Acute Kidney Injury Associated with High Nephrotoxic Medication Exposure Leads to Chronic Kidney Disease after 6 Months

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Objective To assess the development of chronic kidney disease (CKD) after high nephrotoxic medication exposure-associated acute kidney injury (NTMx-AKI) in hospitalized children.

Study design We performed a retrospective cohort study of children exposed to an aminoglycoside for ≥3 days or ≥3 nephrotoxic medications simultaneously for the development of CKD at 6 months. Follow-up data >6 months after acute kidney injury (AKI) were retrieved from electronic health records. Outcomes in children with NTMx-AKI were compared with patients of same age and primary service distribution who were exposed to nephrotoxic medications but did not develop AKI (controls).

Results One hundred patients with NTMx-AKI were assessed (mean age of 9.3 ± 6.9 years). Commonly involved services were bone marrow transplantation/oncology (59%), liver transplantation (13%), and pulmonary (13%). Pre-AKI estimated glomerular filtration rate (eGFR) was 119 ± 14.5 mL/min/1.73 m^2 (range 90-150 mL/min/1.73 m^2). Mean discharge eGFR was 105.1 ± 27.1 mL/min/1.73 m^2. At 6 months after NTMx-AKI, eGFR (n = 77) was 113.8 ± 30.6 mL/min/1.73 m^2. Sixteen (20.7%) had eGFR of 60-90, 2 (2.6%) had eGFR <60, and 9 (11.6%) had eGFR >150 mL/min/1.73 m^2 (hyperfiltration). Twenty-four (68.5%) of 35 patients who were assessed for proteinuria had a urine protein-to-creatinine ratio >0.3 mg/mg, and 29 (37.6%) had hypertension. Twenty-six (33.7%) patients had CKD (proteinuria or eGFR <60 mL/min/1.73 m^2). An additional 28 (36.3%) were considered to be at risk for CKD with hypertension, eGFR between 60 and 90 mL/min/1.73 m^2, or eGFR >150 mL/min/1.73 m^2. CKD, hypertension, and proteinuria were more common in the AKI cohort than in controls.

Conclusions Six months after NTMx-AKI, 70% of patients had evidence of residual kidney damage (reduced eGFR, hyperfiltration, proteinuria, or hypertension). Few underwent a complete evaluation for CKD. With studies showing an association between AKI and CKD, we suggest systematic comprehensive follow-up in children after NTMx-AKI. *(J Pediatr 2014;165:522-7)*.

Acute kidney injury (AKI) is increasingly common in hospitalized children. Based on the definition used and the population studied, the incidence of AKI varies from 4.5% to 82%.[1-3] Recent years have seen a change in the epidemiology of AKI, with secondary causes of ischemia, nephrotoxic medications (NTMx), and sepsis gaining prominence over primary renal disease, with NTMx causing up to 16% of in-hospital pediatric AKI.[4] Between 20% and 33% of children receiving aminoglycosides ≥5 days develop AKI.[5]

AKI was traditionally assumed to be a transient insult without long-term sequelae. There is increasing evidence regarding a strong association between AKI and subsequent chronic kidney disease (CKD).[6] In a meta-analysis, adults with AKI had a significantly higher risk for developing CKD compared with those without AKI (pooled hazard ratio 8.8) and end-stage renal disease (ESRD) (pooled hazard ratio 3.1).[7] Although there are limited data regarding the long-term outcomes of AKI in children, 3 recent observational studies demonstrate 40%-60% of children who survive an AKI episode develop ≥1 sign or symptom of CKD.[8-10] A meta-analysis of >3000 patients with diarrhea-associated hemolytic uremic syndrome showed a pooled incidence of 12% for death or ESRD, and 25% of survivors had long-term renal sequelae (glomerular filtration rate [GFR] <80 mL/min/1.73 m^2, hypertension, or proteinuria).[11]

Most studies on the long-term sequelae of AKI have considered patients with AKI as a homogeneous group or focused on children with primary renal disease. There is limited information available on NTMx exposure-associated AKI (NTMx-AKI). As many as 50% of adults with NTMx-AKI may show permanent kidney damage.[12]

AKI	Acute kidney injury	pRIFLE	Pediatric Risk, Injury, Failure, Loss and End-Stage Kidney Disease
CKD	Chronic kidney disease		
eGFR	Estimated glomerular filtration rate	pRIFLEmax	Maximal pediatric Risk, Injury, Failure, Loss and End-Stage Kidney Disease
ESRD	End-stage renal disease		
GFR	Glomerular filtration rate		
NTMx	Nephrotoxic medication	RRT	Renal replacement therapy
NTMx-AKI	Nephrotoxic medication-associated acute kidney injury	SCr	Serum creatinine
		Up/c	Urine protein-to-creatinine

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To assess the long-term outcomes of children with NTMx-AKI, we aimed to: (1) determine the CKD follow-up and surveillance patterns in patients after an episode of NTMx-AKI; (2) determine the CKD incidence 6 months after NTMx-AKI; and (3) compare renal outcomes in those with NTMx-AKI and those with NTMx exposure without AKI.

Methods

We performed a retrospective cohort study of patients exposed to NTMx in a non–critical care setting at Cincinnati Children's Hospital Medical Center (Cincinnati, Ohio) from June 2011 to June 2012 (**Figure 1**; available at www.jpeds.com). Study patients were identified through a hospital-wide quality improvement project using our electronic health record (Epic, Verdona, Wisconsin) to identify prospectively all children with high-NTMx exposure outside critical care units. We excluded neonates and patients admitted to intensive care units, as AKI can be multifactorial in critically ill children. We also excluded patients with known CKD, kidney transplantation, or urinary tract infection. Patients were defined as having high-NTMx exposure if they received an intravenous aminoglycoside for ≥3 days or ≥3 NTMx simultaneously for 1 day, because previous studies have shown an increased risk of AKI in patients with such NTMx exposure.[13] The list of NTMx was derived from the same study (**Table I**; available at www.jpeds.com).[13] All subjects had a daily serum creatinine (SCr) level checked as part of institutional standard of care for the quality improvement initiative. The results of this initiative have been recently published. There was a 99% adherence to daily SCr monitoring and a 26% AKI rate in children exposed to NTMx in these manners.[14]

In an a priori fashion, we assessed 6-month outcomes in the first 100 patients who developed NTMx-AKI as part of this initiative. Study subjects were included if they developed AKI within 48 hours of exposure as defined by 3 strata (R, I, and F) of the SCr-based pediatric modified RIFLE criteria (pRIFLE: Risk, Injury, Failure, Loss and End-Stage Kidney Disease) (**Table II**; available at www.jpeds.com).[3] After identification of the subjects, the control group was identified from the same quality improvement project. The controls consisted of patients with a similar age and primary service distribution who were exposed to similar medications but did not develop AKI.

We did not use the pRIFLE urine output criteria to define AKI, because NTMx-AKI is typically nonoliguric in nature. We classified all patients based on their maximal pRIFLE (pRIFLEmax) strata during the episode. Individuals who received renal replacement therapy (RRT) met criteria for pRIFLE stratum "F" regardless of creatinine level at the time of RRT. Baseline SCr level was defined as the lowest admission or preadmission value up to 6 months before admission. This project was approved by the Cincinnati Children's Hospital Medical Center Institutional Review Board with a waiver of informed consent.

After identifying the patients with and without NTMx-AKI, we reviewed the electronic health record to determine if each patient had been seen for follow-up in an outpatient clinic at our hospital at least 6 months after a high-NTMx exposure event. We abstracted information from clinic notes and laboratory data regarding SCr, cystatin C GFR,[15] screening for proteinuria, and presence of hypertension that was obtained as part of the patient's care; no additional testing, clinic visit, or assessment was performed as part of this study. Cystatin C was measured in our Division of Nephrology Clinical Laboratory using N Latex Cystatin C (Siemens Healthcare Diagnostics Inc, Newark, Delaware) with a BN II Nephelometer (Siemens Healthcare Diagnostics Inc). Creatinine was measured in the hospital laboratory by using the enzymatic method with standardized isotope dilution mass spectrometry. Hypertension was diagnosed based on the documentation in the clinic note and on whether the patient was being treated with an antihypertensive. CKD was defined as having markers of kidney damage (including persistent proteinuria) or abnormal kidney function (estimated GFR [eGFR] <60 mL/min/1.73 m^2).[16] Those with a decreased eGFR of 60-90 mL/min/1.73 m^2, persistent hypertension, and/or hyperfiltration (eGFR >150 mL/min/1.73 m^2) were defined as being at risk of CKD as previously reported by Mammen et al.[8] GFR was estimated using the modified Schwartz formula (eGFR = 0.413*[height in cm/SCr]).[17] Proteinuria was defined as urine protein-to-creatinine (Up/c) ratio >0.3 mg/mg.

Statistical Analyses

All statistical analyses were performed using SPSS software (version 17.0; IBM SPSS Inc, Chicago, Illinois). Continuous variables were expressed as mean ± SD. Noncontinuous variables were expressed as proportions (percentage). To compare characteristics between those with and without AKI, we used t tests or χ^2 tests as appropriate. $P < .05$ was considered statistically significant.

Results

Data from the first 100 patients who developed NTMx-AKI were analyzed. Baseline characteristics for all patients with AKI including demographics, primary service, pRIFLEmax, and baseline eGFR are listed in **Table III**. Ninety-nine patients with NTMx-AKI had a SCr available 6 months before the AKI episode. The mean eGFR before the AKI episode was 119.2 ± 14.5 mL/min/1.73 m^2; all patients had eGFR between 90 and 150 mL/min/1.73 m^2. Additionally, 15 patients had an evaluation of proteinuria before AKI, none of whom had a Up/c ratio of >0.3 mg/mg.

Mean patient age at the time of AKI was 9.3 ± 6.9 years. The most frequently involved primary service was bone marrow transplantation and oncology (59%); other services were gastroenterology and liver transplantation (16%), pulmonary (13%), and cardiology and surgery (5% each). The pRIFLEmax was "R" in 23 (23%) patients, "I" in 63 (63%), and "F" in 14 (14%). Of the 14 patients with pRIFLE "F," 4