Pediatric RESEARCH

CLINICAL RESEARCH ARTICLE

Defining pediatric community-acquired acute kidney injury: an observational study

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BACKGROUND: Pediatric acute kidney injury (AKI) is associated with long-term morbidity and mortality; however, outcomes improve when AKI is detected earlier. Current definitions of AKI use baseline creatinine; community-acquired AKI (CA-AKI) is difficult to define and detect in the pediatric emergency department (ED) when no baseline creatinine is available. Our objective was to compare age- and gender-based creatinine norms to the traditional baseline (lowest creatinine in previous 3 months) to diagnose CA-AKI.

METHODS: This was a retrospective cross-sectional study conducted in children 1 month–18 years of age seen in the pediatric ED in whom a creatinine was obtained.

RESULTS: Per the Kidney Disease Improving Global Outcomes AKI definition in encounters with baseline creatinine available, 343/2338 (14.7%) had CA-AKI. When the upper limit of the age- and gender-based creatinine norm was applied as a surrogate baseline creatinine, CA-AKI was diagnosed in 1.5% of encounters (239/15,486). Additionally, CA-AKI was diagnosed in 178 cases using the upper limit of age- and gender-based creatinine norms only, as these cases did not have a baseline creatinine.

CONCLUSIONS: Age- and gender-based creatinine norms can be applied as a surrogate baseline to detect CA-AKI in all children regardless of whether baseline creatinine is available, potentially detecting it earlier.

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INTRODUCTION

Acute kidney injury (AKI), regardless of severity, is an independent risk factor for child mortality.[1–3] Few studies report the incidence of pediatric community-acquired AKI (CA-AKI), ranging from 0.26 to 56%.[4–8] Early recognition of AKI allows for the implementation of nephroprotective measures such as timely nephrology consultation and avoidance of nephrotoxic medications, to promote renal recovery.[9–11] Many therapies started in the emergency department (ED) are potentially nephrotoxic and may be modified if AKI is detected early.

Current standardized AKI definitions use duration of oliguria and increase in creatinine from baseline to determine stage of injury. The incidence of AKI varies with definition, specifically method of baseline creatinine selection.[1–8,12–15] Recognition of CA-AKI is particularly challenging in the ED, as a baseline serum creatinine (SCr) is often not readily available and urine output (UOP) difficult to verify or document. The baseline traditionally used in pediatric AKI studies is the lowest creatinine in the previous 3 months, accounting for changes in creatinine with growth and development.[1,2,5,12,15] When baseline creatinine levels are unavailable, approaches to determine AKI frequency have varied from using age- and gender-based norms, assuming normal baseline estimated glomerular filtration rates, using creatinine obtained later during that admission for comparison, or excluding these children from analyses all together.[1–5,12–15]

Variation in the definition of baseline creatinine impacts estimates of AKI incidence.[10] An easily applicable and practical baseline creatinine level is needed in the pediatric ED to improve detection of CA-AKI. Our goals were to determine (1) the incidence of AKI using traditional creatinine baselines and age- and gender-based creatinine norms as surrogate creatinine baselines, (2) compare these norms to traditional baselines, and (3) determine the proportion of children with AKI who would be missed by using baseline creatinine data vs. creatinine norms. Outside the scope of this publication, our ultimate goal with this project is to integrate age- and gender-based creatinine reference ranges into an electronic alert to detect AKI in all children presenting to our ED while minimizing alert fatigue for clinicians.

METHODS

Study design

This was a retrospective cross-sectional study conducted in two pediatric EDs of a quaternary care children's hospital (annual volumes of 75,000 and 45,000; average hospital admission rate 16–17%). Children 1 month–18 years of age seen in the pediatric ED between 1 January and 31 December 2015 in whom a creatinine was obtained were included. Children with known chronic kidney disease (CKD), end-stage renal disease (ESRD), and those who died during their ED encounter were excluded. Patients with CKD and ESRD were identified by cross-referencing our dataset with a monitored list of patients with CKD and ESRD followed by the nephrology service.

Children were diagnosed with CA-AKI if they had relative or absolute changes in creatinine according to the Kidney Disease Improving Global Outcomes (KDIGO) creatinine criteria.[16] UOP was

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Table 1. Population-based normal creatinine ranges by age and gender

Age and gender	Creatinine range (mg/dL)		Upper-limit SCr*	Midpoint SCr[a, b]	Lower-limit SCr[a]
15 days–1 year	0.1–0.4	Sensitivity	18.0% (14.1–22.5%)	30.6% (25.8–35.8%)	76.7% (71.8–81.1%)
2–4 years	0.2–0.4	Specificity	99.1% (98.6–99.5%)	93.9% (92.7–94.9%)	53.3% (51.1–55.5%)
5–11 years	0.3–0.6	PPV	77.5% (67.4–85.2%)	46.3% (40.5–52.1%)	22.0% (20.8–23.3%)
12–14 years	0.5–0.8	NPV	87.5% (87.0–88.1%)	88.7% (88.0–89.4%)	93.0% (91.6–94.2%)
15–18 years, female	0.5–0.8	Positive LR	19.7 (11.8–32.9)	5.0 (4.0–6.3)	1.64 (1.5–1.8)
15–18 years, male	0.6–1.0	Negative LR	0.83 (0.79–0.87)	0.74 (0.69–0.79)	0.44 (0.36–0.53)

LR likelihood ratio, *NPV* negative predictive value, *PPV* positive predictive value, *SCr* serum creatinine
[a]95% Confidence interval within parentheses
[b]Midpoint serum SCr for 15 days–1 year, 0.25; for 2–4 years, 0.3; 5–11 years, 0.45; 12–14 years and 15–18 years, female 0.65; 15–18 years, male 0.8

not used to define AKI, given the infrequency of documentation in the ED.[1,4,5,11,13,15] Similarly, an estimated glomerular filtration rate was not used, as heights are not routinely obtained in our ED. In addition, the time criteria for the KDIGO AKI definition was excluded in our study, similar to other studies,[2,12] as we wanted to identify patients with CA-AKI the moment they presented to our ED. We compared the use of two types of baseline creatinine levels to define AKI. All patients had a surrogate baseline applied, an age- and gender-based creatinine norm (Table 1); and if the patient had a previous creatinine level measured, we used the patient's lowest creatinine in the previous 3 months as well.

Medical records of those with AKI were abstracted for clinical data. Potentially nephrotoxic medications were determined a priori by investigators based on previous studies (Table 2).[17,18] Our clinical laboratory measures plasma creatinine using an enzymatic two-point rate assay on the Vitros 5600 and had created and validated age- and gender-based reference ranges for creatinine using a population study and the Canadian Laboratory Initiative on Pediatric Reference Intervals (Table 1).[19] Baylor College of Medicine review board approval was obtained with a waiver of consent.

The primary outcome was the frequency of CA-AKI among children seen in the pediatric ED using the traditional creatinine baseline (lowest SCr in previous 3 months) and age- and gender-based creatinine norms. Applicability of age- and gender-based creatinine norms compared to baseline creatinine to determine CA-AKI frequency was analyzed. Secondary outcomes included CA-AKI cases that were missed because they did not have baseline creatinine results; the proportion of children with AKI in whom potentially nephrotoxic medications were administered; hospital length of stay (LOS); renal replacement therapy; and mortality during that hospitalization. Further analyses were done on the group of CA-AKI by baseline creatine and those that met CA-AKI using the upper-limit creatinine norm.

Statistical analysis

Continuous data were presented as medians with interquartile ranges and compared using nonparametric tests. Categorical data were presented as frequencies with percentages. Sensitivity, specificity, accuracy, positive predictive value, negative predictive value, and likelihood ratios were calculated and reported with 95% confidence intervals. Analyses were performed using JMP Statistical Software from SAS (JMP 13, SAS Institute, Cary, NC).

RESULTS

CA-AKI using baseline creatinine

Of 15,486 encounters, 2338 (15.1%) had a previous serum creatinine in our electronic medical record. Per the KDIGO AKI definition in encounters with baseline creatinine available, 343/2338 (14.7%) had CA-AKI (Fig. 1). The majority were stage 1 AKI 271/343 (79.0%) (Table 3). Most patients with a baseline creatinine and AKI had a comorbid condition 335/343 (97.7%), malignancy being most common 134/343 (39.0%). A nephrotoxic medication (most commonly an antimicrobial) was used in the ED in 174/343 (50.7%) children with AKI. CA-AKI was recognized by an ED clinician in 20/343 (5.8%) of encounters. Almost 74% (252/343) cases of CA-AKI were admitted.

Table 2. List of nephrotoxic medications[19,20]

Acyclovir	Ifosfamide
Ambisome	Iodixanol
Amikacin	Iohexol
Amphotericin B	Iopamidol
Captopril	Ioversol
Carboplatin	Ketorolac
Cefotaxime	Lisinopril
Ceftazidime	Lithium
Ceftriaxone	Mesalamine
Cefuroxime	Methotrexate
Cidofovir	Nafcillin
Cisplatin	Piperacillin/tazobactam
Colistimethate	Piperacillin
Cyclosporine	Sirolimus
Dapsone	Sulfasalazine
Enalapril	Tacrolimus
Enalaprilat	Ticarcillin/clavulanic acid
Foscarnet	Tobramycin
Gadopentetate dimeglumine	Topiramate
Gadoextate disodium	Valacyclovir
Ganciclovir	Valgangciclovir
Gentamicin	Vancomycin
Ibuprofen	Zonisamide

Comparison of age- and gender-based norms to baseline creatinine

When the upper limit of the age- and gender-based creatinine norm was applied as a surrogate baseline creatinine to all encounters (Table 1), CA-AKI was diagnosed in 1.5% (239/15,486) (Fig. 1). In contrast, CA-AKI was present in 23.1% (3571/15,486) and in 56.4% (8735/15,486) of encounters using the midpoint and the lower creatinine limit, respectively. In order to evaluate which age- and gender-based normal creatinine value to use as baseline, the upper limit, midpoint, and lower limit of normal creatinine were

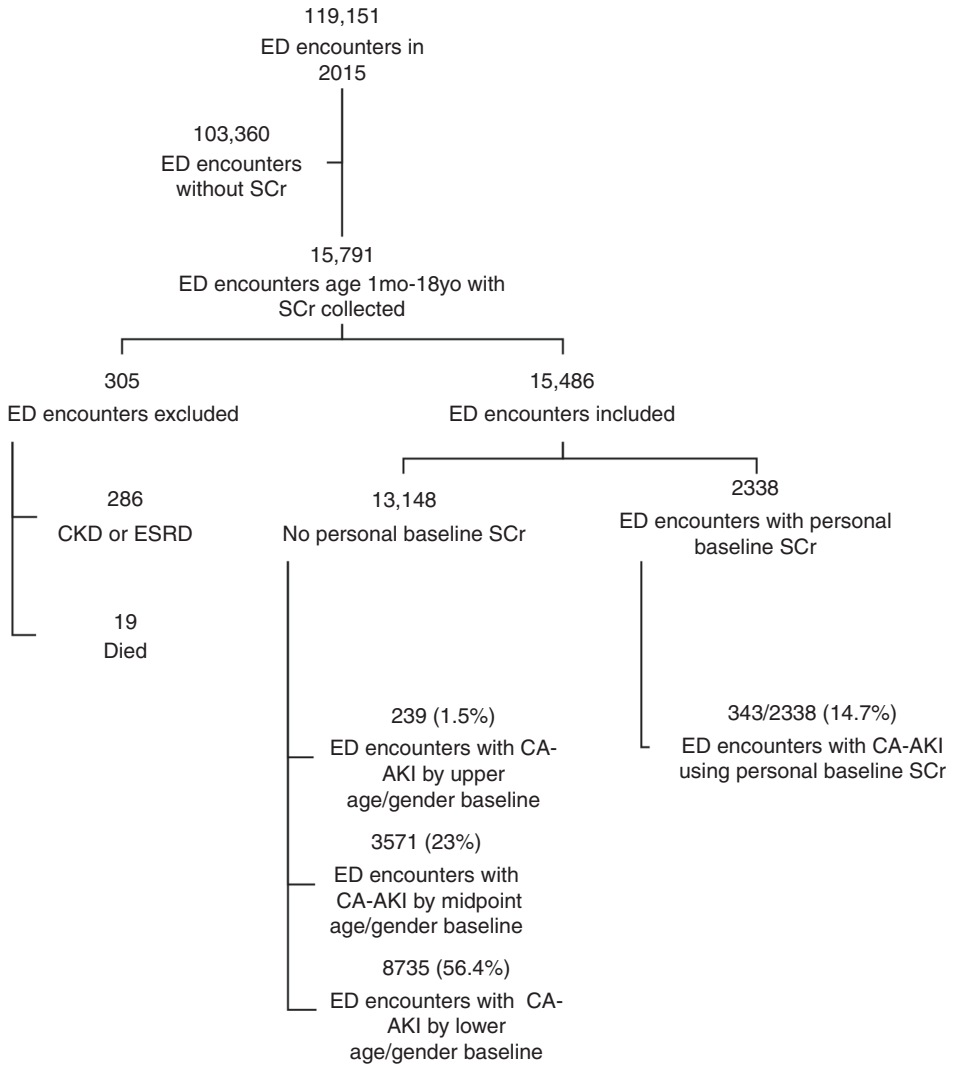

Fig. 1 Flow diagram of pediatric ED encounters and those with CA-AKI. CA-AKI, community-acquired AKI; CKD, chronic kidney disease; ESRD, end-stage renal disease; ED, emergency department; SCr, serum creatinine

compared to a patient's baseline creatinine to define CA-AKI (Table 1). The upper limit of age- and gender-based creatinine normal ranges resulted in a sensitivity of 18.0%, specificity of 99.1%, and positive likelihood ratio of 19.7 (11.8–32.9) (Table 1).

In the 2338 encounters with baseline creatinine levels, 343 (14.7%) had CA-AKI using their baseline creatinine, 79 (2.6%) had CA-AKI using the upper limit of age-/gender-based creatinine norms, 227 (9.7%) had CA-AKI using the midpoint, and 1195 (51.1%) had CA-AKI using the lower-limit creatinine norm.

In the 343 encounters with CA-AKI and baseline creatinine levels: 61 (0.4%) encounters also met CA-AKI by the upper-limit creatinine norm, 105 (0.7%) using the midpoint, and 263 (1.7%) using the lower-limit creatinine norm (Table 4). Using a patient's baseline detected more severe stages of CA-AKI compared to the upper-limit creatinine norms: stage 1 27/61 (44%) vs. 41/61 (67%); stage 2 20/62 (33%) vs. 16/61 (26%); and stage 3 14/61 (23%), vs. 4/61 (6.6 %) (Table 4). Using the midpoint creatine norm resulted in similar AKI staging and the lower-limit creatinine norm identified less severe CA-AKI than the baseline creatinine.

CA-AKI with no baseline creatinine

As most patients did not have baseline creatinine levels, CA-AKI was diagnosed in 178 cases using the upper limit of age- and gender-based creatinine norms only, 3466 cases using the midpoint, and 8499 using the lower-limit creatinine norm. Further reviewing the 178 CA-AKI encounters, 34/178 (19.1%) were diagnosed with AKI by ED clinicians, 148/178 (83%) were admitted, and 61/148 (41%) were diagnosed with AKI by the in-patient team.

DISCUSSION

Incidence of AKI varies with baseline creatinine used. Given that baseline creatinine levels are rarely available in children without medical comorbidities, AKI diagnoses in previously healthy children will be missed. We have demonstrated that age- and gender-based creatinine norms can easily be applied to all children presenting to the ED to detect CA-AKI, regardless of whether they have a previous creatinine level.

The difficulty in diagnosing CA-AKI in the pediatric ED lies in the unavailability of baseline creatinine. In our study, most patients did not have a baseline creatinine. One hundred and seventy eight cases of CA-AKI would have been missed if only traditional baseline creatinine levels were used to define AKI, instead of an age- and gender-based norm, as these patients did not have baseline creatinine levels. Other available methods of determining a surrogate baseline creatinine to detect CA-AKI may not be useful in the pediatric ED. For example, back-calculations using the Schwartz equation are not practical in the ED, where height may

Table 3. Characteristics of the study population encounters with community-acquired acute kidney injury using different baselines

	Upper-limit age/gender baseline SCr ($n = 239$)	Personal baseline SCr ($n = 343$)
Incidence of AKI	239/15,486 (1.5%)	343/15,486 (2.2%)
Characteristics	No. (%) or median (IQR)	
Male patients	135 (56.5%)	172 (50.1%)
Age (years)	11 (4–15)	6 (2–12)
Presented to referral center ED	196 (82.0%)	272 (79.3%)
Presented to community ED	43 (18.0%)	72 (21.0%)
Admitted	202 (84.5%)	252 (73.5%)
Admitted to critical care	76/202 (37.6%)	40/252 (15.9%)
Length of stay (days)	5 (2–10)	4 (2–10)
Nephrotoxic medication exposure	60 (25.1%)	174 (50.7%)
CRRT	4/202 (2.0%)	1/252 (0.4%)
Deaths (during this admission)	5/202 (2.5%)	1/252 (0.4%)
Comorbidities[a]	No. (%)	
Cardiac	33 (13.8%)	48 (14.0%)
Renal or urologic	32 (13.4%)	37 (10.8%)
Oncologic	13 (5.4%)	134 (39.0%)
Endocrinologic	20 (8.4%)	35 (10.2%)
Transplantation	30 (12.6%)	39 (11.3%)
No past medical history	85 (35.6%)	8 (2.3%)
AKI stage	No. (%)	
Stage 1	127 (53.1%)	271 (79.0%)
Stage 2	61 (25.5%)	55 (16.0%)
Stage 3	51 (21.3%)	17 (5.0%)
Correctly diagnosed with AKI	No. (%)	
Diagnosed by ED	46 (19.2%)	20 (5.8%)
Diagnosed by an in-patient team	123/199 (61.8%)	51/252 (20.2%)
Diagnosed by medical team	119/186 (64.0%)	51/249 (20.5%)
Diagnosed by surgical team	4/13 (30.8%)	0/3 (0)
Diagnosed by critical care team	51/76 (67.1%)	17/40 (42.5%)

not be routinely obtained. Height-independent formulas for estimated baseline creatinine have been validated, but would still require a clinician to take extra steps to back-calculate a creatinine and determine if their patient has CA-AKI.[13,14,20,21] Using an admission creatinine as the baseline creatinine would completely miss CA-AKI. Simply removing patients without baseline creatinine levels from ED studies would not be acceptable as an overwhelming majority do not have baseline creatinines.[13,15] Excluding children in whom UOP was unavailable would also underestimate the incidence of CA-AKI, as demonstrated by the AWARE investigators.[2] In addition, UOP is difficult to verify in the ED, and patients do not commonly stay in the ED for long periods of time to measure UOP.[2,12]

Even in the 343 patients with baseline creatinine levels, CA-AKI was infrequently recognized by the ED clinicians (5.8% of the encounters). Given the increased mortality associated with all stages of AKI[13] and amelioration of AKI by early recognition,[10,11] ED-based AKI recognition strategies are needed. This supports the need for more sensitive cut-offs to detect even stage 1 AKI, as the patient outcome will be impacted. Additionally, creatinine does not increase until GFR is significantly decreased, making early subtle elevations in creatinine potentially early indicators of evolving AKI. Zappitelli et al.[15] found that the lower limit of age- and gender-based SCr norms were more sensitive and more closely approximated true SCr.[15] Our study also revealed maximal sensitivity when the lower limit of age- and gender-based creatinine norms were applied as a surrogate baseline creatinine.

Balancing the potential improvement in patient outcomes with more sensitive detection of CA-AKI and the risk of clinician alert fatigue, we plan to use the upper limit of age- and gender-based creatinine norms, with high specificity and low false-positive rates, to detect CA-AKI in our pediatric ED. Although the upper-limit creatinine norm detected a lower incidence and less severe CA-AKI than when using a patient's baseline creatinine, the high positive likelihood ratio of the upper-limit creatinine norm indicates an almost 20-fold increase in the odds of actually having CA-AKI when the age-/gender-based norms indicate CA-AKI. Limitation of CA-AKI detection to only the subpopulation of patients who have a previous creatinine measured introduces selection bias by highlighting patients with comorbidities who are more likely to have lab tests done for a variety of reasons compared to healthy children. The use of the upper-limit creatinine norm would allow for early detection of CA-AKI in all children regardless of whether baseline creatinine is available, but would limit the number of false-positive alerts, in turn limiting alarm fatigue for clinicians. Starting with the upper-limit creatinine norms would allow for a gradual increase in the recognition of CA-AKI, hopefully changing culture in our ED to promote nephroprotective measures and early nephrology involvement, without overwhelming our system.

This study has limitations. Granular data were not available in patients with CA-AKI using the midpoint and lower-limit creatinine

Table 4. Staging of CA-AKI comparing age-/gender-based creatinine norm to creatinine baselines

	Upper-limit and baseline SCr (61)		Midpoint and baseline SCr (105)		Lower-limit and baseline SCr (263)	
	Upper limit	Baseline	Midpoint	Baseline	Lower limit	Baseline
Stage 1	41	27	54	58	82	198
Stage 2	16	20	36	33	92	50
Stage 3	4	14	15	14	89	15

Sixty encounters met CA-AKI by both upper-limit age-/gender-based creatinine norm and baseline creatinine; 105 encounters met CA-AKI by both midpoint age-/gender-based creatinine norm and baseline creatinine; 263 encounters met CA-AKI by both lower-limit age-/gender-based creatinine norm and baseline creatinine

norm limiting insights that might have been gleaned from this subpopulation. We used creatinine norms validated in our local community, and although diverse, these norms may not be applicable to all populations.

In conclusion, CA-AKI is difficult to define and detect in the pediatric ED where baseline creatinine is frequently unavailable. Validated age- and gender-based creatinine reference ranges can easily be used as a surrogate for a baseline creatinine to detect CA-AKI.

AUTHOR CONTRIBUTIONS

E.R.O. designed the study, collected, reviewed, and analyzed data, performed statistical analysis, crafted the manuscript, and critically revised the manuscript. A.T.C. designed the study, performed statistical analysis, and critically revised the manuscript. G.J.B. designed the study, collected, reviewed and analyzed data, and revised the manuscript. L.M. and H.E.S. collected, reviewed and analyzed data, and revised the manuscript. S.D. designed the study and revised the manuscript. L.L.L. designed the study and critically revised the manuscript. A.A.A. designed the study, reviewed and analyzed data, performed statistical analysis, and critically revised the manuscript.

ADDITIONAL INFORMATION

Competing interests: A.A.A. has consulted for Baxter and receives research funding from NIAID. The other authors declare no competing interests.

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