A sustained quality improvement program reduces nephrotoxic medication-associated acute kidney injury

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Exposure to nephrotoxic medication is among the most common causes of acute kidney injury (AKI) in hospitalized patients. Here we conducted a prospective quality improvement project implementing a systematic Electronic Health Record screening and decision support process (trigger) in our quaternary pediatric inpatient hospital. Eligible patients were noncritically ill hospitalized children receiving an intravenous aminoglycoside for more than 3 days or more than 3 nephrotoxins simultaneously (exposure) from September 2011 through March 2015. Pharmacists recommended daily serum creatinine monitoring in exposed patients after appearance on the trigger report and AKI was defined by the Kidney Disease Improving Global Outcomes AKI criteria. A total of 1749 patients accounted for 2358 separate hospital admissions during which a total of 3243 episodes of nephrotoxin exposure were identified with 170 patients (9.7%) experiencing 2 or more exposures. A total of 575 individual AKI episodes occurred over the 43-month study period. Overall, the exposure rate decreased by 38% (11.63–7.24 exposures/1000 patient days), and the AKI rate decreased by 64% (2.96–1.06 episodes/1000 patient days). Assuming initial baseline exposure rates would have persisted without our project implementation, we estimate 633 exposures and 398 AKI episodes were avoided. Thus, systematic surveillance for nephrotoxic medication exposure and near real-time AKI risk can lead to sustained reductions in avoidable harm. These interventions and outcomes are translatable to other pediatric and nonpediatric hospitalized settings.

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Acute kidney injury (AKI) is among the most common comorbidities experienced by hospitalized children.[1] The public health impact of AKI has been the focus of massive global raising-awareness campaigns[2] and publication of international AKI diagnosis and management guidelines.[3] Even though extensive research has been expended in the past 15 years to standardize the AKI definition[4] and identify novel AKI biomarkers to herald kidney damage earlier,[5] AKI rates keep increasing.[6] Exposure to nephrotoxic medications represents a nearly ubiquitous event in the course of hospitalization; 86% of noncritically ill children in 1 study were exposed to ≥1 nephrotoxic medication during their stay, yet screening for nephrotoxic medication-associated AKI (NTMx-AKI) in children exposed to multiple nephrotoxic medication occurred at low rates.[7]

We previously reported the development and validation of a systematic screening program called Nephrotoxic Injury Negated by Just-in-time Action (NINJA), whereby children admitted to a noncritical care unit in our hospital deemed to be at high-risk of NTMx-AKI were recommended to have a daily serum creatinine (SCr) ordered to assess for AKI development.[8] In the first year, we observed a 25% NTMx-AKI rate and a 42% reduction in AKI days per 100 days of nephrotoxic medication exposure. This occurred from a more rapid recognition of AKI, leading the care teams to reduce nephrotoxic medication exposure earlier.

The positive results observed in many quality improvement initiatives are often not sustained, as the intensive resources expended on the project initially are diverted elsewhere, without a transformational plan to keep the initiative viable. Sustainability can only be achieved with reliable systems that become part of the organizational culture.[9–11] Once the early NINJA results were shared with hospital physicians and administrative leadership, we were supported to develop reliable automated processes to identify nephrotoxic medication-exposed patients in near real time,[12] inculcate nephrotoxic medication exposure and AKI assessment discussions and education as part of the daily ward rounds, and empower pharmacists to make screening and nephrotoxic medication adjustment recommendations. We now report on the 3-year sustainability of our project and examine any potential epidemiological shifts that could explain the improved outcomes we observed. We hypothesized that this health

services system would lead to decreased nephrotoxic medication exposure, AKI rates, and AKI duration.

RESULTS

The noncritically ill total patient days, high nephrotoxic medication-exposure episodes, and nephrotoxic medication–AKI cases are depicted for each partial and total calendar year for the project (Table 1). We observed >99% adherence to the daily SCr monitoring recommendation throughout the course of the study. Mean patient age at the time of exposure was 8.7 ± 6.9 years (95% confidence interval [CI]: 8.4–9.1; range 3 days to 30.6 years) and did not differ among the 3 different exposure eras ($P = 0.42$). Over the time course of study, 1749 unique patients accounted for 2358 separate hospital admissions during which a total of 3243 individual episodes of nephrotoxic medication exposure were observed. One hundred seventy patients (9.7%) had ≥2 exposures, and 575 individual AKI episodes were observed over the study period. The primary services caring for each individual exposed patient and the associated AKI rates are listed in Table 2. Similar to our earlier report, patients admitted for bone marrow transplant, gastroenterology/liver transplant, and pulmonary services composed the populations exposed most commonly. The medications/medication classes implicated in exposures are highlighted in Figure 1. Anti-infective medications were related to the most exposures of any medication class during the study.

We observed 2 decreases in nephrotoxic medication-exposure rates (beginning in June 2012 and December 2014) and AKI rates (beginning in January 2012 and December 2014) over the study period (Figures 2 and 3). Overall, the nephrotoxic medication-exposure rate decreased by 38% (11.63–7.24 patients/1000 patient days), and the AKI rate decreased by 64% (2.96–1.06 patients with AKI/1000 patient days). The statistical control process standard met by each of these outcome metrics corresponds to a 99.7% likelihood that the change observed resulted from the improvement intervention. Assuming the initial baseline exposure rates would have persisted without implementation of NINJA, we calculated 633 patient exposure and 398 patient AKI episodes were avoided (Table 1). We did not observe any differences in medications/medication classes or admitting medical/surgical services for exposed patients or AKI patients in the 3- to 6-month period preceding and following each improvement time point (Table 3). The time courses for comparison depended on the study start and end dates and when the improvement occurred (example the second time point improvement of 14 December 2014 occurred 3 months prior to the end of the study observation period). We observed an early decrease in AKI rates per exposure (23.3%–15.4%) and AKI intensity (27.7–19.1 AKI days/100 exposure days) in the first year of study; both of these improvements have persisted for the entire observation period (Figures 4 and 5).

Two hundred forty-eight unique patients comprised 457 separate admissions leading to the 575 individual AKI episodes. The maximum AKI severity distribution for the AKI episodes was Kidney Disease Improving Global Outcomes (KDIGO) stage 1 (271, 47%), KDIGO stage 2 (188, 33%), and KDIGO stage 3 (116, 20%). Nineteen patients received renal replacement therapy at some point in their hospital course after developing NTMx-AKI; 13 received intermittent hemodialysis only, 2 received continuous renal replacement therapy only, and 4 received intermittent hemodialysis and continuous renal replacement therapy. All but three patients initiated renal replacement therapy in the intensive care unit. Of note, 95 patients were discharged from the 457 unique admissions with active AKI or without having documented AKI recovery prior to discharge (44 with stage 1, 37 with stage 2, and 14 with stage 3).

In order to assess for potential negative unintended negative consequences, we assessed for differences in persistent bacterial or fungal infections between the eras of baseline and the 2 decreased nephrotoxic medication-exposure rates (Figure 6). We observed no difference in mean persistent infection rates across the 3 eras (era 1: 0.88 ± 6.7% [SE 0.12], 95% CI: 0.64%–1.1%; era 2: 1.7 ± 9.5% [SE 0.09], 95% CI: 1.5%–1.9%; era 3: 1.2 ± 1.8 % [SE 0.27], 95% CI: 0.0.67%–1.7%; $P = 0.33$).

DISCUSSION

We report the long-term follow-up of our initial validation study to systematically identify children at high risk of NTMx-AKI. Novel outcomes in the current report are reductions in exposure rates and AKI rates along with persistent reductions in AKI intensity. These sustained results over a >3-year period suggest that a substantial percentage of NTMx-AKI is avoidable when health team personnel are

Table 1 | Total patient exposure and AKI census

Measure	2011[a]	2012	2013	2014	2015[a]	Aggregate
Annualized non-critically ill patient days (Actual count)	91,646 (26,133)	91,363	90,627	99,076	109,968 (27,492)	334,691 Census days
Annualized number of patient exposures (Actual count)	1064 (304)	969	837	960	692 (173)	3243 Patient exposures
Annualized number of patients with AKI (Actual count)	266 (74)	169	142	160	116 (30)	575 Patients with AKI
Patient exposures avoided	NA	108	200	219	106	633 Avoided exposures
Patients with AKI avoided	NA	105	113	134	46	398 Avoided AKI events

AKI, acute kidney injury; NA, not applicable.
[a]Data presented for partial year. Annualized values represent whether data were extrapolated to full time period. Study period in 2011 (September–December), in 2015 (January–March). All aggregate data are actual count.

Table 2 | Primary services of patients with exposure and AKI

	Nephrotoxic medication exposure		AKI cases		
Service	Count	%	No	Yes	%
Bone marrow transplant	561	24	340	221	39
Oncology/hematology	357	15	254	103	29
Pulmonary	324	14	266	58	18
Orthopedics	44	2	43	1	2
Cardiology	120	5	103	17	14
Urology	41	2	40	1	2
General surgery	152	6	135	17	11
Gastroenterology transplant	117	5	59	58	50
Gastroenterology	338	14	311	27	8
Ear, nose, and throat	39	2	32	7	18
Neurology	32	1	25	7	22
Nephrology	23	1	14	9	39
Physical medicine and rehabilitation	8	0	2	6	75
Rheumatology	2	0	1	1	50
Adolescent medicine	5	0	5	0	0
Community pediatrics	24	1	23	1	4
Complex care home program	5	0	3	2	40
Hospital medicine	111	5	96	15	14
Trauma	5	0	5	0	0
Colorectal	20	1	17	3	15
Hemangioma vascular malformation	10	0	9	1	10
Critical care[a]	20	1	0	20	100
Total	2358		1783	575	

AKI, acute kidney injury.
[a]Patients covered by the critical care service after they were discharged from the intensive care unit to the general floor.

provided with actionable near real-time data that identify patients at risk for developing NTMx-AKI. Sustained results of this magnitude require fundamental changes to the system. These changes include efficient and reliable data for clinical decision support, intervention built into routine daily operations (rounds), refinement of role descriptions (clinical pharmacists), data regularly shared with clinical teams to demonstrate results, and evaluation of adverse events to identify potential system weaknesses.

There are a number of potential explanations for the observed decrease in NTMx-AKI. The second decrease in the NTMx-AKI rate at the end of the observation period could have resulted from decreased nephrotoxic medication-exposure rates, as the 2 reductions for each occurred in nearly the same time period. However, the first observed NTMx-AKI rate decrease *preceded* the decrease in NTMx-exposure, so a similar explanation is implausible. We did observe an early reduction in the percentage of exposed

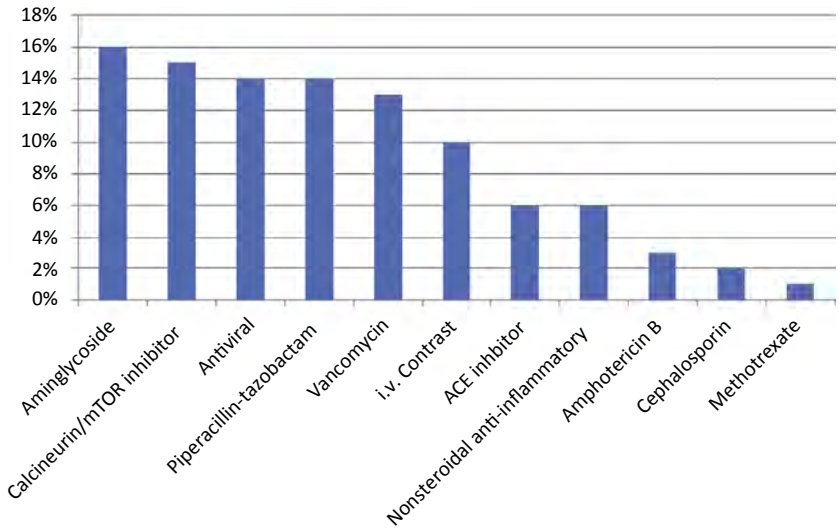

Figure 1 | Percentage of medications/medication classes prescribed to exposed patients. ACE, angiotensin-converting enzyme; mTOR, mammalian target of rapamycin.

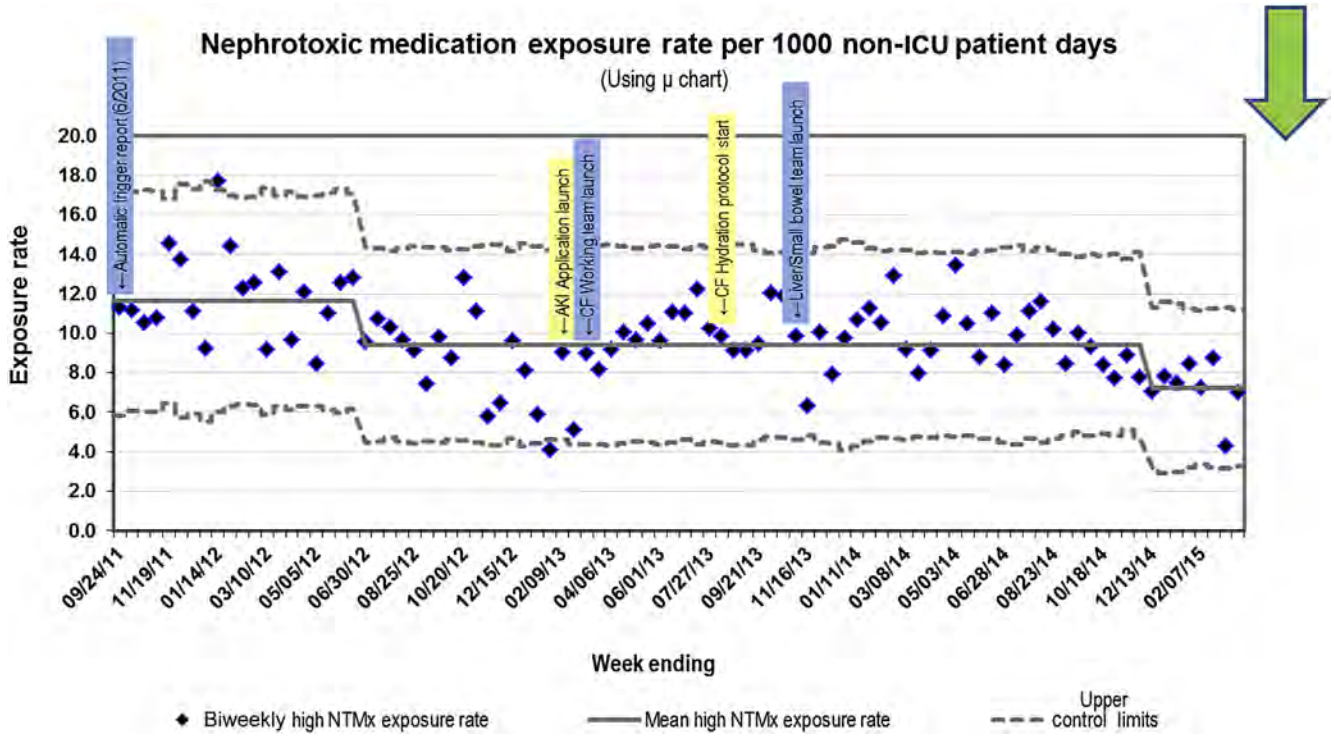

Figure 2| Biweekly average nephrotoxic medication exposure rates as measured by exposed patients per 1000 noncritically ill patient hospital days. The rate decreased from 11.63 to 7.24 admissions per 1000 patient-days over the course of the study, as revealed by 8 consecutive weekly rates below the baseline rate, representing a 99.7% likelihood that a special cause was present. Each data point represents 2 weeks beginning from a Monday to the Sunday occurring 14 days later. The green arrow represents the desired change in direction. AKI, acute kidney injury; CF, cystic fibrosis; ICU, intensive care unit; NTMx, nephrotoxic medication-associated.

patients who developed AKI, and it is possible reduction of very high nephrotoxic medication burden (e.g., from 5 to 4 or 4 to 3 nephrotoxic medications) may have led to the observed improvement, although this was not tracked by our automated system. Whereas a decrease in patient illness severity could have led to decreased exposure and AKI rates, we did not observe a change in medication distribution or primary service distribution in exposed or AKI patients up to 6 months before or after each improvement period. Thus, it is not the case, for example, that fewer patients with bone marrow transplant or less frequent exposure to aminoglycosides were present in the postimprovement periods. Finally, the NINJA project likely increased awareness of the risks of NTMx-AKI, which could have led to specific medication avoidance, but again, we did not assess for such decision making at the bedside as part of this project.

Avoidance of efficacious nephrotoxic medications with a goal of reducing AKI has the potential to lead to unintended harm including delay in, or absence of, treatment response. Because antimicrobials composed a large proportion of the nephrotoxic medications administered to patients, we assessed for treatment failure by determining the rate of persistently positive infections over the time course of study. Despite the 2 decreases in nephrotoxic medication-exposure rates observed in the study, we did not observe an increase in persistent infection rates among the 3 eras. Although this is only 1 measure of a potential unintended consequence, our observation that >98% of all infections were successfully treated within 7 days throughout the 3.5-year period suggests that NINJA did not have a negative outcome on infection treatment.

Several single-site interventions have utilized pharmacist–health care team collaborations to reduce medication-related injury.[13–16] Pharmacist rounding with teams has been associated with reduced injury in single-site studies. Pharmacist counseling on medication management can lead to improved blood pressure control and hospital readmission rates.[13,15] When combined with the use of electronic health records, further reductions in medication-related injury have been reported.[16] In our NINJA project, we informed pharmacists about nephrotoxic medication exposure using electronic health record–based reporting and empowered pharmacists to educate physician teams and patients/families. Qualitatively, our pharmacist team notes that implementation and validation of the electronic trigger has led to significant time reductions in their work, as each pharmacist now spends <20 minutes per weekday validating exposure reports. We have resisted the temptation to rely on an automated alert in each patient record to direct the physician to order the daily creatinine *in lieu* of having the pharmacist discuss the exposure and AKI development on rounds. We believe the continuous interaction among health care team members and patient families has led to increased and pervasive awareness of the common nature of nephrotoxic medication exposure, the acute and chronic implications of nephrotoxic

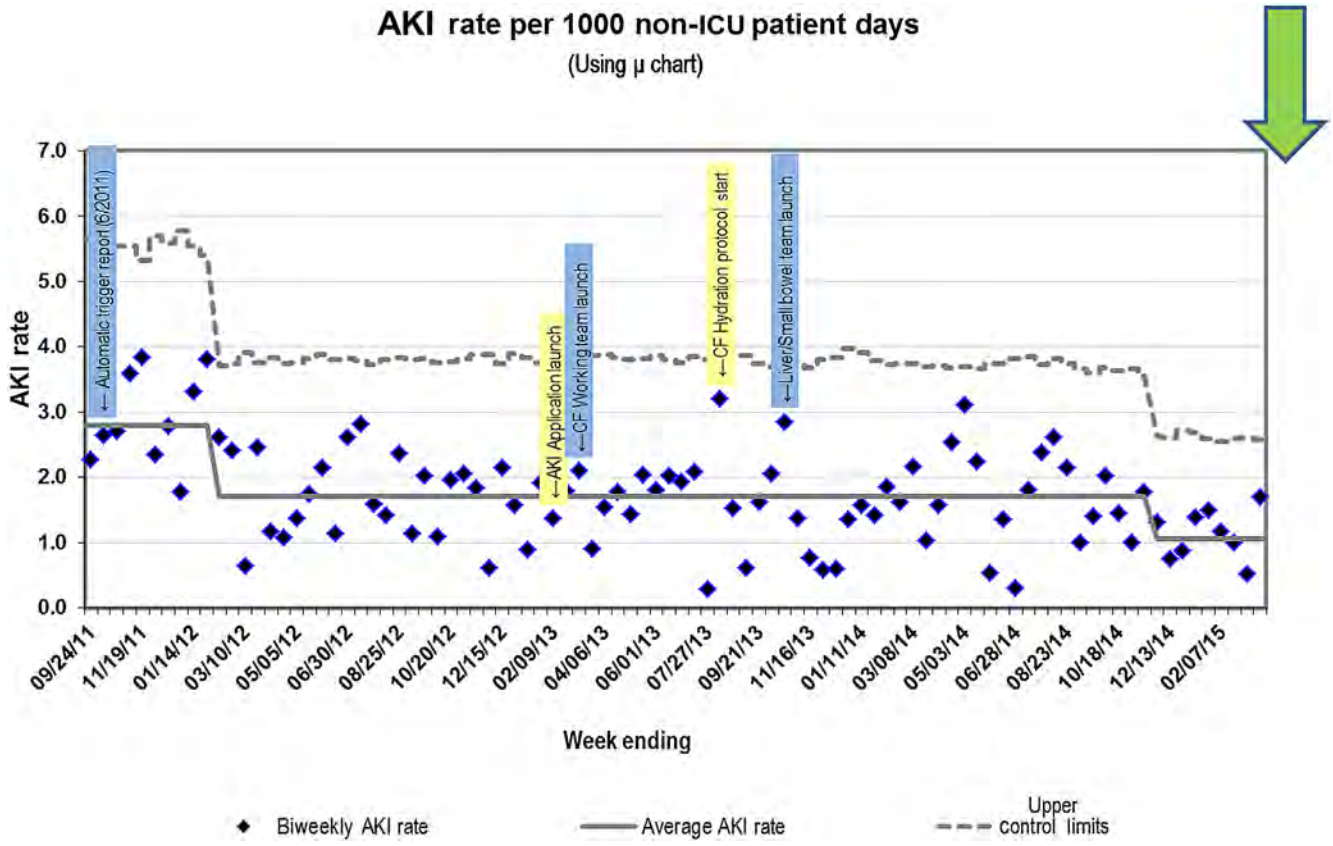

Figure 3 | Biweekly average AKI development rates as measured by patient number with AKI per 1000 noncritically ill patient hospital days. The AKI rates decreased from 2.96 to 1.06 patients with AKI per 1000 patient days over the course of the study as revealed by 8 consecutive weekly rates below the baseline rate, representing a 99.7% likelihood that a special cause was present. Each data point represents 2 weeks beginning from a Monday to the Sunday occurring 14 days later. The green arrow represents the desired change in direction. AKI, acute kidney injury; CF, cystic fibrosis; ICU, intensive care unit.

medication–AKI, which in turn led to enterprise acceptance of daily surveillance.

Our approach and form of clinical decision support (CDS) has been successful, whereas a recent attempt to provide AKI-related CDS to care providers has shown no significant clinical effects and may have, in fact, caused increased health care utilization and expenditures.[17] There are many differences that may have led to these different outcomes. First and foremost, our approach of risk-stratifying patients and providing CDS upstream of actual injury (AKI) provided a larger window of opportunity for elimination or mitigation through earlier clinical action. This occurred despite our intervention being near real time, whereas Wilson *et al.*[17] performed their intervention in real time. Second, we achieved our improvement in outcomes without prescribing or mandating any intervention other than asking providers to order surveillance SCr measurements. The clinical pharmacists embedded in the care teams most certainly did provide guidance, but this was not standardized. The information provided by this project also followed optimal informatics CDS guidelines (utilizing the "The Five Rights of CDS"),[18] by sharing and integrating the (i) right information, with (ii) the right caregivers, (iii) at the right time, via the (iv) right media channel and (v) right format. In effect, this project has taken the first steps toward a more ideal and effective AKI informatics intervention as described in another investigator's commentary on the Wilson study[17]: "In the future, more sophisticated decision-support systems might not only enable detection of acute kidney injury, but be extended to development of algorithm-based predictive, diagnostic, and risk-stratification instruments."[19]

Table 3 | Patient service and medications/medication class distributions before and after observed changes in nephrotoxic medication exposure rates and AKI rates

Cohort	Rate change date	Chi-square	*P*
All patient services	30 June 2012[a]	26.7	0.11
	13 December 2014[b]	18.9	0.33
All patient medications	30 June 2012[a]	29.7	0.11
	13 December 2014[b]	16.7	0.33
AKI patient services	14 January 2012[b]	31.5	0.17
	13 December 2014[b]	15.2	0.36
AKI patient medications	14 January 2012[b]	31.9	0.08
	13 December 2014[b]	10.3	0.67

AKI, acute kidney injury.
[a]Rates compared between the 6 months before and after the rate change date.
[b]Rates compared between the 3 months before and after the rate change date.

The main limitations of our project reside in its single-center design. In fact, in the decade since the release of the

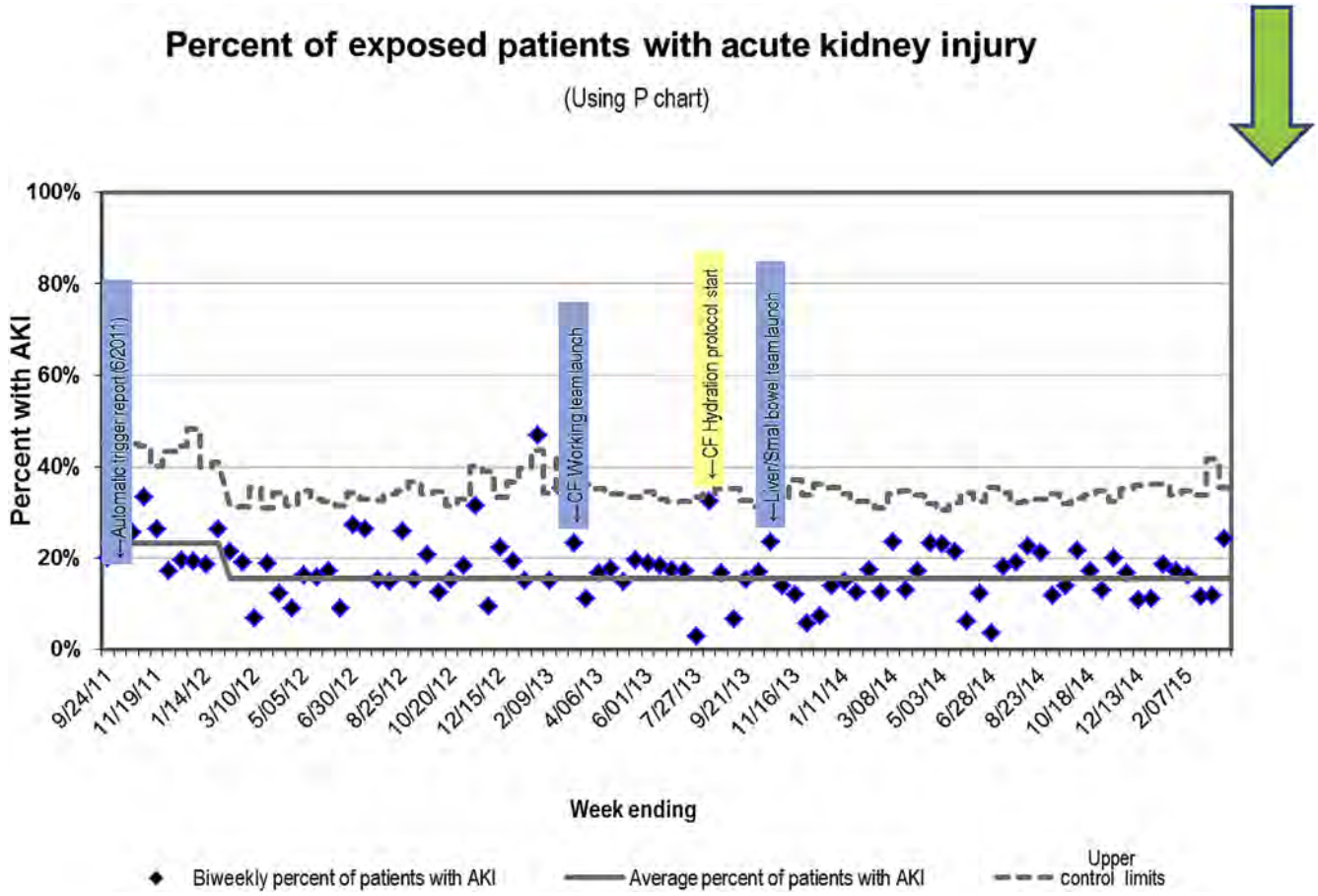

Figure 4 | Biweekly average AKI development rates measured as a percentage of the nephrotoxic medication-exposure patient population. The AKI rate decreased from 23.3% to 15.4% over the course of the study as revealed by 8 consecutive weekly rates below the baseline rate, representing a 99.7% likelihood that a special cause was present. Each data point represents 2 weeks beginning from a Monday to the Sunday occurring 14 days later. The green arrow represents the desired change in direction. AKI, acute kidney injury; CF, cystic fibrosis.

pivotal Institute of Medicine report, *To Err Is Human*, significant hospital, state, and federal resources have been directed toward the study and implementation of patient safety initiatives.[20] Specific hospitals have seen significant improvements in patient safety. For example, through implementation of electronic alerts and change to a "no blame" culture, McLeod Medical Center reduced adverse drug event rates by 90%.[21] However, several publications have commented on the failure to spread success from these few early adopters to other hospitals.[22–25] For instance, in a study of 10 randomly selected North Carolina hospitals, no significant reduction in overall harm or preventable harm was observed from 2002 to 2007.[24] We are currently disseminating the NINJA project to 9 other US pediatric institutions to assess the contextual factors that accelerate or retard implementation at these sites (1R18HS023763-01) with the specific goal of successfully disseminating NINJA to other health care systems. One strategy employed by some of these sites has been to focus on higher risk medical services first to make optimal use of resources and demonstrate an impact before spreading hospital-wide.

We cannot extrapolate our data to intensive care unit populations, as AKI is usually multifactorial in critically ill patients. It is possible that some patients had AKI resulting from causes in addition to nephrotoxin exposure. We suggest this does not invalidate the benefit of our screening algorithm because we detected a high rate of AKI in exposed patients, which would lead to appropriate interventions (dose reduction, medication change) irrespective of AKI cause, a strategy recommended by the KDIGO AKI guidelines.[3] Future work can focus on enriching the NTMx-AKI clinical model with other causes to improve risk stratification. Finally, although we can only speculate as to the reasons for rate changes in our observed metrics, other factors including specific combinations of medications, rates of underlying chronic kidney disease, dehydration rates, and genetic predisposition to nephrotoxic medication–AKI could conceivably confound any attribution to improvement, but these were not part of the intervention (e.g., identification of certain combinations), systematically assessed (chronic kidney disease, dehydration), or modifiable (chronic kidney disease or genetic predisposition).

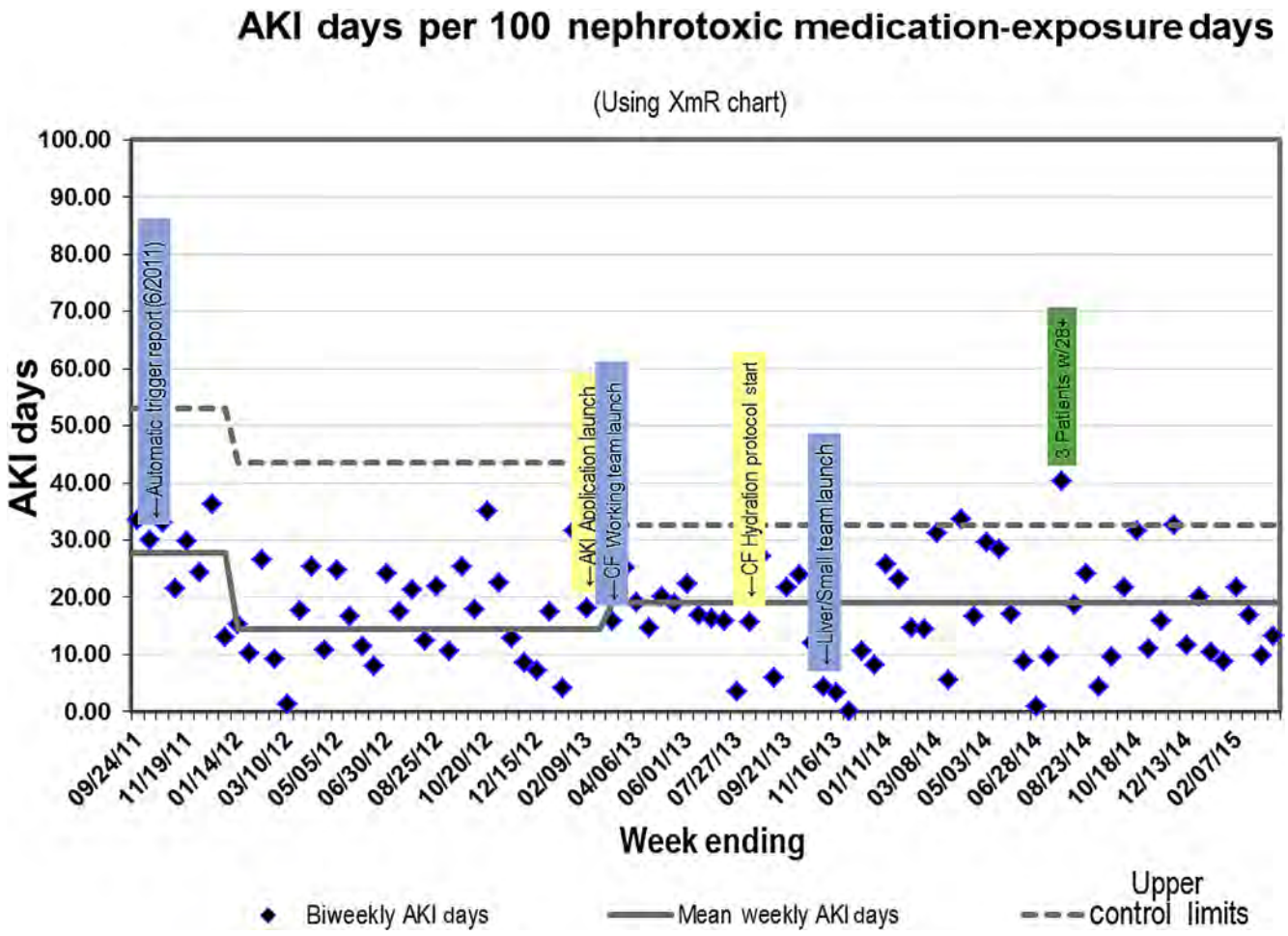

Figure 5 | Biweekly average AKI intensity rates measured as days in AKI by the KDIGO criteria per 100 days of nephrotoxic medication exposure. The mean AKI intensity rate decreased 27.7 to 19.1 AKI days/100 exposure days as revealed by 8 consecutive weekly rates below the baseline rate, representing a 99.7% likelihood that a special cause was present. Each data point represents 2 weeks beginning from a Monday to the Sunday occurring 14 days later. Green arrow represents the desired change in direction. AKI, acute kidney injury; CF, cystic fibrosis; KDIGO, Kidney Disease Improving Global Outcomes; XmR, X-moving range.

MATERIALS AND METHODS

The operational aspects of the NINJA project have been described previously.[8] In brief, this prospective project was undertaken via collaboration among the Cincinnati Children's Hospital Medical Center (CCHMC) Center for Acute Care Nephrology, the James M. Anderson Center for Health Systems Excellence, the Department of Information Services, and the Division of Pharmacy Services. An electronic nephrotoxic medication-exposure trigger program[9] was initially launched September 16, 2011; data reported here are derived through March 31, 2015. The project was approved by the CCHMC Institutional Review Board with a waiver of patient/parental informed consent.

Screening algorithm and trigger process

Every weekday morning, each pharmacist assigned to an inpatient team received an automated report[12] generated from the CCHMC EHR (EpicCare Inpatient, Epic Systems, Verona, WI) identifying all noncritically ill patients with high nephrotoxic medication exposure ("exposure"; see Operational definitions). For the purpose of this report, data managers and pharmacists verified all identified cases daily to ensure data validity. Because we desired to identify nephrotoxic medication exposure as a primary cause of AKI, patients admitted to intensive care units were excluded as AKI is multifactorial in critically ill children, commonly resulting from hypotension or sepsis.[26–29] Patients with chronic kidney disease, kidney transplant, or active urinary tract infection were excluded.

Pharmacists recommended daily SCr monitoring for all exposed patients during morning rounds with the medical team. When clinically appropriate, substitution of a non- or less nephrotoxic medication and/or pharmacokinetic drug concentration monitoring was recommended by the pharmacist, but this was not mandated or monitored by the study team members. Adherence to SCr screening recommendations was recorded daily and reported to the principal investigator (SLG). SLG contacted primary attending physicians who did not agree to daily SCr monitoring to discuss their rationale.

Operational definitions

High nephrotoxic medication exposure (exposure). Exposure was defined at the time a patient received an i.v. aminoglycoside ≥3 days or ≥3 nephrotoxic medications derived from a list used from our previous study (Table 4).[8] Exposure started to be counted on the third day of the aminoglycoside or on the day a third NTMx was

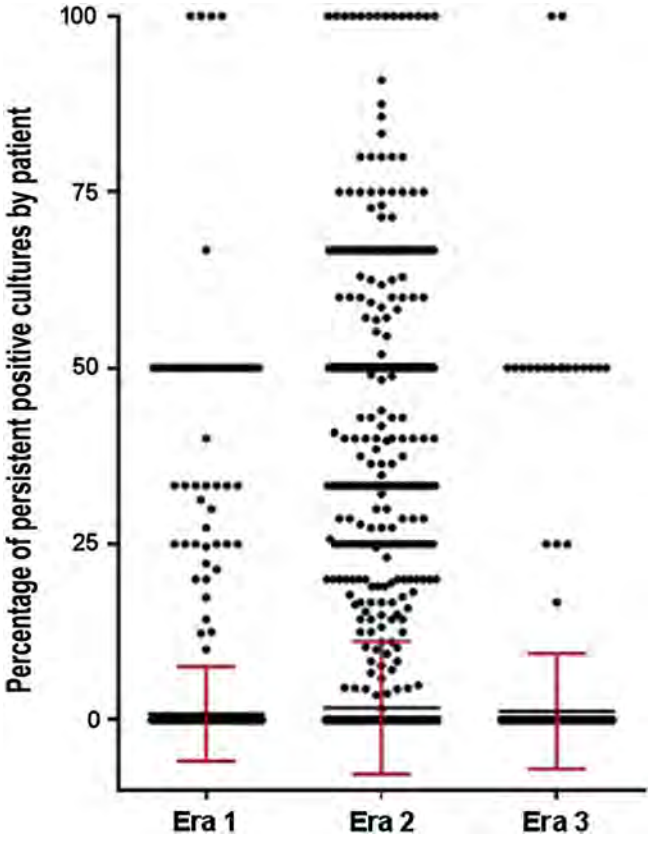

Figure 6 | Persistent positive infection rates over the course of NINJA. Each point represents a single patient infection. A persistent infection is defined as failure to eradicate any bacterial or fungal organism within 7 days of initiation of antimicrobial therapy for a blood, respiratory, soft/deep tissue, or cerebrospinal fluid infection. The red bars depict mean + SD infection rates. NINJA, Nephrotoxic Injury Negated by Just-in-time Action.

administered. Patients were considered exposed for 48 hours after stopping i.v. aminoglycoside or reducing to <3 nephrotoxic medications (Supplementary Figure S1).

Acute kidney injury. AKI was defined by the international KDIGO consensus criteria, using a 50% increase (within 7 days) or a 0.3 mg/dl increase (within 48 hours) over a baseline value obtained within the past 6 months.[3] If a baseline SCr was not available in the previous 6 months, it was calculated based on a presumed estimated creatinine clearance of 120 ml/min/1.73 m^2, which has been validated in the pediatric literature.[30] The AKI duration was defined as a return to baseline SCr for 5 consecutive days or 30 days of AKI, whichever came first. In the case of the "5 day rule," the first of the 5 consecutive days was counted as the end of the AKI episode. The KDIGO AKI urine criteria were not used because nephrotoxic AKI is usually nonoliguric in nature.[31]

Table 4 | List of nephrotoxic medications

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

[a]Medications counted for 7 days after administration toward exposure due to their long half-life. All other listed medications count for 48 additional hours after exposure.

Outcome measures

Table 5 details the outcome measure name definitions used and validated in our previous study, their underlying calculations, and clinical context. To calculate biweekly rates, patients were clustered to the calendar week they became exposed. We grouped nephrotoxic medication by class to identify those associated with the highest exposure and AKI prevalence rates. We also calculated patient exposure and patient AKI episodes potentially avoided over the study period by subtracting the actual exposure and AKI episodes from the projected episodes assuming the initial rates persisted over the course of the study period using actual census data (Table 1).

Table 5 | Outcome measures and definitions

Measure name	Numerator	Denominator	Clinical meaning
High nephrotoxic medication exposure prevalence rate (per 1000 patient-days)	Number of new patients with high nephrotoxic medication exposure each 2 calendar weeks	The total number of noncritically ill patient hospital days standardized per 1000 patient-days each 2 calendar weeks	This measure generates a normalized rate of high nephrotoxic medication exposure cases per 2 study weeks
AKI prevalence rate (per 1000 patient-days)	Number of patients with high nephrotoxic medication exposure who developed AKI	The total number of noncritically ill patient hospital days standardized per 1000 patient-days each 2 calendar weeks	This measure generates a normalized rate of AKI cases per 2 study weeks
Rate of patients with high nephrotoxic medication exposure who develop AKI (%)	Number of patients with high nephrotoxic medication exposure who developed AKI	Number of new patients with high nephrotoxic medication exposure each 2 calendar weeks	This measure generates the fraction of patients with high nephrotoxic medication exposure who develop AKI
AKI intensity rate (per 100 exposed patient-days)	Number of days patients have AKI	The total number of AKI patient-days standardized per 100 exposed-days	This measure depicts a normalized duration of AKI per exposed days

AKI, acute kidney injury.

Statistical analysis

To characterize nephrotoxic medication–AKI epidemiology, we report demographic variables descriptively and compare groups using analysis of variance or chi-square analysis as appropriate using Stata (version 12; StataCorp, College Station, TX). To assess for the effect of NINJA on AKI epidemiology, we used statistical process control methods[32] to identify changes from baseline rates for each metric. We set an *a priori* standard of 8 consecutive weekly metric rates below the baseline rate to qualify as a statistical change (or special cause in process control vernacular), which corresponds to 99.7% likelihood that the change observed resulted from the improvement intervention.[33] This methodology has served as the primary quality improvement assessment measurement to track the serious safety event rates for the past 11 years at CCHMC.[34] The Tukey multiple comparison test was used to assess whether observed rate changes in any of the outcome rates resulted from differences in medication classes or admitting medical/surgical services up to 6 months before and after a change from baseline rates (Stata version 12). To assess for a potentially negative unintended consequence of NINJA, we determined the persistent infections rates among the baseline, first improvement, and second improvement eras. We divided the study into 3 eras to correspond to the 3 nephrotoxic exposure rates observed in Figure 2. We used an outcome of a persistent infection rate defined as a failure to eradicate an organism within 7 days of treatment of a blood, respiratory, soft/deep tissue, or cerebrospinal fluid infection (R Programming Language [version 3.2.3; Vienna Austria]). We compared the persistent infection rates on a per patient basis among the 3 eras by analysis of variance with *post hoc* correction using Dunn multiple comparisons test using GraphPad Prism (version 6.07 for Windows; La Jolla, CA). A *P*-value of <0.05 was considered statistically significant.

Concomitant interventions

During the course of study, we also worked with the Pulmonary Service and the Liver/Small Bowel Transplant Service to identify further modifiable aspects of nephrotoxic medication exposures in these patient populations. Although the results of these initiatives are beyond the scope of this manuscript, we have annotated the statistical process control charts with the dates they commenced with these 2 services.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Figure S1. High nephrotoxic medication exposure and associated acute kidney injury development algorithm used by Cincinnati Children's Hospital for the Nephrotoxic Injury Negated by Just-in-time Action (NINJA) quality improvement initiative. AKI, acute kidney injury; NTMx, nephrotoxic medication-associated; SCr, serum creatinine. Reproduced with permission from Goldstein SL, Kirkendall E, Nguyen H, et al. Electronic health record identification of nephrotoxin exposure and associated acute kidney injury, *Pediatrics.* 2013;132: e756–767.

Supplementary material is linked to the online version of the paper at www.kidney-international.org.

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