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Evaluation of Acute Kidney Injury and Its Risk Factors in Children Admitted with Diagnosis of Nephrotic Syndrome

Anita Kumari[1*], Lehar Sahai[1], Sanjay Kumar[2], Ruchika Bhatnagar[1]

[1]Department of Pediatrics, SRMS Institute of Medical Sciences, Bareilly Uttar Pradesh 243001. Bareilly, India.
[2]Nephrology Division, Department of Medicine SRMS Institute of Medical Sciences, Bareilly Uttar Pradesh 243001. Bareilly, India.

[*]**Corresponding Author**
Dr. Anita Kumari,
Email: anitaneo@gmail.com

Abstract

Background and Aim: Acute Kidney Injury (AKI) is an important complication of Nephrotic Syndrome (NS) associated with adverse outcomes. The frequency of AKI has increased to almost double in the last decade. This study was conducted to determine the incidence of AKI, risk factors, and its association with outcomes in hospitalized children with NS.
Methods: All children aged 1-18 years with a diagnosis of NS from 01 November 2018 to 31 May 2020 were enrolled in the study. AKI was diagnosed using the KIDIGO 2012 guidelines and classified according to the pediatric RIFLE definition.
Results: The mean age of the children was 4.7± 2.8 years. Complications were observed in 67% of the cases. The most frequent complication was anemia (25%) followed by infection (21%). The incidence of AKI was 18.6% in hospitalized children with NS. According to the pRIFLE criteria, 11.6% of the children met stage 1 (risk) criteria, 4.6% met stage 2 (injury) criteria, and 2.3% met stage 3 (failure) criteria. Among all NS children, 53% received nephrotoxic drugs during the hospital stay. On applying multivariate logistic regression analysis, only male gender, associated anemia, and vancomycin use were significant independent risk factor for AKI in nephrotic syndrome patients.
Conclusion: AKI is more frequent in the first episode of NS rather than in any type of relapses. Although nephrotoxic drugs and male gender are known independent risk factors for development of AKI, associated anemia is still not considered as an independent risk factor for AKI in children with NS.

Keywords: Nephrotic Syndrome; AKI; Risk Factors.

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Introduction

Nephrotic Syndrome is a common chronic disease of childhood with an incidence of 20-40 per million populations in developed countries (1). Nephrotic syndrome leads to various complications like anasarca, infections, hypovolemia, thromboembolism, and acute kidney injury.

Among them, the incidence of acute kidney injury (AKI) varies from 0.8-58.6% (2, 3, 4). AKI is a well-known complication for adverse outcomes among hospitalized children in both general and critical care settings. Children with active NS have a number of potential risk factors for the development of AKI, including intravascular

volume depletion, infection, exposure to nephrotoxic medication, and renal interstitial edema leading to vascular congestion (5, 6, 7). AKI is an alarming complication of idiopathic NS. Possible causes of AKI include bilateral renal vein thrombosis, interstitial edema, tubular obstruction, allergic interstitial nephritis, acute pyelonephritis, rapid progression of the original glomerular disease, and acute tubular necrosis secondary to sepsis or hypovolemia

A prospective study was conducted to evaluate the distribution of acute kidney injury in different types of nephrotic syndrome, assess various risk factors associated with acute kidney injury in nephrotic syndrome, and investigate the association of AKI with outcomes in a tertiary care teaching hospital as a cultural and linguistic area situated in the Indian state of Uttar Pradesh.

Methods

The study was conducted in children aged 1-18 years admitted with a diagnosis of nephrotic syndrome to the Pediatric Ward of Shri Ram Murti Smarak Institute of Medical Sciences, Bareilly from November 2018 to May 2020. This study was a hospital-based, prospective, observational study. NS was defined as heavy proteinuria (>40 mg/m2/hour), hypoalbuminemia (≤ 2.5 g/dL), edema and hyperlipidemia (cholesterol >200mg/dl) (1). Steroid-sensitive, steroid-dependent, steroid-resistant, infrequently relapsing and frequently relapsing NS were classified as per standard definitions proposed by the Indian Pediatric Nephrology Group (8). Children with features of nephroto-nephritic syndrome, underlying secondary causes of nephrotic syndrome, and admission for diagnostic renal biopsy were excluded. The study was approved by the Institutional Ethics Committee.

Diagnosis of AKI was made according to KDIGO Guidelines 2012 using serum creatinine and staged according to the pRIFLE score (through creatinine clearance and urine output criteria). The creatinine value was determined using the Modified Jaffe's method and the estimated glomerular filtration rate (eGFR) (ml/min/1.73 m2) was calculated using the original Schwartz formula with a constant of 0.413 (9). According to the KDIGO Guidelines 2012, acute kidney injury is defined as an increase in serum creatinine ≥ 0.3 mg/dL within 48 hours or an increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days, or a urine volume <0.5ml/kg/hr for 6 hours (10). The upper limit of normal range of the serum creatinine value for age was used as the baseline value if no recent serum creatinine value was available. Serum creatinine was evaluated every other day in children if it fell within the normal range until discharge. Serum creatinine was estimated daily if a rising trend was noticed until normalization. Exposure to nephrotoxic agents was considered when a decrease in the urine output and an increase in the serum creatinine value were noticed within one week of such exposure prior to or after admission. Infection was categorized according to the system involved. Pneumonia, peritonitis, gastroenteritis, sepsis and urinary tract infection were confirmed as per the blood count, routine microscopy, and culture sensitivity reports. Cellulitis was diagnosed by pain over the affected area and local signs of inflammation. To rule out dehydration, physical signs of dehydration were evaluated, including dry mucosa, sunken eyes, decreased urine output and return of baseline creatinine within 48 hours after intravenous fluid administration.

Statistical Analyses: Descriptive statistics are shown as frequency and percentage or as mean ± SD as appropriate. The incidence of AKI was measured as a proportion of children developing AKI out of total episodes of hospitalizations with NS. Independent samples t test and chi square or Fischer exact tests were used to test the significance of difference between two means and proportions, respectively. AKI risk factors were analyzed suing univariate and multivariate logistic regression analysis. The p values of less than 0.05 were considered significant. Statistical test applied for qualitative data is student t test using SPSS software version 17.

Results

Of 54 cases admitted, only 43 met the inclusion criteria. The mean age of children in this cohort was 4.7± 2.8 years and male subjects outnumbered female subjects by 72%. The baseline demographic and clinical characteristics are shown in Table 1. Complications were observed in 29 (67%) cases. The most frequent complication was anemia (25%) followed by infection (21%) and AKI (18.6%) in admitted patients.

Most of the complications were in steroid sensitive nephrotic syndrome (96%) compared to dependent or resistant nephrotic syndrome (Table 2). Similarly, in terms of episode, most of the complications occurred in the first episode (55%) followed by frequent relapses (21%).
Among all complications in the steroid sensitive group, only AKI (p – 0.007) and anemia (0.002) had significant associations.

Table 1. Cohort demographic and clinical characteristic

S.No	Category	Number (%), n = 43
1.	Age 1 -3 yrs 4 – 6 yrs 7 – 10 yrs 11 – 18 yrs	 9 (21%) 19 (44%) 11 (25%) 4 (9%)
2.	Gender Male Female	 31 (72%) 12 (28%)
3.	First Episode	21 (48%)
4.	First Relapse	8 (18%)
5.	Frequent Relapse	10 (23%)
6.	Infrequent Relapse	4 (9%)
7.	Steroid sensitive	37 (86%)
8.	Steroid Dependent	6 (14%)
9.	Steroid Resistant	0 (0%)

AKI was seen in 8/43 (18.6%) of the children. These children with nephrotic syndrome and AKI were then staged using the pRIFLE criteria into three stages; including 11.6% in stage 1 (risk), 4.6% in stage 2 (injury), and 2.3% in stage 3 (failure) (Fig. 1) and Table 3 and 4.

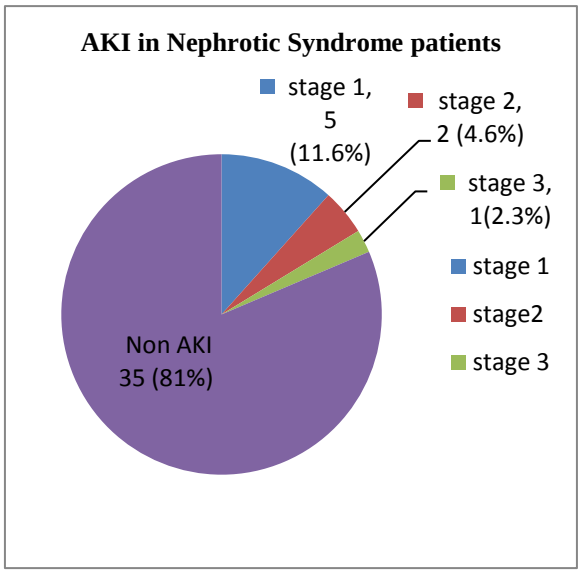

Figure 1. Stages of AKI according to pRIFLE criteria

Table 2. Evaluation of complications in children with nephrotic syndrome in relation to episodes of nephrotic syndrome

Complications of Nephrotic Syndrome	First Episode N (P value)	First Relapse N (p – value)	Frequent Relapse N (p- value)	Infrequent Relapse N (p – value)	Total
Effusions	0(-)	0(-)	0(-)	0(-)	0
Infections	4(1)	2(0.29)	2(0.62)	1(0.299)	9
Acute kidney injury	5(0.007)	1(0.13)	2(0.08)	0(0.3)	8
Thromboembolism	0(0.29)	0(0.29)	1(0.62)	0(0.29)	1
Anemia	7(0.002)	3(0.08)	1(0.04)	0(0.3)	11
Total	16 (55%)	6(21%)	6(21%)	1(3%)	29

Table 3. Univariate analysis of risk factors for acute kidney injury in children with nephrotic syndrome

Parameters	ODDS Ratio	P Value
Sepsis	2.9	0.5
Steroid dependent	1.2	0.8
Peritonitis	2.8	0.3
Drugs	0.8	0.5

Table 4. Multivariate regression analysis of risk factors associated with acute kidney injury in patients with nephrotic syndrome

Clinical Parameters	AKI	Non AKI	P – value
Age (Mean)	7.25	6.0	0.149
Gender (Male)	6	25	0.011
Clinical type			
First Episode	5	16	0.32
First Relapse	1	7	0.63
Frequent Relapse	2	8	0.9
Infrequent Relapse	0	4	0.2
Steroid Response			
Sensitive	7	30	0.8
Dependent	1	5	0.8
Resistant	0	0	-
Complications			
Peritonitis	2	0	0.99
Effusions	0	0	-
Infections	1	11	0.4
Thromboembolism	0	1	4.6
Anemia	3	11	0.00
Nephrotoxic drugs			
Amikacin	3	13	0.6
Vancomycin	2	2	0.002
Furosemide	3	8	0.6
Ace inhibitor	0	3	0.4
Outcome			
Death	0	0	-
Duration of Hospital Stay (mean)	10.6	7.7	0.1

As per the frequency of relapse, five out of eight patients had acute kidney injury in their first episode. Four were at a risk of injury while one had acute kidney injury. In the frequent relapses group, two had AKI (one at risk and the other one had injury) and only one case of first relapse had AKI (failure). Of 43 patients, 23 (53%) received nephrotoxic drugs during the hospital stay. Among nephrotoxic drugs, amikacin (50%) was the most common followed by furosemide (31%). Vancomycin was used in only two patients (8%). None of the risk factors like sepsis, peritonitis, drugs or type of steroid sensitivity had a significant association with AKI. On applying multivariate logistic regression analysis, only gender, associated anemia, and vancomycin use during nephrotic syndrome were significant independent risk factor for acute kidney injury.

Discussion

The mean age of children with NS was 4.7 ± 2.8 years, which was similar to previous studies (11, 12). However, the mean age was slightly higher in a few studies (13). Male predominance (2.5:1) was also noted similar to other studies (14, 15). Overall, complications was observed in 67% of the cases. All these complications were more frequent in the first episode than compared to any type of relapse. This could be due to late presentation to the hospital (secondary to lack of awareness about this disease). Similar to the present study, Krishnan C. et al also noted complications in 67% of cases but unlike us, 73% of complications occurred in relapses (16). In the present study, most of the complications occurred in the steroid sensitive nephrotic syndrome (96%) group rather compared to dependent or resistant nephrotic syndrome. Only a few studies reported acute complications in steroid sensitive nephrotic syndrome group (17). Hjorten R et al only reported long-term complications of steroid sensitive nephrotic syndrome like hypertension, growth failure, overweight, osteoporosis etc (18). The incidence of AKI was 18.6% [according to a KIDIGO 2012 and modern (pRIFLE) definition] in this study while it varies from 0.8 -58.6% in various other studies (2, 3, 4). As per the pRIFLE criteria, 62% of the cases were in stage 1 (Risk), 25% in stage 2 (injury) and 13% in stage 3 (failure) of acute kidney injury. Most of the studies showed similar results, i.e. a higher percentage of patients in the risk category of pRIFLE criteria, but the frequency or the percentage varies. (9, 19, 13) Moreover in the present study, the frequency of acute kidney injury was higher in the first episode of nephrotic syndrome, which was similar to a study done by Sato M. et al where AKI was the most common complication of the first episode of nephrotic

syndrome (20). However, the percentage varies, i.e. 24% of the cases against 62.5% of the cases in the first episode in the present study.

The present study included a larger number of patients with acute kidney injury in the first episode of nephrotic syndrome, probably due to late presentation of patients either in OPD or in casualty as prerenal azotemia from intravascular volume depletion frequently contributes to AKI in children with NS.

Nephrotoxic medication exposure is strongly associated with the risk of AKI. In the present study, it was observed that 23 patients with all types of nephrotic syndrome (53%) received nephrotoxic drugs during the hospital stay. Among the nephrotoxic drugs used, amikacin (53%) was the most common followed by furosemide (34%) and ACE inhibitors (11%). Vancomycin was used in only two patients (8%). Rheault et al found that more than half of all admitted children with any type of nephrotic syndrome were complicated with at least one nephrotoxic drug during the hospital stay, while 20.9% were exposed to at least two, and 5.1% were exposed to three or more (2). In their study, the most common nephrotoxic medications were ACE-inhibitors (27.8%), calcineurin inhibitor (25.5%), and nephrotoxic antibiotics (20.3%).

The rate of exposure to nephrotoxic antibiotics was 58% in our study while it was only 20.3% in the above study. The use of ACE inhibitors was 11% in the present study and 27.8% in the above study. Yaseen A et al found that use of nephrotoxic drugs (43.7%) was the second most common risk factor for acute kidney injury in patients with nephrotic syndrome (13). Drugs included in their study were cyclosporine (31.9%), tacrolimus (9.2%) and ACE inhibitors (2.5%) (13). However, ACE inhibitors were only used in 2.5% in comparison to 11% in the present study. Similar to our study, Prasad BS et al used the same spectrum of nephrotoxic drugs in their study and assessed the use of furosemide (83%), ACE inhibitor (19%), Amikacin (8%), Vancomycin (4%) (9). However, the spectrum of nephrotoxic drug and its frequency varies as per the antibiogram and type of nephrotic syndrome in various studies (2, 13, 9).

This study evaluated whether specific risk factors were significantly associated with the development of AKI. The results of univariate regression analysis for independent risk factor for acute kidney injury showed that none of the parameters i.e. steroid dependent Nephrotic Syndrome, shock, peritonitis, drugs were significant (Table 3). Similarly, Prasad BS et al also observed no significant relationship between sepsis, peritonitis, shock, and steroid dependent nephrotic syndrome with acute kidney injury (9). They found that use of furosemide infusion was the only risk factor for acute kidney injury in children with nephrotic syndrome. Unlike our study, Rheault et al found a significant association between steroid resistant nephrotic syndrome, infection and drugs and acute kidney injury as its risk factors (2). A study by Sharma S et al found that infection and nephrotoxic medication were independently associated with AKI in nephrotic syndrome. Ours study results are not consistent with their study, may be due to the small cohort group in the present study (19).

In the present study, male gender and anemia were independent risk factors for AKI in children with NS in comparison to NS without AKI. In the nephrotoxic medications group, only vancomycin was an independent risk factor for AKI (Table 4). Rheault et al found that race/ethnicity and medication exposure like nephrotoxic antibiotics, calcineurin inhibitors, ACE inhibitors etc. were associated with acute kidney injury (2). However, in the present study, only exposure to vancomycin (not amikacin) was significantly associated with AKI. Calcineurin inhibitors, antivirals, and NSAIDS were not included in our study, while they were investigated in the above study. Prasad BS et al found shock and peritonitis were significantly involved in development of acute kidney injury. Moreover, similar to the present study, they also found that vancomycin was an independent risk factor for AKI (9).

Gender did not have a significant association with AKI in this study (9). Unlike the present study, they also found that the duration of hospital stay was significantly associated with AKI. Anemia was an independent risk factor for acute kidney Injury in the present study.

Anemia is usually due to large loss of serum transferrin in the urine of nephrotic patients (21). Apart from that, a study by Vaziri et al also found that urinary loss of erythropoietin (EPO) caused EPO-deficiency anemia and transferrinuria in nephrotic syndrome patients (22). One study reported an association between anemia (frequent in hospitalized patients) with worse outcomes and AKI (23). The contribution of anemia to AKI is mostly

multifactorial. It has been proposed that lower hemoglobin levels predisposes the patients to renal hypoxia and oxidative stress (24). Moreover, many anemic patients have some subclinical renal disease, which increases the susceptibility to renal injury (25). Shema- Didi et al reported an independent association between anemia and AKI (26). In addition, Malhotra et al. considered anemia as an independent predictor of AKI [OR 1.477 (0.891–2.449), p = 0.13] in the risk prediction score in a prospective study of critically ill patients (27).

Han et al. has identified a hemoglobin threshold for detecting an increased risk of AKI and an association between anemia and AKI and long-term mortality in a retrospective study of critically ill patients (28). However, a review of the literature showed that none of the study investigating childhood idiopathic NS identified anemia as an independent risk factor for acute kidney injury. Although we found that anemia was an independent risk factor for AKI in children with NS, we did not quantify the severity/degree of anemia that predisposes to AKI. Therefore, this is a limitation of the present study, requiring future prospective studies to confirm the role of anemia as a risk factor for NS with AKI and its immediate and long-term consequences.

Conclusion

AKI accounts for 18% of all complications in children with NS. In the steroid sensitive group, only AKI and anemia were significant complications. AKI was more frequent in the first episode compared to frequent and infrequent relapses. Male gender, nephrotoxic drugs (vancomycin), and anemia were independent risk factors for development of AKI. Children with NS and anemia should be closely monitored for development of AKI.

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Conflict of Interest

The author declares no conflicts of interest.

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