Assessment of Worldwide Acute Kidney Injury, Renal Angina and Epidemiology in Critically Ill Children (AWARE): A Prospective Study to Improve Diagnostic Precision

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Received date: Dec 31, 2014; Accepted date: Apr 15, 2015; Published date: Apr 17, 2015

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Abstract

Background: Acute kidney injury (AKI) is associated with poor outcomes in critically ill children. Recent international consensus panels recommend standardized classification systems to improve the precision of AKI diagnosis, but there is a paucity of data to enable this refinement, particularly in pediatric critical care.

Methods/Design: This is a prospective observational study. We anticipate collecting data from more than 5000 critically ill children admitted to 32 pediatric intensive care units (PICUs) across the world, during the calendar year of 2014. Data will be collected continuously for three months at each center on all children older than 90 days and younger than 25 years admitted to the ICU. Demographic, resuscitative, and daily physiological and lab data will be captured at individual centers using MediData Rave™, a commercial system designed to manage and report clinical research data. Kidney specific measured variables include changes in serum creatinine and urine output, cumulative fluid balance, and KDIGO AKI stage. Urinary AKI biomarkers to be measured include: urinary neutrophil gelatinase lipocalin (NGAL), kidney injury molecule-1 (KIM-1), liver-type fatty acid binding protein (l-FABP), and interleukin-18 (IL-18). Biomarker combinations will be created from different pairs and triplets of urinary biomarkers. The primary analysis will compare the discrimination of these panels versus changes in creatinine for prediction of severe AKI by Day 7 of ICU admission. Secondary analysis will investigate the prediction of biomarkers for injury ‘time based phenotypes’: duration (>2 days), severity (KDIGO stage, use of renal replacement therapy), reversibility (time to return of serum creatinine to baseline), association with fluid overload > 10%, and disease association (sepsis, hypovolemia, hypoxemia, or nephrotoxic).

Discussion: The Assessment of Worldwide Acute Kidney Injury, Renal Angina and Epidemiology (AWARE) study will be the largest ever prospective study of any disease process in pediatric critical care. Data from AWARE will enable refinement of AKI classification. AWARE creates the largest ever all-cause pediatric AKI data warehouse and biologic sample repository, providing a broad and invaluable resource for critical care nephrologists seeking to study risk factors, prediction, identification, and treatment options for a disease syndrome with high associated morbidity affecting a significant proportion of hospitalized children. Improving the precision of AKI diagnosis using biomarker combinations provides a foundation for targeted, personalized therapy for different injury phenotypes.

Keywords: Acute kidney injury; Critical care; Paediatrics; Renal angina

Background

Acute kidney injury (AKI) is associated with poor outcomes in critically ill children. The reported incidence rate of AKI in children admitted to pediatric intensive care units (PICUs) range from 8% and 89% [1-6]. The classification of severe AKI (by Kidney Disease Improving Global Outcome (KDIGO) Stage 2-3) has been associated with prolonged hospital stay, progression to chronic kidney disease, and a significantly higher relative risk of in-hospital death [7-10]. The epidemiology and outcomes of adult AKI have been validated through large, multi-center studies describing over 20,000 adult patients [11-13]. Unfortunately, the current pediatric literature lacks such extensive studies. To date, the largest reported experience regarding AKI in children admitted to PICU was a retrospective study by Schneider et al on 3396 children [1]. Aside from a few single center studies, most knowledge of pediatric AKI is gleaned from retrospective studies with relatively small sample sizes and with diverse AKI definitions [2,4,14].

Despite increasing awareness of the prevalence and significance of AKI, effective therapies for this condition are lacking. This, at least in part, stems from imprecise AKI classification. Timely diagnosis by changes in serum creatinine (sCr) and urine output (UOP) [4] is recognized to be limited, but these markers are also unable to provide details about the injury itself [15,16]. The traditional AKI nomenclature “pre-renal” and “acute tubular necrosis”, derived from...
SCr and UOP changes, cannot identify or predict characteristics such as location, duration, and severity of injury. Further, imprecise diagnostics may lead to imprecise therapy. For example, fluid resuscitation, often the first course of action in a patient with severe dehydration, can be quite deleterious in a patient with congestive heart failure, even though both have the same AKI classification of “pre-renal” AKI [16]. Finally, available histologic evidence does not consistently match a necrotic morphology of the renal tubules to a level of renal dysfunction [7].

A number of promising candidate urinary AKI biomarkers have emerged following preliminary proteomic analyses in murine models of renal ischemia [17]. Use of these biomarkers, indicative of different AKI pathophysiology and carrying different temporal profiles in relation to injury, may enhance diagnostic precision [10,11]. The 10th International Acute Dialysis Quality Initiative Consensus conference recommended testing the efficacy of novel AKI biomarkers in combination with functional biomarkers to more precisely delineate and define AKI characteristics [12]. Identification of AKI phenotypes using these biomarkers may be a way to disentangle the AKI syndrome [13,14]. We have recently demonstrated the superior performance of biomarker combinations for improving the precision of AKI diagnosis over changes in serum creatinine in the pediatric population following cardiac bypass [18]. Utilization of combinations of biomarkers to increase the granularity of AKI diagnosis may stratify patients into trials of targeted therapy. For instance, determination of the efficacy of a therapy targeted at restoration of Loop of Henle (LOH) tubular function would ideally be tested in patients with specific LOH dysfunction versus patients with only glomerular functional injury. Biomarker combinations, selective for location and type of injury may facilitate this identification. Proper selection of patients for targeted therapies by injury type or location may assist with most reliable identification of efficacy for a unique treatment – by matching disease positive patients with disease negative patients (and not simply with patients with ‘undifferentiated’ disease). The downstream effect of such targeting would be incorporation of such targeting for actual patient therapy.

Given the paucity of prospective studies directly aimed at investigating pediatric AKI in critical illness, a large and diverse observational study is needed to enrich the field of pediatric critical care nephrology with current data. In this manuscript we describe the methodology of the Assessment of Worldwide Acute Kidney Injury, Renal Angina and Epidemiology (AWARE) study. The AWARE data repository will facilitate the refinement of AKI diagnosis and create more precision for recognition of various phenotypes encompassing the AKI syndrome.

Methods/Design

Design

The design is a prospective, multi-center, observational study of critically ill children admitted to the pediatric intensive care unit (PICU).

Setting

The setting is 32 PICUs across 5 continents and 12 countries. Site investigators are listed in Supplemental File 1.

Population

Eligible participants fulfill all inclusion and no exclusion criteria.

Inclusion criteria

The inclusion criteria are designed to capture as many potential study patients as possible and are inclusive of most patients admitted to the PICU and cardiac intensive care unit (CICU). All inclusion criteria must be met and only patients with an ICU length of stay of at least 48 hours are included in data analysis (other patient data is kept for demographic data repository, but excluded from data analysis or AKI associated outcome).

- In-patient in a PICU or CICU
- Age > 90 days
- Age < 25 years

Inclusion age parameters maximize potential enrolment by maximizing enrolment at ends of the PICU age spectrum: very young patients (accounting for glomerular development as a function of age, estimated filtration of a healthy 3-month old child is ~75-80% of adult glomerular filtration) and the burgeoning population of young adults still cared for at tertiary pediatric institutions (rising upper age limit for admission to tertiary intensive care units, particularly in the United States) [19, 20].

Exclusion criteria

- Maintenance hemodialysis or peritoneal dialysis
- Chronic kidney disease with a baseline estimated glomerular filtration rate (eGFR) of < 15 ml/min/1.73 m^2.
- Kidney transplant within 90 days of PICU/CICU admission
- Post-operative from surgical correction of cyanotic congenital heart disease within 90 days of PICU/CICU admission
- Uncorrected congenital heart disease (does NOT include patients with an isolated atrial or ventricular septal defect, patent ductus arteriosus, or patent foramen ovale).
- Immediately following elective cardiac catheterization.

For exclusion criteria 4-6, patients admitted and then taken to the operating theater for surgical corrections requiring cardiopulmonary bypass are included for study.

Urine collection

For sites that have agreed to collect urine samples, eligible patients for study will have urine collected from an indwelling urinary catheter (foley) or via clean intermittent catheterization twice daily (between 6 and 10 am and between 3 and 7 pm) within the first 48 hours of admission (and then for as many of the regularly scheduled samples as possible within the first 4 days of PICU/CICU admission). Patients are not bagged or catheterized separately/independently for the purposes of this study. Collected urine samples are kept on ice or in 4°C refrigerator within four hours of collection and are stored until they are processed, which occurs within 48 hours. Notations will be made if this processing does not occur within this time frame. During processing, specimens are centrifuged at 3000 RPM at 4°C for fifteen minutes. The supernatants are divided into up to nine 1mL cryovials depending on the collected urine volume and stored at -80°C. The stored urine samples from all participating sites are shipped to the Center for Acute Care Nephrology/Nephrology Center of Excellence Biomarker Core Laboratory in the Division of Nephrology and
Hypertension at Cincinnati Children’s Hospital Medical Center. Until biomarker processing, the samples are kept frozen in a dedicated sub-zero freezer with a multiple redundancy backup paging system alerting machine failure (i.e., freezer failure). All urine samples will be kept in frozen form for 5 years at -80°C, establishing a ‘biorepository’ of urinary samples. Stability of urine for processing and analysis of urinary biomarkers after storage in this manner has been validated [21].

Urinary biomarker sampling

Neutrophil gelatinase associated lipocalin (NGAL), Interleukin-18 (IL-18), Kidney Injury Molecule-1 (KIM-1), liver type-Fatty Acid Binding Protein (l-FABP), alpha-glutathione-S-transferase (α-GST), and pi-glutathione-S-transferase (π-GST) will be measured on the first 3 days of ICU admission. Urine NGAL will be assayed using a human-specific commercially available enzyme-linked immunosorbent assay (ELISA, AntibodyShop, Grusbakken, Denmark). Urine IL-18 and L-FABP will be measured using commercially available ELISA kits (Medical & Biological Laboratories Co., Nagoya, Japan, and CMIC Co., Tokyo, Japan, respectively) per manufacturer’s instructions. Urine KIM-1 is measured by ELISA using commercially available reagents (R&D Systems, Inc., Minneapolis, Minnesota). Urinary GST will be assayed using a quantitative human ELISA (EKF Diagnostics, Magdeburg, Germany).

Variable collection

Data collected per patient encompasses admission demographic data, daily morning hemodynamic parameters, daily laboratory values specific for kidney function, assessments of fluid balance including net fluid in and net fluid out, and use of nephrotoxins or diuretic agents. For admission epidemiology, primary ICU diagnoses are broadly divided into shock/infection/major trauma, medical cardiac, respiratory failure, post-surgical/minor trauma, central nervous system dysfunction, and pain/sedation management. The broad categorization is intentional as it allows initial stratification into major pathophysiologic criteria required for ICU admission. Within each classification, individual patient characteristics, co-morbidities, and specific diagnoses will be collected to allow for further refinement of patient characteristics with a high level of granularity. A full listing of variables is available in Supplemental File 2, the case report form (CRF) used for data collection. Net fluid balance is divided into total fluids and urine flow rates derived per kilogram admission body weight per hour. Net fluid balance includes all form of outputs, including ostomy drainage, stool output, and other drain output. Daily calculated values include:

- Estimated change in creatinine clearance
  
  Calculated as percent change of daily creatinine from baseline creatinine

  Baseline creatinine used is lowest consistent serum creatinine 90 days or more prior to admission

  For patients without a prior baseline, an assumed creatinine clearance of 120 ml/min/1.73m² is used [3].

Figure 1: Anticipated flow map for patients enrolled in AWARE.

- Percent fluid overload
not patient’s ideal body weight or hospital admission weight (for those transferred from a non-ICU hospital bed).

- Fluid corrected serum creatinine
  Calculated as previously described [23]
- KDIGO stage AKI by creatinine
  Based on KDIGO AKI guidelines [24].

Final patient outcomes will be recorded on Day 30 after PICU admission. The anticipated flow of patient data collection is depicted in Figure 1.

### Biomarker panels

Biomarker panels will be created to enable prediction of injury characteristics. For each biomarker, literature based and individual predictive performance derived in this database will be used to determine the optimal cut-off values used to denote “positivity” (Youden’s index). As an example of a potential a priori cut-off that may be used for creation of the panels, a preliminary study of biomarker combinations identified an optimal cut-off value for urinary NGAL of >200 ng/ml [18]. Biomarkers will then be combined in pairs, joining a functional marker with a tubular damage marker in four different combinations (-/-, -/+, +/-, and +/+). Serum creatinine change will be used as the ‘functional’ marker of injury. As this study proceeds with a waiver of consent to maximize enrolment, prospective sampling of serum for Cystatin C (the alternative novel biomarker denoting functional injury) was not considered. All of the urinary markers are considered ‘tubular damage’ markers, but respond to different locations of injury within the nephron [25]. Urinary 1-FAFP is a marker of proximal tubular injury, uNGAL, IL-18, and KIM-1 of overall tubular injury, and GST of distal tubular injury. The damage markers will be joined in pairs together and in triplets (making 8 combinations). Biomarkers representative of injury in different parts of the nephron will also be combined (e.g., NGAL and π-GST).

### MediData Rave®

Data entry of the variables of interest will be performed by the investigators and clinical research coordinators at the participating sites using a web-based data base: MediData Rave®. Rave® is a commercial system designed to capture, manage, and report clinical research data. Through this system, each participating site is assigned a unique code, as identified by the study team. If responses to the initial set of variables that comprise the site principal investigator to ensure data quality and appropriate data entry. Even after repeated inquiry, if patients are missing data, they will be omitted from the study. Data management and statistical analysis will be executed at CCHMC.

### Interventions

AWARE is a non-intervention observational study. Urine collection will occur only for patients that have an indwelling urinary catheter or are scheduled for clean intermittent catheterization.

### Consent

AWARE is proposed as human subject research with a waiver of informed consent/parental permission and assent. This waiver is pursued by the following rationale:

- The research involves no more than minimal risk to the subjects.
- The waiver does not adversely affect the rights and welfare of the subjects.
- The research cannot practically be carried out without the waiver or alteration. Enrolling the maximum number of PICU admissions during the study period yields the greatest and most informative amount of data. Requiring informed consent from every eligible patient causes a significant reduction in enrolment and potentially introduces selection bias into the dataset (i.e., omission of all patients from centers with limited clinical research personnel). Robust quality improvement and process improvement work in patients with acute kidney injury requires that all subjects with acute kidney injury be included in the process. Requiring informed consent leads to incomplete participation, and therefore the data gathered under an informed consent requirement reduces the reliability of the data.
- The research on urine collection and biomarker measurements is reliably and confidentially performed with waiver of consent as long as the following caveats are applied

Only urine intended for discard or waste will be used.

Urine will be collected only from patients with an indwelling urinary drainage system and collection apparatus or scheduled for intermittent catheterization. Patients will not be bagged or catheterized separately/independently for the purposes of this study.

The sites participating in AWARE have obtained appropriate ethical board approval from their respective review consensus boards (Supplemental File 1). No site participating in the study is awaiting approval from an ethical board. Although some institutions have waived the need for consent, some require written, informed consent and this will be obtained as indicated to fulful an additional inclusion criterion. The precedent for obtaining waiver of consent for this type of prospective study was established with our pilot study of renal angina and urinary biomarkers for acute kidney injury (AKI-CHERUB, Clinical Trials.gov: NCT01735162).

### Co-enrolment

Patients enrolled in AWARE may also be enrolled in other studies without exception. As AWARE is non-interventional, there is no overlap in the observation with other CACN or PICU/CICU origin studies.
Primary and secondary outcomes

Our overall objective to improve the precision of AKI diagnosis. Prediction of AKI on Day 3 after admission, defined as KDIGO stage 2 or 3 AKI by creatinine and/or urine output criteria is the primary outcome variable (Day 3 AKI). The primary objective is to compare the prediction of the biomarker panels (on Days 0 and 1) for Day 3 AKI versus changes in SCr from baseline.

Our secondary outcomes are to discern characteristics of Day 3 AKI.

• Determine prediction for severity of AKI (None/KDIGO 1, KDIGO 2/3, requirement of renal replacement therapy).
• Determine prediction of transient AKI (return to baseline creatinine by day 3).
• Determine duration of severe AKI (elevated creatinine past 7 days).
• Determine relation of specific diagnoses with biomarker panel changes on Day 0
• Sepsis
• Nephrotoxin exposure
• Volume depletion
• Cardiopulmonary bypass

• Determine outcome of biomarker “positive” versus creatinine “negative” AKI (both kidney based outcomes and ICU outcomes such as duration of mechanical ventilation, length of stay, and mortality).

Until novel biomarkers become fully integrated into practice, the primary measure of severe AKI will be defined by KDIGO staging (Table 1) or other creatinine based stratification. Given the known limitations of creatinine for phenotype determination, as well as consistency between patients, there is a pressing need for a more sophisticated approach to outcome evaluation. In this study, we will be able to identify the associated consequences of biomarker+/creatinine- patients (pre- and post- biomarker combination analysis). Previous study of such injury indicates that this profile is not a ‘false positive’ of kidney injury, but may typify a different arm of the acute kidney injury spectrum [26]. Longer term outcomes to be followed include duration of mechanical ventilation, use of continuous renal replacement therapy, use of extracorporeal assist devices such as extracorporeal membrane oxygenation (ECMO) or ventricular assist devices (VADs), ICU length of stay, and mortality (Day 30 follow up). Additionally, investigators will ensure that patients without 30 day follow-up are not listed as deceased.

| Criteria                                      | Stage |
|----------------------------------------------|-------|
|                                             | 1     | 2    | 3    |
| Creatinine change (from baseline)           | ≥1.5–1.9x or >10.3mg/dl | ≥2–2.9x | >3x baseline |
|                                             | Initiation of CRRT | eGFR <35ml/min/1.73m² |
| Urine Output (ml/Kg/hr)                      | <0.5 for 6–12 h | <0.5 for >12 h | <0.5 for Or anuria 12 h |
| Duration                                     | 6–12 h | 12 h |

Table 1: Kidney disease improving global outcomes staging criteria for acute kidney injury.

Sample size

The AWARE study will be the largest prospective pediatric AKI study describing global epidemiology, risk factors, and associated outcomes. To date, the largest prospective cohort study of AKI to date was conducted by the Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) investigators [27]. In the BEST Kidney study 18% of 29,269 patients prospectively studied after admission to 54 adult ICUs across 23 countries over 15 months developed AKI. For the AWARE study, we based our sample size estimation on studies of AKI incidence in the PICU [1,5] and internal studies used validate the renal angina index (RAI) [5,28]. We are estimating the average number of enrolled children to be an average of 175 from each participating site with a total of approximately 5,500 children from all sites. Among the participating sites, we estimate one third to participate in urine collection (an estimate derived from data analysis from the single center pilot study for AWARE – “CHERUB” – conducted at Cincinnati Children’s Hospital – Clinical Trials.Gov: NCT01735162), resulting in an expected approximately 2000 patients with urinary biomarkers able to be measured. The RAI is a risk stratification methodology combining AKI risk factors and early signs of injury to optimize biomarker testing and prediction of AKI (in binary fashion) [29]. The primary aim of the biomarker panel arm of the AWARE study is not to re-validate the RAI but to enhance the precision of AKI diagnosis (i.e., increase the granularity). We are allocating each site 3 consecutive months to complete patient enrolment. Data capture can occur after the three months are complete, but no new patients are to be enrolled.

Analysis

Analysis of data will be performed independently based on each specific aim.

• Data for the primary objective of describing the epidemiology of AKI will be presented as a descriptive model. The prevalence on day 0 and incidence of AKI in up to 7 days of ICU admission using KDIGO classification will be calculated for each site cohort to identify the geographical “hot spots” of pediatric AKI. The data then will be pooled into a single cohort to study the outcome of AKI. The whole cohort will be stratified on Day 3 into four sub-populations with: no AKI, AKI-KDIGO Stage 1, AKI-KDIGO Stage 2, and AKI-KDIGO Stage 3. An adjusted and unadjusted survival analysis models using log rank test and cox regression models will be used to compare the mortality rates and the need of renal replacement therapy between the 4 groups.

• Each biomarker will be evaluated as a diagnostic test and sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratios, and receiver operating characteristics (ROCs) will be derived. Youden’s index will be determined to identify optimal cut-off value to denote “positivity”[30]. Biomarker panels will also be subjected to this analysis.

• The biomarkers will be tested in combination for changes in prognostic parameters and comparisons of discrimination using
sites. Other sites will have access only to their enrolled subjects. Data of patients (from over 5 continents), and the inclusion of all ICU at CCHMC will be the only site that can access the data from all other enrolment, consenting (when applicable), processing the urine samples (when applicable), collecting and entering data to RAVE® web browser. The research personnel in every site will be able to access the data of children enrolled from the same site. Only CCHMC research personnel will have access to the data collected for the purposes of this study from all participating sites. CCHMC will be responsible for managing and analyzing the data and testing the urine samples for urinary biomarkers. All participating sites will use the same case report form (CRF). The web-based CRFs will be designed and monitored by the Medidata RAVE® representatives in the Data Management Core at Cincinnati Children’s Hospital Medical Center (CCHMC). As the project coordinators, the Center for Acute Care Nephrology (CACN) at CCHMC will be the only site that can access the data from all other sites. Other sites will have access only to their enrolled subjects. Data management and statistical analysis will be executed at CCHMC.

The AWARE study is a featured study of the Prospective Pediatric Acute Kidney Injury Registry (www.ppaki.org). Founded in 2012, the ppAKI is an international research consortium comprised of pediatric nephrologists and intensivists striving to foster development and advances in the research of pediatric acute kidney injury.

Discussion

The AKI epidemic carries a significant health burden for children [31]. Despite continual diagnostic reclassification over the past 15 years (RIFLE, pRIFLE, AKIN, and KDIGO), novel diagnostic methodologies including risk stratification (renal angina index) and advanced analytics of urinary biomarkers are needed to improve the granularity of injury characterization. The AWARE study will change the field of pediatric AKI and critical care nephrology, directly addressing the current paucity of pediatric data presenting a major hurdle to the advancement of the field towards improving outcomes.

Strengths in the design of this prospective trial include the magnitude of patient enrolment (over 5,500 expected and at the time of this writing over 5,000 enrolled), the broad geographic distribution of patients (from over 5 continents), and the inclusion of all ICU patients – regardless of previously documented AKI risk factors (i.e., sepsis, mechanical ventilation, cardiopulmonary bypass). The repository of data collected will inform critical care nephrologists for many years to come and allow for analysis of many epidemiologic AKI associations. The capture of urine for biomarker analysis is the largest urine biorepository in pediatric critical care to date and the largest ever for the study of AKI. Given the expected population size and data to be prospectively captured, the AWARE study will facilitate analysis of many questions surrounding AKI, both diagnostic and therapeutic. A few examples of targeted questions potentially answerable by mining the database include: a) the association of resuscitative fluids and AKI, b) delineation of predictive and associated factors between transient versus persistent AKI, c) the independent outcomes of fluid overload and oliguria in all critically ill patients, and the d) associations and outcomes of subclinical-AKI.

The design of this prospective study has limitations. We make several assumptions with regards to the expected incidence of AKI per PICU/CICU center. Differing geographic areas included in our enrolment study list and different patient demographics may have greater or less incidence of AKI risk. Many pediatric patients have no ‘baseline’ creatinine measured prior to the time of acute illness. Our assumption of a normal creatinine clearance is based on the use of this paradigm in previous study [4]. Additionally, we assume that 33% or greater of our enrolment sites will be able to capture urine for the biomarker analysis. Perhaps the greatest limitation is that this study is being independent of financial reimbursement. Study coordinators, research coordinators, and data management specialists at each site are not compensated for the exclusive purpose of this study, which has the potential to bias the enrolment strength of each centre (depending on staff enthusiasm and availability). All of these limitations can also be interpreted as strengths of the study, however. Our initial results indicate that the AWARE study will assemble a broad and heterogeneous patient repository and that the pro bono work done by our coordinating sites is robust. It is our expectation that the AWARE study will serve as a model, a proof of concept that resources are in place to facilitate broad based pediatric AKI studies, for future large scale multicenter studies that are funded and sponsored by governmental and private financial support.

AKI is a significant disease syndrome affecting a large proportion of pediatric ICU patients. Existing data indicates that patients are not just dying with AKI, but from AKI [32]. AWARE is a first of its kind and vital study of critically ill children that will inform the pediatric critical care nephrology community of the prevalence and associations of AKI across the globe, offering new perspectives for prediction and detection of disease.

Trial Status

Recruitment is currently active at most centers, but is limited to three consecutive months from the time of initiation at each center. Patient enrolment and data capture is expected to be complete by January 1, 2015.

Acknowledgements

The investigators appreciate the Cincinnati Children’s Hospital Research Foundation’s financial support for the development of the AWARE database platform. AWARE is sponsored by the Center for Acute Care Nephrology at Cincinnati Children’s. This work was supported in part by a grant from the NIH (P50 DK096418). Biomarker measurements will be performed in the lab of Prasad Devarajan MD, principal investigator of the Cincinnati Children’s Hospital Nephrology Center for Excellence.

The authors would like to thank the site investigators and coordinators for their work on the trial. University of Alabama Birmingham, David Askenazi; Children’s Hospital Colorado, Katja Gist; Lucille Packard Children’s Hospital of Stanford University, Scott
References

1. Schneider J, Khemani R, Grushkin C, Bart R (2010) Serum creatinine as stratified in the RIFLE score for acute kidney injury is associated with mortality and length of stay for children in the pediatric intensive care unit. Crit Care Med 38: 933-939.

2. Bailey D, Phan V, Litalien C, Ducrue T, Merouani A, et al. (2007) Risk factors of acute renal failure in critically ill children: A prospective descriptive epidemiological study. Pediatr Crit Care Med 8: 29-35.

3. Zappitelli M, Parikh CR, Akan-Arikan A, Washburn KK, Moffett BS, et al. (2008) Ascertainment and epidemiology of acute kidney injury varies with definition interpretation. Clin J Am Soc Nephrol 3: 948-954.

4. Akan-Arikan A, Zappitelli M, Loisit LL, Washburn KK, Jefferson LS, et al. (2007) Modified RIFLE criteria in critically ill children with acute kidney injury. Kidney Int 71: 1028-1035.

5. Basu RK, Zappitelli M, Brunner L, Wang Y, Wong HR, et al. (2014) Derivation and validation of the renal angina index to improve the prediction of acute kidney injury in critically ill children. Kidney Int 85: 659-667.

6. Seselesi DT, Cornell TT, Heung M, Troost JP, Ehrmann BJ, et al. (2014) Validation of the KDIGO acute kidney injury criteria in a pediatric critical care population. Intensive Care Med 40: 1481-1488.

7. Liao G, Pascual J (1996) Acute renal failure. Madrid Acute Renal Failure Study Group. Lancet 347: 479.

8. Nas K, Haefee A, Hou S (2002) Hospital-acquired renal insufficiency. Am J Kidney Dis 39: 930-936.

9. Venkatachalam MA, Griffin KA, Lan R, Geng H, Saikumar P, et al. (2010) Acute kidney injury: a springboard for progression in chronic kidney disease. Am J Physiol Renal Physiol 298: F1078-1094.

10. Xue JL, Daniels F, Star RA, Kimmel PL, Eggers PW, et al. (2006) Incidence and mortality of acute renal failure in Medicare beneficiaries, 1992 to 2001. J Am Soc Nephrol 17: 1135-1142.

11. Heringlake M, Knappe M, Vargas Hein O, Luft H, Kindgen-Milles D, et al. (2006) Renal dysfunction according to the ADQI-RIFLE system and clinical practice patterns after cardiac surgery in Germany. Minerva Anestesiologica 72: 645-654.

12. Uchino S, Bellomo R, Goldsmith D, Bates S, Ronco C (2006) An assessment of the RIFLE criteria for acute renal failure in hospitalized patients. Crit Care Med 34: 1913-1917.

13. Ostermann M, Chang RW (2007) Acute kidney injury in the intensive care unit according to RIFLE. Crit Care Med 35: 1837-1843.

14. Kendirli T, Ekim M, Ozçakar ZB, Yüksel S, Acar B, et al. (2007) Renal replacement therapies in pediatric intensive care patients: experiences of one center in Turkey. Pediatr Int 49: 345-348.

15. McCullough PA, Bouchard J, Waiker SS, Siew ED, Endre ZH, et al. (2013) Implementation of Novel Biomarkers in the Diagnosis, Prognosis, and Management of Acute Kidney Injury: Executive Summary from the Tenth Consensus Conference of the Acute Dialysis Quality Initiative (ADQI). Contrib Nephrol 182: 1-12.

16. Endre ZH, Kellum JA, Di Somma S, Dui K, Goldstein SL, et al. (2013) Differential diagnosis of AKI in clinical practice by functional and damage biomarkers: workshop statements from the tenth Acute Dialysys Quality Initiative Consensus Conference. Contrib Nephrol 182: 30-44.

17. Devarajan P, Mishra J, Supavekin S, Patterson LT, Steven Potter S (2003) Gene expression in early ischemic renal injury: clues towards pathogenesis, biomarker discovery, and novel therapeutics. Mol Genet Metab 80: 365-376.

18. Basu RK, Hong HR, Krawczeski CD, Wheeler DS, Manning PB, et al. (2014) Combining functional and tubular damage biomarkers improves diagnostic precision for acute kidney injury after cardiac surgery. J Am Coll Cardiol 64: 2753-2762.

19. Edwards JD, Vasiilieks EE, Yoo EJ, Houtrow AJ, Bocardin WJ, et al. (2015) Adults with childhood-onset chronic conditions admitted to US pediatric and adult intensive care units. J Crit Care 30: 201-206.

20. Edwards JD, Houtrow AJ, Vasiileks EE, Dudley RA, Okumura MJ (2013) Multi-institutional profile of adults admitted to pediatric intensive care units. JAMA Pediatr 167: 436-443.

21. Parikh CR, Rutymowicz I, Yu A, Chinchilli VM, Park M, et al. (2014) Urine stability studies for novel biomarkers of acute kidney injury. Am J Kidney Dis 63: 567-572.

22. Goldstein SL, Currier H, Graf Cd, Cosio CC, Brewer ED, et al. (2001) Outcome in children receiving continuous venovenous hemofiltration. Pediatrics 107: 1309-1312.

23. Basu RK, Andrews A, Kravczecki G, Manning P, Wheeler DS, et al. (2013) Acute kidney injury based on corrected serum creatinine is associated with increased morbidity in children following the arterial switch operation. Pediatr Crit Care Med 14: e218-e224.

24. Ethan M Balk (2012) KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney International Supplements 2: 2-138.

25. ge Hur BS, Betjes MG, Bakker J (2012) Biomarkers for the prediction of acute kidney injury: a narrative review on current status and future challenges. Clin Kidney J 5: 102-108.

26. Haase M, Devarajan P, Haase-Fielitz A, Bellomo R, Cruz DN, et al. (2013) The outcome of nephrologists gelatinase-associated lipocalin-positive subclinical acute kidney injury: a multicenter pooled analysis of prospective studies. J Am Coll Cardiol 57: 1752-1761.

27. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, et al. (2005) Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA 294: 813-818.

28. Basu RK, Wang Y, Wong HR, Chawla LS, Wheeler DS, et al. (2014) Incorporation of biomarkers with the renal angina index for prediction of severe AKI in critically ill children. Clin J Am Soc Nephrol 8: 654-662.

29. Goldstein SL, Chawla LS (2010) Renal angina. Clin J Am Soc Nephrol 5: 29.

30. de Geus HR, Betjes MG, Bakker J (2012) Biomarkers for the prediction of acute kidney injury: a narrative review on current status and future challenges. Clin Kidney J 5: 102-108.

31. Haase M, Devarajan P, Haase-Fielitz A, Bellomo R, Cruz DN, et al. (2013) The outcome of nephrologists gelatinase-associated lipocalin-positive subclinical acute kidney injury: a multicenter pooled analysis of prospective studies. J Am Coll Cardiol 57: 1752-1761.

32. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, et al. (2005) Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA 294: 813-818.

33. Basu RK, Wang Y, Wong HR, Chawla LS, Wheeler DS, et al. (2014) Incorporation of biomarkers with the renal angina index for prediction of severe AKI in critically ill children. Clin J Am Soc Nephrol 8: 654-662.

34. Goldstein SL, Chawla LS (2010) Renal angina. Clin J Am Soc Nephrol 5: 943-949.

35. Böhminger D, Bohming H, Holling H (2008) Revisiting Youden's index as a useful measure of the misclassification error in meta-analysis of diagnostic studies. Stat Methods Med Res 17: 543-554.
31. Fortenberry JD, Paden ML, Goldstein SL (2013) Acute kidney injury in children: an update on diagnosis and treatment. Pediatr Clin North Am 60: 669-688.

32. Kellum JA, Bellomo R, Ronco C (2012) Kidney attack. JAMA 307: 2265-2266.