Biol Blood Marrow Transplant 25 (2019) 1654–1658

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Quality of Care

Reduction in Nephrotoxic Antimicrobial Exposure Decreases Associated Acute Kidney Injury in Pediatric Hematopoietic Stem Cell Transplant Patients

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Article history:
Received 11 January 2019
Accepted 24 April 2019

Key Words:
Acute kidney injury
Nephrotoxin
Hematopoietic stem cell transplantation
Pediatric
Quality improvement

A B S T R A C T

Exposure to nephrotoxic medications is a common risk factor for acute kidney injury (AKI) in pediatric stem cell transplantation (SCT). We hypothesized that reducing nephrotoxic antimicrobial exposure for SCT patients would be associated with lower nephrotoxin-associated AKI (NTMx-AKI) rates and no increase in infection treatment failures. We conducted a prospective cohort analysis of all inpatient SCT patients at Cincinnati Children's Hospital Medical Center between January 2014 and December 2017. In January 2016, first line fever coverage was changed from piperacillin-tazobactam to cefepime, acknowledging that the change resulted in a loss of enterococcal coverage, and the duration of antimicrobial exposures was limited, specifically including vancomycin. We collected data using prospective NTMx-AKI and antimicrobial utilization monitoring platforms within the electronic health record. AKI days and severity were extracted for patients exposed to 3+ nephrotoxins, 3+ days of IV aminoglycosides, or 3+ days of IV vancomycin. AKI was identified using KDIGO serum creatinine criteria. We assessed rates of nephrotoxin exposure and NTMx-AKI in all SCT inpatients for 2 years pre- and post-intervention. Data were grouped and analyzed by calendar month, normalized to a denominator of 1000 patient-days. Statistical process control methods were used to monitor adherence to the intervention and identify changes in mean rate of nephrotoxin exposure and NTMx-AKI. Infection rates, alternate antimicrobial usage rates, and the fraction of repeat positive cultures were used to identify treatment failures. PTZ usage decreased from 196 to 33 days/1000 patient days, cefepime usage increased from 62 to 290 days/1000 patient days, and vancomycin usage decreased from 62 to 41 days/1000 patient days. High nephrotoxin exposure decreased by 33% (143 to 96 days/1000 patient days), and NTMx-AKI decreased by 74% (24 to 6 days/1000 patient days). Rates of all KDIGO stages of NTMx-AKI decreased ≥50% after the intervention. Stage 3, the most severe, decreased by >80%. The fraction of repeat positive cultures remained stable between the two eras at .1 (standard deviation 0.21) and .07 (standard deviation 0.17), respectively. There were no increases in infection rates, alternate antimicrobial usage rates, or treatment failures. Reduction of nephrotoxic antimicrobial exposure can decrease the amount and severity of NTMx-AKI in SCT patients without an increase in treatment failures.

INTRODUCTION

Acute kidney injury (AKI) is a common complication in hematopoietic stem cell transplantation (SCT) associated with an increased risk of morbidity and mortality [1-6]. In 2011 Cincinnati Children's Hospital Medical Center initiated a nephrotoxin exposure and nephrotoxin-associated AKI (NTMx-AKI) reduction quality improvement project called Nephrotoxic Injury Negated by Just-in-time Action (NINJA) [7]. The initial data revealed that compared with all other services in the hospital, the SCT service had the highest rate of high-risk nephrotoxin exposures, accounting for 24% of all exposures in the non–acute care setting [8,9]. The SCT service also had 1 of the highest rates of NTMx-AKI, with 39% of exposed patients developing an associated AKI [9]. Of the 5 medications most

Financial disclosure: See Acknowledgments on page 1657.

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https://doi.org/10.1016/j.bbmt.2019.04.022
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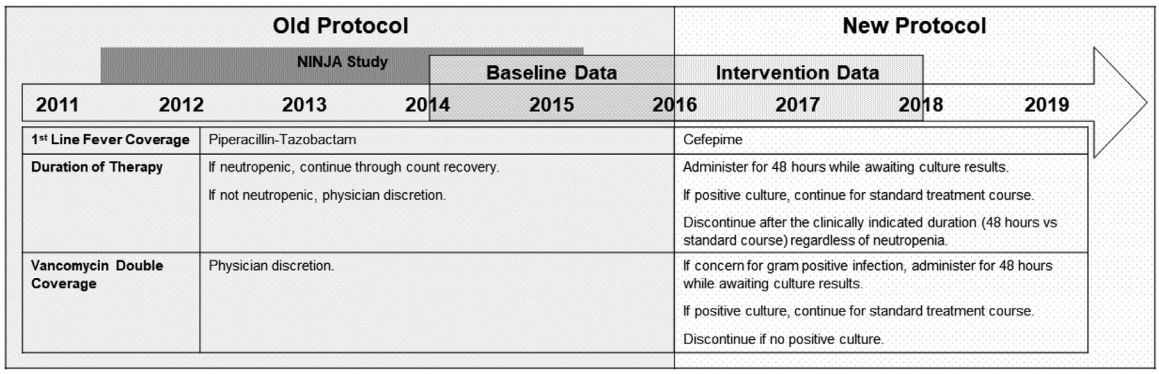

Figure 1. Change in antimicrobial protocol for first-line fever coverage and study timeline. Hospital-wide surveillance of nephrotoxic medication usage and associated AKIs began in 2011. Initial data collected between 2011 and 2015 demonstrated high rates of nephrotoxin-associated AKI in SCT patients. The protocol for first-line fever coverage was revised in 2016 in response. Data collected prospectively between January 2014 and December 2015 were used as a baseline, and the impact of the revised protocol was evaluated from January 2016 through December 2017.

frequently associated with NTMx-AKI, 4 were antimicrobials, including piperacillin-tazobactam (PTZ) and vancomycin [9].

During that time period, standard empiric coverage for fever in SCT patients was PTZ. If a patient was neutropenic, PTZ was continued through immune reconstitution. There were no limitations on the empiric use of vancomycin. Because PTZ and vancomycin were 2 of the top 5 NTMx-AKI–associated nephrotoxins, we hypothesized that reducing exposure to these nephrotoxic antimicrobial medications would be associated with lower NTMx-AKI rates and would not increase infection treatment failures in our SCT patient population.

METHODS

We conducted a prospective cohort analysis of all inpatient SCT patients at Cincinnati Children's Hospital Medical Center between January 2014 and December 2017. During that time the Division of Bone Marrow Transplantation, in collaboration with the Center for Acute Care Nephrology and the Antimicrobial Stewardship Program, changed their antimicrobial usage algorithm, as detailed in Figure 1. The antimicrobial escalation strategy was not adjusted during the study period. Meropenem was used only in the setting of cefepime allergy or critical illness. Double coverage with gentamycin was added (1) as directed by blood culture isolate sensitivity patterns if the clinical condition warranted double coverage and (2) in hypotensive patients without culture results to guide therapy; it was discontinued with clinical stabilization.

Table 1
Nephrotoxins Monitored by the NINJA System [9]

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 are counted during administration and through 48 additional hours after exposure.

* Medications are counted for 7 days after administration is completed because of their long half-life.

Antimicrobial utilization data were collected to confirm compliance with the intervention and to assess for unintended changes in overall antimicrobial usage patterns. Data were extracted from the electronic medical record for all inpatient SCT patients using the VigiLanz clinical surveillance platform (VigiLanz Corporation. Minneapolis, MN). Primary outcome measures were days of PTZ, days of cefepime, and days of vancomycin per 1000 patient days per month. Usage patterns of additional antibiotics (meropenem, ciprofloxacin, gentamicin), antivirals (acyclovir, cidofovir, foscarnet), and antifungals (ambisome, voriconazole, posaconazole) were also assessed.

Nephrotoxin exposure and NTMx-AKI data were collected via the NINJA nephrotoxic medication exposure monitoring platform within the electronic medical record, the operational aspects of which have been previously described [7,9]. Nephrotoxic medications monitored by the platform are shown in Table 1. High nephrotoxic medication exposure was defined as (1) exposure to 3 or more known nephrotoxins in the same calendar day, (2) 3 or more days of intravenous aminoglycosides, or (3) 3 or more days of intravenous vancomycin [8]. Patients were considered exposed until 48 hours after stopping intravenous aminoglycoside and/or vancomycin or after reducing to <3 nephrotoxic medications [9]. AKI was defined using Kidney Disease Improving Global Outcomes (KDIGO) serum creatinine criteria, using a 50% increase (within 7 days) or a .3-mg/dL increase (within 48 hours) over a baseline value obtained within the past 6 month [10]. The KDIGO AKI urine criteria were not used because nephrotoxic AKI is usually nonoliguric in nature [11]. AKI was defined as nephrotoxin-associated if it occurred during an exposure. Outcome measures were days of nephrotoxin exposure and days of NTMx-AKI per 1000 patient days per month.

A normalized duration of AKI per exposed days, called the intensity of NTMx-AKI, was calculated by dividing the days of NTMx-AKI by the days of nephrotoxin exposure. Assuming the pattern of nephrotoxin exposure remains stable except for the intervention, the mean intensity of NTMx-AKI episodes, represented by the number of days of AKI attributed to any 1 exposure, should be stable or decrease. The outcome measure for this was days of NTMx-AKI per 100 days of nephrotoxin exposure per month.

Infectious disease data were extracted using the VigiLanz clinical surveillance platform and were organized into pre- and postintervention eras, called the PTZ era and the cefepime era, respectively. The number of new positive blood cultures growing vancomycin-sensitive and vancomycin-resistant enterococci was assessed, as the change from PTZ to cefepime resulted in a loss of enterococcal coverage and vancomycin use was to be reduced. The number of repeat positive cultures was used to capture treatment failures. A repeat positive culture was defined as a culture that grew the same organism from the same site of an individual patient within 7 days of a prior positive culture. These data were represented as a fraction of repeat positive cultures by dividing the number of repeat positive cultures by the total number of positive cultures. For instance, if a patient had 5 positive blood cultures for *Staphylococcus aureus* 5 days in a row while on antibiotic treatment, 4 of those would be repeat positive cultures, and the fraction of repeat positive cultures would be .8. A similar metric was used in other NINJA publications [9]. These data were summarized as the fraction of repeat positive cultures for each organism across the 2 eras.

Statistical process control methods were used to identify changes in mean rates for each metric [12]. The 24 months of PTZ era data were used to establish baseline rates. We set an a priori standard of 8 consecutive monthly metric rates below the baseline rate to qualify as a statistically significant change. This corresponds to 99.7% likelihood that the change observed

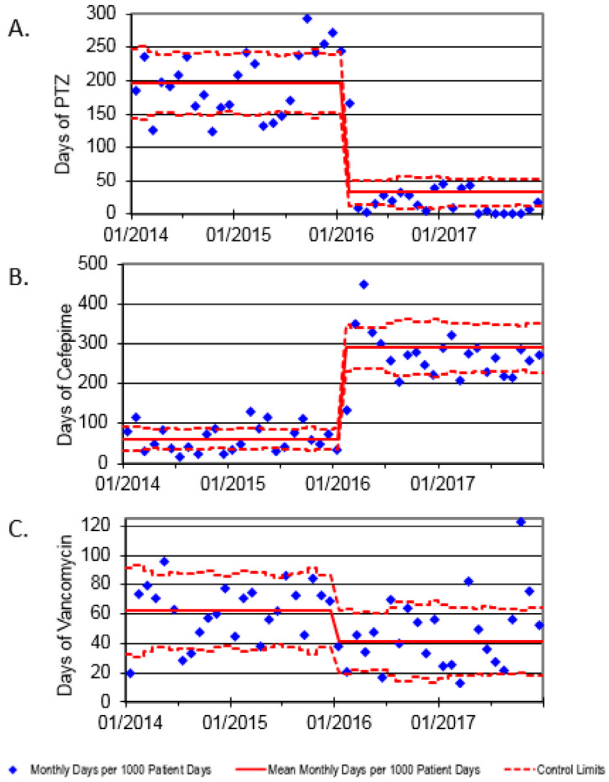

Figure 2. Monthly average antimicrobial usage rate as measured by days of antimicrobial usage per 1000 patient days. (A) The rate of PTZ usage decreased from 196 to 33 days per 1000 patient days. (B) The rate of cefepime usage increased from 62 to 290 days per 1000 patient days. (C) The rate of vancomycin usage decreased from 62 to 41 days per 1000 patient days. Change in the mean usage rate was identified by 8 consecutive monthly rates below the established baseline rate, representing a 99.7% likelihood that a statistically significant shift in the mean rate occurred. Each data point represents 1 calendar month.

resulted from the intervention [13]. This methodology has been used at Cincinnati Children's Hospital Medical Center to track serious safety events for 13 years and is the methodology used by the multicenter NINJA collaborative [9,14]. Twelve months of data were then used to calculate new mean rates. The Mann-Whitney test was used to compare the mean rate of persistent positive cultures in the PTZ and cefepime eras using GraphPad Prism (version 6.07 for Windows; GraphPad, La Jolla, CA). A $P < .05$ was considered to be statistically significant.

The NINJA project was approved by the Cincinnati Children's Hospital Medical Center Institutional Review Board. Patient/parental informed consent was waived.

RESULTS

The mean number of patient days per month across the study period was 786 ± 139, with a minimum of 479 days and a maximum of 1057 days per month. There were 222 SCTs performed in the PTZ era, 157 of which were allogeneic. There were 203 SCTs in the cefepime era, 144 of which were allogeneic. There were no programmatic changes in the types of patients, protocols used, or immunosuppression regimens used between the 2 eras.

PTZ, cefepime, and vancomycin usage data are shown in Figure 2. PTZ usage decreased from 196 to 33 days per 1000 patient days per month, cefepime usage increased from 62 to 290 days per 1000 patient days per month, and vancomycin usage decreased from 62 to 41 days per 1000 patient days per month after introduction of the intervention in January 2016. There was an overall decrease in the days of utilization per 1000 patient days of meropenem, ciprofloxacin, and

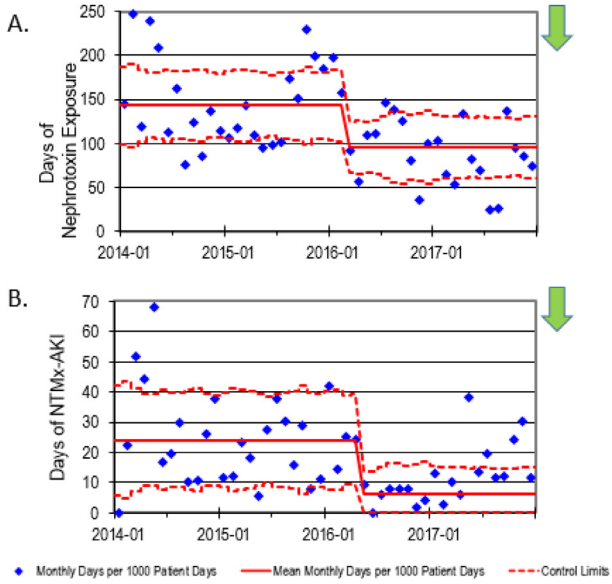

Figure 3. Monthly average nephrotoxin exposure rates and nephrotoxin-associated AKIs measured in days per 1000 patient days. (A) The rate of nephrotoxin exposure decreased from 143 to 96 days per 1000 patient days. (B) The rate of nephrotoxin-associated AKI decreased from 24 to 6 days per 1000 patient days. Change in the mean NTMx-AKI rate was identified by 8 consecutive monthly rates below the established baseline rate, representing a 99.7% likelihood that a statistically significant shift in the mean rate occurred. Each data point represents 1 calendar month.

gentamicin during the cefepime era as well, as shown in Supplementary Figure S1. There was no substantial change in the use of antiviral or antifungal medications across the two eras, as shown in Supplementary Figure S2.

Nephrotoxin exposure and NTMx-AKI data are shown in Figure 3. Nephrotoxin exposure decreased by 33% (143 to 96 days per 1000 patient days) and NTMx-AKI decreased by 74% (24 to 6 days per 1000 patient days). Mean rates of KDIGO stages 1, 2, and 3 NTMx-AKI all decreased ≥50% after the intervention (Table 2, Supplementary Figure S3). NTMx-AKI intensity remained stable across the 2 eras, with 27.8 days of NTMx-AKI per 100 days of nephrotoxin exposure (Supplementary Figure S4).

The frequency of enterococcal infections did not increase in the cefepime era. Only 1 patient in the PTZ era and 1 patient in the cefepime era had vancomycin-resistant enterococci infection. There were no positive blood cultures for any enterococcal species between July 2016 and December 2017 (Supplementary Figure S5). No other changes in antibiotic resistance patterns were noted.

Table 2
Monthly Days of NTMx-AKI Measured per 1000 Patient Days

	PTZ Era Jan 2014 to Dec 2015	Cefepime Era Jan 2016 to Dec 2017
Days of NTMx-AKI	24.1	6.2
Days of stage 1 NTMx-AKI	12.8	3.1
Days of stage 2 NTMx-AKI	8.9	3.9
Days of stage 3 NTMx-AKI	3.0	.5

Values are means per 1000 patient days. The rate of every stage of NTMx-AKI decreased in the cefepime era. Change in the mean NTMx-AKI rate was identified by 8 consecutive monthly rates below the established baseline rate, representing a 99.7% likelihood that a statistically significant shift in the mean rate occurred. Each data point represents 1 calendar month.

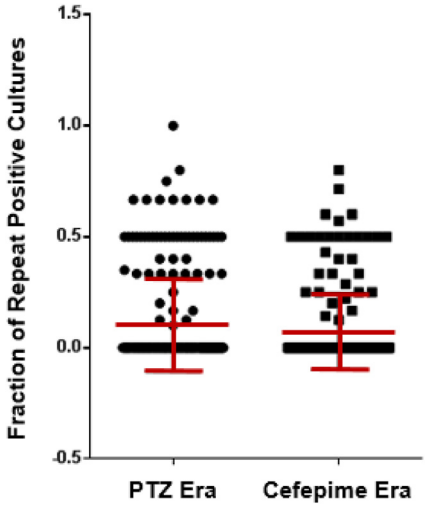

Figure 4. Fraction of repeat positive cultures in the PTZ and cefepime eras. Each point represents a single patient infection. A repeat positive culture was defined as a culture that grew the same organism from the same body site from an individual patient within 7 days of a prior culture. These data were then represented as a fraction of repeat positive cultures by dividing the number of repeat positive cultures by the total number of positive cultures. For instance, if a patient had 5 positive blood cultures in a row for *S. aureus*, 4 of those would be repeats and the fraction of repeat positive cultures would be .8. The mean fraction of repeat positive cultures in the PTZ and cefepime eras, respectively, were .1 (standard deviation, .21) and .07 (standard deviation, .17), as represented by the red lines.

Most infections were cleared after the first positive culture in both eras. The mean fraction of repeat positive cultures remained stable across the 2 eras at .1 (standard deviation, .21) and .07 (standard deviation, .17), respectively ($P = .2$), as shown if Figure 4. There was no increase in treatment failures for any specific organisms including enterococcal infections (Supplementary Figure S6).

DISCUSSION

A significant amount of work has demonstrated the increased risk of AKI with administration of vancomycin and PTZ in adults and children, including specifically in the SCT population [15-18]. The NTMx burden of SCT patients is high compared with most other pediatric inpatient populations, the magnitude of which was quantified for the first time in the initial NINJA quality improvement work [9]. In that study the authors not only demonstrated the high nephrotoxin exposure rate in SCT patients, but also the higher rate of resulting NTMx-AKIs with exposures compared with other pediatric inpatients. Several mechanisms for AKI during SCT, including hypoperfusion, infections, and immunologic injuries, may contribute to their increased vulnerability to nephrotoxic exposures [3].

In this study we built on these findings and identified PTZ and vancomycin as modifiable, high-frequency nephrotoxic exposures. Applying quality improvement methodology, we found that reduction in exposure to these 2 medications was associated with dramatic decreases in all levels of severity of NTMx-AKI, with no associated adverse infectious outcomes. These results demonstrate that nephrotoxin exposure is a modifiable risk factor for AKI and that NTMx-AKI can be reduced even in the complex setting of SCT. These results also demonstrate the power and utility of clinical surveillance platforms for informing real-time quality improvement initiatives.

Enterococcal infections were of particular interest, because there is a loss of enterococcal coverage in the change from PTZ to cefepime. There was no increase in enterococcal treatment failures or in positive enterococcal blood cultures after transitioning from PTZ to cefepime. In fact, there were no positive enterococcal blood cultures between July 2016 and December 2017, when the study ended. One potential explanation for this could be related to preservation of the gut microbiome. Loss of diversity of the gut microbiota has been associated with development of acute graft-versus-host disease and decreased overall survival in pediatric and adult allogeneic SCT patients [19-21]. Specifically, use of PTZ to treat neutropenic fever in allogeneic SCT patients was shown to be associated with an increased risk of graft-versus-host disease–related mortality, and PTZ administration was associated with overgrowth of enterococcus (odds ratio of enterococcal domination, 5.50; 95% confidence interval, 2.03-14.92) in adult intensive care patients [22,23]. Thus, it is conceivable that although substituting cefepime for PTZ removed enterococcal prophylactic coverage, it enabled preservation of critical microbiota that were able to limit enterococcal proliferation. This may also explain why usage of meropenem, ciprofloxacin, and gentamycin all decreased during the cefepime era as well.

Our study is limited by the fact that it is a single-center design. There are now 13 US pediatric institutions contributing data to a NINJA collaborative, and the NINJA project has been accepted for dissemination to the 140 pediatric hospital Solutions for Patient Safety collaborative, so the opportunities for other single-center and multicenter work are growing. Our data only include inpatients on the SCT floor and do not include SCT patients if they moved to the intensive care units. Additionally, we were unable to obtain granular demographic data on the inpatient population. Understanding NTMx-AKI for SCT patients in the critical care setting and identifying SCT patient characteristics associated with NTMx-AKI are both important areas for future research. Finally, we cannot account for every change in practice that occurred over the study period, although the stable NTMx-AKI intensity rate implies that there were not inherent changes to the types or potency of other nephrotoxins during that time.

In summary, PTZ and vancomycin are nephrotoxic, and reduction in exposure to these medications reduced NTMx-AKI in SCT patients without an increase in treatment failures. On a larger scale, NTMx-AKI is a modifiable complication, and data-driven quality improvement initiatives may be able to reduce the morbidity and mortality associated with AKI during SCT.

ACKNOWLEDGMENTS

Financial disclosure: The authors have nothing to disclose.

Conflict of interest statement: Dr. Goldstein receives royalties from Vigilanz Corporation for the NINJA application licensed to Vigilanz from Cincinnati Children's Hospital Medical Center.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2019.04.022.

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