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.