Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.
Background

Although pediatricians participated for two decades in Acute Disease Quality Initiative (ADQI) meetings convened to achieve and disseminate consensus in critical care nephrology and related disease processes, many aspects unique to pediatrics cannot be integrated into adult-focused initiatives. The pADQI Consensus Conference Chairs convened a diverse panel representing relevant pediatric disciplines (nephrology, critical care, pharmacy, nutrition, epidemiology, basic, translational, clinical and health services research) from multiple countries around the world.

Group 1: Integrating Tools for Epidemiology

Optimal consensus diagnostic criteria for pediatric AKI will be based upon biomarkers of injury, rather than solely on functional assessments. Additionally, the concept of an AKI event may be expanded to incorporate diverse AKI phenotypes based upon severity and the etiologic, functional, and temporal aspects of the disease.

A standardized, consensus definition is the foundation of our ability to develop a comprehensive understanding of AKI. The current KDIGO definition employs functional biomarkers (serum creatinine and urine output) as proxies for injury. Ideally, AKI events would be diagnosed based upon biomarkers of injury in conjunction with functional markers using a framework proposed by the ADQI 23 conference and further outlined by Work Group 2. Additionally, consensus around a standard AKI terminology is needed to describe disease characteristics (i.e., transient, persistent, community acquired) and progression (i.e., kidney function recovery, acute kidney disease (AKD), and chronic kidney disease (CKD)). Finally, the current definition presumes AKI is a single entity.
rather than a complex syndrome encompassing a wide array of clinical circumstances which may be differentiated by underlying etiologies, demographics, and co-morbidities. Thus, AKI events should be assessed in the context of the etiologic, functional, and temporal aspects that comprise their AKI phenotype.

Group 2: Utilization of the Electronic Medical Record

Early and accurate diagnosis of AKI is made by both recognition of patient context and clinical/laboratory measurements (such as urine output and functional/structural biomarkers), which may be facilitated by use of available digital health technologies. In healthcare environments that support digital health technology, automated alerts and clinical decision support (CDS) within the electronic health record (EHR) can facilitate recognition of at-risk patients and notify clinicians of abnormal measurements that may predict AKI development or progression. Widespread implementation of EHRs in resource capable settings promises an opportunity to leverage electronically accessible data to enrich risk stratification and provide bedside CDS in real, or near-real time. The promise has been realized partially for children in the intensive care unit setting and for those exposed to multiple nephrotoxic medications. Implementation of standardized risk assessment, AKI surveillance and standardized nephrotoxic medication protocols has been associated with reductions in AKI rates and severity in hospitalized children. Importantly, the epidemiology of AKI and the resources available may be different in developing countries and specific AKI risk assessment and development strategies should be focused accordingly. Given the heterogeneity of the pediatric population, these alerts should be customizable to reflect age-adjusted reference ranges and patient-specific parameters.
Timely recognition of early or subclinical AKI may be expanded to non-resource rich environments by using point of care (POC) testing\textsuperscript{18-20} and digital health technology, when available, for static AKI risk stratification and dynamic automatic continuous review of key variables in children. Recent studies have demonstrated the feasibility of integrating POC testing and protocol-based management for improved recognition and management of patients in resource limited environments.\textsuperscript{21}

**Group 3: Observation to Causality in Fluid Balance**

*The literature describing the association of fluid balance on outcomes is based on observational studies. Evidence from observational data alone cannot establish a causal relationship between fluid balance and outcomes.*

A large body of pediatric literature shows an association between positive fluid balance and adverse clinical outcomes across several clinical contexts and settings.\textsuperscript{22-41} These data are primarily derived from observational cohort studies and have been necessary to describe the potential risk factors, temporal course, and outcomes associated with positive fluid balance and the pathologic state of fluid overload. Observational studies also generate data to support the design and development of clinical trials. However, the evidence from observational data alone cannot establish a causal relationship between fluid balance and outcomes. Observational studies describing the relationship between fluid balance and clinical outcomes are susceptible to potential sources of unmeasured and measured bias. These would include, but are not limited to confounding, competing risks, measurement error, and selection bias. One of the main concerns confounding the association of positive fluid balance with adverse clinical outcomes is that greater fluid volumes are typically administered to the sickest children.

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Group 4: End-points to guide Kidney Support Therapy

Optimal delivery of pediatric acute kidney support therapy (paKST) includes timely and safe initiation, appropriate access placement and maintenance, individualized clearance dose, reliable anticoagulation protocols, modality, appropriate medication and nutrient adjustments, and dynamic prescription of fluid removal rate – all while using pediatric specific and objective indicators of a response to therapy evaluated throughout the treatment course.

All forms of paKST, including peritoneal dialysis (PD), intermittent hemodialysis (IHD) and continuous kidney support therapy (CKST), represent the mainstay of supportive treatment for AKI and fluid overload. Creating and implementing standardized policies and procedures for paKST initiation is essential to prevent complications and assure consistent care. Multiple high-quality adult trials have failed to demonstrate benefit with early KST initiation based on changes in serum creatinine from baseline. Comparable studies are lacking in children. KDIGO staging cannot identify an ideal timepoint for KST commencement. Initiation and maintenance of paKST require timely recognition of the need for paKST, safe insertion of right-sized access, reduction of treatment downtimes with a safe and effective anticoagulation regimen, an appropriate prescription, and well-trained staff. Goals of paKST care should be dynamic and patient-centered, driving decisions on modality, effluent dose, and safe fluid removal rates. Pediatric studies on effluent dosing are lacking and paKST clearance doses are currently extrapolated from adult data.

KST provides a platform to remove harmful endogenous or exogenous substances in non-kidney disease states. Membranes in use for kidney support remove small molecules with low protein-binding and low volume of distribution and have been used for the treatment of inborn errors of metabolism, intoxications, and liver
failure for decades. It will be important to identify clear indications and endpoints for treatment of non-kidney diseases using KST platforms as well as characterizing the key elements of timely, safe, and efficacious therapy for candidate disease states using a KST platform alone or in tandem with other devices.

**Group 5: The Medication Associated AKI Imperative in Children**

*High value, kidney-eliminated medications will be selected for a detailed characterization of their pharmacokinetics, pharmacodynamics, and pharmaco-“omics” in sick children across the developmental continuum, to allow optimization of real-time modelling towards developing improvements in patient care. Concurrently, nephrotoxin stewardship will be identified as an organizational priority and supported with necessary resources and infrastructure.*

Despite the acknowledged complexity, little is known about optimal dosing of medication therapy in sick children. Most evidence guiding the use of kidney-eliminated medications in sick children is extrapolated from studies in non-critically ill adults. High-value medications broadly defined according to healthcare priority for low and middle income countries (LMIC) and high income countries (HIC) alike, regularity of use, therapeutic window, potential benefit, and cost can be selected for detailed pharmacokinetic and pharmacodynamic characterization including attention to novel ‘omics’. Results of such modeling can be utilized to inform drug disposition, dosing and monitoring decisions at the bedside for patients with AKI and those receiving paKST.

Nephrotoxic medication exposure contributes to a 1.7-fold higher risk of AKI in pediatric patients. It is impractical and inappropriate to universally eliminate all potentially nephrotoxic medications from use in sick children. Nephrotoxin stewardship, including strategies to enhance medication safety, ensure kidney health, and avoid
unnecessary costs should be emphasized. These strategies must be tailored to the available resources of the setting (i.e., access to therapeutic drug monitoring, on-site laboratory testing, pharmacist accessibility). Making nephrotoxin stewardship an organizational priority encourages the development of policies and procedures by a multidisciplinary team, development of metrics and monitoring strategies, creation of performance improvement plans, development of solutions to enhance care delivery, engagement of key stakeholders, and widespread education.

Currently, kidney disease research is underfunded. To advance our understanding of pediatric AKI and identify potential therapeutic targets to optimize outcomes throughout the life-course, adequate funding support is required. Aligning and combining research efforts in adult and pediatric nephrology benefits all. Inclusion of children in clinical investigations and collaboration amongst researchers in various specialties optimize the translatability of research investigations.

Group 6: Advanced Methods to Improve AKI-Focused Awareness Initiatives

Advanced communication tools and human partnerships can be leveraged to improve awareness, enhance individualized, longitudinal care across varied settings, and optimize immediate and lifelong outcomes for children after AKI.

Developing effective and meaningful educational programs requires thoughtful preparation, innovative design, and a robust iterative review process, key principles in Education Design Research (EDR). For AKI education, given its diverse spectrum of participants and stakeholders, local problem analysis is imperative. Identifying participants and examining barriers to enhanced awareness and knowledge is a necessary first step. There is a paucity of research on the impact of public, patient, and professional education initiatives on AKI. The nephrology community can learn from other successful initiatives (e.g., diabetes, HIV) where education has improved access.
and quality of care, reduced financial burden, and improved patient health-related quality of life.

Despite improved awareness, there is still risk for under-diagnosis of AKI. Where available, the EHR may employ CDS systems, with automated real-time electronic alerts (e-alert), to improve detection and management. E-alerts work better when bundled with a process that guides next steps; they must be combined with additional education at the healthcare team level.69-72

Telemedicine linkages across settings, both within and between countries, can connect patients in remote, rural, or low-income settings to specialists, with the potential to improve clinical care, optimize follow-up, and expand education to health care workers. In low-resource settings, education of healthcare providers and mobile health technology have been harnessed21 for early identification of high-risk AKI patients, which may improve their clinical course and outcomes.

A unique educational challenge in comprehensive AKI care is the limited scope and availability of KST device related practical and technical references that pertain to pediatric-specific applications. Adaptive use of technology developed for adults has led to the creation of equally adaptive educational products, typically siloed in institutions. “Off-label” use of the technology limits systematic, widely available, and standardized educational and reference material that can be readily disseminated. A network for open sharing of resources, know-how, and other educational material would advance our field supporting the practical application of highly complex treatments in an equitable framework.
Box. Research Agenda for Pediatric Acute Kidney Injury

AKI Epidemiology

1) Insufficient data exist for causality assessment within the epidemiology of longer-term health outcomes following AKI events in childhood. Clarifying the causal nature of longer-term associations requires further high-quality observational study in children (with relevant comparator cohorts and much larger sample size) as well as careful consideration of what defines the most meaningful and measurable longer-term outcomes after pediatric AKI. It is likely that a causative pathway from AKI to longer term negative outcomes is nonlinear and different aspects of AKI, including its etiology, characteristics, and healthcare context, will affect causative trajectories during childhood.

Risk Stratification and Diagnosis

1) While the studies highlighted delineate AKI phenotypes capable of informing prognosis, evidence for a pediatric AKI phenotyping strategy capable of guiding therapy is currently lacking. It is our opinion that clinically important AKI phenotypes should direct personalized management of AKI, and thus, identifying AKI phenotypes that elucidate novel therapeutic targets should be a focus for future research.

2) Further research is needed to determine if POC diagnostic tools can lead to meaningful improvement in clinical outcomes.

Group 3: Fluid Assessment

1) Identify the optimal reference or anchor weight needed to calculate fluid balance measurements to be used through a patient’s clinical course (e.g., premorbid weight, dry weight, admission weight, PICU admission weight (anchor weight), etc.).

2) Systematically study, develop, implement, and evaluate protocols for daily weights in sick children.

3) Evaluate the optimal method and process to adjust anchor weight for patients hospitalized for extended periods of time.
4) Evaluate the optimal method and process to adjust anchor weight for neonates outside of the first 2 postnatal weeks and for sick children with a prolonged duration of hospitalization.

5) Understand the impact of timing and trajectory of positive fluid balance on outcomes across a heterogeneous case-mix of sick children and across varying hospital settings.

6) Identify patient-specific or case-mix thresholds for intervention for fluid overload in sick children.

7) Identify patient-specific strategies to manage positive fluid balance in sick children that directs improved outcomes and care processes.

8) Understand the relationship between positive fluid balance and the development of fluid overload across different ages, case-mix, phase and severity of illness, and hospital settings.

9) Researchers can consider alternative study designs and analyses. Enhanced randomized trials may be needed to better understand the fluid balance and mortality relationship, such as pragmatic trials using cross-over designs, interrupted time series, cluster step-wedge trials, or other quasi-experimental trials. Analysis tools may enhance observational studies by minimizing bias. Incorporating directed acyclic graphs into selection of variables for linear and logistic regression models. Evaluating risk ratios, risk differences, and attributable risks to determine the degree and proportion a specific exposure like abnormal fluid balance may be contributing to mortality in sick children.

**Group 4: Kidney Support and Extracorporeal Therapies**

1) Developing clinical and biomarker risk assessment tools including fluid overload thresholds which can reliably guide pediatric acute kidney support therapy (paKST) initiation

2) Developing guidelines for choosing correct size and type of catheter (temporary vs tunneled) and timing of catheter removal that lead to effective therapies while minimizing catheter-related complications

3) Defining the dose of paKST which optimizes patient outcomes without unwarranted side-effects (e.g., drug/nutrient removal)
4) Comparative pediatric anticoagulation studies addressing safety, efficacy, ease of monitoring and cost-effectiveness (heparin, citrate, prostacyclin, bivalirudin, etc.)

5) Determining strategies to minimize hemodynamic instability during paKST initiation.

6) In addition to the measures outlined in the ADQI XVI consensus document:73
   a. Assessing and stratifying risk for adverse kidney and global outcomes in children who have undergone one or more paKST courses
   b. Identifying clinical and biochemical markers that predict successful or unsuccessful transition from paKST
   c. Characterizing optimal strategies of paKST liberation, de-escalation, and transition to:
      i. Facilitate patient-centered goals of care, including end-of-life care when necessary
      ii. Optimize ICU Liberation Bundle and rehabilitation implementation
      iii. Improve kidney and global functional outcomes in children.
   d. Developing clear guidance on follow-up needs for children after paKST, including frequency and content of follow-up visits and which children may benefit from follow-up with a pediatric nephrologist
   e. Characterizing challenges and best practices for implementation of successful follow-up after paKST across diverse populations and settings.

7) Develop multicenter paKST collaboratives to define, cultivate, and validate QI measures across each domain
   a. Minimum constituents for a paKST program
   b. Minimum acceptable performance/education standards
   c. A comprehensive international quality control initiative
   d. Standardized process improvement to optimize high-priority QI metrics

Group 5: Pathobiology, Nutrition and Pharmacology

1) Incorporating pediatrics into adult-focused research efforts
2) Developing improved pre-clinical models that incorporate development and sex as biological variables in the pathophysiology of AKI
3) Promoting the bench-to-beside research with collaboration between preclinical, epidemiological, and clinical trials researchers

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4) Characterizing the behavior of target medications across the developmental spectrum
5) Developing nephrotoxin stewardship programs that reduce pediatric AKI and reduce long term CKD
6) Identifying appropriate outcome variables to evaluate nutritional intervention

Group 6: Education and Advocacy
1) Future work should begin with an in-depth problem analysis and evaluation of local existing AKI education methods. Following this analysis, design and construction of an educational program should use theoretical frameworks that underpin instructional methods targeted at each unique group of learners (e.g., physicians, nurses, trainees, etc.) and settings (e.g., inpatient, outpatient, rural, urban).
2) Future work should focus on the recognition and improvement of clinical care at the bedside with emphasis on detection and identification of patients with or at risk for AKI.
3) Future work should utilize Education Design Research (EDR), a pragmatic paradigm for creating practical and effective educational solutions. EDR comprises three key phases that yield knowledge and innovation: 1) analysis and exploration, 2) design and construction, and 3) evaluation and reflection. All phases are iterative and participatory, and each generates educational tools that are evaluated and revised in real time.
4) Implementation of pediatric AKI education programs should be followed up with comprehensive program evaluations. The model used for evaluation should be able to assess participant satisfaction, knowledge gained, and subsequent use of this knowledge, in addition to the impact on patient outcomes.
### eTable 1 - Definitions of Fluid Balance

| Terminology                        | Measurement/Equation                                                                 | Duration                        |
|-----------------------------------|--------------------------------------------------------------------------------------|---------------------------------|
| **Cumulative fluid input & output Methodology** \(^{22,26,27,40,74}\) |                                                                                      |                                 |
| Daily Fluid Balance               | Fluid Intake (liters) – Fluid output (liters)                                         | Over 24 hours                   |
| Cumulative Fluid Balance          | \(\sum\) Fluid Intake (liters) - Fluid Output (liters)                                | Over a defined period of time   |
| Percent Cumulative Fluid Balance  | \(\left(\sum [\text{Fluid Intake (liters)} - \text{Fluid Output (liters)}]\right) \times 100\%\) | Over a defined period of time   |
| Anchor weight (kg)                |                                                                                      |                                 |

| **Weight-based Methodology** \(^{23,31,38,75}\) |                                                                                      |                                 |
| Daily Fluid Balance               | Current Weight (kg) – Weight from previous day (kg)                                    | Over 24 hours                   |
| Cumulative Fluid Balance          | Current Weight (kg) – Anchor Weight (kg)                                              | Over a defined period of time   |
| Percent Cumulative Fluid Balance  | \([\text{Current Weight (kg)} - \text{Anchor Weight (kg)}] \times 100\%\) Anchor weight (kg) | Over a defined period of time   |

- **Fluid Intake**: This includes all input of intravenous fluids, blood products, enteral feeds, medications, etc. This does not distinguish enteral versus intravenous input.
- **Fluid Output**: This includes all recorded output including urine, drains, dressings, stool, etc. This does not account for insensible losses.
- **Anchor weight**: The most common anchor weight used in the literature is ICU admission weight. The anchor weight can be customized to specific populations and duration of hospitalization (e.g., pre-operative weight in children undergoing schedule surgery, birthweight in neonates during the first 2 postnatal weeks, hospital admission weight for those never admitted to ICUs or facilities without ICUs, outpatient weight prior to hospitalization, etc.).

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Figure 2.

A. Spectrum of Fluid Balance (FB)

B. Spectrum of Fluid Balance (FB) - Case Mix/Resources Alter Tolerance of the Spectrum

C. Individual Dynamic Spectrum of Fluid Balance (FB)
| Membranes of different pore sizes and/or absorptive materials for sepsis inflammatory response syndrome |
| Use of existing membranes in combination with an added filter with alternative configurations allowing blood to enter/exit the in-flow/outflow dialysis ports designed to modulate the immune response. |
| Addition of albumin to the dialysis fluid to enhance the concentration gradient of protein-bound substances using single-pass albumin dialysis (SPAD) |
| KST in tandem with plasmapheresis |
| KST in tandem with CO₂ scrubbing for hypercarbia |
| Multiple approaches which incorporate an absorbent filter and albumin-enhanced dialysis in conjunction with existing KST membrane/platforms for liver failure and intoxications. |
| KST in tandem with a coated filter that enables extracorporeal pathogen or endotoxin removal. |
### eTable 3. Key components of education and advocacy for children with acute kidney injury (AKI)

| Advocacy                                                                 |
|-------------------------------------------------------------------------|
| ● Engage the government for support- laboratory resources, personnel, dissemination of education |
| ● Involve the community, healthcare workers, hospital administrators  |
| ● Partnership with existing programs like Saving Young Lives, other national/regional healthcare programs (HIV prevention, Malnutrition treatment) |
| ● Support and funding for research programs                               |

| AKI Awareness                                                               |
|---------------------------------------------------------------------------|
| ● Develop checklists for identification and risk stratification            |
| ● Use of electronic health records where available for clinical decision support |

| AKI Education                                                              |
|---------------------------------------------------------------------------|
| ● Training of healthcare workers at all levels                             |
| ● Context appropriate educational programs: can be developed in partnership with international medical community, and medical organizations |
| ● Appropriate checklists and clinical practice guidelines                  |

| Implementation                                                              |
|---------------------------------------------------------------------------|
| ● Improved access to diagnostics                                          |
| ● Expanded use of telecommunication- mobile health technology, telemedicine consults, videoconferencing |

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