Baby NINJA (Nephrotoxic Injury Negated by Just-in-Time Action): Reduction of Nephrotoxic Medication-Associated Acute Kidney Injury in the Neonatal Intensive Care Unit

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Objective(s) To test if acute kidney injury (AKI) is preventable in patients in the neonatal intensive care unit and if infants at high-risk of nephrotoxic medication-induced AKI can be identified using a systematic surveillance program previously used in the pediatric non-intensive care unit setting.

Study design Quality improvement project that occurred between March 2015 and September 2017 in a single center, level IV neonatal intensive care unit. Infants were screened for high-risk nephrotoxic medication exposure (≥3 nephrotoxic medication within 24 hours or ≥4 calendar days of an intravenous [IV] aminoglycoside). If infants met criteria, a daily serum creatinine (SCr) was obtained until 2 days after end of exposure or end of AKI, whichever occurred last. The study was divided into 3 eras: pre-Nephrotoxic Injury Negated by Just-in-time Action (NINJA), initiation, and sustainability. Differences for 5 metrics across 3 eras were compared: SCr surveillance, high nephrotoxic medication exposure rate (per 1000 patient-days), AKI rate (per 1000 patient-days), nephrotoxin-AKI percentage, and AKI intensity (number of AKI days per 100 susceptible patient-days).

Results Comparing the initiation with sustainability era, there was a reduction in high nephrotoxic medication exposures from 16.4 to 9.6 per 1000 patient-days ($P = .03$), reduction in percentage of nephrotoxic medication-AKI from 30.9% to 11.0% ($P < .001$), and reduction in AKI intensity from 9.1 to 2.9 per 100 susceptible patient-days ($P < .001$) while maintaining a high SCr surveillance rate. This prevented 100 AKI episodes during the 18-month sustainability era.

Conclusion(s) A systematic surveillance program to identify high-risk infants can prevent nephrotoxic-induced AKI and has the potential to prevent short and long-term consequences of AKI in critically ill infants. *(J Pediatr 2019;215:223-8)*.

Nephrotoxic medication-induced acute kidney injury (nephrotoxic-AKI) is a common and underdiagnosed morbidity in the hospitalized pediatric population. Approximately 30% of hospitalized noncritically ill children exposed to nephrotoxic medications develop AKI, and those who receive 3 or more concomitant nephrotoxins or are recipient of prolonged intravenous aminoglycoside antibiotics are at increased risk.[1] Nephrotoxic Injury Negated by Just-in-Time Action (NINJA) is a multicenter, quality improvement collaborative whose aim is to reduce nephrotoxic medication exposure and related AKI in the non-intensive care (ICU) setting. In its 2016 single-center sustainability report of noncritically ill hospitalized patients (mean age 8.7 years), the group reported a reduction of nephrotoxic medication exposure rate by 38% and the rate of incidence of AKI by 64%.[2]

Exposure to nephrotoxic medications in neonates admitted to the neonatal intensive care unit (NICU) is even higher, with up to 87% of very low birth weight (VLBW) infants exposed to at least 1 nephrotoxic medication during their hospitalization.[3] About one-quarter of infants admitted to a NICU will develop at least 1 episode of AKI, and neonatal AKI is independently associated with increased mortality and prolonged length of stay.[4,5] Because neonatal nephrogenesis is not complete until 36 weeks postgestational age, many patients in the NICU have an incomplete complement of mature nephrons and glomeruli compared with their full-term counterparts. AKI during times of postnatal glomeruli growth and maturation may have detrimental effects on the

AKI	Acute kidney injury
CKD	Chronic kidney disease
ICU	Intensive care unit
NICU	Neonatal intensive care unit
NINJA	Nephrotoxic Injury Negated by Just-in-time Action
QI	Quality improvement
SCr	Serum creatinine

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long-term nephron development and risk of subsequent chronic kidney disease (CKD).[6-9]

NINJA demonstrated consistent reductions in nephrotoxic medication exposure and nephrotoxic-AKI in the noncritically ill pediatric population, suggesting that stewardship of nephrotoxic medication exposure can reduce AKI, but its implementation and reduction of AKI in the intensive care setting has yet to be determined. Presently, no medicines exist for treatment of AKI in the NICU, and when AKI occurs, acute dialysis may not be feasible in very low birth weight infants (<1500 g). With lack of treatment options in a population at higher risk of CKD, AKI prevention programs focused on reducing neonatal and infantile AKI have the potential for profound impact.

To advance our understanding, prevent nephrotoxic medication exposure, and improve AKI surveillance in the NICU, we performed and reported on a 24-month quality improvement (QI) project in a level IV (nondelivery) NICU entitled "Baby NINJA." Our hypothesis is that improved screening and stewardship of nephrotoxic medication exposures will reduce AKI in the NICU setting.

Methods

This prospective QI initiative project occurred at the Children's of Alabama 48-bed level IV NICU. All admitted infants who met exposure criteria were included except those with end-stage kidney disease who were receiving dialysis. Data were compared across 3 eras (pre-NINJA, initiation, sustainability) and were reported in statistical control charts using aggregate monthly data based on 5 previously established metrics for high nephrotoxic-AKI by the NINJA collaborative.[10] SAS v 9.4 (SAS Institute, Cary, North Carolina) was used for all analyses. The University of Alabama at Birmingham Institutional Review Board reviewed and approved the conduct of the study with waiver of parental informed consent.

Following education and project initiation, each weekday morning an automated screening report of patients with high nephrotoxic medication exposure, defined as ≥3 nephrotoxic medication within 24 hours (**Table I**; available at www.jpeds.com) or ≥4 calendar days of an intravenous (IV) aminoglycoside, was reviewed by the NICU pharmacists who manually verified exposure validity. On weekends, this role was performed by the clinical team without the automated report. If an infant had a high nephrotoxic medication exposure and met study criteria, rounding NICU pharmacists recommended a daily SCr during high nephrotoxic medication exposure and for 2 days postexposure or post-AKI resolution, whichever occurred last. No specific recommendations to adjust medications or alter length of therapy were mandated by the NINJA protocol. Instead, the team discussed possible alternative medications, drug dosages, timing of drug levels, and hydration status based on patient-specific needs. According to a previously published NINJA protocol, a patient encounter was closed for one of the following reasons: 2 days post-end of exposure, 2 days post-AKI with normal SCr, hospital discharge, death, or exposure to high nephrotoxic medication medications for more than 28 days (eg, "reset").[10]

NINJA metrics were captured by a clinical research nurse who verified inclusion criteria, obtained SCr values, and tracked the NINJA metrics previously published (**Table II**; available at www.jpeds.com).[10] SCr compliance was reported as a process metric to monitor SCr adherence as the rates of AKI will drop without ascertaining for this outcome.

Some adaptations to the NINJA protocol were made to address unique attributes of the patient population found in the NICU and used throughout all 3 eras of this project. The first was an extension to those infants who received IV aminoglycoside from 3 days to 4 or more calendar days. The rationale for this adaptation was that many infants who receive ≤48 hours of empiric antibiotic coverage would meet the 3-calendar day criterion (ie, an infant receives a dose at 11 p.m. on day 1, 2 doses on day 2, and 1 dose at 11 a.m. on day 3). The second adaption was to the definition of baseline SCr, because initial SCr values often reflect maternal SCr values in neonates. Baseline SCr value was established based on postnatal days. Therefore, for infants exposed during the first 14 days of life, each SCr value was compared with the lowest previous value. For infants >14 days of life, the lowest previous SCr before exposure was used to compare with all subsequent values. A SCr of ≥0.5 mg/dL was defined as meeting AKI criteria.

Data were reported across 3 different eras. The pre-NINJA era was a 6-month retrospective review of data collected from medical records of all infants who were admitted to the NICU between March 1, 2015 and August 31, 2015. This era established the baseline rates of outcomes prior to any heightened surveillance or change in practice. This was followed by a one month "washout period" (September 2015) during which all clinical staff and pharmacists were trained on NINJA metrics and processes. The initiation era was a 6-month period (October 1, 2015 through March 31, 2016) duing which metrics were evaluated shortly after NINJA implementation. The sustainability era was an 18-month period (April 1, 2016 through September 30, 2017) to capture data after the initial 6 months until the end of the observation period for the project.

Statistical process control charts with mean and upper and lower control limits were created using aggregate monthly data for each metric. Differences by eras were compared for patient characteristics and the NINJA metrics. To assist with the interpretation of the multiple metrics, **Figure 1** consolidates high nephrotoxic medication exposure, nephrotoxic-AKI, and SCr compliance rates grouped by eras.

Statistical Analyses

Continuous variables are reported as mean ± SD and analyzed using a Student *t* test. Categorical variables were

analyzed by proportional difference with the χ^2 test. Poisson regression analysis was performed to detect differences in rates by eras. To evaluate the trigger algorithm's effect on AKI epidemiology, statistical process control methods to detect changes from baseline rates for each metric were used similar to previous NINJA studies.[10] A standard of 6 consecutive weekly metric rates below or above the baseline rate was required to qualify as a statistical change.[10] Upper and lower control limits are denoted on all control charts with lower borders listed instead when the lower control limit was less than zero.

Results

During the 30-month period of Baby NINJA, 476 individual high nephrotoxic exposure events were encountered (432 unique exposures, 44 repeat exposures). Over this time, AKI occurred in 19.7% (94 out of 476) of high nephrotoxic medication exposure events. Of the high nephrotoxic medication exposure events, 52.9% (252 out of 476) occurred in neonates (defined as <28 days of life) and 47.1% (224 out of 476) occurred in infants (≥28 days of life). There was no difference in gestational age or age at exposure among infants across the three eras (**Table III**). From the list of 57 high nephrotoxic medication medications listed for inclusion criteria for NINJA (**Table I**), 17 were used in our NICU (acyclovir, amphotericin B, captopril, cefotaxime, ceftazidime, enalapril/enalaprilat, ganciclovir, gentamicin, ibuprofen, lisinopril, nafcillin, piperacillin/tazobactam, piperacillin, tobramycin, valacyclovir, valganciclovir, vancomycin). The most commonly used medications were vancomycin, gentamicin, and tobramycin. The data are presented in 3 eras, and the delineation between the initiation and sustainability eras coincided with statistically significant differences seen in the control charts for high nephrotoxic medication exposure and AKI rates.

Adherence to the Baby NINJA protocol was gauged by SCr compliance. The SCr compliance rate was lower during the pre-NINJA era vs the initiation era (56.5% vs 90.7%; $P < .001$). SCr compliance remained high during the sustainability era ($\bar{x} = 86.1\%$, range = 75.1%-94.6%) with no statistical difference when compared with the initiation era ($P = .95$) (**Table III** and **Figure 2**; **Figure 2** available at www.jpeds.com).

Compared with the pre-NINJA era, the high nephrotoxic medication exposure rate increased during the initiation era and decreased during the sustainability era, demonstrated by a shift in the mean of the control chart (**Table III** and **Figure 3**). Compared with the initiation era, the nephrotoxic medication exposure rate decreased during the sustainability era as well (**Table III** and **Figure 3**). An evaluation of possible differences in the types of high nephrotoxic medication exposure between eras revealed that a significantly higher percentage of infants met the ≥3 nephrotoxic medication criterion alone in the sustainability era compared with pre-NINJA ($P < .05$) and the initiation era ($P < .05$) (**Figure 4**; available at www.jpeds.com).

Compared with the pre-NINJA era, the AKI rate increased during the initiation era. Compared with the initiation era, there was a reduction in the AKI rate during the sustainability era (**Table III**). These shifts in AKI rates can also be observed in the control chart (**Figure 5**; available at www.jpeds.com).

Compared with the pre-NINJA era, there was no statistically significant change in the percentage of infants with high nephrotoxic medications exposures with AKI (25.2 vs 30.9%; $P = .339$) in the initiation era; however, this rate dropped to 11.0% ($P < .001$) during the sustainability era

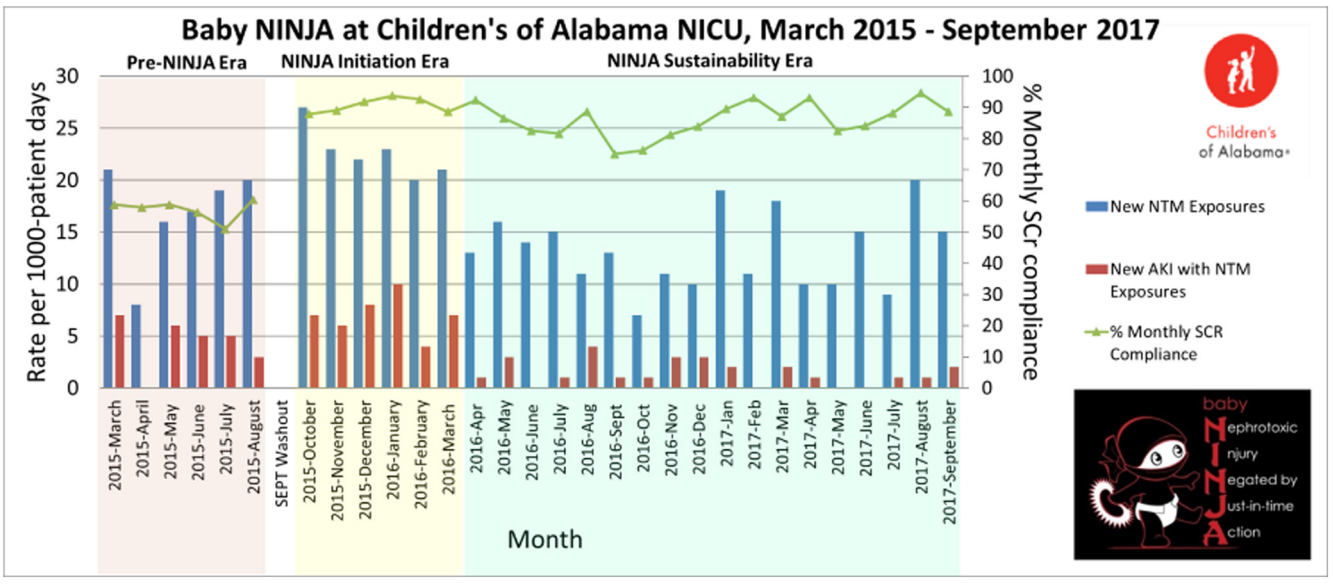

Figure 1. Outcome measures for high nephrotoxic medication exposure and AKI rate in the NICU

Table III. Demographics and outcome measures for high nephrotoxic medication exposure and AKI rate in the NICU

Demographics	Pre-NINJA era	NINJA initiation era	NINJA sustainability era	*P* value*	*P* value†	*P* value‡
Gestational age at birth ($\bar{x} \pm$ SD)	31.2 ± 6.4	31.3 ± 6.6	32.2 ± 6.3	.118	1.305	1.339
Gestational age at exposure ($\bar{x} \pm$ SD)	40.3 ± 10.4	39.1 ± 11.3	39.8 ± 9.2	.841	.650	.442
Age of exposure, d ($\bar{x} \pm$ SD)	62.8 ± 73.4	57.9 ± 117.2	53.9 ± 75.5	.372	.400	1.007
Outcome Measures						
SCr compliance	56.5%	90.7%	86.1%	<.001	.950	<.001
High nephrotoxic medication exposure prevalence rate (per 1000 patient-d)	12.4	16.4	9.6	.034	<.001	.030
AKI prevalence rate (per 1000 patient-d)	3.1	5.1	1.1	.055	<.001	<.001
Rate of patients with high nephrotoxic medication exposure who develop AKI (%)	25.2	30.9	11.0	.339	<.001	<.001
AKI intensity rate (per 100 susceptible patient-d)	6.0	9.1	2.9	.010	<.001	<.001

Simple *t* test for continuous variables, all other statistics performed with Poisson regression analysis with exception of χ^2 for % of high nephrotoxic medication exposure who develop AKI.
*Pre-NINJA era vs NINJA initiation era.
†NINJA initiation era vs NINJA sustainability era.
‡Pre-NINJA era vs NINJA sustainability era.

(Table III). These shifts in the percentage of AKI in those with nephrotoxic medication exposure are similar to those observed in the control chart (Figure 6).

Compared with the pre-NINJA era, the AKI intensity increased in the initiation area. Subsequently, compared with the pre-NINJA and initiation era, the AKI intensity rate decreased significantly during the sustainability era (Table III). These observations are also seen in the shift in the control chart (Figure 7; available at www.jpeds.com).

Discussion

Our study applied the NINJA program to an ICU setting. We demonstrated that using daily SCr surveillance and medication stewardship by the primary ICU team to identify infants at risk for nephrotoxic-AKI significantly reduced the rates of nephrotoxic exposure and AKI.

After implementation of the NINJA protocol, an increase in AKI rates and AKI intensity was observed, likely as a result

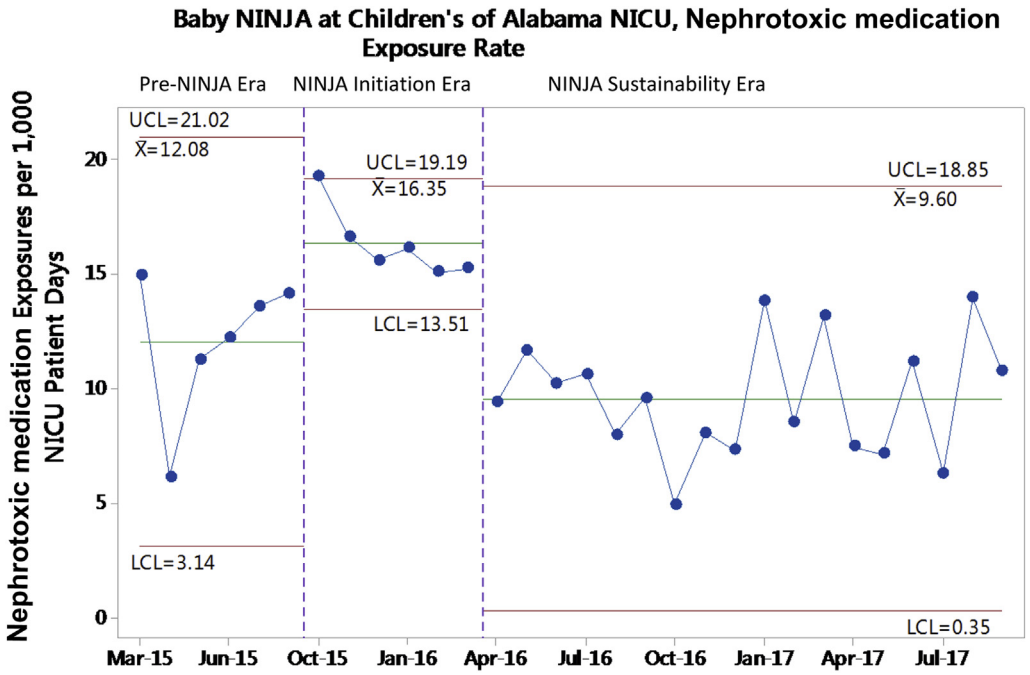

Figure 3. Process control chart of high nephrotoxic medication exposure prevalence rate (per 1000 patient-days) during 3 eras in the NICU.

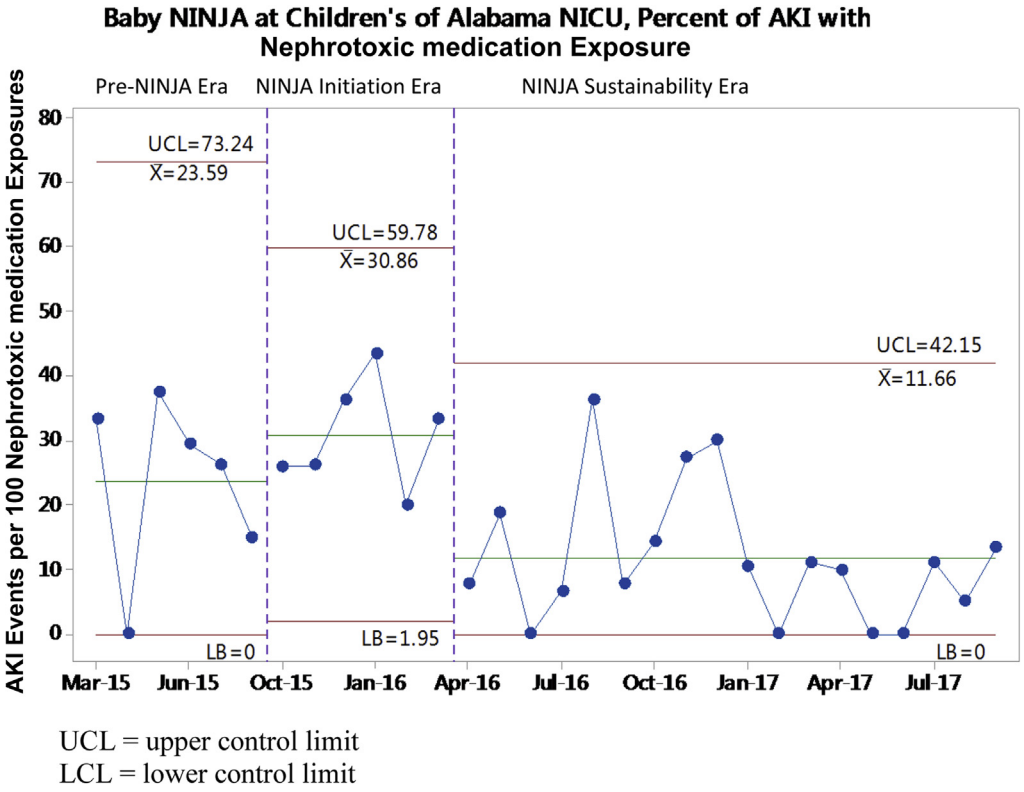

Figure 6. Process control chart of rate of patients with high nephrotoxic medication exposure who develop AKI (%) during 3 eras in the NICU. *LB*, lower border.

of enhanced surveillance. Compared with the baseline levels (established during the initiation era), the rate of high nephrotoxic medication exposures during the sustainability era was reduced by 42%, the rate of AKI by 78%, the percentage of AKI in those with high nephrotoxic medication exposure by 64%, and the number of days in AKI by 68% rate. We estimate this prevented approximately 100 AKI episodes and prevented 157 days of AKI in the NICU in the 18 months of the sustainability era. This was accomplished while maintaining an excellent SCr compliance rate throughout the study period, confirming that the reduction of AKI rates occurred even in the presence of sustained heightened surveillance for AKI. Importantly, no specific medication changes were mandated; rather, the clinical team made patient-specific decisions based on hydration status, considerations of medication adjustment/discontinuation, and alterations in high nephrotoxic medication pharmacologic monitoring.

There was an overall increase in nephrotoxic medication exposure rates and AKI rates following the initiation of Baby NINJA (noted in the initiation era). There are several possible explanations including seasonal variation, increase in patient population complexity, change in practice patterns, and/or ascertainment bias. We found no significant temporal variations or trends of nephrotoxic medication exposure and AKI rates among the 3 eras which covered 30 months of time (**Figure 1**). To evaluate clinical practice variation, differences in the types of high nephrotoxic medication exposure between eras were evaluated. We found that a higher percent of infants met the ≥3 nephrotoxic medication criterion alone in the sustainability era compared with pre-NINJA era and the initiation era (both $P < .05$) (**Figure 4**). This implies that clinicians were more cognizant of prolonged use of aminoglycosides overall and were more aware of prescribing these medications in combination with other nephrotoxic medication medications. Although there are other possible explanations similar to the increase in exposure rate, the most likely explanation for the increasing rates of AKI after initiation of the program is that the rate of SCr compliance increased dramatically, as expected.

Compared with other nephrotoxic-AKI prevention programs, we show a reduction in AKI that is comparable with and perhaps even more impactful than in the non-ICU patient population.[2] In non-ICU patients, Goldstein et al found a 38% reduction of nephrotoxic medication exposure, and we report a 42% reduction. They showed a 64% reduction in the AKI exposure rate, compared with our 78% reduction. They found a 34% reduction in nephrotoxic-AKI, compared with our 64% reduction, and a 31% reduction in the AKI Intensity rate (we showed a 68% reduction). The nephrotoxic medication exposure and AKI rates are higher in the NICU population study, likely because of higher acuity of the patient population in combination with less mature renal physiology.

Attempts by others to reduce AKI using system-wide AKI alerts have shown mixed results. For example, Park et al[11]

demonstrated reduced odds of severe AKI and improved recovery rates when using an AKI alert to initiate a nephrology consultation. As opposed to the nephrology consultation, our project used a pharmacist-physician evaluation that is likely comparable in evaluation and recommendations. Other studies using only an electronic medical record alert report increased AKI detection but were unable to show improvement in outcomes.[12,13] Possible explanations for the success of our project includes focused reduction of known risk factors, multidisciplinary approach within the ICU, "buy-in" from all caregivers, and a systematic approach to care.

Our study has strengths and limitations. First, the utilization of a semi-automated reporting system that identified high exposure patients followed by verification of the reports by pharmacy staff ensured accurate identification of all infants who met enrollment criteria. Internal validity was obtained because all information underwent double verification at a later date by a team member that was not part of the clinical care team. In addition, there was excellent SCr compliance after NINJA initiation which suggests that our AKI rates are accurate. There was superb involvement of all team members with frequent updates that contributed to project adherence. The long sustainability period allowed evaluation of project effectiveness in the presence of potential seasonal and clinical variabilities beyond our control. Nevertheless, there are some limitations of the study. It has limited generalizability as it was a single center project in a level IV NICU which includes numerous medically complex infants many of whom require surgical intervention, including those who undergo extracorporeal membrane oxygenation (ECMO). Although the most widely used SCr-based definition for neonatal AKI was used, urine output was not used in the definition. Furthermore, AKI in the ICU setting can be multifactorial and not solely because of nephrotoxic medication exposures. The variability of SCr values during the first week of life makes determining the baseline SCr values difficult in neonates. Last, because of the lack of NICU pharmacists on weekends and some electronic medical record limitations, a small number of exposures that occurred on weekends relied on clinicians to identify and include those infants who met exposure criteria.

In conclusion, this study demonstrates that that systematic surveillance of high nephrotoxic medication exposure and real-time risk assessment for AKI in the NICU can prevent neonatal and infantile AKI. With the first application of the NINJA QI program to the ICU setting, it is evident that reductions of nephrotoxic medication exposure and AKI can be achieved at similar proportions compared with the noncritically ill patient population. Consistent screening of at-risk infants with serial SCr reveals that many episodes of AKI could be missed if daily systematic evaluation is not implemented. Our approach to identify and evaluate the need for nephrotoxic medications in at-risk patients can reduce the number of AKI events and days spent in AKI. This has the potential to decrease short- and long-term morbidity in neonates/infants, including the risk of CKD on a global level.[8] Application of this approach in other regions and types of NICUs is needed before these findings can be generalized to all NICUs. In the future, we hope to be able to use noninvasive methods to evaluate for nephrotoxic-AKI (such as urine biomarkers) to decrease the need for blood draws. Moreover, identifying additional clinical factors in conjunction with nephrotoxic medication exposure may improve our approach to the care of this high-risk patient population. ■

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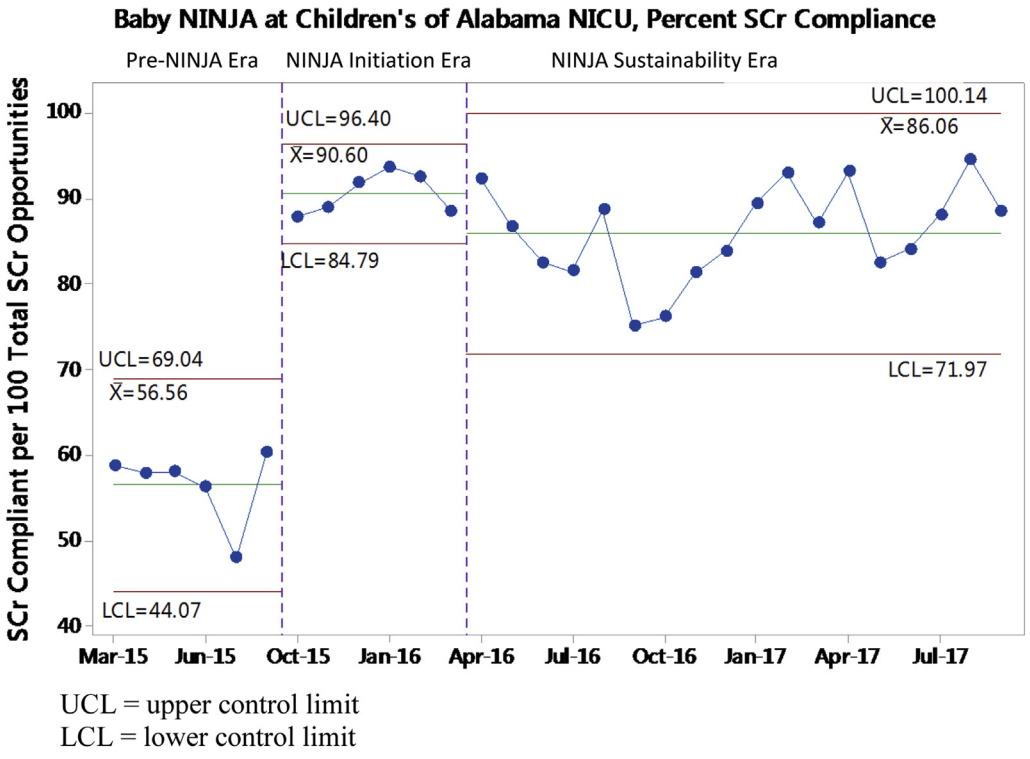
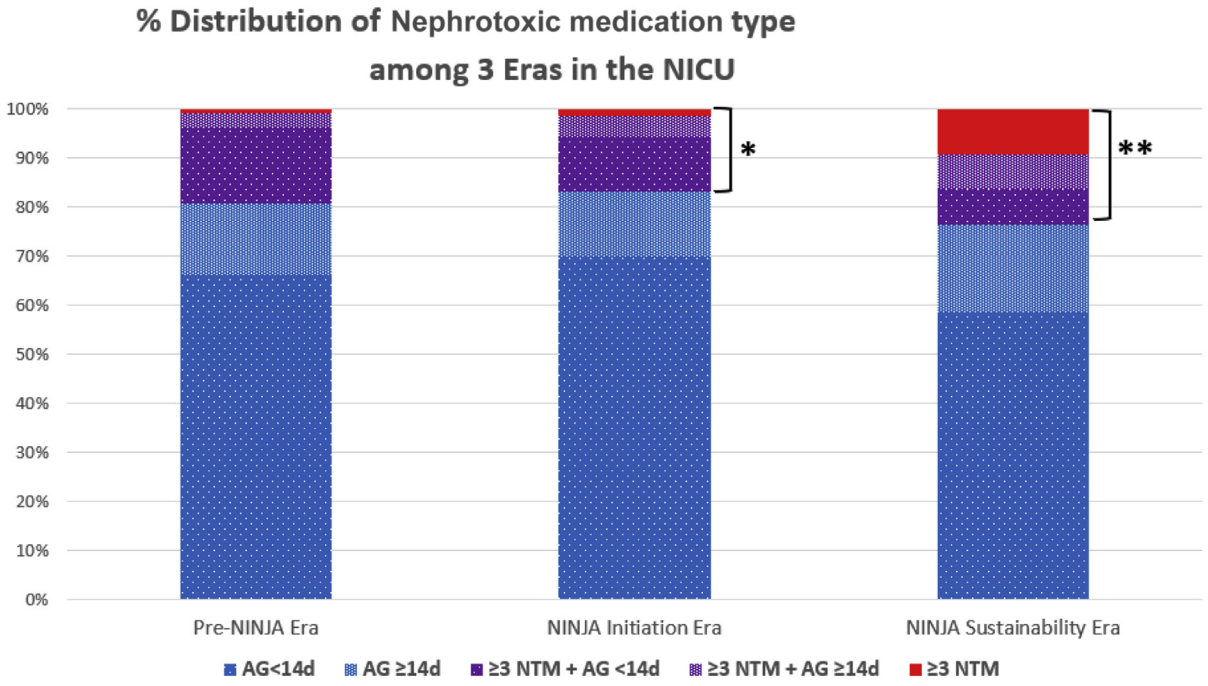


Figure 2. Process control chart of SCr compliance during 3 eras in the NICU.



* ≥3 high Nephrotoxic medication exposures in NINJA Initiation Era vs NINJA Sustainability Era, performed with chi-square analysis, $P<.05$

** ≥3 high nephrotoxic medicationexposures in Pre-NINJA Era vs NINJA Sustainability Era, performed with chi-square analysis, $P<.05$

AG = aminoglycoside

Figure 4. Percent distribution of high nephrotoxic medication exposure type among 3 eras in the NICU.

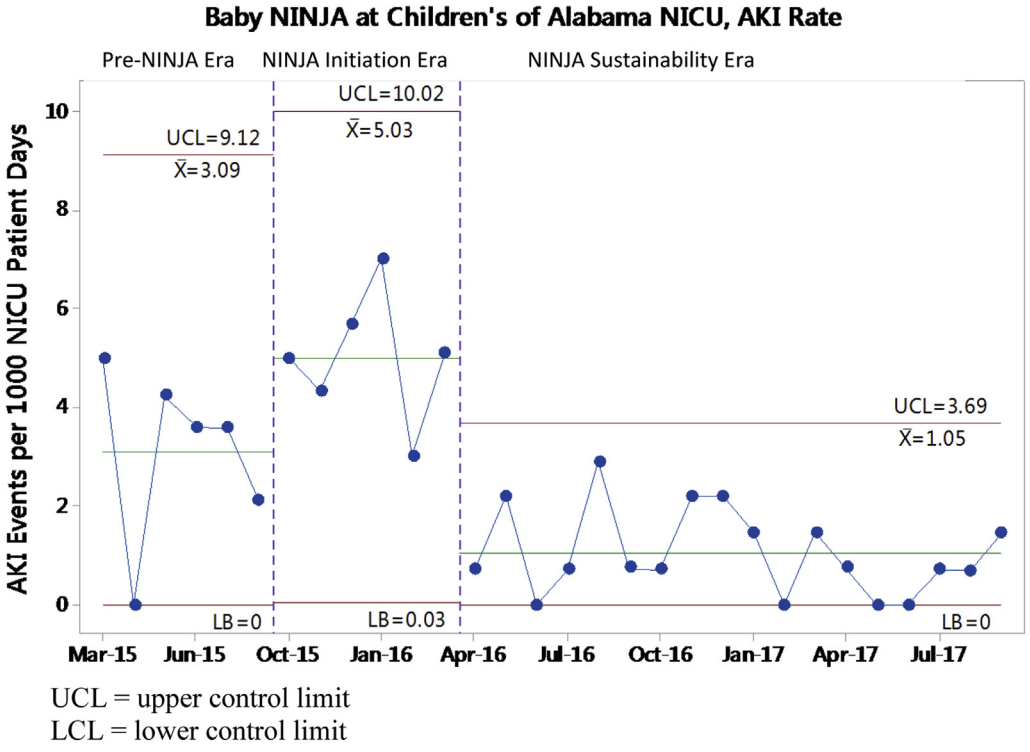


Figure 5. Process control chart of AKI prevalence rate (per 1000 patient-days) during 3 eras in the NICU. *LB*, lower border.

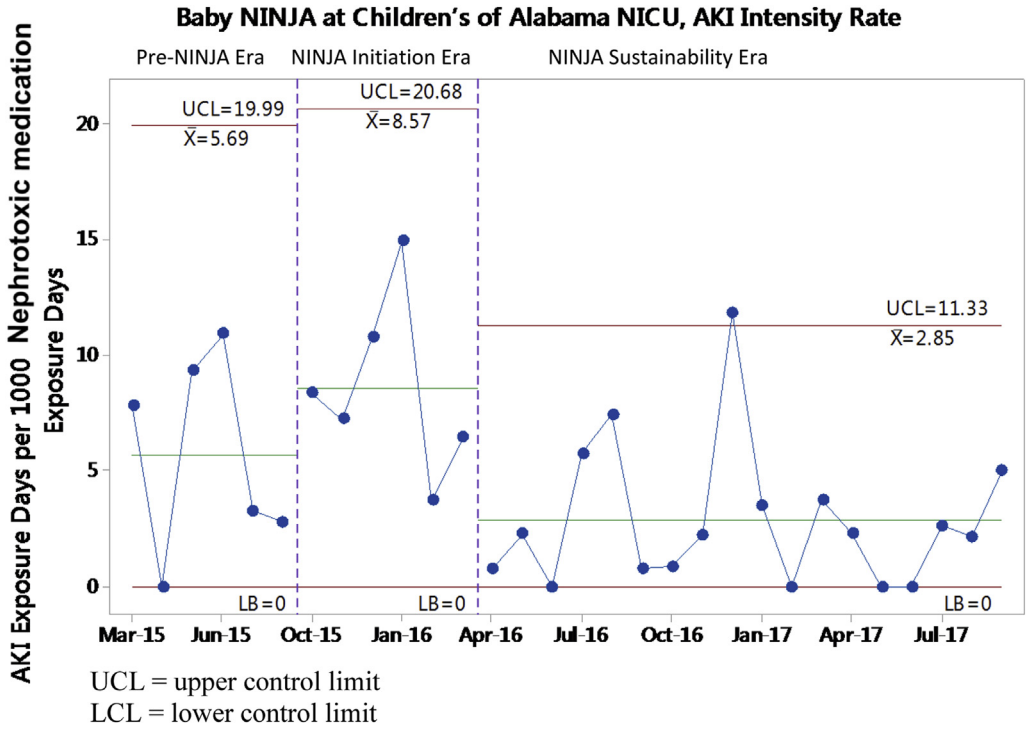


Figure 7. Process control chart of AKI intensity rate (per 100 susceptible patient-days) during 3 eras in the NICU. *LB*, lower border.

Table I. List of nephrotoxic medications

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

*Medications counted for 7 days after administration toward exposure.

Table II. Outcome measures and definitions

Measure names	Numerator	Denominator	Clinical meaning
Process metric			
SCr compliance (%)	Number of SCr values obtained	Number of SCr values that should be obtained per NINJA protocol	This measure generates the fraction of goal SCr values obtained per NINJA protocol
Outcome metrics			
High nephrotoxic medication exposure prevalence rate (per 1000 patient-d)	Number of new patients with high nephrotoxic medication exposure in the calendar wk of study	The total number of patient hospital d standardized per 1000 patient d in the calendar wk of study	This measure generates a normalized rate of high nephrotoxic medication exposure cases per study wk
AKI prevalence rate (per 1000 patient-d)	Number of patients with high nephrotoxic medication exposure who developed AKI in the calendar wk of study	The total number of patient hospital d standardized per 1000 patient d in the calendar wk of study	This measure generates a normalized rate of AKI cases per study wk
Rate of patients with high nephrotoxic medication exposure who develop AKI (%)	Number of patients who develop AKI	Number of new patients with high nephrotoxic medication exposure in the calendar wk of study	This measure generates the fraction of patients with high nephrotoxic medication exposure who develop AKI
AKI intensity rate (per 100 susceptible patient d)	Number of days patients have AKI	The total number of susceptible patient d standardized per 100 susceptible d	This measure depicts a normalized duration of AKI per susceptible d