Reduction of Nephrotoxic Medication-Associated Acute Kidney Injury in Children

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Structured Abstract

Purpose: Nephrotoxic medication (NTMx) exposure is one of the most common causes of acute kidney injury (AKI) in hospitalized children. A single-center harm-reduction program, Nephrotoxic Injury Negated by Just-in-time Action (NINJA), reduced NTMx exposure and associated AKI rates by 38% and 62%, respectively. Our purpose was to 1) Disseminate NINJA at nine pediatric hospitals, 2) measure NINJA's impact on NTMx-AKI in participating hospitals, and 3) assess the association between context measures and reduction in NTMx-AKI by individual hospitals.

Scope: The scope was reduction of NTMx-AKI in noncritically ill children across the collaborative.

Methods: We employed the Institute for Healthcare Improvement Breakthrough Series approach. Outcome measures were the same as those used in the single center: NTMx-exposures per 1000 patient days, NTMx-AKI rates per 1000 patient days, NTMx-AKI rates per NTMX-exposure (%), and NTMx AKI days per 100 NTMx-exposure days. We used statistical process control methods to assess for changes from baseline rates. For context measure assessment, we used qualitative comparative analysis to assess for essential and sufficient factors required for successful implementation of the program.

Results: The collaborative realized reductions in NTMx-exposure (-11.5%), AKI/1000 patient days (-22%), and AKI/NTMx (-28%). Contextual factor assessment is still ongoing.

Key Words: acute kidney injury, nephrotoxicity, children, harm reduction

Purpose

A key limitation to a national reduction in healthcare associated harm is failure to disseminate effective evidence-based interventions from early adopters to the rest of the country. We examined the dissemination of our successful single-center NINJA program[1] in nine pediatric hospitals that are part of The Solutions for Patient Safety, a network of 78 children's hospitals working together to eliminate serious harm caused by healthcare to hospitalized children. Our dissemination proposal was responsive to PA-14-002 in that we 1) focused on communication between pharmacists, nurses, and physicians, 2) used health information technology to improve care coordination and 3) empowered and incorporated pharmacist providers into interdisciplinary team management. We aimed to fulfill the following three specific aims to address the associated hypotheses:

1) Disseminate NINJA implementation at nine pediatric hospitals

H: Using the Institute for Healthcare Improvement Breakthrough Series approach, NINJA will be implemented successfully to support reliable data transmission to the network to calculate NTMx-AKI outcome metrics.

2) Measure the impact of NINJA on NTMx-AKI in participating hospitals

H: There will be a 50% reduction in NTMx-AKI in the NINJA hospitals by the end of the project, as measured using an interrupted time-series evaluation.

3) Assess the association between context measures, including network participation, and reduction in NTMx-AKI by individual hospitals across the network

H: Context measures, process measures (including network participation), and hospital characteristics will be associated with variation in the reduction of NTMx-AKI across participating hospitals using a cohort study that employs qualitative comparative analysis, a method of grouping data sets and identifying causal relationships ideally suited for measuring complex interactions of different context measures in multiple healthcare systems, and employs stratified time-series evaluation.

Scope

BACKGOUND

Nephrotoxic medication (NTMx) exposure is one of the most commonly cited causes of acute kidney injury (AKI) in hospitalized children[2] and is the primary cause of AKI in 16% of cases. More than 80% of noncritically ill children receive at least one NTMx (e.g., aminoglycosides, nonsteroidal anti-inflammatory agents) during their hospitalization.[3] NTMx-AKI is associated with increased hospital length of stay and associated healthcare costs; we found that patients with NTMx-AKI secondary to intravenous aminoglycoside exposure spent a median of 5 additional days in hospital (additional cost of $17,000) compared with children who were exposed but did not have AKI.[4] Furthermore, 10-49% of adults and children who survive an AKI episode develop chronic kidney disease,[5-8] which puts them at risk for hypertension and progression to kidney failure, requiring dialysis or a kidney transplant. The United States Renal Data System, funded by the National Institute of Diabetes and Digestive and Kidney Diseases, the national data registry that collects, analyzes, and distributes information on the end-stage renal disease and chronic kidney disease population in the US, estimates that chronic kidney disease patients incur per person per year costs of just over $23,000[9] compared with $11,000 for patients without chronic kidney disease. Although some research has focused on identifying adults with AKI to optimize their medication dosing in the hospital,[10,11] little attention had been paid to children at risk for NTMx-AKI. We showed that NTMx-AKI rates reach 19-31% in children who receive an aminoglycoside (e.g., gentamicin) for >5 days[4] and that the rate of AKI doubles when children receive three or more NTMx simultaneously.[3] Monitoring kidney function with a basic and inexpensive serum creatinine lab test detects kidney function decline early. Yet, both these single center studies and analysis of a multicenter administrative database[12] of children receiving prolonged aminoglycoside exposure show that kidney function was assessed by the serum creatinine at least once every 4 days only 50-60% of the time. This lack of systematic kidney function monitoring in patients at risk for AKI is a main reason that rates of AKI among hospitalized children are difficult to quantify, leading to a negative ascertainment bias when using administrative coding data to identify AKI,[13,14] such that 70-80% of AKIs are missed by coding data. We recently reported that administrative data missed 44/70 patients (63%) with serum creatinine-based NTMx-AKI.[15] Thus, we suggest that a recent study using ICD-9 codes, reporting 10,322 hospitalized children who suffered from AKI in 2009, may actually reflect a pediatric annual AKI incidence of closer to 80,000-100,000.[16] **This project was responsive to AHRQ's Policy on the Inclusion of Priority Populations in Research, as it focused on children.**

CONTEXT

Through our initial single-center work, **we found that NTMx exposure is potentially modifiable and the associated AKI is an avoidable adverse safety event.** In our single-center, systematic screening system to identify children at risk for AKI, we utilized an electronic health record trigger to improve near-real-time clinical decision support collaboration between rounding physicians, pharmacists, nurses, and patient families.[1] With this systematic screening, we found that our baseline NTMx-AKI rates (2.96 per 1000 patient-days)[1] were similar to published baseline central line bloodstream-[17] and catheter-associated urinary tract infection[18] rates, suggesting that NTMx-AKI is as important as these US hospital-acquired conditions that are national priorities.

Electronic Health Record-based alerts can identify patients at risk for NTMx-AKI

Use of the electronic health record to detect iatrogenic harm retrospectively is well described. Electronic health record-based safety tools include kidney injury triggers, such as the Institute for Healthcare Improvement's Global Trigger Tool,[19] a recent tool using Acute Kidney Injury Network definition,[20] or dosing tools to improve compliance with renal-dosing of medications.[10] Electronic health record-based AKI detection expedites time to interventions and yields a higher percentage of patients returning to baseline kidney function.[21,22] Matheny used retrospective electronic health record data to develop a risk stratification model to predict hospital-acquired AKI.[23] However, no literature existed regarding implementation of a predictive risk stratification trigger to prospectively identify patients exposed to NTMx and provide timely intervention strategies to minimize AKI.

Our project, Nephrotoxic Injury Negated by Just-in-time Action (NINJA), used the electronic health record risk trigger to prospectively identify patients with high exposure to NTMx (defined as receiving an IV aminoglycoside for >3 days or ≥3 NTMx simultaneously) to empower pharmacists to recommend daily serum creatinine monitoring for AKI surveillance or less nephrotoxic medication regimens.

NINJA project results: Combining electronic health record-based triggers and pharmacist-healthcare team communication reduced NTMx-AKI**.**

Through NINJA, our institution achieved a 99% surveillance rate for high-NTMx-exposed patients receiving daily serum creatinine monitoring. AKI occurred in 290/945 (30.7%) exposed admissions in the first year. We observed a stable rate of NTMx exposure of 7.6 admissions per 1000 patient-days from June 1 through September 17, 2011, which increased to 11.6 admissions per 1000 patient-days coinciding with improved detection through implementation of electronic triggers. **Importantly, we observed a 42% decrease in the number of days in AKI per 100 exposure days, and we estimate that this improvement would be associated with 908 AKI days avoided annually at our large pediatric institution.**[1] In the second year of the project, we observed a 19% decrease in nephrotoxic medication exposure from 11.6 to 9.4 admissions per 1000 patient-days and a 42% decrease in AKI rates from 2.96 to 1.71 admissions per 1000 patient days **(Figure 1). We estimate that NINJA implementation prevents AKI in 130 children annually at our institution based on this reduction**.

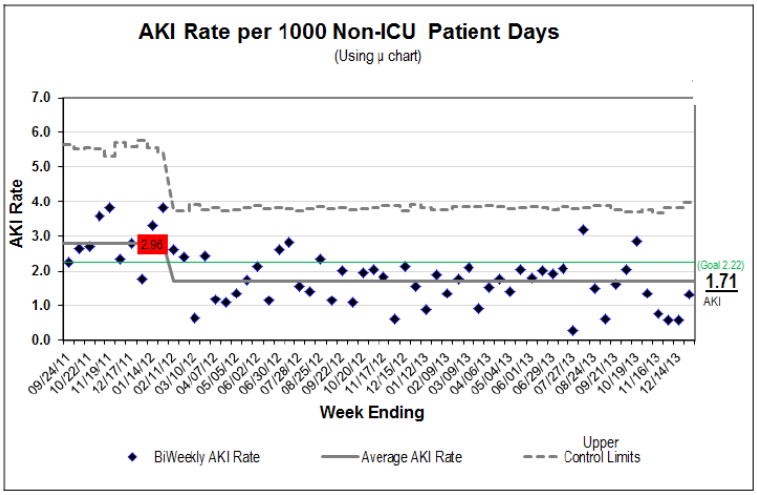


Figure 1 – NINJA is associated with a 42% reduction in NTMx-AKI rates

Pharmacist and physician team collaboration leads to safer medication use

Several single-site interventions have utilized pharmacist-healthcare team collaboration to reduce medication-related injury.[24-27] A pharmacist rounding with teams has been associated with reduced injury in single-site studies. A pharmacist counseling on medication management can lead to improved biological outcomes for patients with chronic conditions.[24,26] When combined with the use of electronic health records, additional reductions in medication-related injury have been reported.[27] In our NINJA project, we informed pharmacists about NTMx exposure using electronic health record alerts, and we empowered pharmacists to educate physician teams and patients/families. In the proposed study, we moved beyond the single site and evaluated the dissemination of this collaborative approach to multiple sites nationally.

Lack of progress in safety linked to failure of spread

In the decade since the release of the 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.[28] 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%.[29] However, several publications have commented on the failure to spread success from these few early adopters to other hospitals.[30-33] 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.[32]

Networks can spread successes and significantly improve safety

There is early evidence that quality improvement networks can overcome the failure to spread improvements. In the Michigan ICU Keystone Project, a collaborative of 108 ICUs worked together to significantly reduce central line-associated bloodstream infections by 50% over 18 months.[34] A national collaborative of pediatric intensive care units began with 29 hospitals and achieved a sustained continual decline in rates of central line-associated

bloodstream infections.[17] During this initial effort, early adopter hospitals were identified and served as peer leaders during subsequent spread and sustain efforts across additional units. We plan to use this early adopter model for the initial dissemination for NINJA. Subsequently, Ohio's eight children's hospitals, led by Dr. Stephen Muething, Cincinnati Children's Vice President of Patient Safety and Co-leader of the Solutions for Patient Safety Network, used an Institute for Healthcare Improvement Breakthrough Series method focused on two adverse events and achieved a 60% reduction in surgical site infections in designated cardiac, neurosurgery, and orthopedic procedures[35] and a 34.5% reduction in overall adverse drug events. These efforts have saved more than 7,700 children from unnecessary harm and avoided $11.8 million in unnecessary healthcare costs since the project's inception. Based on these successes in the Ohio group of children's hospitals, the national Solutions for Patient Safety Network, funded by the Center for Medicare and Medicaid Services, established a network of 78 children's hospitals working together to prevent harm to hospitalized children.

Impact of context on spread of successful interventions

Differences across institutions in the effective implementation of evidence-based patient safety practices may be related to differences in context.[33,36-38] Interventions like NINJA, which was pioneered by members of this team, are designed to improve patient safety and tend to be complex, sociotechnical interventions that target systems, organizations, and groups of individuals. As such, these interventions are sensitive to the context in which they are implemented. In fact, differences in context may explain the lack of external validity seen when a patient safety intervention is implemented successfully in one institution but then fails to be effective when evaluated rigorously in larger, multi-institutional studies.[33,36-38] Studies have identified a range of contextual factors associated with successful implementation of evidence-based patient safety practices, which have been broadly classified into four domains: (1) safety culture, teamwork, and leadership involvement; (2) structural organizational characteristics; (3) external factors; and (4) availability of implementation and management tools.[36] Studies of the effectiveness of quality improvement interventions to implement patient safety practices must, therefore, include an examination of the ways in which contextual factors modify the intervention implementation and effectiveness.[33]

Methods

STUDY DESIGN

Our dissemination approach was grounded in the Institute for Healthcare Improvement Breakthrough Series approach.[39] The nine hospitals worked together to implement NINJA throughout the learning network. We used a similar "all teach, all learn" approach, with increased dependence upon virtual learning supplemented by annual face-to-face meetings. We used a virtual hub, where hospitals shared tools and access to experts as needed by individual hospitals. In order to participate in the collaborative, each hospital had to commit to implementation of the following interventions:

- Engage clinical leaders of key clinical populations
- Develop a system to identify all patients at with high NTMx exposure
- Use standardized serial serum creatinine monitoring in high-NTMx-exposed patients
- Establish real-time pharmacist intervention to adjust usage of NTMx
- Track performance over time with feedback to clinical providers

DATA SOURCES

Implementation Tools - Each network hospital was provided with the tools to support implementation of NINJA, including the NINJA process map, operational definitions, spreadsheets developed at CCHMC to enter and track the individual patient data (NTMx exposure, AKI development), and macros to generate the run charts for the outcome measures. As with our initial work at our institution, the initial implementation of NINJA required manual data entry into these resources that developed expertise among the teams as they detect changes in the data elements or unusual variation in the output metrics.

However, we provided a detailed manual of the electronic health record specifications we used to create our automatic daily trigger report, which we have shown to be extremely reliable in detecting NTMx exposure and harm.[40]

For data sharing and transparency, all centers adopted common outcome definitions for NTMx-AKI and submitted their aggregate data to compute the four metrics to the Cincinnati Children's Hospital Center for Acute Care Nephrology. The aggregate network data were displayed for all group members on a password-protected secure website (www.ppaki.org) that was updated monthly. In addition, each center's individual outcome metric data was discussed transparently among sites on the monthly teleconference/webex calls. Particular emphasis was placed upon those hospitals demonstrating significant improvement and/or significantly better results. These hospitals were asked to share successes and struggles with all hospitals.

For "all teach all learn," we convened monthly teleconference calls/webinars among all hospital stakeholder key personnel to discuss progress, barriers, and facilitators for NINJA implementation. During these calls, hospitals reported the intervention strategies and PDSA progress for each key driver. The goal of the webinars was to expedite the learning that is shared across the hospitals, develop the trust and interaction necessary to establish a true learning environment, build accountability to meeting the shared goals, and sustain/maintain high levels of engagement. The objective for the webinars was to move closer to identifying best practices and to highlight the application of how hospitals are utilizing quality improvement science to address factor that contribute to a hospital's ability to effectively implement NINJA. These communications were collated and cataloged in a repository by the key personnel at CCHMC to serve as the data source for context measure analysis in Aim 3. Key personnel at CCHMC were available to all hospitals for in-depth tutorials with respect to all aspects of NINJA, including building consensus, data abstraction and entry, generation of run charts, electronic health record trigger tool development, etc.

For action periods and learning sessions, this work took place on a monthly cycle with emphasis on rapid cycle change and attention to improvement demonstrated by the transparent sharing of data. This monthly and continuous virtual sharing was supplemented by annual in-person learning sessions as a significant catalyst for learning. This in-person session allowed for more in-depth discussion about the context measures that facilitate and address barriers to NINJA implementation and AKI reduction. The learning sessions leveraged the experience and capability of those hospitals that demonstrated progress to expedite learning quickly across the other hospitals and drive improvements at a faster pace than if done by single hospitals. The learning sessions achieved the goal of transitioning ownership of the NINJA process from CCHMC to the collaborative over the 3 years, as CCHMC became less directive in its role and more responsive in terms of advancing quality improvement expertise.

INTERVENTION

We use the electronic health record risk trigger to prospectively identify patients with high exposure to NTMx (defined as receiving an IV aminoglycoside for >3 days or ≥3 NTMx simultaneously) to empower pharmacists to recommend daily serum creatinine monitoring for AKI surveillance, or less nephrotoxic medication regimens (Figure 2).

Measure the impact of NINJA on NTMx-AKI in hospitals

Overview: We used both statistical process control methods and an interrupted time-series approach to assess the impact of NINJA on the outcome measure rates in the collaborative.

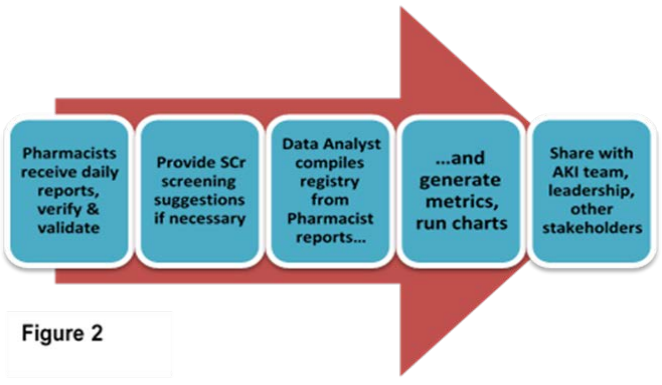


Figure 2

Inclusion criteria: Because we desired to identify nephrotoxic medication exposure as a primary cause of AKI, only noncritically ill patients were included in NINJA,

because AKI is multifactorial in critically ill children, commonly resulting from hypotension or sepsis.[41-44]
Exclusion criteria: Patients with chronic kidney disease, kidney transplant, or urinary tract infection.

MEASURES
Outcome Measures: Our primary outcome was rates of acute kidney injury per 1000 noncritically ill patient days. Our secondary measures are the same as in our single-center study (**Table 1**).

Definitions
High-NTMx-exposure patient: A patient was deemed to have high NTMx exposure (exposed) at the time they receive an IV aminoglycoside ≥3 days or ≥3 NTMx derived from an initial list of 25 medications, based on the work of our previous study. This list was expanded to 45 and then again to 61 medications based on the work of the collaborative. Patients were considered exposed for 48 hours after stopping IV aminoglycoside or reducing to <3 NTMx. Patients were newly identified if placed back on IV aminoglycoside for ≥3 days or ≥3 NTMx simultaneously after the 48-hour window.

Table 1 – Outcome Metrics for NINJA[1]

Measure Name	Numerator	Denominator	Clinical Meaning
High NTMx Exposure Prevalence Rate (per 1000 patient-days)	Number of new patients with high NTMx exposure in the calendar week of study	The total number of non-critically ill patient hospital days standardized per 1000 patient-days in the calendar week of study	This measure generates a normalized rate of high NTMx exposure cases per study week.
AKI Prevalence Rate (per 1000 patient-days) [PRIMARY OUTCOME]	Number of patients with high NTMx exposure who developed AKI in the calendar week of study	The total number of non-critically ill patient hospital days standardized per 1000 patient-days in the calendar week of study	This measure generates a normalized rate of AKI cases per study week.
Rate of Patients with High NTMx Exposure who Develop AKI (%)	Number of patients who develop AKI*	Number of new patients with high NTMx exposure in the calendar week of study	This measure generates the fraction of patients with high NTMx exposure who develop AKI
AKI Intensity Rate (per 100 high exposed patient-days)	Number of days patients have AKI	The total number of susceptible patient days standardized per 100 susceptible-days	This measure depicts a normalized duration of AKI per susceptible days

Acute Kidney Injury: AKI was defined by the recently published international Kidney Disease Improving Global Outcome AKI Consensus Group guideline[45] (S. Goldstein, PI, pediatric KDIGO work group member), which uses a 50% change in serum creatinine over baseline to fulfill AKI criteria. NTMx-AKI is usually nonoliguric in nature,[46] so we did not use the KDIGO urine output criteria. AKI by KDIGO and similar modern AKI definitions has been associated with worse outcomes, including length of stay, mortality, and development of chronic kidney disease, in critically ill and noncritically ill children with AKI.[4-6,8,47]

Analysis
We initially used both the interrupted time-series statistical approach and statistical process control methods to assess for an impact of the NINJA program on the measure outcomes. After assessing both, which showed similar results, we opted for the SPC method, because this is what was used in the published papers on NINJA previously.[1,48,49] We set an *a priori* standard of eight consecutive biweekly measure rates below the established baseline rate to qualify as a statistical change (or special cause in process control vernacular), which corresponds to a 99.7% likelihood that the change observed resulted from the improvement intervention.[50] This methodology has served as the primary quality improvement assessment measurement to track the serious safety event rates for the Solutions for Patient Safety, a national pediatric harm reduction collaborative.[51]

At the conclusion of the first two aims, we were able to quantify the exact impact of NINJA in nine study hospitals compared with baseline, controlling for patient demographics, season, and baseline trends.

Aim 3: Assess the association between context, network participation, and reduction in NTMx-AKI by individual hospitals across the network.

To achieve this aim, we employed both qualitative comparative analysis using the cohort of nine hospitals and time-series regression stratified the data by context measure. Qualitative comparative analysis, *a method of grouping data sets and identifying causal relationships ideally suited for measuring complex interactions of different context measures in multiple healthcare systems,* is used increasingly in healthcare to study complex causality between characteristics of healthcare systems and healthcare quality outcomes; it is designed for studies with five to 50 systems. Qualitative comparative analysis is ideally suited for this aim, as we examine the complex interaction of different context measures in nine healthcare systems.[52,53]

Table 2: Context Measures

Context measure	Data range	Example: CCHMC	Example: another hospital
STRUCTURAL/ORGANIZATIONAL CHARACTERISTICS			
% admissions under 19 years old*	0-100%	95%	20%
Total number pediatric beds	58 – >300	500	50
CHA children's hospital listing	No (0) or Yes (1)	Yes	No
EXTERNAL FACTORS			
Network participation	0-1	1.0	0.3
PATIENT SAFETY CULTURE			
AHRQ Patient safety culture survey[54]			
Item A15. Patient safety never sacrificed to get work done	1-5	4.12	2.29
Item A18. Our procedures and systems are good at preventing errors from happening	1-5	4.11	2.74
AVAILABILITY OF IMPLEMENTATION AND MANAGEMENT TOOLS			
IT capacity[55]	0-7	7	2
Pharmacist time	0-100% FTE	50% FTE	10% FTE

*used as a proxy for being a children's hospital within a general hospital or a freestanding children's hospital

Context Measures: We selected context measures using the framework proposed in the AHRQ framework entitled "Assessing the Evidence for Context-Sensitive Effectiveness and Safety of Patient Safety Practices."[33] Specifically, we included measures for each of the four "high-priority contexts" identified in the report: (1) structural/organizational characteristics, (2) external factors, (3) patient safety culture, and (4) availability of implementation and management tools.[33] The measures we included in each category were based on review of our theoretical model for NINJA and key drivers for the Solutions for Patient Safety Network. To assess structural/organizational characteristics, we included the percent of admissions under 19 years old, the total number of pediatric beds, and the Children's Hospital Association rating as a children's hospital for each participating institution. We assessed our external factor, network participation, by quantifying the participation of each hospital in webinars, in-person meetings, and workgroup calls. We assessed patient safety culture using the AHRQ Patient Safety Culture Survey, in which all items have good response variability and dimension intercorrelations are moderate (0.56) at the hospital level.[54] We chose items A15 and A18 because, according to the article, these are associated with the category "Overall perceptions of safety" and are relevant to our efforts on NINJA.

Finally, we assessed availability of implementation and management tools by measuring two key drivers of successful reduction in NTMx-AKI: IT capacity and pharmacist time. Each site reported pharmacist time as the percent of full-time-equivalent pharmacists participating in NINJA work. Similarly, each site reported institutional information technology capacity using the Health Information Management Systems Society's Electronic Medical Record Adoption Model (http://www.himssanalytics.org/emram/emram.aspx), which quantifies adoption from zero (no electronic medical record in the lab, radiology, and pharmacy) to seven (complete electronic medical record, data warehousing, data continuity with emergency department and ambulatory settings).[55]

Qualitative comparative analysis - Qualitative comparative analysis is a research method that will allow us to identify and distinguish among the different combinations of causal and contextual conditions that lead to success using Boolean algebra to analyze subset relationships. Qualitative comparative analysis offers two main benefits for this study.[52,53] First, it is not subject to degrees-of-freedom limitations and can therefore be used with studies with fewer than 50 healthcare systems. Second, the technique is designed to tease out complex causal relationships, such as when different combinations of conditions lead to the same outcome. Qualitative comparative analysis allows us to identify different approaches that may lead to success. For example, at least a 50% pharmacist full-time equivalent may be necessary to reduce NTMx-AKI at any hospital. At larger hospitals, with a strong culture of safety, this may also be sufficient. At smaller hospitals or those with a weak culture of safety, large network participation and strong information technology capacity along with 50% pharmacist full-time equivalent may be sufficient to reduce NTMx-AKI.

There are three components to a qualitative comparative analysis: (1) data set calibration, (2) testing for necessary conditions, and (3) testing for sufficient conditions. Because qualitative comparative analysis is a set-theoretic technique, all variables in the data set must be converted so as to indicate degrees of set membership. This process is referred to as calibration and seeks to make measures meaningful. For example, our (uncalibrated) "patient safety culture" variable allows us to distinguish hospitals with higher safety culture survey scores from those with lower scores. Properly calibrated, however, the variable will allow us to additionally distinguish between hospitals with strong and weak safety cultures. When calibrated, a score of 1.0 indicates, for example, "fully in the set of hospitals with a strong safety culture," a score of 0.0 indicates "fully out of the set of hospitals with a strong safety culture," and scores in between indicate partial set membership.

The second step involved identifying context measures that are necessary for NINJA to be successful. For example, a certain amount of pharmacist time may be necessary for NINJA to be effective. A necessary condition is an important type of contextual factor: its presence does not ensure that the outcome will occur but, rather, its absence prevents the outcome from occurring all or most of the time. Testing for necessary conditions involves identifying any variables, or combinations of variables, that must be present for the outcome to occur. Necessary conditions can be complex and substitutable: for example, it may be that a certain amount of pharmacist time *or* information technology support is necessary for NINJA to reduce AKI, such that a hospital does not need both but rather one or the other. It is also possible to identify variables that are "almost always necessary." For example, strong network participation may be almost always necessary for NINJA to reduce AKI at study hospitals; that is to say, the absence of strong network participation usually, but not always, prevents NINJA from succeeding. Goodness of fit for necessary conditions is assessed through two measures: consistency, which assesses the strength of the necessary condition and whether it is always, usually, or sometimes necessary, and coverage, which assesses the empiric relevance of the necessary condition and distinguishes between trivial and nontrivial necessary conditions. A trivial necessary condition is something that almost all cases experience and therefore is not explanatory.

Testing for sufficient conditions involves identifying any variables, or combinations of variables, that produce the outcome all or most of the time. An important aspect of qualitative comparative analysis's sufficiency analysis is its sensitivity to causal complexity: it can identify different paths to the same outcome. For example, we do not expect that there is just one way to effectively implement NINJA. Indeed, we expect that, in order to be successful, the program will need to be implemented differently at different hospitals. Qualitative comparative

analysis will enable us to identify both the different contextual factors that affect how NINJA is to be implemented as well as the different ways of successfully implementing NINJA. Consistency and coverage are again used to assess goodness of fit.

Time-series analysis: We analyzed the impact of key contextual factors using time-series analysis. Because our study includes nine hospitals, we limited our stratified time-series analysis to two key contextual factors. We identified key factors using bivariate analysis. We then grouped our data into two groups based on whether or not they have these key factors. We performed stratified time-series analysis of each group of hospitals and compare results by taking the differences of AKI rates by these two groups. We conducted time series modeling on the difference using the same methods described in Aim 2.

At the completion of Aim 3, we will have identified key contextual factors that influence the overall reduction in NTMx-AKI produced by NINJA (analysis still in process). This information will be used to hone a change package, tailored to hospitals in different types of contextual groups, to facilitate spread of NINJA to the remaining 68 Solutions for Patient Safety Network hospitals. In addition, this approach to identifying the influence of complex contextual factors on dissemination of successful safety interventions will be generalized to other Solutions for Patient Safety network endeavors. Finally, this approach will also be generalized to other quality improvement networks.

Results

Individual centers began submitting data in October 2014. In the subsequent 8 months, centers undertook several initiatives and iterative "plan, study, do, act" (PDSA) cycles to pilot the NINJA project to increase the maturity of their programs. We developed a maturity score for the collaborative to track sophistication of the four components of the NINJA program (**Table 3**).

Table 3 – NINJA Maturity Scoring System

	<<<---- MATURITY SCORE---->>>				
Element	**0**	**1**	**2**	**3**	**4**
Type of Trigger Tool[a]	No Report	Manual	Snapshot	Snapshot PLUS	Automated
Medication List[b]	No medication list	25 medications	NA until 6/2016 45 medications after 6/2016	N/A	45 medications until 6/2016 61 medications after 2016
Service Lines Implemented (Capturing all exposures and monitoring serum creatinine)	No services	Less than 50%	50-74%	75%-99%	100%
Capturing Daily Serum Creatinine (Percent of exposed patients getting daily serum creatinine)	Not implemented	Less than 50%	50-74%	75-99%	100%

a. Definitions of Trigger Tools: **Automated** = a comprehensive scheduled report that shows all patients in the institution over all time periods; **Snapshot PLUS** = a combination of an on demand report and a backup system for identifying patients; **Snapshot** = an ad hoc report that users generate on demand or electronic indicators in the system that flag patients that meet exposure criteria at the time the report is reviewed; **Manual** = pharmacist/providers create ad hoc reports while they review med lists; do not have or use a specifically developed report

b. The initial medication list was comprised of the 45 medications used in the single center study. In March 2016, the list was updated by the collaborative to add an additional 16 medications. Sites were given 3 months to update their screening list to attain a full score of 4 in the medication list element of the maturity Score

c. NINJA Maturity Score Calculation Process:
   1. Centers ranks themselves on a scale of 0 to 4 for each maturity measure on a quarterly basis.
   2. Each center can have a max. score of 4 x 4 = 16
   3. The collaborative max. score = 16 x # of centers (9) = 144
   4. Ninja Collaborative Overall Maturity Score (percent) = [(Sum of self-rated total scores for all centers for all maturity measures) / 144] x 100

In May 2015, all nine centers were reliably transmitting data to the collaborative, and the collaborative achieved an aggregate maturity score of least 60. Therefore, May 2015 was considered the time point to set baseline rates for each of the measures. We collected data through June 2017 for the present analysis, comprising a total of 683,179 patient hospitalization days on the noncritical care units.

Overall, 4,898 exposed patients experienced 882 acute kidney injury episodes over the 2-year course of study. Exposure rates experienced an initial decrease from baseline but then increased, coinciding with increased collaborative maturity and the expanded medication list and increased service line participation at the hospitals. The exposure rate then decreased again, although this second decrease was observed with a stable maturity score (**Figure 3**). We observed sustained improvement in two of the other three measures: acute kidney injury rates per 1000 patient days (**Figure 4,** 22% reduction) and acute kidney injury episodes per exposure (28% reduction). Three of the measure rates were all similar to the final rates previously reported from the single center (**Table 4**).[49] Assuming that the initial baseline exposure and acute kidney injury rates would have persisted without implementation of NINJA, we estimate that 644 patient exposure and 346 patient AKI episodes were avoided by implementation of the NINJA program across the collaborative.

Individual Center Assessments

The baseline and end of study exposure and acute kidney injury rates for each center are depicted in **Figure 5**. Of note, five centers had lower baseline exposure and acute kidney injury rates than the aggregate collaborative baseline and end of study rates, and none of these centers demonstrated improvements in exposure or acute kidney injury rates by the end of the study period. However, all the remaining four centers demonstrated improvement in acute kidney injury rates, with three of these centers achieving rates below the aggregate collaborative acute kidney injury rates. Thus, all but one center was able to maintain or achieve an end of study acute kidney injury rate of fewer than 1.25 acute kidney injury episodes per 1000 patient hospitalization days.

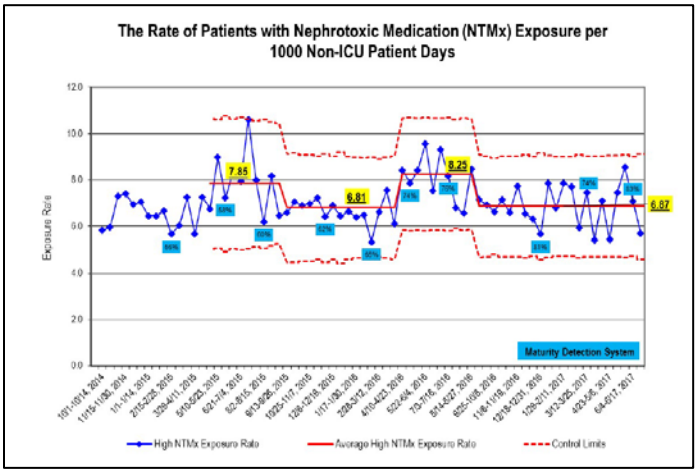


Figure 3 – Biweekly Collaborative Exposure Rates

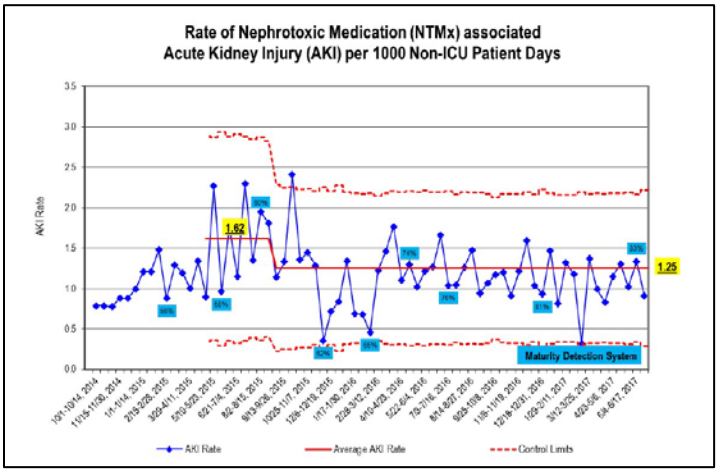


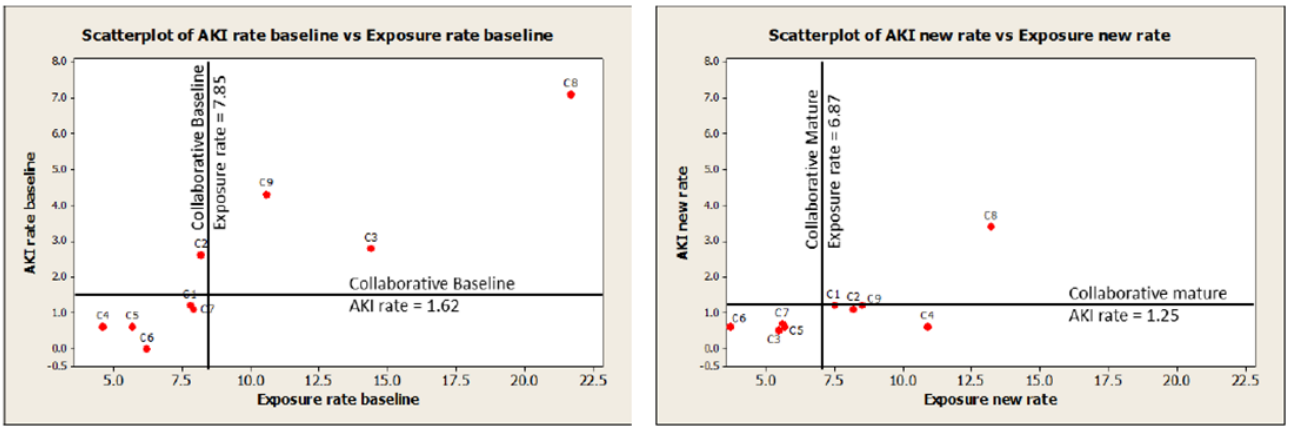
Figure 4 – Biweekly Collaborative AKI Rates

Table 4 - Baseline and End Measure Rates for the Collaborative and the Comparative Pilot Single Center

Measure	Collaborative Baseline	Collaborative End	Collaborative Change (%)	Single Pilot Center Comparator[58]
Exposure rate (per 1000 patient-days)	7.8	6.9	-11.5	7.5
Acute kidney injury rate (per 1000 patient-days)	1.6	1.25	-22	1.1

Measure	Collaborative Baseline	Collaborative End	Collaborative Change (%)	Single Pilot Center Comparator[58]
Acute kidney injury rate (per exposure)	20.8%	15.0%	-28	15.4%
Acute kidney injury Intensity rate (Acute kidney injury days/100 exposure days)	10.9	10.9	0	19.1

Figure 5 - Individual Center Baseline and End of Study Exposure and Acute Kidney Injury Rates



Initial Contextual Factor – Qualitative Comparative Analysis

Although this analysis is still ongoing, our initial analysis has found the following:

- Five out of nine health systems achieved a reduction in AKI over the entire time period.
- It was NECESSARY that, within the first 6 months, the institutional Informative technology department has begun to build reports on nephrotoxic medication exposure.
- It is SUFFICIENT to have achieved the above plus:
  - Have a pharmacist champion with hours and have two or more pharmacists or
  - Have no competing priorities.

DISCUSSION

This large, multicenter initiative that focused on nephrotoxic medication associated acute kidney injury in noncritically ill hospitalized children led to sustained reductions in high nephrotoxic medication exposure and acute kidney injury rates. The ultimate collaborative rates achieved after dissemination were the same or lower than the rates achieved in the single center that pioneered the program. All but one of the collaborative centers were able to achieve an acute kidney injury rate of less than 1.25 episodes per 1000 patient hospitalization days, and all the centers with baseline rates above this threshold were able to reduce their center acute kidney injury rates over the course of the study.

The outcomes of this study demonstrate that a sizable proportion of high nephrotoxic medication burden may be avoidable and therefore should be considered a potentially modifiable adverse safety event, similar to what was observed in the single-center study. Though nephrotoxic medications are often needed as appropriate therapy for a disease state causing hospitalization, the program's trigger to alert the healthcare team of increasing nephrotoxic medication burden likely focused attention on adjudicating which medications were necessary and which one could be discontinued or substituted with an equally efficacious, less nephrotoxic alternative.

A number of findings emanating from this collaborative work are novel in comparison to the single-center study. First, as opposed to the initial study, in which NINJA was implemented reliably across the enterprise with

all service lines participating and plasma creatinine assessed daily >99% of exposed patients, the collaborative started with lower aggregate maturity with respect to service line participation and consistent daily plasma creatinine assessment. Not unexpectedly, the collaborative exposure rates increased as the maturity score increased, likely reflecting the addition of the expanded medication list as well as increased new service lines or better automation in exposure detection. However, decreases in acute kidney injury rates were sustained, even with the improved exposure detection and collaborative maturity. The sustained acute kidney injury rate reductions observed in the collaborative suggests that centers maintained their vigilance on nephrotoxic medication burden and the associated acute kidney injury.

Another novel outcome is the observed individual center exposure and acute kidney injury rate changes from the beginning to the end of the observation period. The fact that all but one center that started above the end of study acute kidney injury rate of 1.25 episodes per 1000 patient days was able to achieve a rate lower than 1.25 episodes per 1000 patient days suggests that this threshold may be a reliable benchmark for future institutions to strive for. Furthermore, the observation that all five centers starting with exposure and acute kidney injury rates below the end of study thresholds did not improve in either measure suggests that these thresholds may be the limit of what can be achieved by solely sharing data and best practices and gaining reliability of a best practice standard. It also projects that achieving further harm reduction will require additional innovation. Such innovation may require assessment of the context that accelerates or provides barriers to implementation, as well as introduction of more intense or disease specific interventions over and above risk identification and daily plasma creatinine surveillance.

Despite the inherent strengths of a multicenter collaborative and the confirmatory nature of the outcomes achieved, this study has a number of limitations. First, we cannot extrapolate our data to critically ill patient populations, as acute kidney injury is usually multifactorial in critically ill patients. Second, it is possible that some patients had acute kidney injury resulting from causes in addition to nephrotoxin exposure. We suggest that this does not invalidate the benefit of our screening algorithm, because we detected a high rate of acute kidney injury rate in exposed patients, which would lead to appropriate interventions (dose reduction, medication change) irrespective of cause, a strategy recommended by the KDIGO Guidelines.[45] Future work can focus on enriching the nephrotoxic-medication-associated acute kidney injury clinical model with other causes to improve risk stratification. Third, though we can only speculate as to the reasons for changes in our observed measures, 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 either not part of the intervention (e.g., identification of certain combinations), not systematically assessed (CKD, dehydration) or not modifiable (CKD or genetic predisposition). Finally, it is possible that we had some unmeasured negative effects of decreasing nephrotoxic medication burden. For example, it is possible that we could have caused decreased infection eradication rates if the medications chosen over nephrotoxic medications were less efficacious, although this phenomenon was not observed in long-term outcome assessment to the single-center study.[49]

In conclusion, we demonstrated successful dissemination and implementation of a program to decrease nephrotoxic-medication-associated acute kidney injury in children to nine pediatric institutions. Given the ubiquitous administration of nephrotoxic medications to hospitalized individuals, we speculate that more widespread dissemination to other pediatric and adult centers could lead to decreased patient morbidity and associated healthcare costs of developing acute kidney injury. ***As a result of this success of this work, the Nephrotoxic Acute Kidney Injury has been selected as the next Hospital-Acquired Condition to be addressed by the Solutions for Patient Safety. Thus, the NINJA program will be disseminated to the 140 pediatric institutions in the SPS Network by 2020.***

List of Publications and Products

Oral Abstract Presentations at the Pediatric Academic Societies Meeting, Toronto, Canada 2018

1. Goldstein SL, Dahale DL, Askenazi D, Somers M, Warady B, Chadha V, Sutherland S, Misurac J, Zaritsky J, Steinke J, Hackbarth R, Yonekawa K, Symons J, Weng P, Mottes T, Muething S, Eric Kirkendall E: Reduction of Nephrotoxic Medication Associated Acute Kidney Injury (NTMx-AKI): The First Report from the Multi-Center NINJA Consortium. Pediatric Academic Societies, May 2018
2. Walsh KE, Kaplan H, Goldstein SL, Daraiseh N, Muething S, Rubinson C, Askenazi D, Warady B, Mottes T, Sutherland S, Steinke J, Hackbarth R, Somers M, Misurac J, Chadha V, Yonekawa K, Symons J, Zaritsky J, Weng P, Dahale D, Kirkendall E: Modifiable Factors that Improve the National Spread of a Safety Intervention to Decrease AKI. Pediatric Academic Societies, May 2018

Planned publication submission

1. Reduction of Nephrotoxic Medication Associated Acute Kidney Injury at Nine Pediatric Hospitals: *The New England Journal of Medicine*. Planned submission date July 2018
2. Development of Medications to Target for a Nephrotoxic Medication Associated Acute Kidney Injury Reduction Project: *Pediatrics*. Planned submission date September 2018

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