
**Objective:** Acute kidney injury occurs early in PICU admission and increases risks for poor outcomes. We evaluated the feasibility of a multicenter acute kidney injury biomarker urine collection protocol and measured diagnostic characteristics of urine neutrophil gelatinase-associated lipocalin, interleukin-18, and liver fatty acid binding protein to predict acute kidney injury and prolonged acute kidney injury.

**Design:** Prospective observational pilot cohort study.

**Setting:** Four Canadian tertiary healthcare PICUs.

**Patients:** Eighty-one children 1 month to 18 years old. Exclusion criteria were as follows: cardiac surgery, baseline severe kidney disease, and inadequate urine or serum for PICU days 1-3.

**Interventions:** PICUs performed standardized urine collection protocol to obtain early PICU admission urine samples, with deferred consent.

**Measurements and Main Results:** Study barriers and facilitators were recorded. Acute kidney injury was defined based on Kidney Disease: Improving Global Outcomes serum creatinine criteria (acute kidney injury serum creatinine) and by serum creatinine and urine output criteria (acute kidney injury serum creatinine+urine output) Prolonged acute kidney injury was defined as acute kidney injury duration of 48 hours or more. PICU days 1-3 neutrophil gelatinase-associated lipocalin, interleukin-18, and liver fatty acid binding protein were evaluated for acute kidney injury prediction (area under the curve). Biomarkers on the first day of acute kidney injury attainment (day 1 acute kidney injury) were evaluated for predicting prolonged acute kidney injury. Eighty-two to 95% of subjects had urine collected from PICU days 1-3. Acute kidney injury serum creatinine developed in 16 subjects (20%); acute kidney injury serum creatinine+urine output developed in 38 (47%). On PICU day 1, interleukin-18 predicted acute kidney injury serum creatinine with area under the curve=0.82, but neutrophil gelatinase-associated lipocalin and liver fatty acid binding protein predicted acute kidney injury serum creatinine with area under the curve of less than or equal to 0.69; on PICU day 2, area under the curve was higher (not shown). Interleukin-18 and liver fatty acid binding protein predicted acute kidney injury serum creatinine+urine output with area under the curve of less than or equal to 0.69; on PICU day 2, area under the curve was higher (not shown). Interleukin-18 and liver fatty acid binding protein predicted acute kidney injury serum creatinine+urine output with area under the curve of less than or equal to 0.69; on PICU day 2, area under the curve was higher (not shown). Interleukin-18 and liver fatty acid binding protein predicted acute kidney injury serum creatinine+urine output with area under the curve of less than or equal to 0.69; on PICU day 2, area under the curve was higher (not shown).

**Conclusions:** Protocol urine collection to procure early admission samples is feasible. Individual biomarker acute kidney injury prediction performance is highly variable and modest. Larger studies should evaluate utility and cost effectiveness of using early acute kidney injury biomarkers.

**Reviewer’s Comments:**
This is one of the first multicentre studies evaluating AKI biomarkers in noncardiac PICU children. A urine collection protocol to obtain early PICU admission urine with deferred consent was feasible. The fact that AKI occurs early in PICU complicates biomarker research. To measure biomarkers during the short therapeutic AKI window (before SCr rise), collecting urine in the first 1–3 PICU days is critical but not easy.
This problem may explain the paucity of PICU AKI biomarker studies. They investigated the impact of UO AKI criteria on biomarker performance. Although adult data suggest that UO-defined AKI is associated with clinical outcomes, little is known on this matter in children. UO criteria are challenging to collect, particularly in patients without urinary catheters. Biomarker performance was worse when including UO criteria. It is possible that a small, temporary UO reduction (i.e., stage 1) may not reflect tubular injury, but rather be a sensitive indicator of temporary volume depletion. It may be that in children, more severe UO reductions are more relevant, in terms of outcome associations or renal tissue injury. Different biomarkers may perform variability by primary disease etiology. Biomarkers may identify tissue injury and help make timely decisions on nephrotoxins and fluid management. They used AKI more than 48 hours to represent prolonged AKI, based previous studies. Future studies may identify alternative “AKI duration” thresholds. Study limitations included low sample size and multiple testing. Better characterization of biomarker performance (timing, subgroups) and more discovery research to identify valid AKI biomarkers in the PICU are needed.


Objectives: To analyse the epidemiology of pediatric acute kidney injury requiring continuous renal replacement therapy and identify prognostic factors affecting mortality rates.

Design: Retrospective analysis.

Setting: PICU of a tertiary medical centre.

Patients: One hundred-twenty three children diagnosed with acute kidney injury requiring continuous renal replacement therapy.

Interventions: None.

Measurements and Main Results:

Vasoactive-Inotropic Score, arterial blood gas analysis, blood chemistry at continuous renal replacement therapy initiation, the extent of fluid overload 24 hours prior to continuous renal replacement therapy initiation, Pediatric Risk of Mortality III score at admission, and need for mechanical ventilation during continuous renal replacement therapy were compared in survivors and nonsurvivors. Out of 1,832 patient admissions, 185 patients (10.1%) developed acute kidney injury during the study period. Of these, 158 patients were treated with continuous renal replacement therapy, and finally, 123 patients were enrolled. Of the enrolled patients, 50 patients died, corresponding to a mortality rate of 40.6%. The survivor group and the nonsurvivor group were compared, and the following factors were associated with an increased risk of mortality: higher Pediatric Risk of Mortality III score at admission and Vasoactive-Inotropic Score when initiating continuous renal replacement therapy, increased fluid overload 24 hours before continuous renal replacement therapy initiation, and need for mechanical ventilation during continuous renal replacement therapy. The percentage of fluid overload difference between the survivors and the nonsurvivors was 1.2% ± 2.2% versus 4.1% ± 4.6%, respectively. Acidosis, elevated lactic acid and blood urea nitrogen, and lower serum creatinine level were laboratory parameters associated with increased mortality. On multivariate analysis, Vasoactive-Inotropic Score, need for mechanical ventilation, blood urea nitrogen, and creatinine level were statistically significant. (Odds ratio: 1.040, 6.096, 1.032, and 0.643, respectively.)

Conclusions: A higher Vasoactive-Inotropic Score, need for mechanical ventilation, elevated blood urea nitrogen, and lower creatinine level were associated with increased mortality in pediatric acute kidney injury patients who underwent continuous renal replacement therapy. Lower creatinine levels may be associated with increased mortality in the context of fluid overload, which is correlated with a reduced chance of survival.

Reviewer's Comments:

Dialysis using CRRT is a safe modality, increasingly used in pediatric AKI patients. This study found that PRISM III score at admission and VIS at CRRT initiation were associated with increased mortality in pediatric acute kidney injury patients who underwent continuous renal replacement therapy. Lower creatinine levels may be associated with increased mortality in the context of fluid overload, which is correlated with a reduced chance of survival.
the nonsurvivor group compared with the survivor group. In addition, increased fluid overload 24 hours prior to CRRT initiation and the need for mechanical ventilation were associated with increased mortality. Among the laboratory findings, acidosis, elevated lactic acid level, and BUN were associated with increased mortality, whereas there was an inverse correlation between creatinine levels and mortality. Interestingly, in this study, the serum creatinine level was higher in the survivor group than in the nonsurvivor group. Serum creatinine elevation is often regarded as a sign of AKI deterioration. However, the higher BUN level and lower creatinine level were associated with an increased risk of death in this study. Lower serum creatinine reflects the extent of fluid overload, which is positively correlated with mortality. In our study, the extent of fluid overload was greater in the nonsurvivor group, and secondary analysis showed that serum creatinine levels were significantly lower in the group with increased fluid overload. Creatinine is often considered not only to be a criterion for defining AKI but also to represent renal function in the clinical fields. However, lower creatinine should not be overlooked. Seemingly, lower serum creatinine level caused by fluid overload may mislead clinicians from meticulously restricting fluid intake. Considering the clinical condition of the patient, clinicians should focus on determining the appropriate timing of CRRT initiation, even where serum creatinine is not raised. A large-scale prospective multicentre study with a standardized CRRT administration protocol is required to elucidate significant prognostic factors. Finally, more sophisticated data, including patient nutritional status and muscle mass, are required to validate the association between serum creatinine levels and increased mortality in CRRT-treated pediatric AKI patients.


Objective: Cardiac surgery-induced acute kidney injury occurs frequently in neonates and infants and is associated with postoperative morbidity/mortality; early identification of cardiac surgery-induced acute kidney injury may be crucial to mitigate postoperative morbidity. We sought to determine if hourly or 6-hour cumulative urine output after furosemide in the first 24 hours after cardiopulmonary bypass could predict development of cardiac surgery-induced acute kidney injury and other deleterious outcomes.

Design: Retrospective chart review.

Setting: Pediatric cardiac ICU.

Patients: All infants younger than 90 days old admitted to the cardiac ICU from October 2012 to December 2015 who received at least one dose of furosemide in the first 24 hours after cardiopulmonary bypass surgery.

Interventions: None.

Measurements and Main Results: Ninety-nine patients met inclusion and exclusion criteria. In total, 45.5% developed cardiac surgery-induced acute kidney injury. Median time between cardiopulmonary bypass and furosemide was 7.7 hours (interquartile range, 4.4-9.5). Six-hour cumulative urine output was 33% lower (p = 0.031) in patients with cardiac surgery-induced acute kidney injury. Area under the curve for prediction of cardiac surgery-induced acute kidney injury was 0.69 (p = 0.002). Other models demonstrated urine output response to furosemide had significant area under the curves for prediction of peak fluid overload greater than 15% (0.68; p = 0.047), prolonged peritoneal dialysis (area under the curve, 0.79; p = 0.007), prolonged mechanical ventilation (area under the curve, 0.79; p < 0.001), prolonged hospitalization (area under the curve, 0.62; p = 0.069) and mortality (area under the curve, 0.72; p = 0.05).

Conclusions: Urine output response to furosemide within 24 hours of cardiopulmonary bypass predicts cardiac surgery-induced acute kidney injury development and other important morbidity in children younger than 90 days old; prospective validation is warranted.

Reviewer’s Comments:
This study support furosemide response as a bedside tool that predicts “functional” CS-AKI in the early postoperative period of infants younger than 90 days old—prior to the discriminative ability of SCr. Identification of CS-AKI in the early postoperative
period may be crucial to mitigate the deleterious impact of its sequelae (especially FO and electrolyte disturbances). Due to delay in SCr rise after kidney injury; current SCr-based definitions of CS-AKI do not achieve this goal. AKI biomarkers have shown promise for early identification of CS-AKI, but they are not readily available for clinical use at this time. UOP response to furosemide is an excellent candidate to assess tubular function early after CPB because it requires active transport across the renal tubular lumen. In this cohort of postoperative cardiac surgical neonates and infants, they found that decreased UOP in response to furosemide in the early postoperative period predicted subsequent diagnosis of CS-AKI. Study suggest UOP response to furosemide provides an objective measure of kidney function, which can predict clinically important CS-AKI and related morbidity in the early postoperative period of children younger than 90 days old. This study was limited by its single center, retrospective design. Small sample size prohibited subgroup analysis with respect to furosemide response performance in different age and surgical risk strata. Authors were not able to completely control for furosemide dosing, timing, or location; consistent timing for initiation of UOP collection after furosemide and/or furosemide treatment indication. Prospective studies investigating the utility of furosemide response alone, or combined with AKI-specific biomarkers for identification of patients at highest risk for clinically important CSAKI is an important future goal.


Objectives: Compare the rates of acute kidney injury in critically ill children treated with vancomycin and piperacillin-tazobactam versus vancomycin and ceftriaxone.

Design: Retrospective cohort study.

Setting: A large tertiary care children’s hospital in an urban setting.

Patients: Children greater than or equal to 2 months old admitted to the PICU who received greater than or equal to 48 consecutive hours of vancomycin and piperacillin-tazobactam or vancomycin and ceftriaxone.

Interventions: None.

Measurements and Main Results: Acute kidney injury was defined as a minimum 50% increase in serum creatinine, adjusted for total fluid balance, from baseline over a 48-hour period. Bivariate analysis compared treatment groups and acute kidney injury groups. A multivariable logistic regression model was fit for acute kidney injury including covariable analysis. The study included 93 children. There were no differences between treatment groups in terms of age, severity of illness, baseline renal function, vancomycin dosing, or vancomycin trough concentrations. Children who received vancomycin and piperacillin-tazobactam had a higher cumulative frequency of acute kidney injury than those who received vancomycin and ceftriaxone 915/58 [25.9%] vs 3/35 [8.6%]; p = 0.041). After controlling for vancomycin trough concentration, age, concurrent nephrotoxin exposure, and use of vasopressors, exposure to piperacillin-tazobactam significantly increased the risk of acute kidney injury (adjusted odds ratio, 4.55; 95% CI [1.11-18.7]; p = 0.035) compared with ceftriaxone. Use of vasopressors (adjusted odds ratio, 3.73 [95% CI, 1.14-12.3]) and a vancomycin trough greater than or equal to 15 mg/dL (adjusted odds ratio, 4.12 [95% CI, 1.12-15.2]) was also associated with acute kidney injury. Length of stay was longer in children with acute kidney injury (median, 18.0 days; interquartile range, 7.76-29.7) compared with those without acute kidney injury (median, 6.21 days; interquartile range, 2.92-15.6; p = 0.017).

Conclusions: In critically ill children, acute kidney injury occurred more in patients treated with vancomycin and piperacillin-tazobactam versus vancomycin plus ceftriaxone. After controlling for covariates, exposure to piperacillin-tazobactam was associated with an increased odds of acute kidney injury development.

Reviewer’s Comments:

Limited pediatric data exist regarding the frequency of AKI in hospitalized children exposed to combination vancomycin and PTZ. To date, most data are limited to
Authors claim that this is the first study to find an increased risk of AKI in 93 critically ill children treated with combination vancomycin and PTZ compared with a similar group treated with vancomycin and ceftriaxone. In this study, of all the measurable risk factors for AKI that were collected, exposure to PTZ with vancomycin was independently associated with four-fold higher odds of AKI. This is additionally supported by the multivariate analysis which indicated that the severity of illness score obtained at admission did not affect the risk of AKI. Clinically, there are circumstances where broad-spectrum empiric antibiotic coverage with vancomycin plus PTZ is reasonable, such as in an immunocompromised patient. Although this study was not designed to investigate the appropriateness of empiric antibiotic therapy, those treating children with vancomycin plus PTZ in the PICU should be aware of the increased risk of AKI. Limitations of this study include its small sample size and single-center nature, which may limit its external validity particularly in areas with different patient demographics and diagnoses. Additionally, as this was a retrospective study, it is difficult to identify those patients who may have been at risk of AKI prior to hospitalization, especially since SCR is an imperfect and delayed marker of renal function. Intensivists treating children with vancomycin and PTZ should be aware of this potential adverse outcome and should critically evaluate the need for broad-spectrum antibiotic coverage with both agents. If warranted, prudent selection of target vancomycin trough concentrations should occur, with close monitoring of kidney function.


Patients: Two hundred ninety-six subjects between 1 day and 18 years old who experienced in-hospital or out-of-hospital cardiac arrest between July 1, 2003, and December 31, 2004.

Interventions: None.

Measurements and Main Results: Our primary outcome was development of acute kidney injury as defined by the Acute Kidney Injury Network criteria. An ordinal probit model was developed. We found six critical explanatory variables, including total number of epinephrine doses, postcardiac arrest blood pressure, arrest location, presence of a chronic lung condition, pH, and presence of an abnormal baseline creatinine. Total number of epinephrine doses received as well as rate of epinephrine dosing impacted acute kidney injury risk and severity of acute kidney injury.

Conclusions: This study is the first to identify risk factors for acute kidney injury in children after cardiac arrest. Our findings regarding the impact of epinephrine dosing are of particular interest and suggest potential for epinephrine toxicity with regard to acute kidney injury. The ability to identify and potentially modify risk factors for acute kidney injury after cardiac arrest may lead to improved morbidity and mortality in this population.

Reviewer’s Comments:

AKI after CA in children is a common event with important implications for both morbidity and mortality. Identifying risk factors for AKI, particularly those that may be subject to intervention or modification, may significantly improve outcomes in this challenging population. Authors claim that this was the first analysis of incidence and potential risk factors for AKI after pediatric CA. Authors identified the total number of epinephrine doses as an important association with AKIN stage after pediatric CA. Number of epinephrine doses correlates with total epinephrine dosage. These findings generally affirm those in adult studies. This study failed to demonstrate a statistically reliable relationship between CPR duration and AKIN stage. This study has several limitations. First, it is a post hoc, retrospective review of a larger dataset, which was not designed to
address questions about changes in renal function in association with CA. Second, the dataset was generated over 10 years ago, and in that time, there have been significant changes in both post-CA and AKI care, including changes to American Heart Association resuscitation guidelines, renewed emphasis on improving resuscitation quality, increased awareness of AKI, and improving post-CA outcomes. Third, the challenges in using creatinine as a marker of renal function in non steady state conditions are well-described and include a significant time lapse between renal injury and a rise in serum creatinine. Further studies to verify our findings, to clarify relationships among variables, and to identify additional important modifiers are needed.

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