary neutrophil gelatinase associated lipocalin (uNGAL) have been validated in several populations to separate functional vs. damage-associated AKI (22–24). In addition, the classification of "sub-clinical" AKI, damage without measurable changes in SCr, has been made possible and is associated with worse overall outcomes, both with regards to kidney function and overall patient status (22, 25–27). The 16th ADQI recommended study (including risk scores, functional markers, and use of biomarkers) to identify, predict, and further characterize patients with persistent AKI (i.e., $\geq$48 h of SCr elevation or oliguria) and to consider SCr elevation with return to baseline in the first 48 h to be considered separately from actual AKI (28). Risk stratification systems such as the renal angina index can identify the patients with the highest pretest probability (risk) for evolution into severe AKI after 72 h (29). Meanwhile, matching aberrancies in hemodynamic and bioenergetic drivers of AKI with the kidney's response to insult, as assessed by the adaptive or maladaptive responses to injury, has opened the door to diagnostics matching the phase of illness (30).

Biomarkers demonstrate time-dependent profiles reflective of injury pathology. A broad adult study of multiple biomarkers following cardiac surgery demonstrated unique temporal profiles of the most commonly cited individual biomarkers: NGAL, interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), and liver-fatty acid binding protein (31–33). An important conclusion of these data and more recent individual population study data is the concordance of specific biomarkers for specific characteristics of AKI. For instance, the profile of KIM-1 appears to be reflective of AKI with high risk of chronic kidney disease (34, 35); in fact, follow-up studies of patients with cardiac surgery associated AKI demonstrate persistent elevation of KIM-1 in patients with chronic kidney disease following AKI. The temporal profile of a biomarker reflective of kidney "stress," the cell-cycle arrest, marker tissue inhibitor of matrix metalloproteinase-2/insulin-like growth factor binding protein-7 demonstrates marked variation in relation to different drivers of potential AKI (i.e., nephrotoxins, non-steroidal anti-inflammatory agents, and cardiac surgery) (36, 37). Finally, case examples of sequential uNGAL identifies fluid-based AKI phenotypes reflective of not only AKI diagnosis and prognosis but also theragnosis (38). The negative or positive deflection of the biomarker appears to be predictive, specifically, of response to diuretic therapy and function of the tubule for clearance of solute and fluid.

In the absence of novel biomarkers, simply assessing changes in SCr or UOP in a new manner may yield informative, actionable information. SCr in the mathematical construct of kinetic estimated glomerular filtration rate offers insight as to trajectory of filtration injury or recovery (39, 40). Adjustment of the kinetic estimated glomerular filtration rate for total body volume, often significantly labile in critically ill patients, may further refine the prognostic value of this methodology (41). Correction of SCr for fluid balance and as the fluid balance changes may delineate the independent effects of AKI and fluid overload (FO), identifying unique AKI-FO phenotypes (42, 43). Recent data from both adults and children demonstrate the importance of close monitoring of urine output early in ICU course (19, 20). As accumulation of fluid can be a proxy for reduced UOP, and evidence indicates excessive positive fluid balance (FO) is associated with poor outcome (44), attention to how UOP and FO change over time may offer a point of intervention earlier than changes in SCr. To this end, the furosemide stress test (FST), a standardized metric to gauge urine flow after a single diuretic dose, may be valuable to phenotype renal reserve and tubular function (36, 45, 46).

In total, diagnostic assessment of AKI should mirror the pathology of the syndrome. The biology of AKI is manifest in different segments of the nephron and via different mechanistic underpinnings. The manifestation of AKI itself varies considerably as well. Currently, the focus rests squarely upon clearance of solute and fluid, but a significant body of

evidence supports the extrarenal distant organ effects of isolated AKI—demonstrating wide ranging physiological perturbation. Following biomarkers in a multiplicative fashion and as they change over time will likely facilitate a deeper understanding of what injury is actually occurring under the umbrella diagnosis of AKI and potentially the trajectory of these injuries.

A DYNAMIC MULTIDIMENSIONAL APPROACH TO AKI: THE AKI BIOMARKER COMPOSITE

ICU management is multidimensional and dynamic. The care for a patient suffering sepsis or respiratory failure is guided by not only patient exam and context but also a series of diagnostic evaluations that occur in multiplicative fashion over the time of ICU course. As an example, respiratory failure from ARDS is assessed, managed, and treated in a sequential, iterative way. Multiple diagnostic inputs ranging from physical exam, radiography, blood gas assessment, capnography, and pulse oximetry are used over time to personalize the approach to a patient. Unique interventions are also specifically directed toward improving oxygenation, augmenting ventilation, reducing secretion load, and mitigating bronchospasm—all within the paradigm of monitoring the syndrome as it changes over time using a diagnostic platform that concurrently changes. Similarly, to track the progression of septic shock, markers such as lactate and central venous oxygen saturation (S_vO_2) are followed longitudinally; measurement at a single timepoint only does not allow for adjudication of management or make it possible to track effects of therapy (**Table 1**). A dynamic diagnostic approach to AKI, mirroring the approaches used for respiratory failure or septic shock, may ultimately lead to more precise and effective therapeutic options.

An AKI biomarker panel may facilitate simultaneous patient monitoring and targeting. Akin to a blood gas assessment for the purposes of tracking and managing respiratory failure, an ABC can be constructed to parallel biology and mechanistic characteristics of the injury (**Figure 1**). Urine output reflects homeostasis and overall organ function, while SCr serves as a reflection of filtration. This parallels a blood gas: pH is used as the first arbiter of homeostasis in respiratory failure, while partial pressure of oxygen (pO_2) is a marker of filtration of oxygen along the alveolar–capillary endothelial border. A marker of tubular epithelial injury mirrors the marker in the lungs of alveolar epithelial function—the ability to exchange gas (O_2 for carbon dioxide—CO_2). Damage markers such as uNGAL may identify renal tubular epithelial cell dysfunction, similar to the imputation of alveolar epithelial functionality determined by an arterial partial pressure of carbon dioxide (pCO_2). The furosemide stress test as mentioned earlier reflects renal functional reserve and can be utilized as a functional capacitance marker, identifying the amount of reserve left in the renal system. Incorporation of FO% into the composite is a real-time assessment of compensation in relation to AKI,

TABLE 1 | Comparison of common diagnostics used for ICU syndromes.

Syndrome	Prevalence in ICU patients	Effective management	Risk stratification	Diagnosis	Surveillance and therapeutic monitoring
Sepsis	5–10%	Antibiotics Early Goal Directed Therapy	APACHE-III SOFA, qSOFA PRISM I, II, III, IV PELOD 1, 2 PIM 1, 2	Mental Status Temperature HR, RR MAP WBC Lactate SvO2 Blood Culture/GS CSF Cx/GS Urine Cx/Analysis	Physical Exam Lactate pH Base deficit or excess S_vO_2 Urine Output Coagulation Profile Echocardiogram C-reactive protein ESR Procalcitonin NIRS Oximetry Cytokine profile IVC POCUS
ARDS	6–10%	Low tidal volume ventilation Neuromuscular blockade Prone Positioning	Berlin Criteria OI S/F ratio P/F ratio Co-morbidity	CXR Chest CT S_pO_2 P_aO_2 Echocardiogram Sputum Culture	CXR S_pO_2 pCO_2 pH Lung Ultrasound Respiratory Secretions
AKI	25–30%		Creatinine	Creatinine Urine Output	Creatinine Urine Output

Common ICU injury syndromes with associated characteristics related to prevalence, management and detection. APACHE-III = Acute Physiology, Age, Chronic Health Evaluation. SOFA, Sequential Organ Failure Assessment; PRISM, Pediatric Risk of Mortality; PELOD, Pediatric Logistic Organ Dysfunction; PIM, Pediatric Index of Mortality; HR, heart rate; RR, respiratory rate; MAP, mean arterial pressure; WBC, white blood cell count; SvO_2, venous oxygen saturation; GS, gram stain; CSF, cerebrospinal fluid; Cx, culture; ESR, erythrocyte sedimentation rate; NIRS, near infrared spectroscopy; IVC POCUS, inferior vena cava point of care ultrasound; OI, oxygenation index; S/F, saturation of oxygen/fraction of inspired oxygen; P/F, partial pressure of oxygen/fraction of inspired oxygen; CXR, chest radiograph; CT, computed tomograph; SpO_2, oxygen saturation; pCO_2, partial pressure of carbon dioxide.

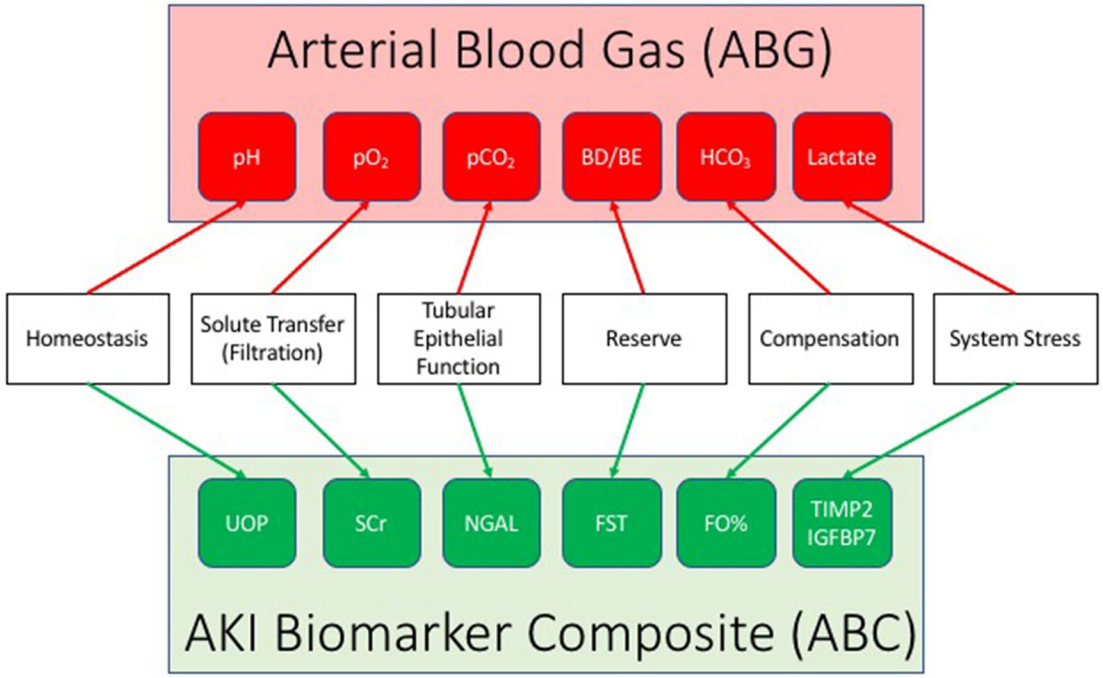

FIGURE 1 | The AKI biomarker composite (ABC). Drawing a parallel to the arterial blood gas, the ABC integrates a series of individual AKI biomarkers to facilitate the status and progression of acute kidney injury (AKI). An AKI biomarker composite integrates a marker of homeostasis (urine output: UOP), filtration (serum creatinine: SCr), tubular function (urine neutrophil gelatinase associated lipocalin: NGAL), renal reserve (furosemide stress test: FST, renal functional reserve: RFR), renal compensation (percent fluid overload: FO%), and stress (tissue inhibitor of matrix metalloproteinase-2/insulin like growth factor binding protein 7: TIMP2/IGFBP7).

potentially an analog to the base excess or deficit on a blood gas. Finally, tissue inhibitor of matrix metalloproteinase-2*insulin-like growth factor binding protein-7 may identify varying levels of renal stress, just as serum lactate is used for shock to adjudicate the balance between supply and demand in the setting of oxygen metabolism. The ABC offers the possibility of identifying how much stress exists on the system, the change from homeostatic conditions, aberrancies within the system for clearance of fluid and solute, and how much renal reserve exists—and does so concurrently—as opposed to testing individual biomarkers in isolation and/or at a single point in time. Although untested at this time, and theoretic in nature, this multidimensional combination of markers used simultaneously and over time may provide a dynamic system for tracking AKI—prognosis, diagnosis, and theragnosis. The concept could be implemented in a manner analogous to the use of arterial blood gas sampling for the purposes of respiratory failure—iterative to guide intervention on the ventilator (e.g., fluid balance management) or as an adjudication of a daily trend. Significant work will be required to demonstrate validity to this approach; however, the justification remains simple—the existing diagnostic paradigm is simply too generic, imprecise, unsophisticated, and cannot reasonably be expected to match the heterogeneity and complexity of AKI.

The AKI syndrome affects critically ill patients of all ages and requires a personalized medicine approach. A contemporary and appropriately personalized diagnostic paradigm is possible, practical, and may ultimately identify opportunities to target and manage specific aspects of injury in real time.

CONCLUSION

In summary, critically ill patients suffering from AKI need a modern and personalized approach to care. Use of a conventional and one-size-fits-all diagnostic approach to AKI will likely perpetuate the poor outcomes associated with AKI. The potential exists to refine the understanding of AKI and improve diagnostics using sophistication and precision. A dynamic and multimodal approach to AKI, paralleling the approach used for other critical illnesses, may make it possible to identify newer and targeted therapeutic possibilities in the future.

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The author confirms being the sole contributor of this work and has approved it for publication.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2019.00535/full#supplementary-material

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Pediatric Acute Kidney Injury—The Time for Nihilism Is Over

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Nihilism has been pervasive in the acute kidney injury field for decades, given that no studies, had been able to reduce AKI rates in hospitalized patients. Furthermore, children with AKI comprise an orphan population, where there is little incentive to develop diagnostics, therapeutics or devices specifically for them. The 3rd International Symposium on Acute Kidney Injury in Children, held in Cincinnati in October 2018, provided a platform to demonstrate the advancements in the diagnosis and treatment of children with, or at-risk for AKI, and also highlighted barriers to advancing care for this population. The progress made in the pediatric AKI since the 2nd International Symposium in 2016, highlighted the positive outcomes emanating from federal agency, private foundation and corporate sponsor investment in pediatric AKI. As a result, the time should be over for nihilism in the pediatric field.

Keywords: acute kidney injury, children, renal replacement therapies, biomarkers, nihilism

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INTRODUCTION

Nihilism comes from the Latin *nihil*, or *nothing*. It is the belief that values are falsely invented. The term nihilism can also be used to describe the idea that life, or the world, has no distinct meaning or purpose. Nearly 20 years ago, Kellum and Angus wrote a landmark editorial reviewing the current state of acute renal failure (1). This editorial contained six foundational statements:

- A commonly held belief among intensivists and nephrologists is that patients die with, and not of, acute renal failure (ARF);
- Although this may seem a trivial distinction, its implications are far reaching;
- This raises the rather obvious but tricky questions of "why" and "what can we do to improve the situation"?
- Preventing the development of ARF in at-risk populations is an attractive but difficult goal;
- Well-powered studies have failed to demonstrate that drugs, such as low-dose dopamine or diuretics, can prevent onset or deterioration of renal function in the critically ill, and some studies have even suggested harm;
- The best advice to date is disappointingly empirical—avoid hypotension, dehydration, and exposure to nephrotoxins.

Implicit in these statements a heralding of a turning point from in the perspective from ignorance to nihilism, which in many cases, persists today. However, these statements also reflect the authors' hope that since patients are dying *from* and not just *with* their acute renal failure, it is incumbent upon clinician researchers in the field to not give into nihilism, but do something about it.

PROGRESS IN PEDIATRIC AKI

The 3rd International Symposium on Acute Kidney Injury in Children, held in Cincinnati in October 2018, provided a platform to demonstrate the advancements in the diagnosis and

treatment of children with, or at-risk for acute kidney injury. Selected advancements are highlighted in this issue of *Frontiers in Pediatrics*. A tangible demonstration of the proverbial needle moving forward was a detailing of the fulfilled expectations from the end of the 2nd International Symposium held in 2016. At the end of the 2nd Symposium, I highlighted a number of areas I "hoped" we would be discussing in 2018:

(1) AKI biomarker directed care algorithms;
(2) Renal replacement therapy devices specifically designed for and/or targeted for uses in children with the plan for FDA clearance for use in children in the United States;
(3) Dissemination of the successful single center nephrotoxic medication associated AKI program NINJA (2, 3), to multiple pediatric centers.

The progress toward each of these goals is detailed below.

AKI Biomarker Directed Care Algorithms

Meersch and colleagues employed use of the cell-cycle arrest biomarkers, TIMP-2-IGBP7 (Nephrocheck™, Biomerieux, Inc.), to direct a care bundle in patients with an elevated biomarker product after cardiac surgery (4). Although this study was conducted in adults, the investigators demonstrated a significant reduction in AKI rates in the patients who received the bundle of care. Our team is currently conducting a prospective study in the pediatric ICU population to integrate a real time AKI risk assessment algorithm, the renal angina index (5–7), with urine AKI biomarker assessment (Neutrophil Gelatinase Associated Lipocalin, NGAL, BioPorto, Inc.), to guide fluid management and renal replacement therapy initiation (TAKING FOCUS 2, NCT03541785, 2P50 DK096418-06). Initial results were presented at the 3rd International Symposium showing patients who were RAI+ (with a score $\geq$8) and NGAL+ (with a concentration >150 ng/ml), comprised an overwhelmingly majority of patients who developed >10% fluid overload and required renal replacement therapy. The importance of using an AKI biomarker in these studies is to enrich the sample of patients to include only those who would be truly at increased risk for AKI development. These studies should serve as a trial design template for future interventional trials aimed at preventing AKI or mitigating its effects.

Renal Replacement Therapy Devices Specifically Designed for and/or Targeted for Uses in Children With the Plan for FDA Clearance for Use in Children in the United States

Currently, three different devices have completed studies and/or have applications in process with the FDA for a pediatric indication. The HF20™ CRRT circuit (Baxter Healthcare, McGaw Park, IL), would represent that small dedicated CRRT circuit available in the US. It has been used in countries outside of the United States for over 10 years (8). A five center US pediatric consortium completed a prospective study with the HF20™ in 2018 with the aim of FDA clearance (NCT02561247). The Cardiorenal Pediatric Emergency Dialysis Machine (CARPEDIEM™, Medtronic, Inc., Mirandola Italy) is a CRRT machine designed specifically for neonates with AKI and is available in Europe (9, 10). The FDA is currently reviewing a submission for the CARPEDIEM™ for clearance for use in the United States. The Selective Cytopheretic Device (SCD, Seastar, Inc., San Diego, CA), has been demonstrated to improve outcomes in adult patients with AKI receiving CRRT, where the circuit ionized calcium is maintained at <0.4 mmol/L (11). The SCD is use in tandem with CRRT and its mechanistic effect is by immune modulation. Currently, a 5 center US consortium is prospectively evaluating the SCD in pediatric patients (NCT02820350, R01FD005092). In addition, since the time of the 2018 Symposium, a multicenter retrospective US study has detailed the use and associated outcomes of an ultrafiltration device (Aquadex™, CHF Solutions, Inc, Minneapolis, MN) to support children with AKI and/or fluid overload (12). Thus, these studies clearly demonstrate that despite significant challenges, devices are being made specifically for children, or successfully adapted for them. Hopefully, the devices under consideration at FDA will be cleared and made available in the US.

Dissemination of the Successful Single Center Nephrotoxic Medication Associated AKI Program NINJA, to Multiple Pediatric Centers

Nephrotoxic medication exposure represents one of the most common causes of AKI in hospitalized children. Our center realized a 38% reduction in nephrotoxic medication exposure and a 62% reduction in associated AKI after implementation of the Nephrotoxic Injury Negated by Just in time Action (NINJA) program (3). NINJA identifies patients in near real time who are exposed to three or more nephrotoxic medications on the same day or receiving an IV aminoglycoside or IV vancomycin for three or more days. Exposed patients are then recommended to have a daily serum creatinine to assess for AKI development systematically. A nine center collaborative recently completed a 3 year implementation of NINJA (1R18HS023763-01) to determine if NINJA could be successfully disseminated to these centers and to ascertain the contextual factors that accelerated or hindered successful implementation. Preliminary data presented at the 3rd International Symposium showed a 23.8% reduction in AKI rates across the collaborative. Other data from this effort assessed projected health care cost reductions associated with NINJA, and various AKI rates in different service lines in the NINJA collaborative.

CONCLUSIONS

While the nihilistic perspective Kellum and Angus were concerned about nearly 20 years may still persist in some circles, the advancements in AKI clinical care, research and investment in pediatric AKI research and devices, suggests the tide may be finally turning. The progress made in the past 2 years has been especially dramatic, as highlighted in the pages of this Golden Research Topic volume. With persistence and determination,

a brighter future should be realized to improve outcomes for children with, or at-risk for AKI. In the not too distant future, the time for nihilism will be over.

DISCLOSURE

Industry sponsors mentioned in this manuscript, Baxter Healthcare, Medtronic, BioPorto and CHF Solutions provided unrestricted educational grants for the 3rd International Symposium on AKI in Children. Dr. Goldstein serves as a consultant for all of the industry sponsors as well.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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frontiers in Pediatrics

REVIEW
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AWAKEN-Ing a New Frontier in Neonatal Nephrology

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In 2013, literature about the epidemiology of neonatal acute kidney injury (AKI) was limited to primarily retrospective, single center studies that suggested that AKI was common and that those with AKI had higher rates of mortality. We developed a 24-center retrospective cohort of neonates admitted to the NICU between January 1 and March 31, 2014. Analysis of the Assessment of Worldwide Acute Kidney Epidemiology in Neonates (AWAKEN) cohort, has allowed us to describe the prevalence, risk factors and impact of neonatal AKI for different gestational age cohorts. The ample sample size allows us to provide convincing data to show that those with AKI have an increase *independent* higher odds of death and prolonged hospitalization time (1). This data mirrors similar studies in pediatric (2) and adult (3) critically ill populations which collectively suggest that patients do not just die with AKI, but instead, AKI is directly linked to hard clinical outcomes. This study has allowed us to answer multiple other questions in the field which has expanded our understanding of the risk factors, complications, impact of fluid overload, the definition of neonatal AKI and suggests interventions for improving outcomes. Furthermore, this project brought together neonatologist and nephrologist within and across centers. Finally, the AWAKEN project has enabled us to build relationships and infrastructure that has launched the Neonatal Kidney Collaborative http://babykidney.org/ on its way to accomplish its stated mission to improve the health of newborns with or at risk for kidney disease through multidisciplinary collaborative research, advocacy, and education.

Keywords: acute kidney injury, neonate, acute renal failure, collaborative, epidemiology, outcomes, survival

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On April 9, 2013, the National Institute of Health sponsored a workshop in Washington DC with the following objectives (1) review the state-of-the-art knowledge of acute kidney injury (AKI) in neonates; and (2) determine the feasibility of studying this group in an organized prospective manner. This conference brought together experts from the fields of pediatric nephrology, neonatology, general pediatrics, industry, and professional organizations to get a broad perspective on the issues to be considered. Two white papers were published. The first, reports a framework whereby the scientific community can answer critical questions about how and when to evaluate neonates at risk for chronic kidney disease (4). The second, focused on the definition of neonatal AKI (5). Furthermore, this meeting solidified the need to develop a multi-center, multi-disciplinary, neonatal kidney collaborative.

Up until this time, the field of neonatal AKI was limited to small single center studies. The use of the staged AKI criteria had only just begun to be used in neonatal studies. Using these staged AKI definitions, small single-center neonatal studies of very low birth weight neonates (6–11), term asphyxiated infants (12–15), those who underwent extra-corporeal membrane oxygenation (16–18), and cardiac pulmonary bypass surgery (19–22) had rates of AKI between 10 and 83%.

Consistently in these manuscripts, those with AKI had higher mortality than those without AKI; however, due to their relative small sample size, it was difficult to surmise the independent impact of AKI on survival after accounting for confounders.

At the American Society of Nephrology meeting in Atlanta Georgia on November 7, 2013, a group of pediatric nephrologist agreed to form a collaborative (27 and 5/7 weeks after conception at the NIH Neonatal AKI workshop). The following Spring at the Pediatric Academic Society in Vancouver, Canada we had our first official Neonatal Kidney Collaborative meeting. At this meeting interested neonatologist and nephrologist began to develop the mission, vision, strategy, and necessary infrastructure for sustained collaboration. Shortly thereafter, researchers who attended the NIH workshop, and those who were doing single-center neonatal AKI studies joined the group. The only criteria to join was a commitment to participate in a retrospective multi-center study, and an identified neonatology and pediatric nephrologist at the institution willing to work together on the project. Our short-term goals were simple: first, to develop an infrastructure for communication and knowledge acquisition; second, to perform a multi-center epidemiology study that would improve our understanding of the practice patterns, incidence, and outcome in neonates spanning the gestational age spectrum who were critically ill. Our long-term goal was to improve the short and long-term outcomes for neonates at risk for kidney disease.

With commitments from 24 centers, the Neonatal Kidney Collaborative worked to develop the questions, the data forms, the database and the committee infrastructure for our inaugural project, the Assessment of Worldwide Acute Kidney Epidemiology in Neonates (AWAKEN)[1]. This acronym symbolizes our intention to "wake up" the community to the need to better understand neonatal kidney disease. Fortunately we had support from many. We partnered with Dr. Stuart Goldstein, who had recently completed the collection of data from children admitted to the pediatric intensive care unit in a study called Assessment of Worldwide Acute kidney injury and Renal Angina Epidemiology (AWARE). Leveraging these resources, we developed a web based data entry system for the AWAKEN study.

We outlined the most important questions we could answer through a multi-center retrospective study. One of the most important decisions we had to make up front was to determining the inclusion and exclusion criteria. Recognizing that many babies who are only in the NICU for a short duration (i.e., transient tachypnea of the newborn) do not get assessed for kidney disease, we chose to only look at infants who received intravenous fluids for more than 48 h as a key inclusion criteria. In addition we chose to only include infants who were admitted to our NICU's within the first 2 weeks of life, and we excluded those who had severe congenital heart disease requiring heart surgery within the first perinatal week, those who died within 48 h (as we could not assign them to having AKI or not), those with lethal chromosome anomalies, and those with severe bilateral congenital kidney disease. Of the infants who were admitted to the hospital, about 50% met inclusion/exclusion criteria. Thus, the AWAKEN study should not be generalized to all neonates, nor all who are admitted to the NICU; instead, the AWAKEN study can be generalized only to sick infants who need extensive support beyond 48 h after birth. The methods for the study were published prior to data analysis (23).

As of December 2019, we have published 13 original manuscripts from this cohort which we summarize in **Table 1**. We are planning additional manuscripts as we continue to pose and test specific hypotheses. All manuscripts have neonatology and nephrology representation, and most have a neonatologist and nephrologist as first and last authors pairs. Most first-author for these manuscripts have been led by early academic investigators, medical students, and fellows. The first four sets of questions (epidemiology, risk factors, fluid balance, and definition) were determined prior to the data abstraction and were led by the Neonatal Kidney Collaborative steering committee. The rest of the manuscripts below were developed via the secondary analysis manuscript process.

The primary hypothesis for AWAKEN was that AKI was independently associated with mortality after controlling for numerous confounders. Using the Neonatal KDIGO AKI definition, we found that ∼30% of the cohort had at least one episode of AKI. Interestingly, the incidence differed across the gestational age in a "U" distribution. The incidence of AKI was 43% in those <29 weeks GA, 18% in those between 29 and 36 weeks GA, and 37% in the those >36 weeks GA. Of the 605 infants with AKI, 59 (9.7%) died compared to only 20/1,417 (1.4%) who did not have AKI. Even after controlling for numerous confounders known to be associated with neonatal mortality, the adjusted OR for death in those that had AKI was 4.6 times higher the odds of death in those who did not have AKI. Furthermore, those with AKI had an adjusted 8.8 more hospital days compared to those without AKI (1). These relationships held true when we explored subsets of patients categorized by gestational age.

One of the unique parts of this study was that for the first time, we are able to compare the risk factors of AKI in neonates of different GA ranges, and in different time points of the hospital course. We published on these risk factor of early neonatal AKI (first perinatal week) where we showed how perinatal risk factors (maternal and infant demographics, APGAR scores, perinatal medications) are closely associated with AKI (24). Next we reported the risk factors of late AKI (after the post-natal week). After the first week, the perinatal factors are less as important in predicting AKI, but a previous episode of AKI, sepsis, surgery, and nephrotoxin medications are risk factors for AKI (25). For both of these timeframes, we describe the risk factors by different gestational age groups. Currently, we are also describing how anemia, hypoalbuminemia, and dysnatremias are associated with early neonatal AKI (presented as abstracts—not yet in press).

The impact of fluid balance in critical illness is one of the most important questions in critical care nephrology. Besides a few reports on neonates who required extra-corporeal membrane oxygenation and those who had cardio-pulmonary bypass surgery, there is a paucity of data on

[1]**Supplementary Presentation 1** is a slide-deck used as part of a presentation on AWAKEN presented at the 3rd pAKI meeting in Cincinnati Ohio in October 2018.

TABLE 1 | Original manuscript published as of January 2020 from the AWAKEN Study.

Author	Journal	Article name	Summary of findings	DOI
Starr et al.	American Journal of Perinatology, November 2019	Acute Kidney Injury and Bronchopulmonary Dysplasia in Premature Neonates Born <32 Weeks' Gestation.	Moderate or severe broncho-pulmonary dysplasia (BPD) occurred in 214 of 546 (39%) infants, while death occurred in 32 of 546 (6%); the composite of moderate or severe BPD/death occurred in 246 of 546 (45%). For infants born ≤29 weeks of gestation, the adjusted odds ratio (OR) of AKI and the primary outcome was 1.15 [95% confidence interval (CI) = 0.47–2.86; $p = 0.76$]. Infants born between 29 and 32 weeks of gestation with AKI had four-fold higher odds of moderate or severe BPD/death that remained after controlling for multiple factors (adjusted OR = 4.21, 95% CI: 2.07–8.61; $p < 0.001$). Infants born between 29 and 32 weeks of gestation with AKI had four-fold higher odds of moderate or severe BPD/death that remained after controlling for multiple factors (adjusted *OR* = 4.21, 95% CI: 2.07–8.61; $p < 0.001$).	doi: 10.1055/s-0039-3400311
Starr et al.	American Journal of Perinatology, November 2019	Acute Kidney Injury is Associated with Poor Lung Outcomes in Infants Born >32 Weeks' Gestation.	Chronic Lund Disease (CLD) occurred in 82/1,348 (6.1%) infants, while death occurred in 22/1,348 (1.6%); the composite of CLD/death occurred in 104/1,348 (7.7%). Infants with AKI had an almost five-fold increased odds of CLD/death, which remained after controlling for GA, maternal polyhydramnios, multiple gestations, 5-min Apgar's score, intubation, and hypoxic-ischemic encephalopathy [adjusted odds ratio (OR) = 4.9, 95% confidence interval (CI): 3.2–7.4; $p < 0.0001$]. Infants with AKI required longer duration of respiratory support (count ratio = 1.59, 95% CI: 1.14–2.23, $p = 0.003$) and oxygen (count ratio = 1.43, 95% CI: 1.22–1.68, $p < 0.0001$) compared with those without AKI.	doi: 10.1055/s-0039-1698836
Selewski et al.	Pediatric Research, September 2019	The impact of fluid balance on outcomes in premature neonates: a report from the AWAKEN study group.	One hundred and forty-nine (14.8%) were on mechanical ventilation (MV) at post-natal day 7. The median peak Fluid Balance (FB) was 0% (IQR: −2.9, 2) and occurred on post-natal day 2 (IQR: 1,5). Multivariable models showed that the peak FB (aOR 1.14, 95% CI 1.10–1.19), lowest FB in first post-natal week (aOR 1.12, 95% CI 1.07–1.16), and FB on post-natal day 7 (aOR 1.10, 95% CI 1.06–1.13) were independently associated with MV on post-natal day 7. In a similar analysis, a negative FB at post-natal day 7 protected against the need for MV at post-natal day 7 (aOR 0.21, 95% CI 0.12–0.35).	doi: 10.1038/s41390-019-0579-1
Stoops et al.	Neonatology, August 2019	The Association of Intraventricular Hemorrhage and Acute Kidney Injury in Premature Infants from the Assessment of the Worldwide Acute Kidney Injury Epidemiology in Neonates (AWAKEN) Study.	AKI was documented in 22.2% (183/825) of infants and Intraventricular hemorrhage (IVH) in 14.3% (118/825). Infants with AKI ($n = 183$) were more likely to have IVH (26.8%, 49/183) than those without AKI ($n = 642$) who had IVH (10.7%, 69/642, $p < 0.0001$). After controlling for 5-min Apgar score, vasopressor support within the first week of age, and gestational age, infants with AKI had 1.6 times higher adjusted odds to develop any grade IVH (95% CI 1.04–2.56). Furthermore, infants of gestational age of 22–28 weeks had 1.9 times higher adjusted odds to develop IVH (OR 1.87, 95% CI 1.08–3.23).	doi: 10.1159/000501708
Charlton et al.	Clinical Journal of American Society of Nephrology, February 2019	Incidence and Risk Factors of Early Onset Neonatal AKI.	In over 2,000 patients, early AKI (≤7 days) occurred in 21% of neonates. Infants with early AKI had higher risk of death (aOR 2.8, 95% CI 1.7–4.7) and longer length of stay (7.3 days, 95% CI 4.7–10). Risk factors for early AKI are: outborn delivery; resuscitation with epinephrine; admission diagnosis of hyperbilirubinemia, inborn errors of metabolism, or surgical need; frequent kidney function surveillance; and admission to a children's hospital. Protective factors were: multiple gestations, cesarean section, and exposures to antimicrobials, methylxanthines, diuretics, and vasopressors.	doi: 10.2215/CJN.03670318
Harer et al.	JAMA Pediatrics, April 2018	Association Between Early Caffeine Citrate Administration and Risk of Acute Kidney Injury in Preterm Neonates: Results from the AWAKEN Study.	Of 675 preterm infants ≤33 weeks, AKI occurred less frequently in neonates who received caffeine than those who did not [50 of 447 (11.2%) vs. 72 of 228 (31.6%), $P < 0.01$]. After multivariable adjustment, the number needed to treat to prevent one case of AKI was 4.3 and those receiving caffeine were less likely to develop high grade AKI (stage 2 or 3, OR 0.20, 95% CI 0.12–0.34).	doi: 10.1001/jamapediatrics.2018.0322

(Continued)

TABLE 1 | Continued

Author	Journal	Article name	Summary of findings	DOI
Kraut et al.	Pediatric Research, May 2018	Incidence of neonatal hypertension from a large multicenter study [Assessment of the Worldwide Acute Kidney Injury Epidemiology in Neonates (AWAKEN)].	Of over 2,000 infants, hypertension was documented in 1.8% and an additional 3.7% were defined as having undiagnosed hypertension. Hypertension was associated with a diagnosis of AKI and other risk factors for HTN were hyperbilirubinemia, Caucasian race, outborn, vaginal delivery, and congenital heart disease. Protective factors were small for gestational age, multiple gestation, and maternal betamethasone.	doi: 10.1038/s41390-018-0018-8
Kirkley et al.	Pediatric Research, August 2018	Acute kidney injury in neonatal encephalopathy: an evaluation of the AWAKEN database.	Of 113 patients with neonatal encephalopathy, 41.6% developed AKI. Risk factors for AKI were outborn, Intrauterine growth retardation, and presence of meconium at delivery. AKI resulted in longer hospital stays (8.5 days, 95% CI 0.79–16.2).	doi: 10.1007/s00467-018-4068-2
Selewski et al.	Pediatric Research, September 2018	The impact of fluid balance on outcomes in critically ill near term/term neonates: a report from the AWAKEN study group.	The median peak fluid balance was 1.0% and occurred on post-natal day 3. Multivariable models showed the peak fluid balance, lowest fluid balance in 1st post-natal week, and fluid balance on post-natal day 7 were independently associated with need for mechanical ventilation on post-natal day 7.	doi: 10.1038/s41390-018-0183-9
Askenazi et al.	Pediatric Research, December 2018	Optimizing the AKI definition during the first post-natal week using Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates (AWAKEN) cohort.	The absolute rise in serum creatinine of 0.3 mg/dL outperformed a ≥50% rise in serum creatinine during the first week of life for predicting mortality. The optimal serum creatinine thresholds to predict AUC and specificity were ≥0.3 and ≥0.6 mg/dL for ≤29 weeks gestational age and ≥0.1 and ≥0.3 mg/dL for >29 week gestational age. The maximum serum creatinine value provides great specificity.	doi: 10.1038/s41390-018-0249-8
Charlton et al.	Pediatric Research, December 2018	Late onset neonatal acute kidney injury: results from the AWAKEN study.	*n* over 2,000 patients, late AKI (>7 days after birth) occurred in 9% of neonates. Infants with late AKI had increased risk of death (aOR 2.1, $p = 0.02$) and longer length of stay (21.9, $p < 0.001$). Risk factors for late AKI are: intubation, oligo- and polyhydramnios, mild-moderate renal anomalies, admission diagnoses of congenital heart disease, necrotizing enterocolitis, surgical need, exposure to diuretics, vasopressors, and NSAIDs, discharge diagnoses of patent ductus arteriosus, necrotizing enterocolitis, sepsis, and urinary tract infection.	doi: 10.1038/s41390-018-0255-x
Jetton et al.	Lancet Child Adolescent Health. September 2017	Incidence and outcomes of neonatal acute kidney injury (AWAKEN): multicenter, multinational, observational cohort study.	In over 2,000 infants admitted to the NICU on IVF for at least 48 h, 30% developed AKI based on the neonatal KDIGO definition. AKI varies by gestational age at birth: 48% for those born 22–29 weeks, 18% for 29–35 weeks, and 37% for babies ≥36 weeks. Babies with AKI have higher mortality (OR 4.6, 95% CI 2.5–8.3) and longer length of hospital stay (8.8 days, 95% CI 6.1–11.5) after adjusting for multiple confounding factors.	doi: 10.1016/S2352-4642(17)30069-X
Jetton et al.	Frontiers in Pediatrics, July 2016	Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates: Design of a Retrospective Cohort Study.	Describes the formation of the NKC and establishment of the AWAKEN cohort and database—the largest most inclusive neonatal AKI study to date.	doi: 10.3389/fped.2016.00068

the impact of fluid balance and neonatal outcomes. The AWAKEN study allows us to explore these relationships as we show that different fluid balance parameters during the first perinatal week predict the need for mechanical ventilation at 7 days, even after controlling for multiple potential confounders in premature neonates (26) and in near-term/term neonates (27).

One of the most challenging aspects to the evaluation and clinical research on neonatal AKI is the complexity of interpreting the normal SCr patterns seen during the first perinatal weeks and the pragmatic approach to defining neonatal AKI. We use the AWAKEN database to show that different GA groups have different optimal SCr cutoffs at different timepoints after birth to predict mortality. In addition, we show that the addition of a percent rise in SCr does not add any important information to an absolute SCr rise in the ability to predict mortality. This has allowed us to propose a framework for future investigations in understanding how to diagnose neonatal AKI, which will need to be tested in other large clinical cohorts (28).

In a manuscript published in JAMA-Peds, we show that despite the fact that infants who received caffeine (commonly done to keep infants from needing to get intubated) were sicker, those who received caffeine had a much lower adjusted odds of developing AKI than those who were not exposed to caffeine (number needed to treat = 4.3) (29). Other ancillary studies include a report the association of AKI and Hypertension (30), a study showing the association between AKI and mortality in those with severe neonatal encephalopathy (31), the association of AKI and Intra-ventricular hemorrhage (32), the association of AKI and Chronic Lung Disease in premature (33) and near term/term infants (34).

IMPLICATIONS FOR THE FUTURE

The AWAKEN study has allowed us to answer multiple previously unanswered questions, and has "AWAKEN'ed" the field of Neonatal Kidney Disease. We have shown that AKI is very common in sick critically ill neonates, and those who have AKI have a much higher mortality risk than those without AKI. Thus, it is no longer acceptable for the medical community to say that neonatal AKI is rare and carries no sequalae. We have identified that caffeine may prevent AKI, which may have implications not only in neonates but for other populations. Furthermore, we have shown a wide disparity in evaluating for AKI using SCr, and not surprisingly, those centers who measure SCr often have much higher rates of AKI, suggesting a wide practice variation. We have described the potential consequences of impaired kidney function in the neonate (impaired fluid balance, blood pressure control) and its associations with chronic lung disease and intra-ventricular hemorrhage. Finally, this dataset allows centers to compare their current practice to the group as a whole as we provided center-specific data in relation to the AWAKEN cohort collectively.

Importantly, we have supported the ability for medical students, residents, fellows and young attendings to lead manuscripts, and participate in the project. We hope that this experience will stimulate their academic careers with an emphasis on neonatal nephrology, thereby enriching the field with talented, young academicians with strong mentors from the group. Importantly, AWAKEN has provided neonatologist and nephrologist interested in neonatal nephrology an opportunity to problem-solve, study, interpret data, and share ideas together. Finally, the answer to these questions stimulates researchers to ask the next set of questions and motivation us to improve outcomes in this vulnerable population.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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SUPPLEMENTARY MATERIAL

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OPINION
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Opportunities and Barriers to Innovation in Acute Care Pediatrics

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Keywords: acute care pediatrics, investment, academic incentive, ROI, clinical trials network

INTRODUCTION

Drug development is largely an exercise in failure punctuated with infrequent, and rarely, dramatic successes. In general, only 1 in 10,000 compounds assessed for medical use go on to become Food and Drug Administration (FDA) approved drugs (1). This attrition rate is exacerbated by the fact that drug development is usually a long-term project. In general, the time from initial compound development to FDA approval requires 10–15 years. Added to the poor success rate and long duration, drug development requires compounds that are produced under good manufacturing practice (GMP), requires animal and toxicology studies, that must conform to good laboratory practice (GLP), and require successful clinical studies in patients that conform to good clinical practice (GCP). All of these provisions add cost and time to the process. On average, the development cost for a drug which eventually gains FDA approval is $30–150 million (2). Thus, it is clear that drug development is capital intensive and requires both patience and perseverance to achieve success.

With this background in mind, recognize that the capital-intensive portion of this equation sets the stage for which therapeutic areas are pursued and which are ignored. Investors do not mind long-term investments so long as they achieve a good return on the investment (ROI). Why does an investor choose drug development as an investment over something more banal such as purchasing the stock of a large stable company (i.e., a large utility company)? The answer lies in the ROI—better ROI justifies taking more risk. The companies that decide on which therapeutic areas to pursue are cognizant of these factors and tend to pursue drugs that will generate a good ROI; thus, cultivating the requisite investment.

These factors conspire to make pediatric acute care medicine less attractive than other therapeutic indications. For purposes of this exercise, we will use a 20-year timeline which assumes 10 years to drug approval (a rapid time frame to get a drug approved) and 10 years to make profits and recoup the investment. In order to illustrate this point, let's look at a conservative investment of 100 million dollars in a safe high-yielding utility stock that generates a reliable 4% annual dividend (assume annual compounding of the interest) and assume that the stock price does not change for 20 years. At the end of 20 years, an investor who invested in this utility company would have 219 million dollars. Therefore, in order for an investor to decide to place their investment in drug development instead, the investor expects a better ROI. In terms of investment, any factor which increases the time of drug development, increases the risk of failure, or decreases the ability to recoup profits will make an investment less attractive. The question at hand is simply this: does acute care pediatrics increase the time of development, have a higher risk of failure, and does it decrease profit potential? The answer is yes on all counts.

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PEDIATRIC RESEARCH AND IMPACT ON THE FINANCES OF DEVELOPMENT

How does pediatric acute care decrease the *expected* ROI. First, in order to bring a drug into Phase 1 studies (humans), the drug must undergo comprehensive toxicology studies in two species of animals (there can be exceptions, but this the standard guidance). Any drug destined for investigation in children requires juvenile toxicology studies which add both time and money to the equation. In addition, pediatric trials have a higher failure rate than adult studies and they take longer to enroll. Moreover, since children are generally in good health, there are fewer sick patients available to study. Studies in in children typically require different dose formulations, and drug production work of these smaller formulations need to be done before pivotal trials can be done. If these hurdles were not enough, drug companies make more money on outpatient drugs than acute care drugs. One reason for this is that acute care is shorter in duration, whereas in chronic diseases the drugs are taken for a longer duration of time (i.v. antibiotics vs. statins) (**Figure 1**).

For purposes of investment decision making, let's assume the average ROI in a portfolio of drugs is 8% (double the safe utility company) and assume the stock price does not change and drug is guaranteed to succeed. Now if we take the same 100-million-dollar investment and change the ROI from 20 years and add a 5-year delay for acute care pediatrics the value proposition is quite different. In the first case of a 20-year timeline, 100 million dollars invested at 8% pays off 466 million. If that same 466 million was earned over 25 years instead of 20, the interest rate return is 6.35% instead of 8%—a difference of 1.65% or 165 basis points. This may not seem like a big difference, but if it was your own mortgage payment, that difference would be meaningful. For an investor with 100 million dollars, the difference is much larger. Assessed another way, 100 million dollars invested over 20 years at 6.35% yields 342 million whereas 8% yields 466 million for a difference of 124 million dollars. If it was your money, would you invest in the acute care pediatric drug, or the drug for adult type II diabetics? Since most investors are capitalists, they tend to invest in chronic prevalent adult disease and avoid acute diseases.

The FDA is aware of these issues and has attempted to incentivize pediatric development. If a drug gains a pediatric indication after the initial adult indication, the exclusivity of the drug is increased by 6 months. The FDA has also placed incentives such as priority review vouchers to incentivize pediatric research on drug development on rare diseases. Nonetheless, the brutal truth is this—acute care pediatrics is a higher risk investment with worse ROI compared to adults with a chronic disease. In my view, these are key factors that drive the general neglect felt by most acute care physicians particularly pediatricians.

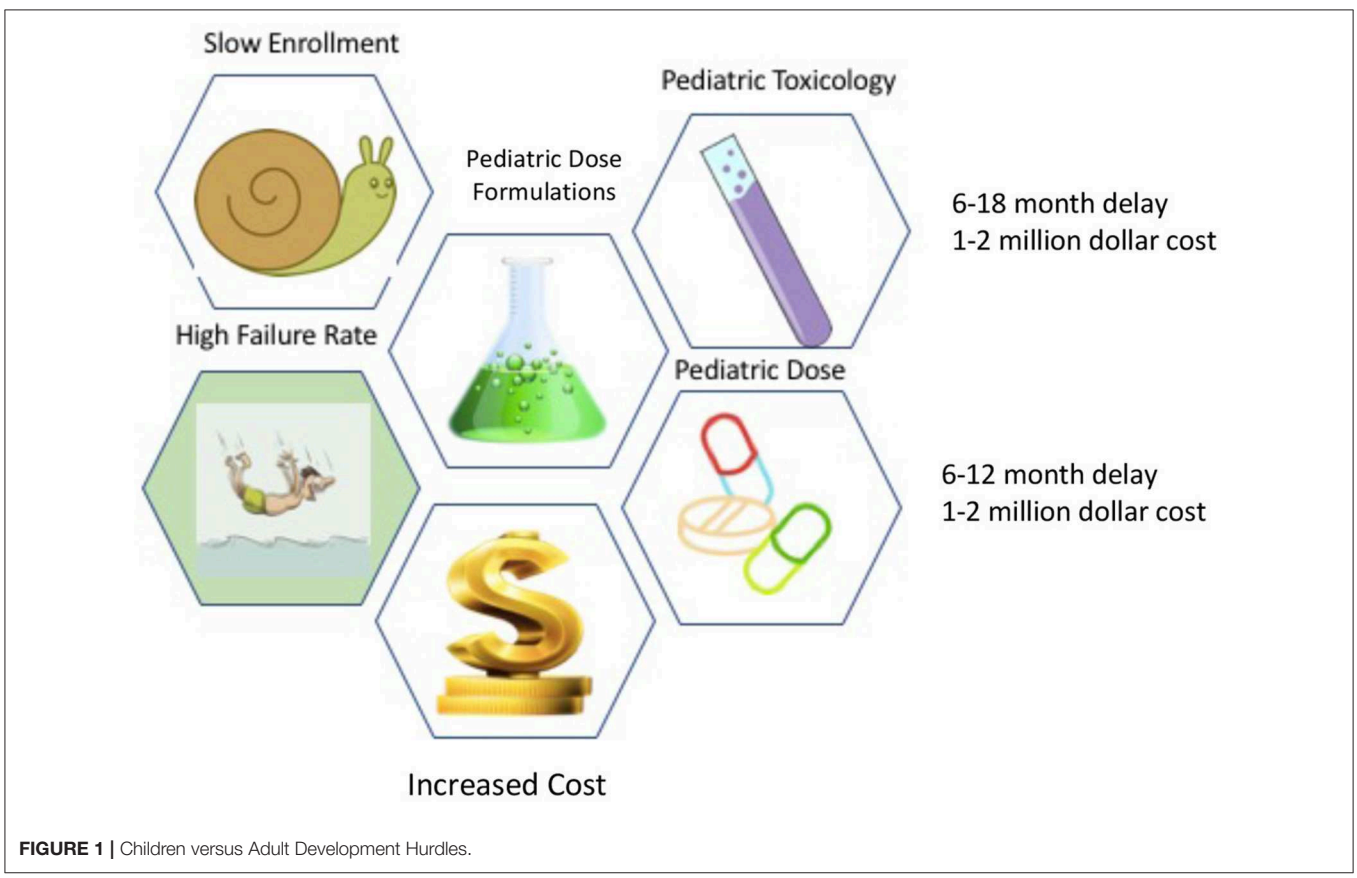

FIGURE 1 | Children versus Adult Development Hurdles.

TABLE 1 | Strategies to improve enrollment time and efficiency.

Strategic Investment	Reasons
Standing acute care pediatric trial networks	Avoids the feast/famine of investigator and coordinator personnel and budgets
Enrollment Screening Tools that are linked to the EMR	Improve efficiency of planning trials and enrollment
Use of precision diagnostics	The routine availability of these diagnostics makes them actionable for study enrollment. The use of these diagnostics for research purposes only increases cost and time
Alignment of incentives	Promotion and academic advancement must align with the needs of improvements in clinical trial enrollment and efficiency. The failure to align these incentives precludes the ability to retain talent.

DISCUSSION

What can be done to mitigate these factors? Simply put, the acute care pediatric community can only directly control one of these many factors. The ability to recoup profits from the chronic outpatient vs. the acute inpatient is a structural issue and will require policy initiatives. However, the probability and time to success can be improved. In order to improve the time to completion of acute care pediatric studies, I would offer four suggestions (**Table 1**). One, clinical trial networks involving many pediatric-centered hospitals must be organized and maintained so that when a drug is ready to be tested, the infra-structure is already in place. Two, screening tools that leverage electronic medical records in order to facilitate timely and efficient enrollment of patients should be put into place as a part of routine practice. Third, the acute care pediatric community must embrace precision diagnostics into their regular clinical practice; thus enabling identification of patients that may benefit from an investigational drug. All too often, the nihilistic view is that since there is no drug for this disease, I don't need to diagnose it in a precise or timely fashion and these diagnostics are not put into routine practice. Fourth, academic centers must create financial and promotion incentives to support clinical investigators so that the talent is brought to the bedside and not pushed into the lab. Incentives matter, and currently the incentives at academic centers is to get government and non-profit research to increase the coveted indirect funding dollars and avoid industry trials. Indirect funding is good for an academic center's bottom-line, but in order to gain FDA approval, the sponsor must be a company that can make the drug to the FDA standard. The National Institutes of Health, Gates Foundation, and other luminary institutions do not manufacture drugs even though they may fund billions in research dollars. Plainly stated, if the acute care pediatric care community wants to alter the financial equation and shepherd investment into this therapeutic area, they must enroll their trials faster and cheaper while maintaining high quality and safety.

In conclusion, the nature of pediatric acute care drug development creates a tendency for under-investment. Some of the factors that contribute to this are structural and hard to change. However, initiatives that foster collaboration, academic promotion incentives for investing in clinical trials personal/infra-structure, and improved trial enrollment may help offset these hurdles.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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MINI REVIEW
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Does Your Program Know Its AKI and CRRT Epidemiology? The Case for a Dashboard

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Current acute kidney injury (AKI) literature focuses on diagnosis, treatment, and outcomes. While little literature exists studying the quality of care delivered to patients with AKI. However, improving outcomes for patients is dependent on the specifics of the delivered care (i.e., the who, what, when, and how). Therefore, it is necessary to direct attention to process measures to assess the relationship between care and outcomes. The application of quality improvement science to the care of AKI, uses a series of metrics encompassing both processes and outcomes to better understand, evaluate, and ensure the delivery high quality care.

Keywords: acute kidney injury (AKI), continuous renal replacement therapy (CRRT), quality improvement (QI), dashboard, standardization, epidemiology

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INTRODUCTION

Recent pediatric epidemiology and prevalence studies reported AKI developed in 26.9% of critically ill children, with severe AKI occurring 11.6% (1). The current management for AKI is support with interventions that target improving hemodynamics, removing the potential sources of the renal injury, and the utilization of renal replacement therapy in the setting of severe AKI (2). While diagnosis and treatment of AKI is well-described in the literature, very few studies focused on the quality of care delivered in the AKI care continuum. There is an assumption that care delivery is consistent between institutions, as well as within an institution. However, when examined further significant practice variations exist across the AKI care continuum (3, 4). Analyzing the relationship between process measures, outcomes measure, and patient outcomes is the foundation of quality improvement (QI) science. QI science performs a series of metrics encompassing both processes and outcomes to better understand, evaluate, and ensure the delivery high quality care. Process measures reflect adherence to the standardized steps and practices performed by health care staff members that are necessary to ensure quality care is delivered to every patient (5). Literature is skewed heavily toward understanding the associations between care and outcome measures (e.g., mortality). However, improving outcomes for patients is dependent on the specifics of the delivered care (i.e., the who, what, when, and how). More attention is now given to process measures, understanding how the degree of variability in the process of delivering care is associated with patient outcome.

Aimed at reducing practice variation and standardizing care for managing AKI, the 5Rs approach was recently introduced (6). The 5Rs approach identifies area for interventions along the AKI care continuum; Recognition, Response, Risk identification, Renal support, and Rehabilitation (6). Interventions in each category may include the use of electronic health record alerts to identify patients, provide clinical decision support algorithms for care delivery, implementation of care bundles to reduce variation, and development of a QI dashboard for reporting. Studying these process measures and the association with patient outcomes is the foundation for improving care.

STANDARDIZE CARE DELIVERY AND QI METHODOLOGIES

QI practices are grounded in understanding how care delivery processes (and variation in processes) impact patient outcomes. Practice variation and its association with poor outcomes is well-described in the literature (7–9). For example, central line infections (outcome measure) are directly associated with mortality (patient outcome), so focus is given to measuring the performance of providers in actions aimed to reduce the infections such as bundles of care and infection prevention standards (process measures). This kind of quality improvement analysis is also evident in other complex therapies such as cardiopulmonary resuscitation—a reported process measure is depth of compressions in relation to published guidelines (10, 11). In these investigations, measuring process outcomes is leading to the understanding that the quality, consistency, and reproducibility of the care provided (and adherence to existing guidelines or benchmarks) is itself important. Therefore, the logical first step in applying QI strategies to an AKI/CRRT program is establishing standardized practices for the delivery of care. Standardization of practice is achieved by developing detailed recommendations to guide practitioners in providing appropriate evidence-based interventions [e.g., standard practice guidelines (SPG), care pathways, or care bundles].

The benefits of standardization are two-fold. Establishing a standard of care ensures each patient receives high quality consistent care, as well as providing a platform for standardizing team expectations and communication (12). For example, a SPG recommends performing a blood prime initiation procedure for patient weighing <10 kg. However, the orders are not consistent with the SPG. The team members recognize the variation in practice and communicates this with ordering practitioner, preventing an error and potential harm. It is important to acknowledge that SPG are meant to provide recommendations for care and do not limit the practitioner from using expertise to modify interventions or therapies based on patient responses.

Following the implementation of standardized practices, the next steps are data collection, data analysis, and preparing and distributing reports. An essential component of data analysis is identifying deviations from established benchmarks or goals. Upon the detection of a deviation, a "deep dive" is done to investigate for potential causes through factor analysis of patient (selection criteria, initiation, size and body habitus, special circumstances), equipment (inclusive of access catheter and machine), technical proficiency (nursing care and pharmacy), and the prescription of the therapy (modality, dose, anticoagulation) (2). Interventions, if necessary, are based on the final results of the "deep dive."

QUALITY IMPROVEMENT IN AKI

Recognition (Early)/Response/Risk Identification

The early recognition of AKI has been associated with improved patient outcomes. Forde and colleagues report earlier diagnosis of AKI and improvement AKI management following targeted education and implementation of a checklist (13). The AKI checklist/bundle uses a simple acronym ABCDE; Address drugs, Boost blood pressure, Calculate fluid balance, Dip urine, and Exclude obstruction (13). The primary aim, diagnosing AKI within 24 h, improved from 30 to 100%. The checklist was implemented 75% of the time in the post-education period.

Other early recognition QI programs utilize the electronic health records to detect patient at risk for AKI or have AKI. The electronic health record identified the target population and alerts the practitioner. However, the literature suggests that alerting practitioners alone, does not improve patient outcomes (14). A systematic integration of clinical decision support with the alert is necessary to influence patient outcomes (15). The ideal AKI QI initiative aimed at recognition involves detected AKI, followed by an alert to the appropriate personnel and recommends intervention of preventative and therapeutic measures.

Renal Support

As previously discussed, there is a paucity of literature studying the delivery of renal replacement therapy (RRT). The majority of the research is focused on patient characteristics, indications for RRT, and patient outcomes (16–18). The care is continuous in nature and involves numerous processes for safe, effective care to be delivered. Studying process measures, both categorical and temporal, provides an index of quality by providing a quantifiable level of adherence to accepted performance standards.

Activity

Activity metrics are tracked to study the relationship between frequency of therapies and other process measures. Specifically, assessing if available resources are sufficient to deliver high quality of care.

Filter Survival

The optimal delivery of CRRT is contingent on maintaining a well-functioning CRRT circuit. However, filter life is multifactorial and therefore is assessed using two process measures: filter life and unplanned filter changes (UPC).

Filter life

Filter life is defined as the duration of time, measured in hours, an individual filter or circuit is delivering therapy to the patient (2, 19).

Unplanned filter changes

UPC is defined as any filter changed prior to 60 h, censored for patient procedures, emergent events or patient death (2, 19).

Prescription

Prescribed and achieved CRRT effluent doses are an important process measures and provides an objective assessment of the delivered care. Variations between prescribed and delivered was quantified by simultaneously measuring both values and calculating % delivered (2, 19).

Minimum prescription

The minimum prescription is defined as the total number of CRRT hours and the total effluent measured in mL normalized to patient body surface area. The standard prescription for pediatrics is 2,000 ml/1.73 m^2/h. Therefore, prescription below this dose were identified as a deviation from the standard.

Average treatment time

The average treatment time is the quantified average of time the CRRT delivered therapy for an individual patient treatment course on CRRT (2).

Fluid balance

Fluid as a metric, is separated into fluid status at initiation and achievement of daily fluid goals. Fluid accumulation is expressed as percent fluid overload (% FO). The formula for calculating fluid overload is: [((Intake (liters) from ICU admission to CRRT start – Output (liters) from ICU admission to CRRT start)/1000))/ICU admission weight (kg)] (20).

Achieved Fluid Goal (Desired Total Fluid Output) is defined as achieving the established fluid goal within the acceptable range of a fluid goal is ±10% of target. Calculation of the variability from the target fluid goal assumes the actual 24-h total output will be equivalent to the total 24-h intake minus the net 24-h fluid balance goal (2).

Rehabilitation

The final R in the AKI continuum is Rehabilitation. Recent literature report patients who recover from an AKI event have an increase in risk for developing chronic kidney disease (CKD) (21, 22). Therefore, using QI strategies to ensure adequate follow-up for AKI survivors is essential. Currently, there is a lack of evidence that answers the questions regarding follow-up (e.g., who, what, when, and how). Recent literature reported the use of an algorithm for establishing follow-up standards and well as what patient measures to assess (22).

CONCLUSION

The use of an AKI dashboard provides and ongoing assessment of process measures and facilitates analyses of variations and deviations from standards of care. Assumptions about how effective the therapy is cannot be made simply by whether a patient survives. Ultimately, process metrics are valuable to study in and of themselves but are likely directly impactful to the traditional hard patient outcomes specific to the kidney, to morbidity, and to mortality.

AUTHOR CONTRIBUTIONS

TM collected, analyzed and interpreted the data for quality improvement in CRRT, as well as a major contributor in writing the manuscript.

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The Current State of the Art in Acute Kidney Injury

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Decades of pre-clinical research have revealed biologic pathways that have suggested potential therapies for acute kidney injury (AKI) in experimental models. However, translating these to human AKI has largely yielded disappointing results. Fortunately, recent discoveries in AKI molecular mechanisms are providing new opportunities for early detection and novel interventions. This review identifies technologies that are revealing the exceptionally complex nature of the normal kidney, the remarkable heterogeneity of the AKI syndrome, and the myriad responses of the kidney to AKI. Based on the current state of the art, novel approaches to improve the bench-to-bedside translation of novel discoveries are proposed. These strategies include the use of unbiased approaches to improve our understanding of human AKI, establishment of irrefutable biologic plausibility for proposed biomarkers and therapies, identification of patients at risk for AKI pre-injury using clinical scores and non-invasive biomarkers, initiation of safe, and effective preventive interventions of pre-injury in susceptible patients, identification of patients who may develop AKI post-injury using electronic triggers, clinical scores, and novel biomarkers, employment of sequential biomarkers to initiate appropriate therapies based on knowledge of the underlying pathophysiology, use of new biomarkers as criteria for enrollment in randomized clinical trials, assessing efficacy, and empowering the drug development process, and early initiation of anti-fibrotic therapies. These strategies are immediately actionable and hold tremendous promise for effective bench-to-bedside translation of novel discoveries that will change the current dismal prognosis of human AKI.

Keywords: acute kidney injury, electronic triggers, clinical scores, biomarkers, anti-fibrotic therapies

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INTRODUCTION

Acute kidney injury (AKI) is a growing global epidemic, afflicting about 30% of children in neonatal and pediatric intensive care units and at least 5% of non-critically ill pediatric hospitalizations. Impressive improvements in the clinical care of hospitalized children have inexorably shifted the AKI epidemiology from primary renal diseases toward a consequence of systemic illnesses and their treatments and nephrotoxin exposure. In contrast with AKI in adults, pediatric AKI typically strikes early in the course of a critical illness, but it is more often reversible in the absence of major comorbid complications. However, AKI is independently associated with increased mortality and morbidity, including the development of chronic kidney disease, in all age groups. Several decades of intense pre-clinical and translational research have uncovered biologic pathways and mechanisms that have suggested promising therapeutic approaches in animal models. However, the

translational efforts in human AKI have largely yielded disappointing results, and the incidence of and the complications from human AKI remain unacceptably high, with no satisfactory preventive or therapeutic solutions in sight. Fortunately, recent discoveries in AKI molecular mechanisms are shifting old paradigms and providing new approaches for early detection and intervention. This review will focus on the state-of-the-art technologies that are revealing the exceptional complexity of the normal kidney, the remarkable heterogeneity of the AKI syndrome, and the myriad responses of the kidney to AKI. Novel approaches to improve the bench-to-bedside translation of novel discoveries will be proposed—at the present time, these remain largely the author's personal opinions that have not been systematically studied.

THE UNEXPECTED COMPLEXITY OF THE NORMAL KIDNEY

Our understanding of the normal kidney has advanced dramatically during the past decade, with the advent of unbiased gene, protein, and metabolome expression analysis, propelled by the enabling technologies of molecular nephrology (1, 2). In particular, single-cell RNA sequencing (scRNA-seq) can now uncover the expression level of every gene in every cell type, enabling the rapid determination of serial gene expression changes in many thousands of cells, identification of previously unknown cell populations, and even novel heterogeneity within a given cell type. For example, the scRNA-seq analysis of the developing collecting duct has newly identified sub-cluster cell types that include principal cells, β-intercalated cells, and other previously unknown cell subtypes (3). Similar studies in the fully developed collecting duct have revealed a novel crosstalk between signal transduction pathways as well as an improved understanding of physiologic regulatory pathways (4). A comprehensive scRNA-seq analysis of adult mouse kidneys has identified novel cell types that remain to be fully characterized (5). An examination of human kidney transplant biopsies has uncovered 16 distinct cell types and novel cell states within endothelial cells as well as pro-inflammatory parenchymal responses in the rejecting kidney (6). Thus, scRNA-seq techniques are identifying new categories of known cell sub-types as well as previously unknown cell types that are improving our understanding of the developing, mature, and diseased kidney at an unprecedented level of detail.

THE UNANTICIPATED HETEROGENEITY OF ACUTE KIDNEY INJURY

Decades of meticulous clinical phenotyping have taught us that all AKIs are not created equal. As clinicians, we have become adept at recognizing several AKI subtypes, including pre-renal, intrinsic, ischemic, hypoxic, nephrotoxic, septic, inflammatory, and obstructive forms. An improved understanding of the molecular underpinnings of AKI subtypes was ushered in two decades ago with the advent of transcriptome profiling technologies. Data mining of gene expression profiles from 150 microarray experiments performed in 21 different models of AKI (including mouse, rat, pig, and human models) identified novel upregulated genes that have now been well-characterized and are now considered "usual suspects" in AKI parlance—including *LCN2* (encoding lipocalin 2 or NGAL), *KIM-1* (kidney injury molecule-1), *CCL2* (chemokine ligand 2 or MCP-1), *HMOX1* (heme oxygenase), *TNF* (tumor necrosis factor), and *CLU* (Clusterin) (7). Downstream translational analyses in animal and human AKI are now beginning to yield pathways for therapeutic targeting, as well as excellent non-invasive assays for the early diagnosis of AKI and its sequelae (1).

More recent deep sequencing studies have identified significant differences in the responses between the AKI subtypes. For example, there exists a remarkable diversity of changes in the kidney genomic response to ischemic and septic injuries (8). While *TNF* and *LCN2* are dramatically upregulated in both ischemic and septic AKI, *KIM-1* is induced primarily in ischemic injury and *ICAM-1* in sepsis only (8). Furthermore, a comparison of the ischemic and the volume depletion models of AKI, often considered to be a continuum and therefore predicted to have similar gene expression response, unexpectedly showed that <10% of the expressed genes were differentially regulated in the two models despite identical elevations in serum creatinine (9). Volume depletion induced metabolic pathways and anti-inflammatory molecules. By contrast, ischemic injury activated hundreds of known and novel inflammatory, coagulation, and epithelial repair pathways, including the "usual suspects" *LCN2, KIM-1, CXCL1*, and *IL-6*, all of which were totally unchanged in the volume depletion model (9). For added complexity, different nephron segments responded with distinct signatures to different injuries. For example, volume depletion predominately affected the inner medulla, whereas ischemic changes were noted primarily in the outer medulla. In addition, ischemic injury induces mRNA expression of *KIM-1* specifically in the proximal tubule and, in contrast, *LCN2* specifically in the distal nephron (9). Hence, different insults lead to diverse responses reflecting alterations in segment-specific pathophysiology.

Recent metabolomic approaches have further validated additional dramatic differences in the response of the kidney to injuries that were previously thought to be closely related. For example, experimental models of ischemia–reperfusion injury display the rapid appearance of alanine, leucine, and glucose in urine, with a downregulation of urinary creatinine and nicotinamide (10). In marked contrast, hypoxic injury rapidly induces the urinary excretion of benzoate and fructose, while citrate and isothionate are suppressed (11). The differential appearance of these metabolites in the urine may hold important clues toward etiology-specific biomarkers and therapeutic targets in humans.

Additional recent metabolomic studies in a mouse model of ischemic AKI have identified a deficiency in the urinary and intra-renal nicotinamide adenine dinucleotide (NAD), an essential component of energy generation via glycolysis and the Kreb's cycle (12). In a phase I study of oral NAM supplementation (which generates NAD via a salvage pathway) in adults undergoing cardiac surgery, the rise in serum creatinine

was prevented compared to placebo (12). Additional studies are underway.

STRATEGIES TO IMPROVE BENCH-TO-BEDSIDE TRANSLATION IN AKI

Thus, different etiologies of AKI elicit dramatically divergent responses. Additional basic and translational studies, too numerous to be elucidated here, have yielded characteristic structural, functional, and regenerative responses to each AKI stimulus. However, animal studies do not faithfully recapitulate the human AKI phenotype, rendering bench-to-bedside translation enormously challenging. Despite promising pre-clinical data, the human AKI literature is littered with numerous disappointing treatment failures—including forced diuresis and RGD peptides for tubular obstruction, ATP donors (ATP-Mg, thyroxine) for intracellular ATP depletion, natriuretic peptides and dopamine for vasoconstriction, reactive oxygen species scavengers and iron chelators for oxidative stress, anti-ICAM antibodies for endothelial–leucocyte adhesion, anti-apoptotic agents, growth factors (IGF-1, HGF, FGF, and erythropoietin), anti-inflammatory agents (α-MSH), and regenerative factors (mesenchymal stem cells) (13). The strategies proposed by the author to close this bench-to-bedside chasm are detailed below.

Use Agnostic Approaches to Better Understand AKI in Animal and Human Models

We recommend the use of unbiased approaches to identify AKI susceptibility genes in humans. Large-scale genome-wide association studies (GWAS) can identify potentially pathogenic genomic sequences that are statistically enriched in AKI cases compared to controls. A recent GWAS analysis of a discovery cohort of 1,400 adults with critical illness (760 with AKI) followed by a separate replication cohort of 200 AKI cases (14) has yielded two single-nucleotide polymorphisms (SNPs) involving the transcription factor interferon regulatory factor 2 (IRF2) and an additional two SNPs close to the transcription factor T-box 1 (TBX1). The identification of SNPs near IRF2 suggests a potential role for the immune system in AKI, a concept with already strong biologic plausibility. TBX1 is expressed during kidney development, and this finding supports the intriguing concept that ontogeny recapitulates phylogeny after kidney injury, whereby genetic programs involved in nephrogenesis that become dormant after birth are once again reactivated and are essential for the recovery process after injury in post-natal life. Additional GWAS studies with even larger cohorts of control and AKI subjects are underway and may yield new AKI susceptibility genes of critical biological significance.

We recommend the employment of dramatic advances in single-cell RNA sequencing to examine both animal and human AKI models (15, 16). A recent comprehensive analysis of a mouse model of ischemia–reperfusion AKI using whole kidney total mRNA sequencing has already identified time-dependent changes in the expression of genes involved in tubular injury/repair, fibrosis, and innate and adaptive immunity (17). As an extension to humans, the NIH-funded Kidney Precision Medicine Project will analyze human AKI kidney biopsies based on elevations in serum creatinine and a urinary biomarker (based on the "usual suspects" previously mentioned). Single-cell RNA-seq and other advanced deep sequencing studies are expected to yield a detailed molecular atlas of the human kidney and potentially identify new pathways for future therapies.

Establish Irrefutable Biologic Plausibility in Multiple Animal Models Prior to Embarking on Etiology-Specific Human Studies

We recommend detailed molecular analyses of animal models most pertinent to human AKI, followed by bioinformatic determination of both common and etiology-specific pathways, and downstream confirmation of biologic significance with additional techniques. Such studies will begin to address the enormous complexity of human AKI, which is often multifactorial, with overlapping components—in addition to volume depletion, ischemia–reperfusion injury, and nephrotoxins, clinicians have to worry about hypoxia, sepsis, inflammation, obstruction, and primary kidney diseases, to name a few situations. All of these induce comparable elevations in serum creatinine levels, the current highly flawed "gold standard" for the diagnosis and staging of AKI, a major limiting factor in AKI diagnostics today (1).

Recent publications validate this recommendation. Reliable animal models have now been developed to recapitulate many human AKI pathophysiologies, including the AKI-to-CKD transition (18). A careful analysis of these models has begun to elucidate the myriad responses at the structural and the molecular levels (17). In a murine bilateral ischemia–reperfusion survival model that recapitulated the human AKI-to-CKD transition, serum creatinine peaks after 2 days. However, histology at day 1 already revealed characteristic tubular changes in the outer medullary region that mimic the human phenotype. At 6 months after the injury, cortical fibrosis is the predominant finding. At 1 year later, additional cystic changes and a severe chronic interstitial nephritis appear, all reminiscent of end-stage kidney disease in humans. At the molecular level, the earliest changes included a significant expression of immediate early response and stress-related genes that are conserved between mouse and humans and are also activated soon after transplanting deceased donor kidneys (17). Within 24 h of injury, elevation of genes regulating apoptosis and proliferation, which persisted for weeks after injury, was prominently noted, attesting to the critical significance for the balance between cell death and cell survival during recovery from AKI. Most prominent among these were the genes encoding NGAL and KIM-1, both crucial to the processes of cellular regeneration and repair, lending ample biological plausibility for their roles as early non-invasive biomarkers (1, 7).

Animal models of ischemia–reperfusion AKI have additionally identified diverse epigenetic changes that in

turn control AKI gene expression (8). For example, histone acetylation (which results in a transcriptionally permissive chromatin structure) was significantly associated with *Tnf* gene expression. Similarly, changes in histone methylation (which provides docking sites for chromatin modifiers) were identified in *Tnf*, *Kim-1*, and *Ngal* genes (8). These and other epigenetic changes are potentially reversible with appropriate pharmacotherapy and provide novel targets for drug design in AKI.

A translational molecular analysis of septic AKI has been limited by the fact that most animal models of this condition do not faithfully mimic the human condition (19). Murine models have utilized cecal ligation and puncture, fecal implantation in the abdomen, and lipopolysaccharide (LPS) injections and have resulted in varying degrees of structural and functional AKI. Despite these limitations, recent studies have revealed dramatic differences in gene transcription and in epigenetic changes in the kidney following LPS injection vs. ischemia–reperfusion (8). While the *Tnf* and *Ngal* genes are strongly induced in both models, *Kim-1* and *Tlr4* were upregulated only in ischemia–reperfusion and *Icam-1* only after sepsis. Many genes such as *Klotho* and *Netrin1* were downregulated only after ischemia–reperfusion, while several angiogenic genes exhibited a decreased expression following LPS injection. Understanding the heterogeneity of genetic and epigenetic responses in etiology-specific animal models will contribute to the discovery of interventions tailored to the cause of AKI.

Identify Patients at Risk for AKI Pre-injury

We recommend the use of clinical scoring systems to predict AKI pre-injury. For example, to predict AKI in adults, clinical risk factors have been incorporated into the well-known Cleveland Clinic Score (for cardiac surgery) and Mehran Score (for contrast agents). These scores can be adapted for use in pediatrics. Indeed in a prospective multicenter analysis of children undergoing cardiac surgery, risk factors associated with a greater AKI incidence included lower age, weight, body surface area, and preoperative serum creatinine (20). Longer bypass time was also associated with AKI development. Those that had a bypass time $>$180 min showed a nearly 8-fold greater odds of developing AKI when compared to those with a bypass time $<$60 min (20).

We recommend the use of non-invasive pre-procedural biomarkers to predict AKI in children at risk. One of the best studied pre-operative biomarkers is uromodulin, a well-established nephroprotective protein—uromodulin knock-out mice are more susceptible to ischemia–reperfusion kidney injury and are more likely to experience tubular inflammation and necrosis, especially in the highly susceptible S3 segment of the proximal tubule (21). In a recent analysis of 101 children undergoing cardiac surgery with bypass, 47% developed AKI, and only 8% of the patients in the highest quartile of preoperative urinary uromodulin (uUMOD) concentrations developed AKI, in contrast with 92% of the participants in the lowest quartile (22). Preoperative uUMOD strongly predicted postoperative AKI, with area under the curve (AUC) of 0.90 (22). These results suggest that if pre-operative uUMOD is used to identify patients at risk for AKI after bypass, preventive measures might minimize post-operative AKI.

Initiate Preventive Interventions Pre-injury in Susceptible Patients

We recommend the initiation of safe and inexpensive preventive measures in context-specific susceptible patients. One well-studied example is the use of N-acetyl cysteine (NAC) to prevent contrast-induced AKI. While this remains controversial, it is safe and orally effective. It is our practice to administer NAC (in addition to intravenous hydration and urinary alkalinization) in children scheduled for a contrast study with underlying chronic kidney disease stage 3 or greater who have a history of contrast-induced AKI (23).

Although intense renal vasoconstriction and vasospasm are well-known pathogenic processes in many forms of AKI, vasodilator therapies such as the natriuretic peptides and dopamine have been ineffective in preventing human AKI and are not recommended (23). However, the use of fenoldopam, a short-acting selective dopamine-1 receptor agonist (which the renal vasculature is particularly enriched in) with additional anti-inflammatory properties, is intriguing. In a prospective randomized double-blind trial of 80 children undergoing cardiac surgery, 40 received placebo and 40 were treated with fenoldopam intra-operatively (24). The fenoldopam group displayed a significant reduction in urinary biomarkers of AKI (NGAL and cystatin C) and a reduced need for diuretics and other vasodilators in the post-operative period. These data are promising but need independent confirmation in larger studies.

Identify Patients Who Are at Risk for AKI Post-injury Early

We recommend the use of clinical scoring systems to predict AKI post-injury or when the timing of injury is unknown. The Renal Angina Index (RAI) has emerged as a useful scoring system in children who are critically ill (25). The RAI combines validated clinical risk factors (ICU admission, solid organ or stem cell transplant, mechanical ventilation, and vasopressor need) with evidence for decreased kidney function (increases in serum creatinine or degrees of fluid accumulation) to stratify patients at risk for subsequent severe AKI. Importantly, the incorporation of urinary biomarkers further improves the predictive ability of the RAI (26). In a prospective study of 184 children admitted to the pediatric ICU, a positive RAI (score $\geq$8) was present in 33% of patients at day 0 and predicted day 3 AKI with an AUC of 0.80. Inclusion of admission urinary NGAL further increased the AUC to predict day 3 AKI to 0.97. The RAI has thus emerged as an important tool to direct biomarker measurements in select patients who are most likely to benefit from such determinations.

We recommend the use of non-invasive biologically plausible urinary and plasma biomarkers to predict AKI and its severity in all clinical settings that portend a risk for AKI development. The most extensively studied such biomarker is NGAL, which is rapidly induced in the distal nephron following a variety of injurious stimuli and exerts a profound nephroprotective effect due to its anti-apoptotic, pro-proliferative, and bacteriostatic

properties (1, 7, 27–29). A myriad of prospective studies, many in children, have now established the highly predictive role of NGAL as a biomarker to predict AKI and its complications in numerous clinical settings including critical illness, sepsis, cardiac surgery, nephrotoxins, and organ transplants (30–33). Following an analysis of many thousands of subjects and many thousands of AKI events in the literature, we now have six large meta-analyses attesting to the diagnostic properties of NGAL measurements for AKI prediction, with a consistent area under the curve of over 0.8 for a urinary NGAL value >150 ng/ml (34–38).

The combination of two biomarkers of cellular stress, namely, TIMP-2 and IGFBP-7, has also recently emerged as a promising early biomarker of AKI, particularly in adults with critical illness. In a recent meta-analysis of five studies with 1,619 critically ill patients, urinary TIMP-2 × IGFBP7 cutoff points of 0.3 (ng/ml)/1,000 had an AUC of 0.75 for AKI prediction (39). The pediatric experience with TIMP-2 and IGFBP-7 has been limited to date to small studies in which these biomarkers have been promising but are somewhat delayed predictors of AKI in comparison to NGAL (40, 41).

Use Automated Electronic Health Records Plus Early Biomarkers to Assess for AKI

We recommend employing automated electronic health record (EHR) systems to direct measurements of serum creatinine and other predictive AKI biomarkers in children at risk for AKI. The utility of this approach is best exemplified by a prospective single-center study in which the EHR identified hospitalized children receiving aminoglycosides for more than 3 days or more than three nephrotoxins simultaneously (42). This triggered the pharmacists to recommend daily serum creatinine monitoring in exposed patients. During the study period, the exposure rate decreased by 38%, and the AKI rate decreased by 64%. An estimated 633 exposures and 398 AKI episodes were avoided. Thus, EHR-based surveillance for nephrotoxic medication exposure can lead to sustained reductions in nephrotoxin use and AKI. These interventions have now been translated to 30 other pediatric centers.

We recommend the use of the EHR-based serum creatinine increases to trigger biomarker measurements. In our clinical practice, urine NGAL is measured automatically in critically ill children with 50% or greater increase in serum creatinine. The results drive an early nephrology consultation as well as rational initial management, depending on the presence of intrinsic structural AKI (NGAL $\geq$ 150 ng/ml) or volume-responsive functional AKI (NGAL $\leq$ 50 ng/ml).

Use Sequential Biomarkers to Initiate Context-Specific Therapies

We recommend the use of temporally sequential biomarkers to establish the time of initial injury as well as to initiate appropriate therapies based on knowledge of the underlying pathophysiology. Experimental AKI proceeds in four sequential phases: initiation, extension, maintenance, and recovery. During the initiation phase, there is profound intracellular ATP depletion and generation of reactive oxygen molecules and labile iron. Vasodilator, ATP-donor, anti-oxidant, and iron chelation therapies may be effective during this phase, and the appearance of the earliest non-invasive biomarkers such as NGAL may be used to trigger such therapies. Several published studies in humans, including children with AKI (41, 43), have documented the appearance of NGAL in the urine and the blood very early after ischemic, nephrotoxic, or septic structural kidney injury (but not in pre-renal functional injury). In the extension phase, tubules undergo reperfusion-mediated cell death, and the injured endothelial and epithelial cells amplify the inflammatory cascades. This phase may be marked by intermediate biomarkers such as L-FABP, and therapeutic interventions might include anti-apoptotic and anti-inflammatory strategies. During the maintenance phase, cell regeneration predominates. Slightly delayed markers with high specificity, such as the cell cycle biomarkers (TIMP-2 and IGFBP-7), may trigger therapeutic measures such as growth factors and stem cells that accelerate repair. These concepts are illustrated in **Figure 1** and are ready for implementation since both NGAL and the cell cycle biomarkers are now widely available for clinical use.

Use Injury-Specific Biomarkers as Eligibility Criteria for Clinical Trial Enrollment

We recommend the use of widely available early AKI biomarkers such as NGAL to enroll patients in AKI clinical trials. This concept is illustrated in **Figure 2**, whereby patients known to have clinical risk factors for AKI are triaged using a biomarker measurement (irrespective of the serum creatinine value). Using early biomarker elevation to enroll subjects in AKI trials can increase the proportion of patients enrolled early in the course of AKI and decrease the sample size required, thereby dramatically reducing trial cost. This concept has been validated in recent publications using hypothetical simulations (44). In patients undergoing cardiac surgery, by using a combination of a known clinical risk factor (prolonged bypass time) and injury markers (IL-18 or NGAL), the authors showed that an AKI therapeutic trial cost could be decreased by 64% (44).

Furthermore, we recommend the use of AKI biomarkers to assess the response to therapies and as outcome measures to identify the therapies that warrant further testing in larger, multicenter trials. In this concept, a reduction in biomarker concentration can be considered as an initial success—this will once again decrease the cost of completing initial proof-of-principle AKI trials and will identify the best context-specific agents for more definitive trials that include widely accepted longer-term outcomes such as the "three Ds" (death, dialysis, and doubling of serum creatinine) and "MAKE" (major adverse kidney events).

Use Injury-Specific Biomarkers in the Drug Development Process

We recommend the use of injury-specific biomarkers in the pre-clinical phases of drug development, specifically for the early identification of nephrotoxic AKI independent of the serum

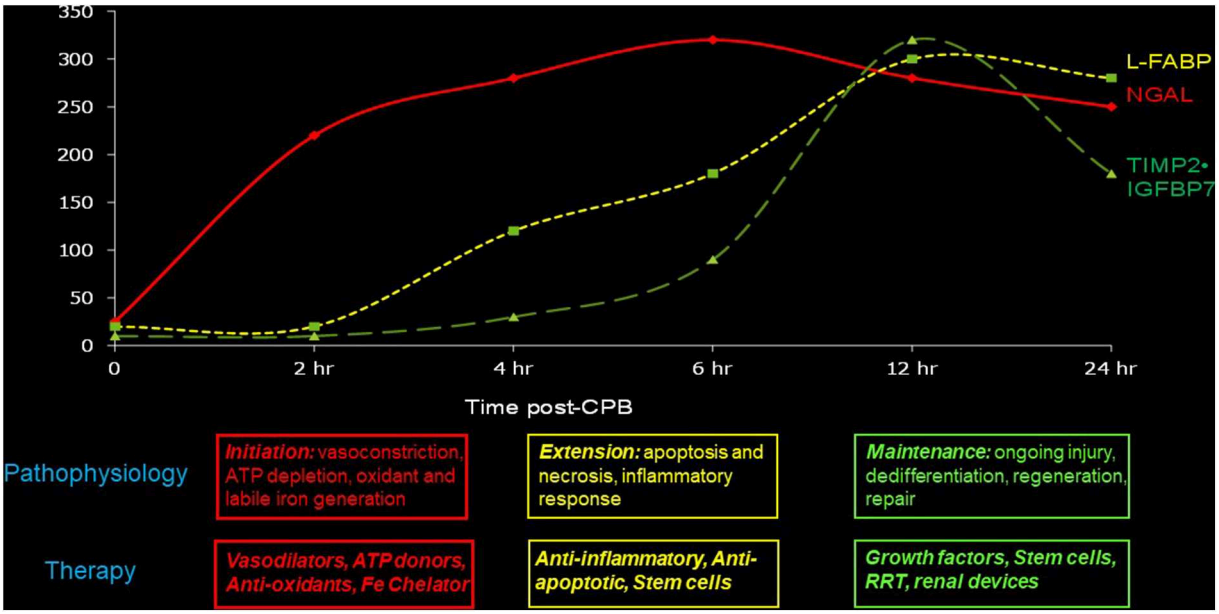

FIGURE 1 | Sequential biomarkers to establish the time of initial injury as well as to initiate appropriate therapies based on knowledge of the underlying pathophysiology.

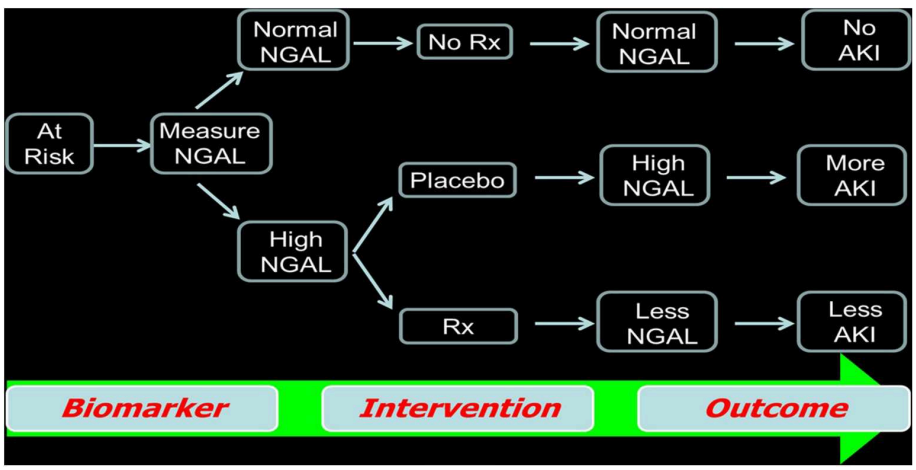

FIGURE 2 | Use of biomarkers as criteria for enrollment in randomized clinical trials as well as to assess the efficacy of the agent being studied.

creatinine. Extensive pre-clinical studies by the academia and the industry have revealed highly specific urinary biomarkers that predict structural nephrotoxic AKI in the absence of serum creatinine increase. In 2008, the Food and Drug Administration (FDA) and the European Medicines Agency approved the use of seven safety biomarkers in pre-clinical drug toxicity, and this initial roster was extended in 2016 to include NGAL. Consequently, in 2018, a safety biomarker panel was approved by the FDA (including clusterin, cystatin C, KIM-1, NAG, NGAL, and osteopontin) to detect kidney tubular injury in healthy human volunteers participating in phase 1 clinical trials (45). It is hoped that the use of this safety biomarker panel can be extended to phases 2 and 3 AKI clinical trials, not only to identify any nephrotoxic injury or lack of therapeutic response (whereby biomarker concentration would increase) early but also to establish therapeutic efficacy (evidenced by a downward trajectory in biomarker concentration).

Early Initiation of Anti-fibrotic Therapies

We recommend for clinical trials to investigate the early initiation of anti-fibrotic therapies. Recent publications validate this recommendation. Clinical evidence for the progression of pediatric AKI to CKD is now abundant. Animal models have now been developed to recapitulate many human AKI

pathophysiologies, including the AKI-to-CKD transition (18). A careful analysis of these models has begun to challenge the dogma that the fibrotic response of the kidney to injury is a late and final common pathway. In a murine bilateral ischemia–reperfusion survival model that recapitulated the human AKI-to-CKD transition, the serum creatinine peaks after 2 days, and kidney sections at day 1 revealed surprising segment-specific responses. While significant acute tubular damage was noted in the outer medullary region, the same regions adjacent to the damaged S3 segments also unexpectedly revealed significant fibrosis (17). In the ensuing weeks, the outer medullary fibrosis extended further, with the additional appearance of cortical fibrosis.

Encouraging new experimental data suggest that this early fibrotic response can be prevented. In murine AKI due to ischemia–reperfusion, an intraperitoneal administration of a peptide (pUR4) that binds fibronectin and inhibits fibronectin polymerization (an early event in the fibrotic cascade) soon after injury dramatically attenuated the early fibrotic response (46). The pUR4 peptide was devoid of any adverse effects, rendering its translational application to human AKI a very realistic possibility.

CONCLUSION

Propelled by the enabling technologies of molecular nephrology, this review has identified ten strategies that hold tremendous promise for effective bench-to-bedside translation to change the current dismal prognosis of pediatric AKI. These strategies are immediately actionable and well within the reach of the nephrology community. We are optimistic that this "call to arms" will be heeded, tested, and implemented.

AUTHOR CONTRIBUTIONS

PD is responsible for the concepts and contents of this publication.

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Conflict of Interest: PD is a co-inventor on patents submitted for the use of NGAL as a biomarker of kidney injury.

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OPINION
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Experience With Pediatric Medical Device Development

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Keywords: child, medical device, humanitarian use device, orphan diseases, renal replacement therapy, immunomodulation

PEDIATRIC MEDICAL DEVICES: UNDERSERVED AND LARGELY IGNORED

Few FDA approved medical devices are specifically designed for children's needs. FDA approval for clinical indications of medical devices specify procedures and not patient ages. Accordingly, the majority of both devices and drugs in pediatric patients are used for off-label indications. Data suggests that 60–75% of medical devices or drugs in pediatric patients are used for off label indications (1). This approach has drawbacks including safety and performance concerns with lack of proper education and instructions for the use of an adult device for a pediatric patient.

Barriers to pediatric medical device development arise from the small numbers of pediatric patients, numbered in the thousands vs. hundreds of thousands in the adult market. The number of cancer patients in pediatrics is ∼2,000 vs. 600,000 adult patients; the number of defibrillators use in pediatrics is 1,600 vs. 200,000 in adult cardiology (1). Due to the low volume of patients, clinical trials in children have much slower enrollment than adult trials. Parental consent also complicates the enrollment of children in clinical research protocols. Liability concerns, although not discussed openly, may be another detriment for pediatric drug and device innovation.

To encourage pediatric device development, Congress and FDA established the Pediatric Medical Device Safety and Improvement Act of 2007 (PL-110-85). This allowed the FDA to designate a Humanitarian Use Device (HUD) designation for disorders with 4,000 patients annually and allowed a Humanitarian Device Exemption (HDE) marketing approval by the FDA for a device. This approval is based upon "safety and probable benefit" rather than the FDA standard Premarket Approval (PMA) process based upon randomized control trials demonstrating statistically significant "safety and effectiveness." This approach was due to the low number of patients in many pediatric diseases to perform randomized control trials in a reasonable time frame. The elimination of the profit restriction on devices approved under an HDE also promoted financial incentives for pediatric device development (2). On December 2016 the twenty-first Century Cures Act (PL-114-255) changed the population estimate required to qualify for HUD designation from "fewer than 4,000" to "not more than 8,000" to further incentivize pediatric device development.

Even prior to these Congressional mandated incentives for pediatric devices, the passage of the Orphan Drug Act in 1983 (PL-97-414) also encouraged the development and approval of drugs for rare diseases. This Act established the Orphan Products Clinical Trials Grant Program in the FDA's Office of Orphan Products Development (OOPD) to support developing drugs and devices to treat orphan diseases. An orphan disease is defined as a disorder affecting fewer than 200,000 patients in the United States. Since developing a new drug or device is costly with inherent risk, large pharmaceutical drug companies have had little interest due to small market size and difficulty in recruiting sufficient number of subjects to study safety and efficacy of a new compound or device. Accordingly, this Act and its subsequent amendments in 1984, 1985, 1988, and 2007, provided a number of incentives for companies to develop compounds to treat rare diseases, including tax credits for the costs of clinical research, 7-year period of exclusive marketing after an orphan drug is approved, and waiver of Prescription Drug User Fee Act (PDUFA) filing fees (over $1 million).

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With these incentives interest in orphan disease indications have occurred over the last decade (3, 4). This interest is driven also by the facts that there are ∼7,000 rare diseases affecting 30 million people in the United States and 400 million worldwide and the recognition that many of these rare diseases have no effective treatments. Accordingly, small biotechnology companies have been formed with funding from private equity to develop new approaches to the unmet medical needs of orphan diseases due to high potential returns on investment. In fact, drugs to treat orphan diseases have commanded high price tags due to the small number of patients and non-competition (5). A recent study has shown that companies with regulatory approved orphan drugs are more profitable and are more attractive investment opportunities than companies without orphan drugs (6). With this background, the development of a potentially transformative device to treat adult and pediatric ICU patients with acute kidney injury requiring continuous renal replacement therapy(CRRT) provides an illustration of how the regulatory environment and the congressional legislation described above resulted in a pivoted focus on pediatric rather than adult indications. This opinion is based upon a singular experience in the bumpy road to commercialization of an immunomodulatory device named the Selective Cytopheretic Device (SCD).

A SERENDIPITOUS DISCOVERY

Many scientific discoveries have occurred due to chance observations by scientists with detailed background knowledge and an honest curiosity to understand the unexpected results of planned experiments (7). In this regard, an unanticipated result in a clinical trial led to a platform discovery to immunomodulate the detrimental effects of the activated innate immunologic system in both acute and chronic organ failures. This resulted in the development of a Selective Cytopheretic Device.

The SCD originated from the clinical evaluation of a tissue engineered Renal Assist Device (RAD) (8) containing adult human renal epithelial cells as a component of a bioartificial kidney to provide more complete renal replacement therapy (RRT). The use of the metabolic activity of renal tubule cells was evaluated to assess whether this addition could improve the poor outcomes of ICU patients with severe acute renal failure requiring RRT. After safety and efficacy signals in Phase I/II and Phase II clinical trials, a change in clinical protocol was made in the RAD Phase IIb clinical study. Subsets of patients were treated with a cell containing RAD or a sham (non-renal cell containing) RAD cartridge (9). The Phase IIb study was a randomized control, blinded multicenter study in ICU patients with Acute Renal Failure secondary to Acute Kidney Injury (AKI) undergoing continuous renal replacement therapy (CRRT). The clinical study was suspended after an interim analysis due to an unanticipated high survival rate of the sham device arm. In retrospective analysis of the sham control groups, the improved survival rate was demonstrated in the presence of regional citrate anticoagulation (RCA) when compared to systemic heparin anticoagulation (10). Subjects were divided into four groups: (1) RAD with citrate anticoagulation, (2) sham device with citrate anticoagulation, (3) RAD with heparin anticoagulation, and (4) sham device with heparin anticoagulation. The 28-day survival rate in the heparin sham patient group was 50 vs. 75% in the citrate sham group ($n = 12$ for each treatment arm), and the 90-day survival rate was 25% (heparin) vs. 67% (citrate). The baseline demographics for the two subsets were comparable, with similar sequential organ failure assessment (SOFA) scores (13.4 $\pm$ 1.1 vs. 12.2 $\pm$ 0.9), organ failure number (4.17 $\pm$ 0.46 vs. 3.93 $\pm$ 0.36) and incidence of sepsis (58 vs. 58%) for the citrate vs. heparin sham groups, respectively (10). This clinical result, although unexpected, was consistent with a potential clinical benefit of the fiber based sham device without cultured renal cells (RAD sham), when used with RCA, which later became known as SCD therapy (**Figure 1**).

The therapeutic benefit afforded by this combination of a device and a compound (citrate) on a systemic clinical disorder can be better understood from the following: (1) Microscopy of the sham cartridges (future SCD) after patient treatment demonstrated adherent leukocytes on the outer surface of the membranes of the cartridge along the blood flow path (**Figures 2A,B**) (9). The attached leukocytes were dominated by neutrophils and monocytes (**Figure 2C**), which preferentially adhere, compared to other leukocytes such as lymphocytes (11). The ability of leukocytes to adhere to the outer walls of the hollow fiber membranes rather than the inner walls, which is the conventional blood flow path for renal dialysis/hemofiltration applications, was due to the shear forces of blood flow. The shear stress of blood along the outer wall of the membrane was near capillary force of <1 dyne/cm^2 compared to the shear stress of 100 dyne/cm^2 for blood flowing along the conventional luminal surface of the hollow fiber membranes. (2) RCA lowers the iCa in blood within the circuit to <0.4 mM, a level which inhibits the coagulation system, has an inhibitory effect on leukocyte and platelet activation (11, 12), and also affects the calcium-dependent selectin and integrin mediated interactions between leukocytes and the membrane (13, 14). Extravasation of neutrophils and monocytes from the systemic circulation into tissues is a highly regulated process. In a low shear force environment like that found in capillaries or created within the SCD, neutrophils and monocytes roll along surfaces and are slowed via selectin binding followed by integrin mediated firm adhesion prior to diapedesis (13).

Data from an *in vitro* blood study utilizing flow chambers to visualize leukocyte interactions with fiber materials suggested that leukocytes roll, then adhere to fibers, are retained for a significant time period (11) (referred to as sequestration) and are then released. Binding selectivity for more activated leukocytes in the SCD is increased in the low iCa environment where calcium dependent selectin rolling, integrin binding, and downstream conformational changes of attached cells are inhibited (15). Neutrophils (16, 17) and monocytes (18, 19) mobilize intracellular stores of CD11b, to the cell surface as they become (primed) activated. Measurement of CD11b, allows for real time measurement of systemic acute neutrophil (priming) and monocyte activation. Additionally, monocyte populations are heterogeneous in their expression of CD11b, with $CD14^{hi}CD16^{-}$ being the highest, and $CD14^{low}CD16^{+}$ being

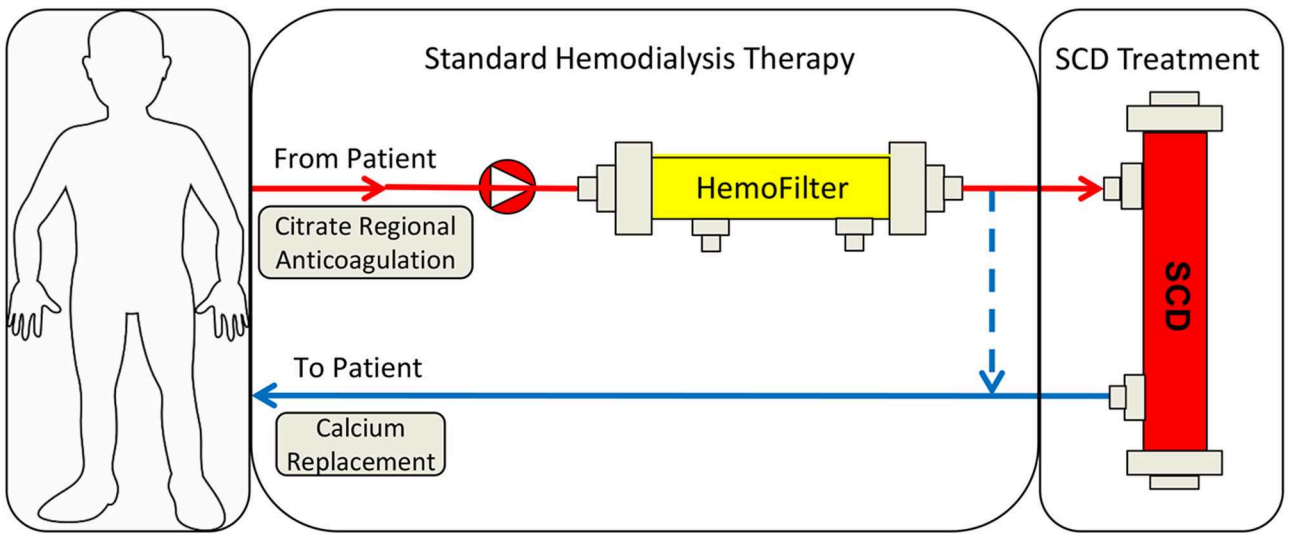

FIGURE 1 | Schematic representation of the circuit used for selective cytopheretic device therapy.

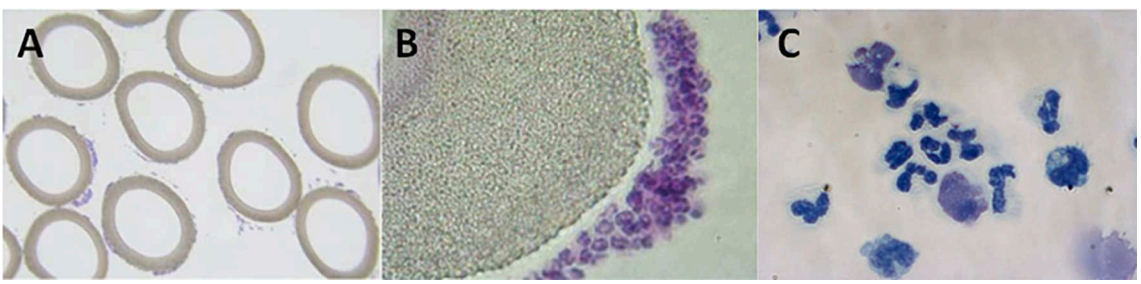

FIGURE 2 | Micrographs of cross-sectional area of sham, acellular cartridges (as part of the regional citrate anticoagulation arm of the Renal Assist Device clinical trial now known as the selective cytopheretic device) **(A,B)**. Low-power micrograph showing adherent cells around each fiber (**A**, 4× objective). Higher-power micrograph showing clustering of bound leukocytes (**B**, 20× objective). High-power micrograph of a cytospin prepared from adherent cells washed from the outer membrane of the SCD after 24 h of therapy on the first pediatric patient (**C**, 63× objective). Patient treatment demonstrated adherent leukocytes with a predominance of neutrophils and monocytes on the outer surface of the membranes along the blood flow path which translated into patient benefit.

the lowest (20). It follows that the preferential sequestration of inflammatory $CD14^{hi}$ monocytes is enhanced in the low iCa environment. The selectivity of binding of the highest activated leukocytes has been repeatedly observed in preclinical animal models where systemic CD11R3: the porcine analog of human CD11b (21), levels decrease through the treatment course (10, 11, 22, 23). This effect was measured directly in a clinical trial by comparing the CD11R3 relative fluorescence of the circulating cells in the peripheral blood to those directly associated with the SCD (24). These results when taken together (10, 11, 22–25), suggest a SCD mechanism of action with a simultaneous, combination effect to transiently sequester activated circulating neutrophils and monocytes, with enhanced selectivity for inflammatory leukocytes, which alters the overall activation of bound and processed leukocytes. Clinical efficacy in AKI with Multi-Organ Dysfunction (MOD) may be due to sequestration and immunomodulation of leukocytes in the SCD. This process appears to block the inflammatory sequence associated with accumulation and aggregation of leukocytes in the peritubular capillaries and reduce infiltration into interstitial spaces, that when unchecked promotes kidney injury following systemic inflammatory response syndrome (SIRS).

CLINICAL DEVELOPMENT OF THE SCD: ADULT TRIALS

Preclinical large animal studies confirmed the efficacy of the SCD in a porcine model of septic shock with concomitant acute tubular necrosis (26). Product development continued with successful Phase I/II and Phase II clinical studies which demonstrated safety and strong signals for efficacy in ICU

patients with AKI (11, 27). Accordingly, a phase III multi-center, randomized, controlled, pivotal study to assess the safety and efficacy of a SCD in patients with AKI (IDE G090189, Protocol SCD-003) (28)was initiated. The primary objective of this study was to determine whether CRRT+SCD therapy, compared to CRRT alone, results in a clinically relevant and statistically significant improvement in all-cause mortality through day 60. Secondary objectives included assessment of RRT dependency at day 60, mortality at day 28, number of ventilator free days at day 28, and mortality at day 60 of the subset of patients with severe sepsis. This study was a two-arm, randomized, open-label, controlled multi-center pivotal study that enrolled 134 patients at 21 US medical centers. ICU AKI patients of each participating hospital were randomized to treatment undergoing CRRT or CRRT+SCD. Each participating clinical site used their established RCA protocol for the CRRT+SCD circuits (Study Arm) and for the CRRT only (Control Arm). The recommended iCa (riCa) level (measured post SCD) in the CRRT and SCD circuit was specified to be between 0.25 and 0.4 mmol/L.

During the second quarter of the enrollment period, a national calcium shortage occurred in the US from FDA related quality manufacturing issues of the major US supplier. This shortage resulted in most centers unable to recruit to the study, since injectable calcium is required for RCA. Due to reliance of the SCD on a narrow intra-circuit iCa range for functional efficacy and the concern that patients randomized to SCD therapy were not getting effective therapy, the interim analysis was performed early-after enrollment of 134 patients. Enrollment was paused on May 24, 2013, to assess the clinical impact of the calcium shortage on study endpoints. The shortage of calcium infusion solutions resulted in a tendency to minimize citrate infusion rates. Accordingly, iCa levels within the blood circuit tended to be above the recommended (r)iCa of 0.25–0.40 mmol/L. Subsequently, the injectable calcium shortage resulted in 9 of the 21 open clinical sites being unable to enroll patients due to low hospital inventories of injectable calcium, contributing to the early termination of the study. Of the 134 patients in the analysis, 69 received CRRT alone and 65 received SCD therapy. No significant differences were noted between the control and treatment groups in baseline characteristics. No statistically significant difference was found between the treated and control patients with a 60-day mortality of 39% (27/69) and 36% (21/59), respectively, with six patients lost to follow up. The amount of time the patients in both the control and treatment group were maintained in the riCa range (0.25–0.40 mmol/L), as specified in the study protocol, was substantially lower than expected due to the injectable calcium shortage. Of the 134 patients enrolled at the time of the interim analysis, 19 SCD patients and 31 control patients were maintained at riCa for $\geq$90% of the therapy time. Furthermore, none of the significant adverse events (SAE) were considered device related per the principal investigator and the Data Safety Monitoring Board. Comparison of these subgroups of patients revealed 60-day mortality was 16% (3/19) in the SCD group compared to 41% (11/27) in the control group ($p = 0.11$). Dialysis dependency showed a borderline statistically significant difference between the SCD vs. control patients maintained for >90% of the treatment in the protocol's riCa target range with values of 0% (0/16) and 25% (4/16), respectively ($p = 0.10$). When the riCa SCD and control subgroups were compared for a composite index of 60-day mortality and dialysis dependency, the percentage in SCD subjects was 16 vs. 58% in the control subjects ($p < 0.01$). When the riCa subpopulation was considered, a statistically significant difference was detected in several parameters: log urine output substantially increased, and absolute leukocyte and neutrophil counts diminished in the SCD vs. control groups over time (28).

ADULT CLINICAL TRIALS SUMMARY

The observation that, in those patients who had the riCa level >90% of the time of SCD treatment, mortality improved from 41 to 16%, is clinically compelling. In addition, the observation both that in SCD clinical trials no patient receiving appropriate SCD therapy was dialysis dependent at day 60 is also compelling. Previous large prospective clinical studies in AKI with MOD had >20% incidence of dialysis dependency of patients followed for 60 or more days (29, 30). The effect of SCD therapy to modulate excessive leukocyte activation most likely plays a critical role in the recovery of renal function after a substantive AKI event. The relationship of ongoing inflammation in the kidney after AKI and chronic progressive kidney disease and dialysis dependency has been demonstrated (31, 32). In this patient population, immunomodulation by SCD therapy appears to positively promote kidney healing as evidenced by the lack of dialysis dependency at day 60. Additionally, improvement in overall mortality may suggest improved immune balance that persists through the late SIRS process to ameliorate the compensatory anti-inflammatory response which follows the excessive systemic pro-inflammatory state in AKI and MOD (33). Furthermore, the significant decrease in absolute leukocyte and neutrophil counts, as well as the improvement in urine output over time corroborates the mechanistic and pilot studies previously published (11, 27, 34).

PIVOT TO PEDIATRIC DEVICES

With this compelling *post-hoc* analysis, the company, Cytopherx, which licensed this technology from the University of Michigan to commercialize this therapy, underwent a diligent attempt to obtain private equity to undertake a final Premarket Approval (PMA) clinical trial to use the composite index of 60-day mortality and dialysis dependency for FDA approval and rights to market this device in the United States. This effort proved to be difficult with venture capital and private equity firms hesitant to commit tens of millions of dollars to undertake a final multicenter randomized, control study which failed in the initial attempt. Despite the compelling *post-hoc* analysis, and the lessons learned regarding careful control of the circuit iCa in the recommended range of 0.25–0.4 mM, the perception of a previously failed trial (minimizing the *post-hoc*

analysis) and the risk of capital was too high of a hurdle to obtain commitment to fund the clinical program to achieve FDA approval.

With the failure to obtain funding commitments but being convinced from the compelling preclinical and the safety and efficacy clinical data from adult trials, our group considered testing SCD therapy in the pediatric population for a number of reasons. Since the pediatric patient with AKI and MOD usually is not saddled with various chronic diseases which may cause mortality within 60 days of recovery from AKI and dialysis, this patient population would have less obfuscating co-morbidities. An efficacy signal would be apparent in lesser number of patients, thereby confirming the *post-hoc* analysis of the Phase III adult trial. In addition, the route to FDA approval would not require a large number of patients due to a Humanitarian Use Designation (HUD) since there are <8,000 pediatric patients with AKI and MOD requiring CRRT annually in the United States. Upon demonstrating safety and probable benefit in this HUD pediatric trial, a Humanitarian Device Exemption (HDE) approval by the FDA will allow marketing and commercial sale of the SCD in the United States. Upon HDE approval, funds derived from private equity or public markets to carry out the PMA adult clinical trial would be more readily obtained.

With this strategy, our group contacted the prospective pediatric (pp) CRRT consortium (35, 36) directed by Dr. Stuart Goldstein, who agreed that this direction was feasible. Accordingly, our group with the collaboration of Dr. Goldstein, submitted an FDA Office of Orphan Products Development (OOPD) grant to carry out this clinical study. Funding was received in 2014 and the trial was initiated in 2015.

Accordingly, similar to the adult AKI clinical trial, a multicenter US study of the SCD in critically ill children (>15 kg, age up to 22 years) with AKI and MOD receiving CRRT as part of standard of care was initiated and is ongoing under the FDA approved IDE#G150179 (clinicaltrials.gov NCT02820350). Mortality rates in pediatric patients with AKI and MOD requiring CRRT has historically approached 50% (35–37). In this clinical trial, pediatric patients have received SCD therapy for up to 7 days or when CRRT is discontinued, whichever comes first. Interim analysis of the 14 patients treated with the SCD revealed compelling safety and efficacy data similar to the *post-hoc* analysis of the Phase III adult SCD study of patients treated per protocol with the recommended iCa levels below 0.4 mM ninety percent of treatment time. The 14 treated patients had an age range between 5 and 20 years, had multiorgan failure between 2 and 5 organs, averaging 2.92 organ failures as a group. Eight of fourteen treated patients also presented with severe sepsis or septic shock. All patients received RCA per protocol with the recommended iCa levels below 0.4 mM for 90% of measured values during treatment. When compared to the historical control standard of care CRRT treatment of pediatric patients with AKI/MOD, SCD therapy reduced both 60-day mortality and ICU length of stay. No patient was dialysis dependent at 60 days. These results, therefore, support a plan to submit an HUD/HDE application to the FDA. These data also strongly support the *post-hoc* analysis of the adult study. A final IDE adult study using a composite outcome measure of 60-day mortality or 60-day dialysis independence has been approved by the FDA and successful fundraising is anticipated to move this therapy back to the large adult market which comprises of 160,000 patients in the U.S. on an annual basis.

SUMMARY

This case study demonstrates that creative strategic planning, recognition of FDA pathways and support for pediatric devices can coalesce to promote the development of a life saving device reaching the bedside to save lives and save hospital costs with decreasing length of stays. The product development of pediatric therapies may provide a unique opportunity to more clearly demonstrate the potential effectiveness of a therapy with a smaller population due to the lack of complications and comorbidities as is often seen in adult disease. The development of a pediatric therapy not only is ethically sound, but can also lead to easier and faster transition into the adult market negating the initial hesitancy from a perceived limited market. This case study provides a perspective of the clinical development of a pediatric device as an important step in the commercialization of an innovative therapy.

AUTHOR CONTRIBUTIONS

HH developed the main conceptual ideas of this manuscript. HH and AW contributed to the design, implementation of the supporting research, and writing the manuscript.

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Conflict of Interest: HH retains equity interest in Innovative BioTherapies and SeaStar Medical (formerly Cytopherix), the company licensed by the University of Michigan to commercialize the Selective Cytopheretic device technology described in this review. AW has equity interest in SeaStar Medical.

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