Urine Neutrophil Gelatinase-Associated Lipocalin and Kidney Injury Molecule-1 to Detect Pediatric Cisplatin-Associated Acute Kidney Injury

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Key Points
• Urine neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1) were high in patients with AKI. Clinical usefulness and associations with late kidney outcomes should be evaluated.
• Urine NGAL and KIM-1 were modest at discriminating for cisplatin-associated AKI in children.
• There is a need to identify other tubular injury biomarkers in children treated with cisplatin.

Abstract
Background Few studies have described associations between the AKI biomarkers urinary neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1) with AKI in cisplatin-treated children. We aimed to describe excretion patterns of urine NGAL and KIM-1 and associations with AKI in children receiving cisplatin.

Methods Participants (n=159) were enrolled between 2013 and 2017 in a prospective cohort study conducted in 12 Canadian pediatric hospitals. Participants were evaluated at early cisplatin infusions (at first or second cisplatin cycle) and late cisplatin infusions (last or second-to-last cycle). Urine NGAL and KIM-1 were measured (1) pre-cisplatin infusion, (2) post-infusion (morning after), and (3) at hospital discharge at early and late cisplatin infusions. Primary outcome: AKI defined by serum creatinine rise within 10 days post-cisplatin, on the basis of Kidney Disease Improving Global Outcomes guidelines criteria (stage 1 or higher).

Results Of 159 children, 156 (median [interquartile range (IQR)] age: 5.8 [2.4–12.0] years; 78 [50%] female) had biomarker data available at early cisplatin infusions and 127 had data at late infusions. Forty six of the 156 (29%) and 22 of the 127 (17%) children developed AKI within 10 days of cisplatin administration after early and late infusions, respectively. Urine NGAL and KIM-1 concentrations were significantly higher in patients with versus without AKI (near hospital discharge of late cisplatin infusion, median [IQR] NGAL levels were 76.1 [10.0–232.7] versus 14.9 [5.4–29.7] ng/mg creatinine; KIM-1 levels were 4415 [2083–9077] versus 1049 [358–3326] pg/mg creatinine; P<0.01). These markers modestly discriminated for AKI (area under receiver operating characteristic curve [AUC-ROC] range: NGAL, 0.56–0.72; KIM-1, 0.48–0.75). Biomarker concentrations were higher and better discriminated for AKI at late cisplatin infusions (AUC-ROC range, 0.54–0.75) versus early infusions (AUC-ROC range, 0.48–0.65).

Conclusions Urine NGAL and KIM-1 were modest at discriminating for cisplatin-associated AKI. Further research is needed to determine clinical utility and applicability of these markers and associations with late kidney outcomes.

Introduction
AKI is associated with increased morbidity and mortality in children (1). AKI occurs in 0%–77% of children treated with cisplatin; 1%–94% experience electrolyte abnormalities (2–7). Cisplatin causes tubular cell death by various mechanisms, including oxidative stress, inflammation, and mitochondrial and microvascular dysfunction (8,9). One reason there is no treatment for AKI in humans is that the current diagnostic test for AKI, serum creatinine (Scr), rises days after injury, limiting early identification and interventions to mitigate injury (10,11).

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Many urinary kidney damage biomarkers have been studied (12). In animals, neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1) are upregulated and released by kidney tubules with ischemic AKI or cisplatin-associated AKI (13–16). NGAL is a 25-kD protein involved in injury and repair of tubular cells and iron transport, and is expressed in proximal and distal tubules (13,16,17). KIM-1 is a proximal tubule transmembrane protein involved in cell regeneration and removal of apoptotic/necrotic bodies (14,15,18). Both biomarkers have been validated for early AKI diagnosis in adults and children in various non-cancer populations (15,19–22). However, little data exist on NGAL and KIM-1 in children receiving nephrotoxic chemotherapy (7,23,24). Cisplatin is a useful model to evaluate AKI biomarkers because the timing and mechanism of injury and dose of toxin are known. Given the kidney segments where NGAL and KIM-1 indicate injury, they may aid in early diagnosis of cisplatin-associated AKI (8,15,16).

We aimed to describe urine NGAL and KIM-1 excretion in cisplatin-treated children and determine whether these biomarkers are diagnostic and predictive of AKI (defined using SCr and electrolyte abnormalities) at two separate cisplatin infusions.

Materials and Methods

Study Cohort

From May 2013 to March 2017, we prospectively enrolled children with cancer from 12 Canadian pediatric hospitals in the Applying Biomarkers to Minimize Long-Term Effects of Childhood/Adolescent Cancer Treatment (ABLE) Nephrotoxicity Study (2,25). Methods and recruitment details were published (2,25). Inclusion criteria included age <18 years at cancer diagnosis and receiving one or more cisplatin infusion (no minimum dose) (2,25). Exclusion criteria included kidney transplant and GFR <30 ml/min per 1.73 m² (2,25). This analysis excluded participants with no AKI biomarker measurement available. Informed consent (and/or assent) was obtained from patients or guardians. Sites obtained research ethics board approval. The study adhered with the Declaration of Helsinki.

Study Procedure

Specimen Collection

Recruitment occurred shortly after the decision to initiate cisplatin was made (2,25). Participants were evaluated at two cisplatin infusion time points: (1) at the first or second cisplatin cycle of cancer treatment (early visit), and (2) at the last or second last cycle (late visit) (2,25). With each visit, urine (30 ml) and blood (3 ml) were collected at three time points: (1) pre-infusion, i.e., on the same day, but before cisplatin infusion (day 1); (2) post-infusion, i.e., on the morning after infusion (day 2); and (3) discharge, i.e., just before hospital discharge (at most, day 5 post-infusion).

Data Collection

Baseline (pre-cisplatin) data were collected retrospectively (demographics, cancer details, kidney history, medications, routine GFR tests). From 3 days before to 10 days after study cisplatin infusions, data were collected prospectively, including daily SCr and electrolyte values and medications. Data were collected throughout cisplatin treatment (between first and last cisplatin infusion: monthly SCr and electrolytes, dialysis need, intensive care unit admissions, infections).

Laboratory Measurements

Sites centrifuged blood specimens (1000×g, 10 minutes, 21°C). Serum and urine were aliquoted and stored at −80°C until shipment. Specimens were shipped biannually to Montreal (central site). Urine specimens were thawed, centrifuged (1000×g, 10 minutes, 21°C), aliquoted, and frozen (−80°C) for batched analysis. Samples were stored for <2 years before analysis. Urine and blood were measured for creatinine (SCr: isotope dilution mass spectrometry–traceable assay), potassium, magnesium, and phosphate at the McGill University Health Centre (MUHC; Montreal, Canada).

Biomarkers were measured at the Cincinnati Children’s Hospital Medical Center Biomarker Laboratory (Cincinnati, OH) using commercial ELISA kits (NGAL ELISA Kit 036; Bioporto, Grusbakken, Denmark; KIM-1, Duoset DY1750; R&D Systems Inc., Minneapolis, MN) in three batches (between December 2014 and February 2018) (22,26). Inter- and intra-assay coefficients of variation were <11%. Biomarkers were measured once at each study time point and expressed as a ratio to urine creatinine. Biomarkers were measured from frozen aliquots that did not undergo any additional freeze-thaw cycles. Personnel measuring biomarkers were blinded to data. When biomarker values were below the reportable range, lower limits were used.

AKI Definition

The primary outcome (SCr-AKI) was defined on the basis of the Kidney Disease Improving Global Outcomes (KDIGO) guidelines SCr criteria (KDIGO stage 1 or higher) (27). Stage 1 was a ≥50% SCr rise from baseline or a ≥0.3 mg/dl rise by 10 days post-cisplatin; stage 2 was SCr doubling; stage 3 was SCr tripling or ≥4.0 mg/dl rise, requiring dialysis, or GFR <35 ml/min per 1.73 m² (27). Similar to a previous study (28), a 10-day period was used to ascertain AKI due to the known toxicity window and to allow variable routine follow-up times of laboratory measurements post-cisplatin. KDIGO urine output criteria were not used because cisplatin-associated AKI is typically nonoliguric (27). Baseline SCr at the early visit was the lowest 3 months pre-cisplatin; for participants with previous cisplatin exposure, SCr values 3 days before the early visit cisplatin infusion were also used. For the late visit, baseline SCr was the lowest 3-day pre-cisplatin infusion level. Severe SCr-AKI was defined as KDIGO stage 2 or higher (27).

A secondary AKI definition, termed electrolyte-AKI (eAKI), was defined using electrolyte criteria adapted from the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (29). The novel term “eAKI” was chosen to reflect electrolyte abnormalities occurring due to kidney tubular injury. eAKI was any grade 1 (less than the lower limit of normal for age) or higher electrolyte abnormality (hypophosphatemia, hypokalemia, or hypomagnesemia) using nadir electrolyte values within 10 days post-infusion (29).
A composite of SCR-AKI and eAKI (SCR+eAKI) definitions was also evaluated. Routine care and study-specific laboratory measures were used to assess AKI.

Statistical Analysis
We assessed variable associations using distribution-appropriate tests (two-sample t test, Mann–Whitney test, Kruskal–Wallis test, Spearman correlation, chi-squared, or Fisher exact test). AKI rates were calculated. The Skillings–Mack test and Wilcoxon signed-rank test were used to compare biomarker concentrations across time points in participants with/without AKI. Biomarker concentrations were divided into quartiles to evaluate associations with log odds of AKI using chi-squared test for homogeneity and linear trend. Area under the receiver operating characteristic curve (AUC-ROC) with 95% CIs, sensitivity and specificity for AKI discrimination (ability of biomarker to detect presence of SCR-AKI), and prediction were calculated. For AKI prediction analyses, only participants without AKI or participants who had not yet developed AKI on the day of measurement were included. Logistic regression–derived AUC-ROCs were used to evaluate biomarker combinations for AKI diagnosis. Only participants with nonmissing biomarker data were included in analyses. We performed four sensitivity analyses: (1) using raw biomarker concentrations, (2) only including participants with biomarkers available at all visit time points, (3) including only participants who were cisplatin naive at the early visit, and (4) only including participants who performed the late visit at their last cisplatin cycle. P<0.05 (two tailed) was considered statistically significant. Analyses were performed using Stata version 15.1 (Stata; College Station, TX).

Results
Study Cohort and AKI Development
Of the 159 patients enrolled in the ABLE Nephrotoxicity study (2), 156 (median [interquartile range (IQR)] age of 6 [2–12] years; 78 [50%] girls) and 127 (median [IQR] age of 6 [2–12] years; 62 [49%] girls) had early and late visit biomarker data available, respectively (Figure 1). The early visit occurred at the first cisplatin cycle for 89 (57%) participants and at the second cycle for 67 (43%) participants. The late visit occurred at a median (IQR) of the third (second to fourth) cisplatin cycle. At the early and late visit, 46 of the 156 (29%) and 22 of the 127 (17%) children developed SCR-AKI, respectively. At the early visit, SCR-AKI onset occurred at a median (IQR) of 4 (2–6) days; at the late visit, it occurred at 3 (2–5) days. Eleven of the 156 (7%) and seven of the 127 (6%) children developed severe SCR-AKI at the early and late visit, respectively. Table 1 shows patient characteristics at each visit, stratified by SCR-AKI status. At the early visit, 30 of the 156 (19%) children developed SCR+eAKI; at the late visit, 15 of the 127 (12%) children developed SCR+eAKI.

Associations between AKI Biomarkers and Participant Characteristics
AKI biomarker concentrations were higher in participants aged <3 years (Supplemental Table 1). Urine NGAL was two- to three-fold higher in females versus males, whereas KIM-1 was not associated with sex (Supplemental Table 1). KIM-1 was positively correlated with cisplatin infusion dose (in milligrams per meter squared; Spearman ρ range, 0.136–0.480). NGAL was not correlated with cisplatin dose (Supplemental Table 1).

Biomarker Excretion at Early and Late Visits
Samples collected near hospital discharge at the early and late visit were collected a median (IQR) of 3 (2–4) days and 2 (2–4) days post-cisplatin infusion, respectively. Figure 2 shows NGAL was significantly higher in participants with versus without SCR-AKI near time of hospital discharge during the early visit and at all late visit time points. KIM-1 was significantly higher in participants with versus without SCR-AKI near time of hospital discharge from early and late visits and post-infusion of the late visit (Figure 2). In participants with and without SCR-AKI, KIM-1 rose significantly across time points from pre-infusion to hospital discharge at early and late visits, whereas NGAL only rose significantly in participants with SCR-AKI at the early visit (doubling from pre-infusion to discharge; Figure 2). Supplemental Table 2 details statistical significance in biomarker concentration differences between individual time points. Overall, biomarkers were higher at the late visit relative to the early visit (Figure 2). When biomarkers were classified into quartiles, participants in the highest post-infusion biomarker quartile had the highest SCR-AKI rate (Supplemental Table 3). Biomarker excretion by SCR-AKI severity stage is displayed in Figure 3; biomarker concentrations were highest in participants with stage 2 or 3 SCR-AKI.

Biomarker Performance for AKI Discrimination and Prediction
Overall, AUC-ROCs to discriminate for presence of SCR-AKI were higher at the late visit (AUC-ROC range of 0.54–0.75, depending on time point) compared with the early visit (AUC-ROC range of 0.48–0.66; Table 2). The highest AUC-ROC for SCR-AKI diagnosis was KIM-1 measured near hospital discharge of the late visit (AUC-ROC, 0.75; 95% CI, 0.63 to 0.86; Table 2).

When evaluating biomarkers to predict SCR-AKI development before SCR rise, neither biomarker was predictive at the early visit. NGAL and KIM-1 measured near hospital discharge of the late visit were predictive of SCR-AKI (AUC-ROC for NGAL, 0.94 [95% CI, 0.87 to 1.00]; for KIM-1, 0.80 [95% CI, 0.59 to 1.00]), but sample size was lower, with few events (Supplemental Table 4).

Biomarker Associations with SCR+eAKI and Severe SCR-AKI
NGAL measured at post-infusion and hospital discharge at the early visit, and NGAL and KIM-1 measured near hospital discharge at the late visit, were two- to four-fold higher in participants with versus without SCR+eAKI (Table 3). NGAL and KIM-1 concentrations at all late visit time points were three- to 11-fold higher in participants with versus without severe SCR-AKI (Table 3). AUC-ROCs for SCR+eAKI discrimination ranged from 0.53 to 0.73 (Supplemental Table 5). For severe SCR-AKI, AUC-ROCs...
ranged between 0.50 and 0.64 at the early visit, and between 0.73 and 0.87 at the late visit, being highest near hospital discharge (Supplemental Table 6).

**Biomarker Combinations**

When biomarkers from two time points were considered, pre-infusion NGAL combined with discharge KIM-1 at the late visit achieved the highest AUC-ROC for SCR-AKI discrimination (0.75, 95% CI, 0.63 to 0.87; Table 4). For SCR-AKI prediction, pre-infusion KIM-1 combined with discharge NGAL at the late visit yielded the highest AUC-ROC (0.96; 95% CI, 0.90 to 1.00; Table 4). AUC-ROCs for discrimination of SCR+eAKI at early and late visits ranged between 0.57 and 0.74 (Table 4). For discrimination of
severe SCR-AKI, AUC-ROCs for biomarker combinations at the late visit ranged between 0.73 and 0.87 (Table 4).

**Sensitivity Analyses**

When biomarkers were not normalized to urine creatinine, excretion and AUC-ROCs were similar in direction and magnitude (Supplemental Table 7). We found similar results in direction and magnitude when analyzing only participants with biomarkers measured at *all* early/late visit time points (Supplemental Table 8). Results did not differ substantially when evaluating only participants who were cisplatin naive at the early visit (Supplemental Table 9), or those who did the late visit at their last cisplatin cycle (Supplemental Table 10).

**Discussion**

This multicenter, prospective study evaluated NGAL and KIM-1 for early AKI diagnosis in children receiving cisplatin. Biomarker concentrations were higher in patients with AKI compared with those without. Although NGAL and KIM-1 modestly discriminated for SCR-AKI, biomarkers

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**Table 1. Characteristics of study participants at early and late cisplatin visits by SCR-AKI status**

| Characteristic                                      | Early Visit          | Late Visit           |
|-----------------------------------------------------|----------------------|----------------------|
|                                                     | SCR-AKI (n=46)       | No SCR-AKI (n=110)   |
|                                                     | SCR-AKI (n=22)       | No SCR-AKI (n=105)   |
| Male                                                | 22 (48)              | 56 (51)              |
| White race                                          | 38 (83)              | 78 (71)              |
| Cancer diagnosis<sup>a</sup>                        |                      |                      |
| CNS tumor<sup>b</sup>                               | 18 (39)              | 38 (35)              |
| Neuroblastoma                                       | 18 (39)              | 24 (22)<sup>b</sup>  |
| Osteosarcoma                                        | 2 (4)                | 31 (28)<sup>c</sup>  |
| Germ cell tumor                                     | 3 (7)                | 11 (10)              |
| Hepatoblastoma                                      | 4 (9)                | 5 (5)                |
| Other<sup>e</sup>                                   | 1 (2)                | 1 (0.9)              |
| Cancer involves one or both kidneys                 |                      |                      |
| Kidney medical history<sup>d</sup>                  | 8 (17)               | 5 (5)<sup>d</sup>    |
| Nephrotoxic drug before first cisplatin<sup>f</sup> | 11 (24)              | 15 (14)              |
| Vancomycin in 2 weeks pre-cisplatin<sup>g</sup>     | 5 (11)               | 3 (3)<sup>b</sup>    |
| Immediate before/day of the early/late visit infusion|                      |                      |
| Age at early/late visit, yr, median (IQR)           | 3 (2–7)              | 8 (3–13)<sup>d</sup> |
| Age at early/late visit <3 years, n (%)             | 25 (54)              | 25 (23)<sup>f</sup>  |
| Cisplatin naive at the early visit, n (%)           | 29 (63)              | 60 (55)              |
| Pre-visit eGFR, ml/min per 1.73 m², median (IQR)<sup>h</sup> | 165 (138–206)       | 133 (117–155)<sup>c</sup> |
| The late visit was the last cisplatin cycle of cancer treatment, n (%) | N/A                  | N/A                  |
| Cumulative cisplatin dose before early/late visit, mg/m², median (IQR)<sup>i</sup> | 82 (77–127)<sup>i</sup> | 107 (77–119)<sup>i</sup> |
| Early/late visit cisplatin infusion dose, mg/m², median (IQR) | 59 (50–77)           | 59 (50–74)           |
| Infection before early/late visit, n (%)           | 6 (13)               | 14 (133)             |
| PICU admission before early/late visit, n (%)      | 1 (2)                | 1 (0.9)              |
| SCR-AKI episode before early/late visit, n (%)     | 11 (24)              | 8 (7)<sup>d</sup>    |
| Days between early visit and late visit, median (IQR)<sup>j</sup> | N/A                  | N/A                  |
| Concurrent nephrotoxins at early/late visit, n (%)<sup>k</sup> | 3 (7)                | 20 (18)              |

<sup>a</sup> CNS tumor includes optic glioma.

<sup>b</sup> Excretion and AUC-ROCs were similar in direction and magnitude when biomarkers were not normalized to urine creatinine.

<sup>c</sup> Numbers in parentheses denote the percentage of the total population.

<sup>d</sup> Cancer diagnosis includes CNS tumor, neuroblastoma, osteosarcoma, germ cell tumor, hepatoblastoma, and other.

<sup>e</sup> Cancer diagnosis includes CNS tumor, neuroblastoma, osteosarcoma, germ cell tumor, hepatoblastoma, and other.

<sup>f</sup> Numbers in parentheses denote the percentage of the total population.

<sup>g</sup> Numbers in parentheses denote the percentage of the total population.

<sup>h</sup> Pre-visit eGFR was measured within 48 hours before the early/late visit infusion.

<sup>i</sup> Cumulative cisplatin dose includes cisplatin given before and on the day of the early/late visit infusion.

<sup>j</sup> Numbers in parentheses denote the percentage of the total population.

<sup>k</sup> Concurrent nephrotoxins include vancomycin, antibiotics, or other nephrotoxic drugs.
exhibited good performance for severe SCr-AKI discrimination at the late visit. Biomarkers were higher and performed better at the late visit relative to the early visit.

Most AKI biomarker studies in patients receiving cisplatin have been performed in adults, at single institutions, with small sample sizes (30–33). Few studies have evaluated AKI biomarkers in children treated with cisplatin (7,23,24). Some studies report high diagnostic ability of urinary NGAL or KIM-1 for detecting cisplatin-associated SCr-AKI (AUC-ROCs between 0.73 and 0.94) (23,24,33–37), whereas the same studies or others report poor discrimination (AUC-ROC range of 0.37–0.66) (7,33,37,38). In a small pilot study (n = 21), we previously reported that urine NGAL measured within 24 hours post-chemotherapy was not diagnostic of SCr-AKI in children receiving cisplatin or carboplatin (7). Another study involving 30 children showed urine NGAL measured 1 week post-chemotherapy initiation predicted SCr-AKI at chemotherapy end (AUC-ROC, 0.85; 95% CI, 0.74 to 0.96) (24). In a study of 64 children receiving methotrexate or cisplatin, urine KIM-1 measured 24 hours post-chemotherapy had good SCr-AKI discrimination (AUC-ROC, 0.82; 95% CI, 0.66 to 0.95) (23). We found NGAL and KIM-1 were modest for SCr-AKI discrimination. Reasons for this are likely multifactorial; our results may differ from other studies due to patient differences (e.g., age, cancer type, timing of specimen collection), and we exclusively evaluated cisplatin-based chemotherapy. Biomarker combinations that included the hospital discharge time point of the late visit had excellent SCr-AKI predictive characteristics (AUC-ROC range of 0.82–0.95) (23,24,33–37). In a study of 64 children receiving methotrexate or cisplatin, urine KIM-1 measured 24 hours post-chemotherapy had good SCr-AKI discrimination (AUC-ROC, 0.82; 95% CI, 0.66 to 0.95) (23). We found NGAL and KIM-1 were modest for SCr-AKI and SCr+eAKI discrimination. Reasons for this are likely multifactorial; our results may differ from other studies due to patient differences (e.g., age, cancer type, timing of specimen collection), and we exclusively evaluated cisplatin-based chemotherapy. Biomarker combinations that included the hospital discharge time point of the late visit had excellent SCr-AKI predictive characteristics (AUC-ROCs ≥0.88). Biomarker combinations at the late visit had good discriminatory ability for severe SCr-AKI (AUC-ROC range of

| Characteristic | Early Visit | Late Visit |
|---------------|-------------|------------|
| Cancer treatment details | SCr-AKI (n=46) | No SCr-AKI (n=110) | SCr-AKI (n=22) | No SCr-AKI (n=105) |
| Early/late visit total cisplatin cycle dose, mg/m², median (IQR) | 100 (77–193) | 107 (77–122) | 82 (76–155) | 100 (75–120) |
| Any flank (left or right), whole abdomen, pelvic, or total body radiation planned, n (%) | 10 (22) | 11 (10)b | 3 (14) | 10 (10) |
| Postcisplatin | | | | |
| Early/late visit length of hospital stay, d, median (IQR) | 6 (5–21) | 5 (4–6)c | 5 (4–11) | 5 (3–6) |
| Nephrotoxins in 10 days after early/late visit, n (%)d | 5 (11) | 7 (6) | 1 (5) | 9 (9) |

Percentages are based on the total for each column. SCr-AKI, serum creatinine–defined AKI; CNS, central nervous system; N/A, not applicable; IQR, interquartile range; PICU, pediatric intensive care unit; CKiD, Chronic Kidney Disease in Children; SCr, serum creatinine.

ACNS tumors at the early visit: astrocytoma (n=3), choroid plexus tumor (n=2), ependymoma (n=1), medulloblastoma (n=38), primitive neuroectodermal tumor (n=7), atypical teratoid/rhabdoid tumor (n=3). CNS tumors at the late visit: astrocytoma (n=2), choroid plexus tumor (n=2), ependymoma (n=1), medulloblastoma (n=32), primitive neuroectodermal tumor (n=7), atypical teratoid/rhabdoid tumor (n=3).

*bP<0.05, significant difference between AKI and non-AKI groups for that time point.

**P<0.01, significant difference between AKI and non-AKI groups for that time point.

*Other cancers at the early visit: lymphoma and nasopharyngeal carcinoma. Other cancer at the late visit: nasopharyngeal carcinoma.

Evidence of hypertension, treatment with antihypertensives, family history of kidney disease, CKD, dialysis, congenital renal anomaly, kidney stones, vesicoureteral reflux, urinary tract infection, serum electrolyte abnormality requiring treatment, or AKI by chart review.

Receipt of acyclovir, amphotericin, aminoglycosides (gentamicin, tobramycin, amikacin), vancomycin, angiotensin-converting enzyme inhibitor, ganciclovir/valganciclovir, ifosfamide, or methotrexate in 2 weeks precisplatin.

If age <18 years at visit, GFR was estimated using updated CKiD equation. If age >18 years, the average of the updated CKiD equation and the Chronic Kidney Disease Epidemiology Collaboration SCr–based equation was used.

Patients with SCr-AKI with data, n = 17; Patients without SCr-AKI with data, n = 50. These are the numbers of patients who were not cisplatin naive at the early visit.

To ascertain SCr-AKI before early/late visit, all routine and study-measured SCr values that occurred before cisplatin infusion of early/late visit were used. Peak SCr was the highest SCr occurring before early/late visit infusion but occurring after the baseline SCr. For SCr-AKI before the early visit, baseline SCr was the lowest routine value in 3 months precisplatin initiation. For AKI between the early and late visit, baseline SCr was the lowest routine or study-measured value in 3 months precisplatin initiation.

Acyclovir, amphotericin, aminoglycosides (gentamicin, tobramycin, amikacin), ifosfamide, or chemotherapy protocol indicating a nephrotoxin (aldesleukin, busulfan, carboplatin, dinutuximab, gemcitabine, lomustine, melphalan, methotrexate, radiotherapy, rituximab, stem cell transplant, or temsirolimus) was given within 24 hours of cisplatin infusion.

Acyclovir, amphotericin, aminoglycosides (gentamicin, tobramycin, amikacin), ifosfamide.
Bidimensional performance might have been better e.g., other nephrotoxic medications), leading to further kidney injury. At the late visit, patients may have received multiple prior cisplatin doses, potentially causing unresolved or cumulative tubular damage, enhancing susceptibility to further injury (39,40). SCr-AKI may underestimate the severity of cisplatin kidney injury. Perhaps, in some patients, functional injury (SCR-AKI) at the early visit increased susceptibility for tubular injury (rise in biomarkers) at the late visit. The proportion of patients with SCR-AKI at the late visit was lower compared with the early visit; however, there may be subclinical kidney injury (without a rise in SCR) at the late visit. This suggests SCR as a biomarker of AKI may become less useful as cancer treatment progresses, possibly due to loss of muscle mass as cancer treatment progresses or due to a chronic poor nutritional state leading to lower muscle mass and impaired kidney repair processes (41). Future research should consider evaluating other AKI biomarkers (e.g., cystatin C) to assess AKI more accurately and evaluate associations between biomarkers and clinical outcomes (e.g., mortality, long-term kidney outcomes).

The urine NGAL concentrations we identified as being optimal to detect SCR-AKI are below recognized pediatric thresholds (100–135 ng/ml) (42). The KIM-1 thresholds we deemed optimal for SCR-AKI detection are similar to published pediatric thresholds (500–2000 pg/mg creatinine)
However, most thresholds were developed in intensive care unit or cardiac surgery populations, which likely have higher illness severity and more infections. Our study indicates a lower threshold for NGAL and KIM-1 is likely needed for children treated with cisplatin. Further research is needed to identify optimal biomarker thresholds.

It remains unclear whether biomarker concentrations recover between cisplatin cycles. In children with SCr-AKI, pre-infusion NGAL concentrations at the late visit did not return to early visit pre-infusion levels, suggesting sustained subclinical injury with subsequent cisplatin administration. Conversely, pre-infusion KIM-1 levels at the late visit were similar to early visit pre-infusion levels. This is contrary to a previous adult study, where KIM-1 levels did not return to pre-cisplatin baseline levels after subsequent cisplatin cycles (30). Cisplatin is a heavy metal, detectable up to 20 years after administration (46). Kidney repair and recovery may more likely be transitory at earlier cisplatin cycles and more sustained at later cycles. Research evaluating biomarker associations with AKI in different populations and settings is needed.

Biomarker concentrations were highest near hospital discharge, perhaps indicating NGAL and KIM-1 are later markers of cisplatin kidney injury or cumulative tubular damage. After pediatric cardiac surgery, NGAL rises earlier (within 0–12 hours) than KIM-1 (12–48 hours) (20,21,47). However, adult data suggest biomarker excretion time courses differ in cisplatin nephrotoxicity (31,48,49). Excretion patterns may be distinct in different clinical settings, highlighting the importance of validation across patient populations. Our findings suggest a potential utility of...
Table 2. SCr-AKI diagnostic characteristics of AKI biomarkers at early and late cisplatin visits

| Time Point | Area Under Receiver Operating Characteristic Curve (95% Confidence Interval) | Optimal Biomarker Concentration Cutoffa | Sensitivity (%) | Specificity (%) | Biomarker Associated Concentration for >85% Sensitivity (%) | Sensitivity (%) | Specificity (%) |
|------------|---------------------------------------------------------------------------|----------------------------------------|----------------|----------------|-------------------------------------------------|----------------|---------------|
|            | Time Point                                                                 |                                                        |                |                | Time Point                                       |                |               |
|            | Pre-infusion (n=150)                                                      | 0.56 (0.46 to 0.67)                      | 36.7           | 39             | 0.58 (0.46 to 0.67)                              | 31             | 65            |
|            | Post-infusion (n=148)                                                     | 0.60 (0.49 to 0.70)                      | 8.7            | 74             | 0.65 (0.49 to 0.70)                              | 19             | 25            |
|            | Discharge (n=146)                                                        | 0.65 (0.54 to 0.75)                      | 15.5           | 71             | 0.71 (0.57 to 0.80)                              | 57             | 57            |
|            | Pre-infusion (n=150)                                                      | 0.48 (0.36 to 0.59)                      | 3269           | 15             | 0.56 (0.45 to 0.67)                              | 100            | 119           |
|            | Post-infusion (n=148)                                                     | 0.60 (0.45 to 0.70)                      | 573            | 42             | 0.61 (0.51 to 0.71)                              | 78             | 91            |
|            | Discharge (n=146)                                                        | 0.61 (0.51 to 0.71)                      | 1649           | 63             | 0.69 (0.56 to 0.82)                              | 38             | 38            |
|            | Pre-infusion (n=120)                                                      | 0.64 (0.52 to 0.77)                      | 77             | 65             | 0.71 (0.57 to 0.80)                              | 74             | 74            |
|            | Post-infusion (n=123)                                                     | 0.67 (0.55 to 0.80)                      | 150            | 62             | 0.74 (0.62 to 0.91)                              | 55             | 55            |
|            | Discharge (n=116)                                                        | 0.69 (0.56 to 0.82)                      | 412            | 44             | 0.77 (0.63 to 0.90)                              | 43             | 43            |

SCr-AKI, serum creatinine-defined AKI; NGAL, neutrophil gelatinase-associated lipocalin; discharge, hospital discharge; KIM-1, kidney injury molecule-1.

*Optimal biomarker concentration cut-off: maximum combined sensitivity and specificity. Units for urine NGAL, mg/mg creatinine. Units for urine KIM-1, pg/mg creatinine.
biomarkers in evaluating kidney cell damage in future cisplatin nephrotoxicity prevention drug trials.

Combining NGAL and KIM-1 did not substantially increase AKI prediction compared with each biomarker alone. Pediatric cardiac surgery studies have reported combinations of up to five biomarkers were strongly associated with AKI (21). Other AKI markers should be considered for cisplatin-associated AKI evaluation (12,30,32,33). A panel of validated AKI biomarkers could be useful in improving clinical care of patients treated for cancer, by allowing for earlier and more specific avoidance of other nephrotoxic medications, fluid management, and for further cisplatin cycle dosing.

The prospective and multicenter design and rigorous specimen collection protocol were study strengths. Use of standardized AKI definitions and evaluating AKI with electrolytes and SCr enabled a comprehensive AKI evaluation. This study had limitations. Because patients receiving cisplatin often receive other nephrotoxic medications, and cisplatin is emetogenic, which may cause SCr rise or electrolyte disturbances through mechanisms unrelated to its tubular toxicity, it might be challenging to attribute all AKI to cisplatin. However, given the pathophysiology of cisplatin nephrotoxicity, we believe a term similar to eAKI should be acknowledged to reflect electrolyte disturbances occurring due to cisplatin injury. Although this is a large pediatric cohort, we could not perform subgroup analyses due to a relatively small sample size. Larger studies should evaluate other factors (e.g., age, sex, cisplatin dose, dose, and duration of other nephrotoxic medications) affecting biomarkers in multivariable analyses. Our findings are not applicable to non-pediatric cancer populations. Although we found similar results when using urine creatinine corrected and uncorrected biomarker levels, fluid status can affect SCr levels and AKI assessment, which indirectly affects biomarker performance. Moreover, timing of specimen collection may have influenced biomarker levels. To balance feasibility and specimen collection, NGAL and KIM-1 were assessed once per day at most. Some biomarker rises may have been missed. NGAL has been shown to peak within 0–12 hours post-cardiac surgery, thus we may have missed an earlier NGAL rise in some patients (20,21,47). Future studies should evaluate kinetics of urine NGAL and KIM-1 with cisplatin nephrotoxicity. We acknowledge that multiple comparisons were evaluated which may lead to spurious statistical significance of some analyses; however all analyses were planned a priori.

Few studies have described and characterized associations between urinary tubular injury biomarkers and AKI in children treated with cisplatin (7,23,24). Our findings suggest NGAL and KIM-1 have modest SCr-AKI discrimination ability. Additional research is needed to determine clinical utility of AKI biomarkers in children receiving chemotherapy. Future research should determine whether incorporating kidney injury biomarkers in the AKI definition improves patient management and care, and whether biomarkers are associated with later kidney outcomes.

Disclosures

T.D. Blydt-Hansen reports having ownership interest in Apple, Hydrogenics, and Royal Bank of Canada; receiving honoraria from Astellas Canada; receiving research funding from Astellas Canada, Canadian Institutes of Health Research, Child and Family Research Institute, Children’s Hospital of Manitoba Research Institute, and

Table 3. Urine AKI biomarker excretion at early and late cisplatin visits for SCr+eAKI and severe SCr-AKI

| Time Point          | Non-AKI | AKI   | Severe SCr-AKI | Non-AKI | AKI   |
|---------------------|---------|-------|----------------|---------|-------|
| **Early visit (ng/mg creatinine)** |         |       |                |         |       |
| Pre-NGAL            | 120; 14.4 (6.2–27.5) | 30; 23.8 (7.3–62.3) | 139; 14.5 (6.3–30.4) | 11; 41.6 (11.0–133.5) |       |
| Post-NGAL           | 121; 10.0 (5.3–25.8) | 27; 23.1 (10.2–115.7) | 138; 12.1 (5.6–28.7) | 10; 20.7 (8.70–136.7) |       |
| Discharge NGAL      | 119; 13.1 (5.5–38.5) | 27; 58.7 (16.5–96.2) | 136; 15.4 (6.7–47.2) | 10; 47.6 (3.8–184.8) |       |
| **Late visit (ng/mg creatinine)** |         |       |                |         |       |
| Pre-NGAL            | 106; 14.3 (5.5–34.3) | 14; 35.7 (5.3–91.2) | 113; 13.7 (5.3–38.5) | 7; 36.7 (12.7–170.1) |       |
| Post-NGAL           | 108; 11.9 (5.2–29.6) | 15; 23.6 (8.8–187.1) | 116; 11.5 (5.2–28.4) | 7; 57.2 (23.6–407.8) |       |
| Discharge NGAL      | 101; 15.1 (5.6–30.1) | 15; 53.8 (7.4–279.9) | 109; 14.9 (5.6–30.8) | 7; 174.7 (53.8–279.9) |       |
| **Early visit (pg/mg creatinine)** |         |       |                |         |       |
| Pre-KIM-1           | 120; 397 (185–812) | 30; 376 (167–1563) | 139; 397 (185–836) | 11; 249 (157–3420) |       |
| Post-KIM-1          | 121; 225 (155–569) | 27; 315 (167–3147) | 138; 240 (167–610) | 10; 301 (91–2585) |       |
| Discharge KIM-1     | 119; 1468 (374–3703) | 27; 2019 (458–5696) | 136; 1526 (403–3846) | 10; 1984 (307–4343) |       |
| **Late visit (pg/mg creatinine)** |         |       |                |         |       |
| Pre-KIM-1           | 106; 505 (202–1085) | 14; 580 (185–1818) | 113; 483 (192–1001) | 7; 1571 (533–5771) |       |
| Post-KIM-1          | 108; 337 (185–924) | 15; 357 (257–1549) | 116; 334 (185–839) | 7; 1549 (357–18974) |       |
| Discharge KIM-1     | 101; 1108 (421–3389) | 15; 4079 (2069–10545) | 109; 1253 (428–3759) | 7; 8240 (3204–12957) |       |

SCr+eAKI; composite outcome of SCr-AKI and electrolyte-AKI; SCr-AKI, serum creatinine–defined AKI; IQR, interquartile range; Pre-, preinfusion; NGAL, neutrophil gelatinase-associated lipocalin; Post-, postinfusion; discharge, hospital discharge; KIM-1, kidney injury molecule-1.

*P<0.01, significant difference between AKI and non-AKI groups for that time point.

**P<0.001, significant difference between AKI and non-AKI groups for that time point.

***P<0.05, significant difference between AKI and non-AKI groups for that time point.
Table 4. Combinations of urinary AKI biomarkers and AKI discrimination and prediction at early and late cisplatin visits

| Time Point | Area Under Receiver Operating Characteristic Curve (95% Confidence Interval) |
|------------|--------------------------------------------------------------------------------|
|            | SCR-AKI Discrimination | SCR-AKI Prediction | SCR+eAKI Discrimination | Severe SCR-AKI Discrimination |
| Early visit| NGAL (pre)+KIM-1 (pre)   | 0.54 (0.43 to 0.65) | 0.54 (0.43 to 0.65) | 0.60 (0.48 to 0.73) | 0.65 (0.44 to 0.85) |
|            | NGAL (post)+KIM-1 (post) | 0.60 (0.49 to 0.71) | 0.55 (0.41 to 0.69) | 0.70 (0.58 to 0.82) | 0.62 (0.41 to 0.83) |
|            | NGAL (discharge)+KIM-1 (discharge) | 0.64 (0.55 to 0.73) | 0.46 (0.31 to 0.62) | 0.66 (0.54 to 0.77) | 0.60 (0.43 to 0.78) |
|            | NGAL (pre)+KIM-1 (post)  | 0.62 (0.51 to 0.72) | 0.57 (0.43 to 0.71) | 0.71 (0.59 to 0.83) | 0.70 (0.50 to 0.90) |
|            | NGAL (post)+KIM-1 (pre)  | 0.55 (0.43 to 0.66) | 0.47 (0.33 to 0.61) | 0.64 (0.51 to 0.77) | 0.59 (0.36 to 0.82) |
|            | NGAL (pre)+KIM-1 (discharge) | 0.59 (0.48 to 0.69) | 0.56 (0.37 to 0.75) | 0.61 (0.49 to 0.74) | 0.66 (0.44 to 0.89) |
|            | NGAL (discharge)+KIM-1 (pre) | 0.56 (0.44 to 0.67) | 0.60 (0.40 to 0.80) | 0.69 (0.57 to 0.81) | 0.65 (0.42 to 0.89) |
|            | NGAL (post)+KIM-1 (discharge) | 0.63 (0.54 to 0.73) | 0.55 (0.35 to 0.74) | 0.67 (0.55 to 0.78) | 0.60 (0.42 to 0.79) |
|            | NGAL (discharge)+KIM-1 (post) | 0.62 (0.51 to 0.73) | 0.55 (0.35 to 0.75) | 0.73 (0.62 to 0.84) | 0.67 (0.44 to 0.91) |
| Late visit | NGAL (pre)+KIM-1 (pre)   | 0.56 (0.40 to 0.71) | 0.56 (0.40 to 0.71) | 0.57 (0.38 to 0.75) | 0.73 (0.50 to 0.96) |
|            | NGAL (post)+KIM-1 (post) | 0.70 (0.56 to 0.84) | 0.65 (0.46 to 0.83) | 0.65 (0.47 to 0.82) | 0.83 (0.65 to 1.00) |
|            | NGAL (discharge)+KIM-1 (discharge) | 0.72 (0.58 to 0.86) | 0.94 (0.86 to 1.00) | 0.74 (0.60 to 0.88) | 0.84 (0.72 to 0.97) |
|            | NGAL (pre)+KIM-1 (post)  | 0.62 (0.47 to 0.77) | 0.60 (0.46 to 0.75) | 0.59 (0.42 to 0.76) | 0.80 (0.61 to 1.00) |
|            | NGAL (post)+KIM-1 (pre)  | 0.62 (0.45 to 0.78) | 0.64 (0.48 to 0.80) | 0.58 (0.38 to 0.78) | 0.77 (0.55 to 0.99) |
|            | NGAL (pre)+KIM-1 (discharge) | 0.75 (0.63 to 0.87) | 0.89 (0.72 to 1.00) | 0.73 (0.59 to 0.87) | 0.86 (0.75 to 0.97) |
|            | NGAL (discharge)+KIM-1 (pre) | 0.71 (0.54 to 0.89) | 0.96 (0.90 to 1.00) | 0.66 (0.46 to 0.86) | 0.85 (0.72 to 0.98) |
|            | NGAL (post)+KIM-1 (post) | 0.75 (0.62 to 0.87) | 0.88 (0.68 to 1.00) | 0.72 (0.56 to 0.87) | 0.87 (0.76 to 0.99) |
|            | NGAL (discharge)+KIM-1 (post) | 0.72 (0.56 to 0.88) | 0.95 (0.88 to 1.00) | 0.70 (0.52 to 0.87) | 0.83 (0.68 to 0.97) |

Combinations of biomarkers were estimated with logistic regression models. Up to two biomarkers were included in each model. SCR-AKI, serum creatinine–defined AKI; SCR+eAKI, composite outcome of SCR-AKI and electrolyte-AKI; NGAL, neutrophil gelatinase–associated lipocalin; pre, preinfusion; KIM-1, kidney injury molecule-1; post, postinfusion; discharge, hospital discharge.
the study: Ms. Pina Giuliani, Ms. Karen Mazil, Ms. Jessica Scheidl, Ms. Susan Talmey, and Mr. Tao Wang (Alberta Children’s Hospital, Calgary, Alberta, Canada); Ms. Octavia Choi, Ms. Cecilia Crosby, Ms. Jessica Davis, Ms. Fatima Dharsee, Mr. Mateo Farfan, Mr. Rohan Kakkar, Ms. Nicole Kelly, Ms. Alecia Lim, Ms. Alicia Oger, Ms. Ritu Ratan, Ms. Jennifer Sergeant, and Ms. Grace Tam (British Columbia Children’s Hospital, Vancouver, British Columbia, Canada); Ms. Nancy Coreas, Ms. Megan Friesen, Ms. Rebekah Hiebert, Ms. Jodi Karwacki, Ms. Krista Mueller, Ms. Ashley Ouelette, and Ms. Kiera Unger (CancerCare Manitoba, Winnipeg, Manitoba, Canada); Ms. Barbara Desbiens, Ms. Melanie Ernst, Ms. Marie-Christine Gagnon, and Ms. Nadine Roy (Centre Hospitalier Universitaire de Québec - Université Laval, Quebec, Quebec, Canada); Ms. Ernestine Chablis, Ms. Blanka Courcelle, Ms. Angélique Courtade, Ms. Catherine Desjean, Mr. Marc-Antoine Nadeau, Ms. Marie Saint-Jacques, Ms. Martine Therrien, and Ms. Caroline Tra (Centre Hospitalier Universitaire Sainte-Justine, Montreal, Quebec, Canada); Ms. Sandra Blamires, Ms. Tianna Deluzio, Ms. Becky Malkin, Ms. Mariam Mikhail, and Ms. Leslie Paddock (Children’s Hospital, London Health Sciences Centre, London, Ontario, Canada); Mr. Nathan Adolphe, Ms. Brooke Bowerman, Ms. Isabelle Laforest, Ms. Oluwatoni Adeniyi, Ms. Kelly-Ann Ramakko, and Ms. Jenna-Lee Tremblay (Children’s Hospital of Eastern Ontario, Ottawa, Ontario, Canada); Ms. Mandy Bouchard (IWK Health Centre, Halifax, Nova Scotia, Canada); Ms. Shawde Harris and Ms. Rachel Simpson (McMaster Children’s Hospital, Hamilton, Ontario, Canada); Ms. Anelise Espiritu Santo, Ms. Jackie Girgis, Ms. Dominique Lafrenière, Ms. Martine Nagy, and Ms. Sandra Pepin (Montreal Children’s Hospital, MUHC, Montreal, Quebec, Canada); Ms. Linda Churcher, Ms. Dianne Cortez, Mr. Kevin Dietrich, Ms. Brenda Ennis, Ms. Nicholas Howe, Ms. Crystal Lefebvre, Ms. Nicole Orrell, and Ms. Holly Sykora (Stollery Children’s Hospital, Edmonton, Alberta, Canada); and Ms. Abongwne Abianui, Ms. Rachel Arix, Ms. Beren Avci, Ms. Aparna Bhan, Mr. Eric Lee, Ms. Darshika Mistry, Ms. Niwethaa Nadesan, Mr. Nicholas Pasquale, Ms. Subitha Rajakumaran, Ms. Grace Tran, Ms. Megan Wood, and Ms. Elyze Yamasaki (The Hospital for Sick Children, Toronto, Ontario, Canada). Thank you to Ms. Debbie Boyko and the EPICORE Centre team (Departments of Pharmacology and Medicine, University of Alberta, Edmonton, Canada) for data support, entry, queries, and management. We would like to thank Ms. Anat Halevy (University of British Columbia, Vancouver, Canada) for the ABLE Study support. Thank you to Mr. Michael Pizzi and Mr. Olivier Pouliot (Research Institute of the MUHC team members) for their contributions. We also thank Ms. Jasmine Lee and Dr. Asaf Lebel (Hospital for Sick Children, Toronto, Canada) for their contributions. Thank you to Mr. Qing Ma and Dr. Michael Bennett (Cincinnati Children’s Hospital Medical Center) for their help with biomarker measurements. All individuals were compensated for their time.

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Supplemental Material
This article contains supplemental material online at http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.0004802021/-/DCSupplemental.

Supplemental Table 1. Associations between AKI biomarkers and participant characteristics at early and late cisplatin visits.
Supplemental Table 2. Wilcoxon signed-rank test P values comparing biomarker values between timepoints within participants with AKI and without AKI at the early visit and the late visit.
Supplemental Table 3. Rate of SCr-AKI by AKI biomarkers quartiles at post-infusion of early and late cisplatin visits.
Supplemental Table 4. AKI biomarkers to predict SCr-AKI development at early and late cisplatin visits.
Supplemental Table 5. SCr+eAKI diagnostic characteristics of AKI biomarkers at early and late cisplatin visits.
Supplemental Table 6. Severe SCr-AKI diagnostic characteristics of AKI biomarkers at early and late cisplatin visits.
Supplemental Table 7. Raw urine AKI biomarker excretion and AKI diagnostic characteristics at early and late cisplatin visits for SCr-AKI, SCr+eAKI and severe SCr-AKI.
Supplemental Table 8. Urine AKI biomarker excretion and AKI diagnostic characteristics at early and late cisplatin visits for SCr-AKI, SCr+eAKI and severe SCr-AKI only in patients with biomarker values at all sample timepoints.
Supplemental Table 9. Urine AKI biomarker excretion and AKI diagnostic characteristics at the early cisplatin visit for SCr-AKI, SCr+eAKI and severe SCr-AKI only in cisplatin naïve patients.
Supplemental Table 10. Urine AKI biomarker excretion and AKI diagnostic characteristics at the late cisplatin visit for SCr-AKI, SCr+eAKI and severe SCr-AKI only for patients who did their last cisplatin visit at their last cisplatin cycle.

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Received: July 21, 2021 Accepted: October 29, 2021

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