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Original Research Article

Association of nephrotoxic medication exposure and nephrotoxic medication induced acute kidney injury in hospitalised non-critically ill children: single centre study

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ABSTRACT

Background: Acute kidney injury (AKI) in children is increasingly linked to nephrotoxic medication exposure, particularly in hospitalized patients. Although nephrotoxic drugs contribute substantially to AKI incidence, especially with multiple-agent exposure, data on their prevalence and associated AKI risk in non-critically ill pediatric populations remain limited. This study assessed the prevalence of nephrotoxic medication exposure in non-critically ill children per 1000 patient-days of hospitalization, and the prevalence of nephrotoxic AKI among these patients.
Methods: This prospective study evaluated nephrotoxic medication exposure and the development of nephrotoxic AKI in non-critically ill hospitalized children aged 1 month to 12 years. Baseline kidney function was assessed and serum creatinine levels were monitored during and after the exposure period. AKI was defined according to KDIGO criteria. Upon AKI occurrence, nephrotoxic medications are substituted with less harmful alternatives.
Results: The study included 3,264 children with bronchopneumonia (29.4%), acute gastroenteritis (26%), and tropical fever (22.4%) as common hospitalization causes. Nephrotoxic medication exposure was identified in 3.1% of cases, yielding a prevalence rate of 5.02 per 1000 patient days. Most exposed children were aged 3 to 12 years (58.4%), with a nearly equal gender distribution (males: 51.5%). Among those exposed, 70.3% received one nephrotoxic medication, while 29.7% received two, resulting in an AKI prevalence of 5.94%. AKI resolved within an average of 11±4 days following the substitution of non-nephrotoxic drugs. The most frequently administered nephrotoxic drugs were vancomycin (38.6%), acyclovir (26.7%), and amikacin (17.8%).
Conclusions: The findings indicate that nephrotoxic medication exposure among non-critically ill children was minimal, with a low prevalence rate of nephrotoxic AKI. Vancomycin, acyclovir, and amikacin are the most commonly used nephrotoxic drugs.

Keywords: Nephrotoxic medication exposure, Nephrotoxic acute kidney injury, Children, NINJA program

INTRODUCTION

Acute kidney injury (AKI) in the pediatric population can lead to severe clinical consequences and is an independent predictor of poor outcomes in affected patients.[1,2] Moreover, long-term monitoring of children who have experienced an AKI episode has revealed notable renal complications.[3] The epidemiological landscape of pediatric AKI is evolving, with secondary causes, particularly those associated with systemic illnesses or their treatments, now surpassing the incidence of primary renal diseases.[4] A key factor contributing to this shift is the rising prevalence of nephrotoxic medication use, which currently accounts for approximately 16% of pediatric inpatients with AKI.[3,4] Despite this, the specific risk of AKI upon initiation of any nephrotoxic drug, as well as the

cumulative risk when multiple nephrotoxic agents are administered, remains unclear. Identifying children at an increased risk of medication-induced AKI could potentially improve clinical outcomes. Accordingly, adapting monitoring protocols and optimizing drug selection may be necessary to reduce the risk of adverse outcomes associated with nephrotoxic agents.

The incidence, prevalence, and cause of AKI in children remain poorly characterized. Retrospective pediatric studies have reported AKI incidence rates in pediatric intensive care units (PICU) ranging from 8% to 30%.[5,6] Neonates, particularly those who undergo cardiac surgery, experience severe asphyxia, or are born prematurely, exhibit higher rates of AKI.[7] Two prospective studies conducted on children admitted to the PICU reported AKI incidence rates of 4.5% and 2.5%.[8,9] In a study by Bailey et al, excluding neonates, the most frequent diagnoses among children with AKI were hemolytic uremic syndrome (18.2%), oncologic diseases (18.2%), and cardiac surgery (11.4%). Although the univariate analysis in this study showed a higher frequency of nephrotoxic drug use in children with AKI, the multivariate analysis failed to establish nephrotoxic drugs as an independent risk factor for AKI.[10]

A 2005 report from Houston, Texas, USA, identified renal ischemia (21%), pharmacological agents (16%), and sepsis (11%) as the leading causes of AKI in hospitalized children, with primary renal disease accounting for only 7% of the cases.[4] Additionally, this study linked nephrotoxic medications were linked to AKI, primarily in older children and adolescents.

Exposure to nephrotoxic medications is a major cause of AKI in hospitalized children, increasing the cost and length of hospital stay. When children receive three or more nephrotoxic medications on the same day, the rate of AKI doubles. In some patients, the damage is permanent, leading to chronic kidney disease. Goldstein and colleagues developed the nephrotoxic injury negated by just-in-time action (NINJA) program in the hopes of decreasing nephrotoxic medication exposure and the development of nephrotoxic AKI.[11]

This study aimed to evaluate the exposure to nephrotoxic medications and the development of nephrotoxic AKI in non-critically ill hospitalized pediatric patients aged 1 month to 12 years.

METHODS

This prospective observational study was conducted on pediatric patients aged 1 month to 12 years at the Department of Nephrology, Department of Pediatrics.

Inclusion and exclusion criteria

Non-critically ill children aged 1–12 years were included. Patients admitted to the intensive care unit, with a hospital stay of <72 hours, pre-existing chronic kidney disease, and congenital kidney anomalies were excluded.

Ethical approval was obtained from the institutional review board on 01/12/2022 (EC registration number: ECR/131/Inst/TN/2013/RR-22), and informed consent was obtained from the parents or guardians of all children.

Baseline kidney function

Before the administration of nephrotoxic medications, baseline kidney function was assessed. Serum creatinine (SCr) levels were measured and other relevant clinical and demographic data were collected, including age, gender, underlying illness, and concurrent use of other medications (Figure 1).'

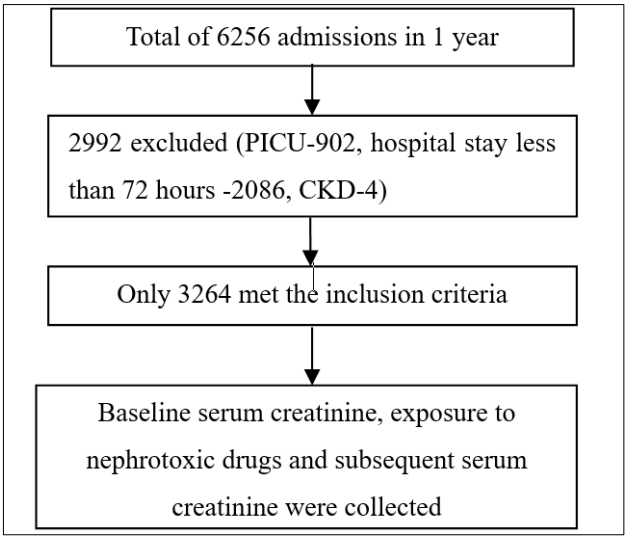

Figure 1: Flow of participants in the study.

Monitoring nephrotoxic medications and AKI

Serum creatinine levels were monitored to assess renal function. SCr measurements were taken at baseline and baseline eGFR by Schwartz equation was obtained in these patients. Serum Creatinine level was obtained on alternate days in these exposed patients, for the duration of and after two days after exposure ends to monitor any delayed effects. In cases where serum creatinine increased by 50% or more from baseline, AKI was diagnosed using the kidney disease: improving global outcomes (KDIGO) criteria. AKI was defined based on the KDIGO guidelines as an increase in serum creatinine by ≥0.3 mg/dl within 48 hours, an increase of ≥50% from baseline within 7 days, or urine output <0.5 ml/kg/hour for 6 hours.

Intervention and replacement of medications

For patients who developed AKI during the study period, nephrotoxic medications were promptly discontinued or replaced with alternative agents that were considered less harmful to renal function. The pediatric team was blinded

to this study to avoid bias in not using nephrotoxic medications. Only when AKI developed was the clinical decision to replace medication made in collaboration with the attending paediatrician and nephrologist.

Statistical analysis

Data were prospectively collected and entered into a predesigned database. Continuous variables, including serum creatinine levels and age, are expressed as mean±standard deviation (SD), while categorical variables are presented as frequencies and percentages. The incidence of AKI was calculated as the proportion of the total cohort. Statistical analysis was performed using statistical package for the social sciences (SPSS) 20.0, with statistical significance defined as $p<0.05$.

RESULTS

The age distribution showed that the majority of hospitalized children were between 3 and 12 years old, representing 75.1% of the total cases. Children aged 2 months to 2 years constituted 18.5% of the cases, while infants aged between 1 and 2 months constituted the smallest proportion, accounting for 6.4%.

Table 1: Demographic distribution, reasons for hospitalization, and exposure to NTMx in pediatric cases.

Variables	Number of cases	%
Age group		
1 to 2 months	208	6.4
2 months to 2 years	604	18.5
3 years to 12 years	2452	75.1
Gender		
Male	1733	53.1
Female	1531	46.9
Reason for hospitalization		
Bronchopneumonia	961	29.4
UTI	102	3.1
Tropical fever	730	22.4
Acute gastroenteritis	848	26
Nephrotic/nephritic syndrome	34	1
SAM	23	0.7
CNS infection, GBS	27	0.8
Others- hepatitis, tonsillitis, pancreatitis, varicella	59	1.8
Others – poisoning, snake bite, scorpion sting, leukemia	28	0.9
Surgical – appendicitis, intussusception /abscess	52	1.6
Seizure disorder/ breakthrough seizures	400	12.3
Exposure to NTMx		
Yes	101	3.1
No	3163	96.9

The gender distribution of the hospitalized children was nearly balanced, with males slightly outnumbering females. Males accounted for 53.1% of the cases, showing a relatively equal male-to-female ratio.

Bronchopneumonia emerged as the most common reason for hospitalization and was responsible for 29.4% of cases. Acute gastroenteritis followed closely, comprising 26% of hospitalizations, while tropical fever accounted for 22.4% of hospitalizations. Other notable causes included seizure disorders (12.3%), urinary tract infections (UTIs) (3.1%), less frequent conditions, such as nephrotic or nephritic syndrome (1%), severe acute malnutrition (SAM) (0.7%), and central nervous system (CNS) infections, such as Guillain-Barré syndrome (0.8%). A small number of cases were attributed to surgical conditions (1.6%) and other causes such as poisoning, snake bites, and oncologic issues (0.9%).

Among the study population, 3.1% of the children were exposed to nephrotoxic medications (NTMx), while the remaining 96.9% were not (Table 1). NTMx exposure was more frequent in older children, with 58.4% of exposed patients aged 3–12 years, followed by 24.8% in the 2 months to 2 years age group, and 16.8% in infants aged 1–2 months. Gender distribution of NTMx exposure was fairly even, with males comprising 51.5% and females 48.5%.

Among children exposed to nephrotoxic medications, acyclovir was the most commonly administered drug (17.8%), followed by vancomycin (13.9%), amikacin, and enalapril (12.9% each). Combination therapies such as acyclovir with methotrexate (5%) or vancomycin (4%) and amikacin with vancomycin (5%) were also noted. Other drugs included aspirin (5%), ganciclovir (2%), ibuprofen (3%), and intravenous immunoglobulin (IVIG) (2%). The less frequently used medications were liposomal amphotericin (1%) and a combination of piperacillin-tazobactam (piptaz) and vancomycin (15.8%) (Table 2).

The prevalence of NTMx was 5.02, and the overall AKI prevalence was 0.29. However, the AKI prevalence rate was significantly higher among patients exposed to NTMx (5.4) (Table 3). Among those patients exposed to NTMx, the mean age in the AKI group was 4.07 years and in the non-AKI group, the mean age was 4.76 years. The mean baseline eGFR in the AKI and non-AKI group was 91.33 49 ml/min/1.73 m^2 and 115.49 ml/min/1.73 m^2 respectively.

Regarding the intensity of medication exposure among the patients, 70.3% were exposed to one nephrotoxic medication, whereas 29.7% were exposed to two nephrotoxic medications.

Among the NTMx administered, vancomycin was the most frequently prescribed, accounting for 38.6% of the cases, followed by acyclovir at 26.7%. Amikacin and enalapril were used in 17.8% and 12.9% of the cases,

respectively. Aspirin accounted for 5% of cases, while methotrexate (Mtx) was noted in 5%. Ganciclovir and IVIG were less commonly used, each accounting for 2%, and ibuprofen constituted 3%. Liposomal amphotericin was the least prescribed NTMx, representing only 1% of cases (Table 4 and Figure 2).

Table 2: Overall incidence of cases exposed to nephrotoxic medications.

Exposure to NTMx	Number of cases	%
Age group		
1 to 2 months	17	16.8
2 months to 2 years	25	24.8
3 years to 12 years	59	58.4
Gender		
Female	49	48.5
Male	52	51.5
Drug exposure		
Acyclovir	18	17.8
Acyclovir and methotrexate (Mtx)	5	5
Acyclovir and vancomycin	4	4
Amikacin	13	12.9
Amikacin and vancomycin	5	5
Aspirin	5	5
Enalapril	13	12.9
Ganciclovir	2	2
Ibuprofen	3	3
IVIG	2	2
Liposomal amphotericin	1	1
Piptaz and vancomycin	16	15.8
Vancomycin	14	13.9

Table 3: NTMs exposure prevalence rate per 1000 patient days.

Variables	Prevalence rate
NTMx exposure prevalence rate	5.02
AKI prevalence rate	0.29
AKI prevalence rate in NTMx exposure	5.4

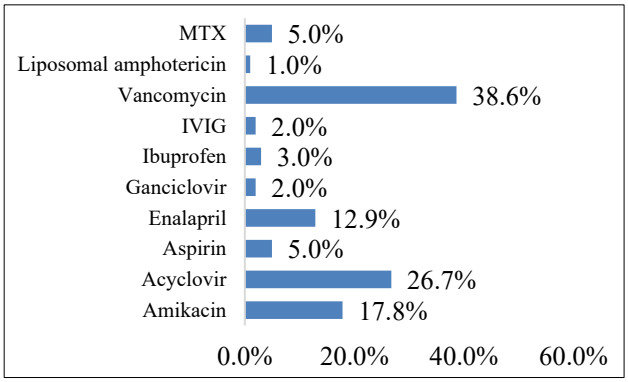

Figure 2: Overall use of NTMx drugs.

Table 4: Medication exposure intensity and NTMx drug usage in pediatric cases.

Variables	Number of cases	%
Medication exposure intensity		
1	71	70.3
2	30	29.7
NTMx drug		
Amikacin	18	17.8
Acyclovir	27	26.7
Aspirin	5	5
Enalapril	13	12.9
Ganciclovir	2	2
Ibuprofen	3	3
Intravenous immunoglobulin (IVIG)	2	2
Vancomycin	39	38.6
Liposomal amphotericin	1	1
Mtx	5	5

Serum creatinine monitoring rates in nephrotoxic drug-exposed babies were 100% till day 7, after which the monitoring rates gradually decreased because the discharge of patients after clinical improvement was only 55% on day 17 (Table 5).

Table 5: Serum creatinine monitoring rates.

Day	Monitoring rates (%)
Day 3	100
Day 5	100
Day 7	100
Day 9	83
Day 11	69
Day 13	64
Day 15	59
Day 17	55

DISCUSSION

This study showed the hospitalization trends and NTMx exposure among children, revealing significant insights into age distribution, gender balance, primary causes of hospitalization, and the relationship between NTMx exposure and AKI. An increased prevalence of nephrotoxic medication exposure is associated with an increased risk of AKI. Synergistic nephrotoxic effects can occur when multiple nephrotoxic medications are administered. This may be due to various drug-related mechanisms for nephrotoxicity acting synergistically.[12]

The majority of hospitalized children fell within the age group of 3–12 years, highlighting a vulnerability in this demographic that could inform targeted health interventions and preventive measures. Previous studies have indicated that nephrotoxic drugs are becoming a more frequent cause of acute AKI in hospitalized children.[13-15]

The gender distribution of the study population was relatively balanced, with a slight male predominance. This aligns with the existing literature, which often reports a higher prevalence of certain illnesses among males during early childhood. The leading cause of hospitalization was bronchopneumonia, which accounted for nearly one-third of all cases. Acute gastroenteritis and tropical fever were also prevalent, indicating that infectious diseases remain a significant burden on children's health, particularly in endemic regions of our country. However, the study conducted by Moffett et al. to determine the odds of nephrotoxic medication exposure reported contrasting findings, as in our study. The study included a total of 1660 patients, and their study on AKI and nephrotoxic drug exposure showed that >80% of the study population, with or without AKI, was exposed to at least one nephrotoxic medication, of which 561 were diagnosed with AKI (33.8%) with a male predominance (50.8%). As exposure to nephrotoxic medication increases, the number of patients who develop AKI also increases.[12]

Despite the low overall prevalence of NTMx exposure (3.1%), it is concerning that exposure was significantly associated with increased rates of AKI, increasing to 5.4% in the exposed group. To avoid confounding factors regarding the aetiology of AKI, this cohort consisted of non-critically ill children, making it quite clear that the renal dysfunction that occurred in this group was due to nephrotoxic medication in the entirety. This highlights the need for careful monitoring of kidney function in children receiving nephrotoxic treatments, particularly vancomycin and acyclovir, which are frequently used in hospitals. The high occurrence of nephrotoxicity associated with these drugs emphasizes the importance of cautious usage and ongoing renal assessment. Moffett et al reported that patients with AKI were 1.7 times more likely to have been exposed to one or more nephrotoxic medications than those without AKI (95% confidence interval, 1.04 to 2.9; p=0.03). Additionally, the severity and duration of exposure to nephrotoxic medications increased the risk of developing AKI.[12]

Several studies have reported that increasing age helps as a protective factor, and infants are at a sensitive risk of developing AKI following exposure to nephrotoxic medications.[16] Studies indicate that the incidence of AKI in pediatric intensive care units (PICUs) ranges from 8% to 30%, with higher rates observed in neonates.[17]

The NTMx exposure prevalence rate was 5.02 per 1000 patient days. In the Goldstein et al study, the NTMx exposure prevalence rate was 7 and 6.9 per 1000 patient days. The AKI prevalence rate was 0.29 per 1000 patient days. The study reported a contrasting finding that the AKI prevalence rates were 1.7 and 1.3 per 1000 patient days, which were high compared to this study.[11]

In a study by Almedia et al, the incidence of AKI associated with nephrotoxic medication use in critically ill children was reported to be 42.4%, highlighting the critical nature of monitoring drug interactions and increasing exposure. The most commonly implicated drugs include vancomycin, aminoglycosides, and furosemide.[18]

In our study, acyclovir was the most commonly administered drug (17.8%), followed by vancomycin (13.9%), amikacin and enalapril (12.9% each).

Limitations

The limitations of this study include the fact that the data were drawn from a single institution, which may affect the generalizability of the findings to a broader population. There may also be unmeasured confounding factors, such as underlying health conditions and severity of illness at admission, which could impact both medication exposure and AKI rates.

CONCLUSION

Our study demonstrated that exposure to nephrotoxic medications in non-critically ill children is minimal, and the prevalence rate of nephrotoxic AKI is also low. The most commonly used nephrotoxic drugs are vancomycin, acyclovir, and amikacin. While the overall prevalence of nephrotoxic medication exposure in hospitalized children is relatively low, its association with increased AKI rates warrants attention. The regular practice of monitoring serum creatinine to detect AKI earlier in patients receiving nephrotoxic medications potentially allows for more expeditious dose adjustment and decreased length of hospitalization in those patients. With bronchopneumonia identified as the leading cause of hospitalization, it is essential to continue efforts to enhance preventive care strategies for respiratory infections and closely monitor the effects of nephrotoxic medications. Additional research is necessary to investigate the long-term effects of nephrotoxic medication exposure and to develop guidelines for safer pediatric medication management.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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