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Use of the NINJA (Nephrotoxic Injury Negated by Just-in-Time Action) Program to Identify Nephrotoxicity in Pediatric Patients with Cystic Fibrosis

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OBJECTIVE This study aims to use and evaluate the Nephrotoxic Injury Negated by Just-in-time Action (NINJA) program in hospitalized patients with cystic fibrosis (CF) at Children's Healthcare of Atlanta.

METHODS This was a single-center study evaluating patients with CF who were hospitalized and admitted to the pulmonary service 4 months pre- and post-NINJA implementation. Postimplementation patients with high nephrotoxic medication (NTMx) exposure were identified using an electronic reporting tool that triggered the pharmacist to alert the medical team and recommend Monday/Wednesday/Friday serum creatinine (SCr) monitoring. High NTMx exposure was defined as 3 or more NTMxs given concurrently, or at least 3 consecutive days of IV aminoglycosides or vancomycin. Outcomes assessed were rate of SCr monitoring, NTMx exposure, and days of acute kidney injury (AKI) pre- and post-NINJA implementation.

RESULTS A total of 19 patients and 25 high-NTMx exposures were identified both pre- and post-NINJA implementation. The SCr monitoring increased from 13% to 50% of NTMx exposure days in the pre- versus post-NINJA time frame. More NTMx exposure days occurred in the post-NINJA time frame, from 250 exposure days per 1000 patient days pre-NINJA to 521 post-NINJA. An increased incidence of AKI events and AKI days were noted post-implementation; however, these differences were not significantly different between the 2 groups.

CONCLUSIONS Increased SCr monitoring for patients with NTMx exposure using NINJA uncovered more episodes of AKI. Increased prevalence of NTMx use was associated with increased rates of AKI. Increased SCr monitoring as a result of NINJA implementation may allow for earlier detection of AKI.

ABBREVIATIONS AKI, acute kidney injury; CHOA, Children's Healthcare of Atlanta; CF, cystic fibrosis; ICU, intensive care unit; IV, intravenous; NINJA, Nephrotoxic Injury Negated by Just-in-time Action; NTMx, nephrotoxic medication; NTMx-AKI, nephrotoxin-associated AKI; pRIFLE, pediatric Risk, Injury, Failure, Loss and End-Stage Kidney Disease; SCr, serum creatinine

KEYWORDS acute kidney injury; cystic fibrosis; nephrotoxic medication–associated acute kidney injury; pediatrics; quality improvement; serum creatinine

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Introduction

Acute kidney injury (AKI) is defined as an abrupt decline in renal function and is assessed by clinical biomarkers, such as serum creatinine (SCr) and urine output.[1] Nephrotoxic medication-–associated AKI (NTMx-AKI) has been identified as the primary cause of 16% of pediatric AKI cases.[2] Moffett et al[3] found that NTMx-AKI rates reach 19% to 31% in children who receive an IV aminoglycoside for more than 5 days, and the rate of AKI doubles when children receive 3 or more NTMxs simultaneously. Certain patient populations, such as those with cystic fibrosis (CF), are routinely exposed to NTMx during hospitalization for pulmonary exacerbations. The use of aminoglycosides as first-line therapy for CF patients has become a standard of care due to their pharmacologic activity against the most common offending respiratory pathogen in CF patients, *Pseudomonas aeruginosa*.[1] A similar study published by Askenazi et al[4] found that approximately one quarter of hospitalized patients with CF will develop AKI, suggesting that the incidence of AKI in this patient population is higher than what has previously been reported in the literature.[4]

In 2011, the team at Cincinnati Children's Hospital pioneered the Nephrotoxic Injury Negated by Just-in-time Action (NINJA) program, a quality improvement initiative that aims to improve safety and avoid harm from NTMx exposure in hospitalized children. NINJA aims to increase awareness and prevent NTMx-AKI by recommending daily monitoring of SCr and reducing nephrotoxin exposure when possible. The overarching goal is to ensure children only receive the NTMx they

Table 1. Nephrotoxic Medication List[6]

Acyclovir	Diatrizoate sodium*	Ioxaglate meglumine*	Piperacillin
Amikacin	Enalapril	Ioxaglate sodium*	Piperacillin/tazobactam
Amphotericin liposomal*	Enalaprilat	Ioxilan*	Polymixin B
Amphotericin B	Foscarnet	Ketorolac	Sirolimus
Aspirin	Ganciclovir	Lisinopril	Sulfasalazine
Captopril	Gentamicin	Lithium	Tacrolimus
Carboplatin	Ibuprofen	Losartan	Tenofovir
Celecoxib	Ifosfamide	Mesalamine	Ticarcillin/clavulanic acid
Cidofovir*	Indomethacin	Methotrexate	Tobramycin
Cisplatin	Iodixanol*	Mitomycin	Topiramate
Colistimethate	Iohexol*	Nafcillin	Valacyclovir
Cyclosporine	Iopamidol*	Naproxen	Valsartan
Deferasirox	Iopromide*	Pamidronate disodium	Vancomycin
Diatrizoate meglumine*	Ioversol*	Pentamidine	Zoledronic acid
			Zonisamide

* Medications counted for 7 days after administration toward exposure.

Table 2. Pediatric Risk, Injury, Failure, Loss, End-Stage Kidney Disease (pRIFLE) Stratification Based on Changes in Serum Creatinine Values and Urine Output

pRIFLE Category	Estimated CrCL*	Urine Output, mL/kg/hr
Risk	Decrease by 25%	<0.5 for 8 hr
Injury	Decrease by 50%	<0.5 for 16 hr
Failure	Decrease by 75% or <35 mL/min/1.73 m^2	<0.3 for 24 hr or anuric for 12 hr
Loss	Loss of renal function >4 wk	
End-Stage	End-stage renal disease	

CrCL, creatinine clearance

* Estimated with Schwartz equation[8]: 0.413 × Ht (cm)/SCr

need for the duration they need them.[5] Currently at Children's Healthcare of Atlanta (CHOA), the NINJA program has been implemented in the Hematology/Oncology Unit and the Bone Marrow Transplant Unit because these are areas associated with high nephrotoxin exposure. The purpose of this quality improvement study was to implement and evaluate the NINJA program in hospitalized CF patients at CHOA.

Methods

This single-center study piloted the NINJA program in CF patients at CHOA and was implemented on October 1, 2018. Pre-NINJA implementation data were collected from June 1, 2018, through September 30, 2018, by means of retrospective chart review. This was followed by 4 months of prospective data collection post-NINJA implementation. Patients were included in this study if they were admitted to the pulmonary service, were 0 to 21 years of age, and had a diagnosis of CF. The pioneer NINJA study done at Cincinnati Children's Hospital excluded patients admitted to the ICU; hence, patient data were excluded if they were transferred to an ICU. Because we were seeking to identify NTMx exposure as the primary cause of AKI, an additional reason for the exclusion of patients admitted to ICUs was the fact that AKI is multifactorial in critically ill children.[5]

Definitions. High NTMx exposure was defined as ≥3 NTMxs (Table 1)[6] given within the same 24-hour time period, or at least 3 consecutive days of IV aminoglycosides or vancomycin. To define AKI, we used the pediatric Risk, Injury, Failure, Loss and End-Stage Kidney Disease (pRIFLE) criteria (Table 2).[7] Serum creatinine was estimated using the Schwartz et al[8] equation. Baseline SCr was denoted as the patient's lowest SCr value within the previous 6 months.

SCr Monitoring. The pharmacist covering CF patients received an automated daily report generated from the electronic health records. After reviewing the report and verifying patients with high NTMx exposure, the pharmacist would alert the medical team and recommend Monday/Wednesday/Friday SCr monitoring for all exposed patients. Standard practice prior to NINJA included once weekly SCr measurement for CF patients

Table 3. Patient Demographics for Both the Pre- and Post-NINJA (Nephrotoxic Injury Negated by Just-in-time Action) Groups

Demographic	Pre-NINJA (n = 19)	Post-NINJA (n = 19)	p value
Age, mean ± SD, yr	14.2 ± 4.6	13.6 ± 5.0	0.704
Sex, male, n	10	9	0.746
Exposure, days*	250	521	0.025

* per 1000 patient days

groups there were patients with more than 1 hospital admission, ultimately resulting in 25 cases of high NTMx exposure per group. There was no significant difference between the types of NTMx exposure (Table 4). Two cases of AKI were noted pre-implementation, whereas 5 cases of AKI ensued post-implementation. In our study, we observed an initial AKI rate of 2.6 per 1000 patient days, which increased to 11.7 per 1000 patient days after implementation (Figure). Intensity of AKI was similar between the two groups. Serum creatinine monitoring increased from 13% to 50% of NTMx exposure days in the pre- versus post-NINJA time frame. In the subset of patients with AKI, tobramycin

Table 4. Patient Characteristics Related to Nephrotoxic Medication (NTMx) Exposure and Acute Kidney Injury (AKI) In Both Pre- and Post-Implementation Groups

Characteristic	Pre-NINJA (n = 25)	Post-NINJA (n = 25)	p value
Exposure type			
≥3 NTMx	3	3	1.000
≥3 days IV of an aminoglycoside	21	21	1.000
≥3 days IV vancomycin	1	1	1.000
AKI episode category			
Risk	2	5	0.221
Injury	0	0	
Failure	0	0	
AKI, mean ± SD, days	1 ± 0	1.2 ± 0.4	0.576

NINJA, Nephrotoxic Injury Negated by Just-in-time Action program

who were receiving an IV aminoglycoside. If a patient had AKI, the pharmacist would recommend daily SCr monitoring until resolution of AKI for 48 hours, at which point they could resume Monday/Wednesday/Friday monitoring. All NINJA patients were monitored for 48 hours post-exposure or until hospital discharge (whichever came first).

Outcome Measures and Statistical Analysis. Outcomes assessed included SCr monitoring rates, NTMx exposure rate per 1000 patient days, AKI incidence rate per 1000 patient days, and AKI intensity rate (days of AKI per 100 susceptible days). The 2 groups were used to compare 4 months of pre- versus post-NINJA data. Descriptive statistics were used to report patient demographics. The groups were compared using χ^2 analysis for sex, exposure type, and AKI or Student *t* test for age, exposure days, and AKI days. A p value of <0.05 was considered statistically significant.

Results

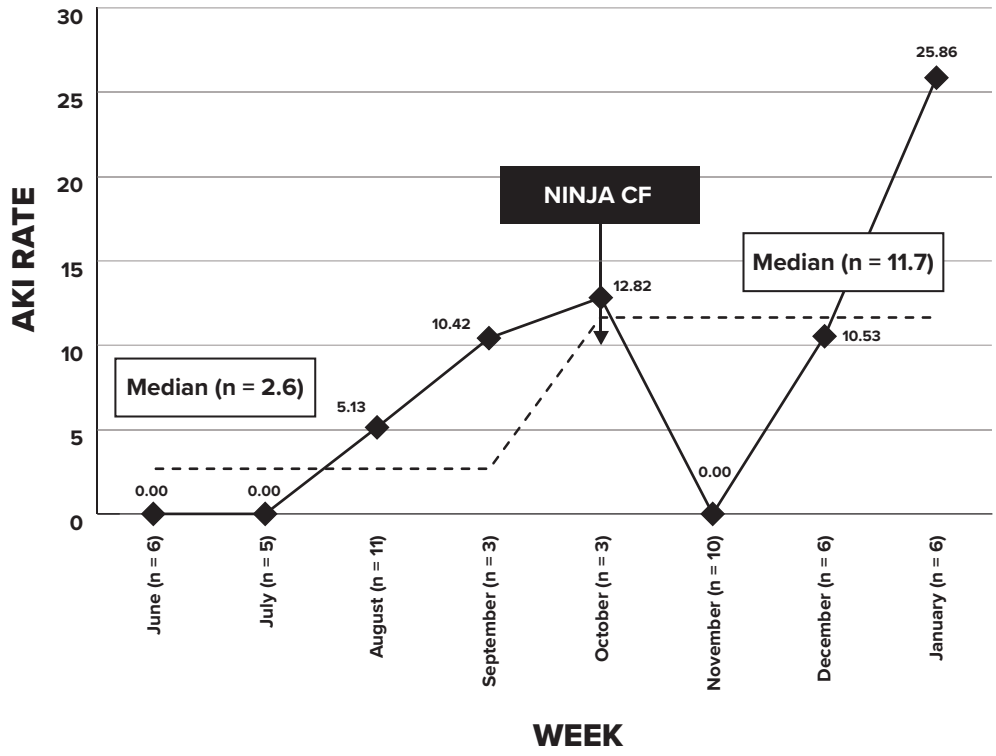
There were 19 patients identified both pre- and post-NINJA implementation (Table 3). The mean age was similar between the groups (p = 0.704). Results revealed significantly more NTMx exposure days in the post-NINJA era, at 521 exposure days per 1000 patient days compared with 250 pre-NINJA. In both was used alone or in conjunction with other NTMx in 5 of 7 cases of AKI. Other NTMx included tacrolimus (n = 1), piperacillin/tazobactam (n = 1), colistin (n = 1), ibuprofen (n = 1), ketorolac (n = 1), and gentamicin (n = 1).

Acute kidney injury rates were reanalyzed in the post-NINJA data set using the pre-NINJA practice of weekly SCr monitoring, which revealed only 3 cases of AKI and 3 AKI days total.

Discussion

Increased SCr monitoring for CF patients with high NTMx exposure uncovered more episodes of AKI compared with previous less frequent monitoring. Interventions to help reduce the risk of AKI were made for these patients. Interventions in our study included the following: 1) recommending discontinuing ibuprofen or ketorolac orders and using an alternate therapy for pain, such as acetaminophen; 2) checking tobramycin trough serum concentrations to monitor for accumulation in patients with AKI; and 3) providing maintenance fluids for the NINJA patients who did not already have them ordered. By removing the extra SCr monitoring in our post-implementation group, 2 AKI cases and 3 AKI days may have gone undetected. Increased prevalence of NTMx use was associated with increased rates of AKI in our study. Rates of AKI were fairly low, which may

Figure. Monthly average acute kidney injury (AKI) development rates measured as patients with AKI per 1000 non–critically ill hospital days.



CF, cystic fibrosis; NINJA, Nephrotoxic Injury Negated by Just-in-time Action program

—◆— Rate of patients – – – Median rate

be due to low rates of concomitant aminoglycoside and vancomycin use at our center. A limitation of this study was a small sample size due to the short duration of time for data collection. Extrarenal factors that are known to influence renal function, such as fluid status, were not accounted for. In addition, thrice weekly SCr monitoring was a deviation from the NINJA recommendation of daily SCr monitoring for NTMx exposed patients. The less frequent monitoring was agreed upon by pulmonology and pharmacy at our institution.

Conclusion

This study revealed that increased SCr monitoring as a result of using the NINJA program may allow for earlier detection of AKI among CF patients. Increased prevalence of NTMx use was associated with increased rates of AKI. Results of this study were shared with the pulmonology group at our institution. As a result, all CF patients who receive an aminoglycoside have thrice weekly SCr monitoring, ordered as a standing order by the pharmacist who is providing clinical coverage for these patients. All members of the health care team, including physicians, advanced practitioners, and nurses, have become more keenly aware of NTMx and their potential detrimental impact to the kidneys.

Discussion of other ways to prevent AKI have been ongoing. In July 2019, the method of monitoring aminoglycosides in CF patients changed from a 1-point to a 2-point system. By using a 2- and 6-hour drug level, an area under the curve and peak level are calculated, which gives providers a better idea of aminoglycoside exposure, resulting in better safety and efficacy. Another potential method to minimize risk of AKI in our CF patient population is implementation of a hydration protocol using urine specific gravity and fluid boluses. In 2020, the NINJA program spread to all non-ICU floors of the hospital. With the aid of pharmacists and the NINJA program, an increasing awareness of NTMx-AKI can continue to grow.

Article Information

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