AIMS Medical Science

AIMS Medical Science, 9(1): 18–31.
DOI: 10.3934/medsci.2022004
Received: 17 November 2021
Revised: 09 January 2022
Accepted: 16 February 2022
Published: 09 March 2022

http://www.aimspress.com/journal/medicalScience

Research article

Acute kidney injury in children with nephrotic syndrome at the University of Abuja Teaching Hospital, Abuja, Nigeria: 2016 to 2021

Emmanuel Ademola Anigilaje* and Ishola Ibraheem

Nephrology Unit, Department of Paediatrics, University of Abuja Teaching Hospital, Abuja, Nigeria

* **Correspondence:** Email: demolaanigilaje2@gmail.com; Tel: 2348033833839.

Abstract: Background: Information regarding acute kidney injury (AKI) is scarce among Nigerian children with nephrotic syndrome (NS). This study describes the prevalence, risk factors and outcomes of AKI among children with NS at the University of Abuja Teaching Hospital (UATH), Abuja, Nigeria. **Materials and methods:** This is a review of children with NS, from January 2016 to October 2021 at the UATH. AKI was classified by the paediatric RIFLE criteria. **Results:** Of the 75 children with NS, aged 13 months to 18 years, with a mean age of 10 ± 18 years, and majorly (64, 85.3%) males. AKI occurred in 19 of 75 (25.3%) subjects comprising Failure in 15 (78.9%), Injury in 3 (15.8%) and Risk in 1 (5.3%). Regarding risk factors of AKI at hospital admission; subjects with no sepsis were at reduced odds of AKI (OR = 0.01, 95% CI = 0.02–0.06, $p < 0.001$); and the risk of AKI was reduced among subjects without gross haematuria (OR = 0.07, 95% CI = 0.01–0.66, $p = 0.004$). The likelihood of AKI increased in the presence of peritonitis (OR = 7.91, 95% CI = 2.15–29.15, $p < 0.001$) and urinary tract infections (UTIs) (OR = 2.55, 95% CI = 1.39–4.66, $p < 0.001$). Subjects with historical exposure to nephrotoxic medications (NTM) were also at risk of AKI (OR = 1.79, 95% CI = 1.13–2.84, $p = 0.001$). The only 2 deaths (2.6%) observed in the short term was among those with AKI (2/19, 10.5%) but full renal recovery occurred in the majority (16/19, 84.2%). **Conclusions:** AKI is common in our children with NS. Sepsis, gross haematuria, peritonitis, UTIs and NTM were its identified risk factors. It is prudent to have a suspicion of AKI among children with NS with these risk factors in our setting.

Keywords: acute kidney injury; nephrotic syndrome; children; Abuja; Nigeria

1. Introduction

Nephrotic syndrome (NS) is the commonest chronic glomerular disease in children characterized by heavy proteinuria with attendant hypoalbuminaemia, hyperlipidemia, and generalized oedema [1]. In children with NS, steroid responsiveness is the key determinant of prognosis and it differs across geographical regions reflecting varying histopathological lesions, ethnogenetic, and environmental factors [2]. In Europe and North America, minimal change disease (MCD) represents 85% of the NS cases with steroid responsiveness seen in more than 90% of the MCD [3]. In Africa, MCD NS with steroid responsiveness also predominates in temperate regions [3]. In tropical Africa, from the 1960s to 1980s, steroid-resistant non-MCD, including quartan malaria nephropathy was the dominant histopathology type [3]. However, in the years after 1989, proliferative glomerulonephritis, MCD, and focal segmental glomerulosclerosis (FSGS) predominate [3]. The earlier studies in Nigeria reported children with NS to be majorly steroid unresponsive [4]; however, recent studies are documenting high and increasing prevalence rates of steroid-sensitive NS (SSNS) [5–8].

NS manifests with some acute life-threatening complications including infection, hypovolaemia, venous thromboembolism (VTE), and acute kidney injury (AKI) [9,10]. Although the clinical implications of infection and VTE on children with NS are clear, the epidemiology and outcomes of AKI in NS remain unclear [11]. AKI is an abrupt decline in kidney excretory function characterized by a reversible increase in the blood concentration of creatinine and nitrogenous waste products, often accompanied by a decrease in urine output and by the inability to regulate fluid and electrolyte homeostasis [12]. AKI remains a major cause of childhood morbidity and mortality [13,14]. In addition to a prolonged hospital stay, AKI in NS also necessitates the need for intensive care in children [11]. The possible aetiopathogenesis of AKI in children includes acute tubular necrosis from hypovolaemia and infection, renal interstitial oedema with vascular congestion, bilateral renal vein thrombosis, acute pyelonephritis, rapid progression of the original glomerular disease, and exposure to nephrotoxic medications (NTMs) [15–18]. Children with NS are inevitably exposed to NTMs either because of the need to treat the underlying glomerular lesions (calcineurin inhibitors) or the need to treat oedema, hypertension and infections (diuretics, angiotensin-converting enzyme inhibitors and antibiotics) [19]. Whereas the studies of AKI in NS are commoner in adult populations [17,18], a standardized definition of AKI in children [Pediatric Risk, Injury, Failure, Loss, End-Stage Renal Disease (pRIFLE) Staging] is allowing for more reports of AKI in childhood NS. Studies have reported incidences of AKI in children with NS to be 0.8–58.6% [11,18,20,21]. AKI is a recognized precursor of chronic kidney disease (CKD) and its epidemiology needs to be well described in all subgroups of childhood illnesses including those with NS.

To the best of the authors' knowledge, there has been no published report of AKI among Nigerian children with AK.

In the light of the foregoing, this study describes the hospital-based prevalence of AKI (using the pRIFLE definition) and its risk factors among children with NS at the University of Abuja Teaching Hospital Abuja (UATH), from January 2016 to October 2021.

2. Materials and methods

Ethical consideration followed the Helsinki Declaration of 1975, as revised in 1983. Permission to use the data was obtained from the Research and Ethics Committee of the UATH, Abuja. All

children with NS (including those with or without AKI) aged 1 month to 18 years from January 2016 to October 2021 at the Nephrology Unit of the Department of Paediatrics, UATH, were included in the study. We have previously published the details of investigations and management of childhood AKI at the UATH, Abuja [22]. Management of AKI is mostly supportive [17]. Mild AKI tends to resolve with remission of NS with steroids [17]. The need for dialysis was after the failure of conservative management that includes intravascular volume repletion, treatment of infection, and removal of NTMs [17,22]. Specifically, indications for dialysis include hypervolaemia and hypertension with congestive heart failure and pulmonary oedema failing to respond to treatment, AKI with multisystem failure, uraemic symptoms (encephalopathy, pericarditis, intractable vomiting, and haemorrhage), symptomatic severe anaemia, and anuria of more than 24 hours [22]. Biochemical indications for dialysis include hyperkalemia >6.5 mmol/L and increasing serum creatinine levels despite conservative management, severe hyponatraemia (Na < 118 mmol/L with oliguria), severe hypernatraemia (Na > 160 mmol/L with oliguria), severe hypocalcaemia [total Ca (corrected) < 1.75 mmol/L, ionized Ca < 0.8 mmol/L] not responding to therapy, severe hyperphosphataemia (PO4 > 1.7 mmol/L), hyperuricaemia (serum uric acid > 15 mg/dL), and severe intractable acidosis (plasma bicarbonate < 10 mmol/L) [22]. Choice of acute dialysis is either intermittent haemodialysis or peritoneal dialysis (PD). PD was opted for small-sized patients (weight < 25 kg), when vascular access cannot be secured in a bigger child, in uremic diathesis, and when there was cardiovascular instability [22].

Definition of terms: AKI and its severity were as described by pRIFLE criteria using urine output and serum creatinine estimation measured by Jaffe's method [23]. Although AKI was diagnosed at hospital admission, the maximum serum creatinine level reached in each patient on or before post-admission Day 7 was used for the final AKI severity as per Injury or Failure. Estimation of glomerular filtration rate (eGFR) was by Schwartz's formula and adequacy of urinary output was based on the bodyweight [23]. AKI/risk was defined as a decrease of at least 25% in eGFR and/or a urine output of <0.5 mL/kg/h for >8 h [24]. The injury was a decrease of at least 50% in eGFR and/or a urine output of <0.5 mL/kg/h for 16 h [24]. Failure was a decrease of at least 75% in eGFR or eGFR <35 mL/min/1.73 m^2 and/or urine output <0.3 mL/kg/h for 24 h or if the child was anuric for 12 h [24]. It is important to emphasize that this is a description of children with NS (some of whom had AKI as described by pRIFLE above) coming to our hospital for the first time, therefore, their baseline serum creatinine was unknown, and a baseline GFR of 100 mL/min/1.73 m^2 was assumed [22,24,25].

NS was defined as the presence of oedema, massive proteinuria of spot urine protein creatinine ratio ≥200 mg/mmol, hypoalbuminaemia (serum albumin ≤ 25 g/L) and hypercholesterolemia (serum cholesterol > 5.2 mmol/L) [26–28]. In this study, massive proteinuria of spot urine protein creatinine ratio ≥200 mg/mmol was the sine qua non of NS diagnosis [28]. Secondary NS (SNS) refers to proven aetiology extrinsic to the kidney [26]. Thus, SNS includes autoimmune and vasculitic diseases, such as systemic lupus erythematosus, infectious diseases such as malaria, human immunodeficiency virus (HIV), hepatitis B and C, and sickle cell anaemia [26]. Idiopathic NS (INS) is when NS is not congenital, infantile or secondary [26]. Complete remission/steroid responsiveness is when urine dipstick albumin becomes negative or a trace for 3 consecutive days [29]. Partial remissions (PR) is a proteinuria level of 1+/2+ proteinuria by dipstick for 3 consecutive days [29]. Initial or earlier responder (steroid-sensitive NS-SSNS): An attainment of complete remission within the initial 4 weeks of prednisolone therapy as defined by the International Study of Kidney Disease in Children (ISKDC) [29]. Initial resistance (steroid-resistant NS-SRNS) was a failure to achieve complete remission after 8 weeks of prednisolone therapy as defined by ISKDC [29]. The ISKDC

steroid regimen used was 60 mg/m^2 once daily (single morning maximum dose of 60 mg of prednisolone) for 28 days, followed by 40 mg/m^2 (maximum dose of 40 mg of prednisolone) given on an alternate day for a further 28 days [30]. We extended alternate-day prednisolone from 28 days to 56 days (8 weeks) for subjects who had partial remission to prednisolone after 28 days of induction prednisolone. Steroid resistance was treated with cyclosporine or mycophenolate. We used mycophenolate rather than cyclosporine in children with a reduced eGFR at presentation. Supportive treatment includes the use of cimetidine and omeprazole while on steroid therapy 40–60 mg/m^2, diuretics (frusemide, spironolactone and hydrochlorothiazide) for oedema, intravenous hydralazine and nifedipine/amlodipine for hypertension, and angiotensin-converting enzyme inhibitors for SRNS. Biopsy was warranted for SRNS and those who did not respond to standard conservative management for AKI. Hypertension was defined as systolic and or diastolic blood pressure greater than the 95th centile for age, gender and length using nomogram published in the fourth report of the National High Blood Pressure Education Group [31]. Socioeconomic status (SES) stratification was done using the one proposed by Oyedeji which employs the educational status and occupation of parents [32]. SES was classified into high, medium and low based on the occupation and level of education of the parents. Sepsis in children conformed with its description including the presence of two or more of the following: abnormal temperature (< 36.0 °C or > 38.3 °C) or age-specific tachycardia (>140 beat/min for 0–2 years, >120 for 2–6 years, and >110 for >6 years) or acute altered mental status; with a clinical suspicion of new infection including cough/chest pain and or abdominal pain/distension/diarrhoea and/or dysuria and or headache with neck stiffness and/or presence of cellulitis/wound infection/joint infection [33]. Malaria diagnoses were confirmed by the presence of asexual forms of Plasmodium falciparum on peripheral blood film. Urinary tract infection (UTI): It is defined as a positive test result for pyuria by either microscopy (10 white blood cells per microliter or ≥5 white blood cells/high power field in uncentrifuged urine specimen) or dipstick test (positive leukocyte esterase test) and positive growth on the culture of at least 50,000 colony-forming unit (CFU)/mL of a single uropathogen in urine specimen obtained by catheterization or >100,000 CFU/mL of a single uropathogen in clean-catch urine specimen or any uropathogenic growth in urine obtained supra-pubically [34]. Short-time mortality was the number of children with AKI that died while on admission and within the first four weeks of follow-up. Renal recovery was defined as the number of children who survived AKI and became independent from dialysis, with progressive improvement in eGFR to values ≥100 mL/min/1.73 m^2 [22,24,25]. Strictly, the term AKI applies for impaired eGFR and clinical conditions ≤7 days, acute kidney disease (AKD) applies for >7 days to <90 days, and chronic kidney disease (CKD) applies for ≥90 days with impaired eGFR and proteinuria [12]. Therefore, at 3 months of follow-up, children with eGFR <100 mL/min/ 1.73 m^2 who did not require dialysis were closely monitored for evidence of chronic kidney damage (e.g., nephrotic range proteinuria or albumin excretion rate of ≥30 mg/24 h) and were managed as per their subsequent stage of the CKD (eGFR in mL/min/1.73 m^2 G1; ≥ 90, G2; 60–89, G3a; 45–59, G3b; 30–44, G4; 15–29 and G5 ≤ 15) [35]. Subjects were bled for serum creatinine (GFR estimation) on the morning of their 3 months follow-up before the commencement of the out-patient nephrology clinic.

3. Statistical analysis

Categorical variables were described in frequencies and percentages and were compared using the chi-square test or Fisher's exact test as appropriate. For continuous variables, QQ plots were used to describe the normality of distribution. The age, serum albumin, serum cholesterol, packed cell volume, and body weight were normally distributed and their means and standard deviations were compared using an unpaired student t-test. Spot urine protein creatinine ratio and serum creatinine distribution were skewed and comparisons of their medians and interquartile ranges (IQR) were made with the Mann-Whitney test. AKI and its severity were described by pRIFLE criteria [16]. Subjects were dichotomized into AKI and non-AKI groups. Risk factors with a p-value < 0.05 were described for odds ratios and confidence intervals (CI) set at 95% level. All analyses were performed using SPSS, version 20 (IBM Corp., Armonk, NY, USA).

4. Results

Table 1. Baseline socio-demographic characteristics of the children with nephrotic syndrome.

Characteristics	Number	Percentages
Age groups in years		
0–5	28	37.3
6–10	27	36.0
≥ 11	20	26.7
Gender		
Male	64	85.3
Female	11	14.7
Ethnicity		
Igbo	22	29.4
Fulani	16	21.3
Yoruba	12	16.0
Bassa	5	6.7
Idoma	4	5.3
Others	16	21.3
Socioeconomic class		
High	25	33.3
Medium	20	26.7
Low	30	40.0
Steroid sensitivity		
Steroid-sensitive nephrotic syndrome	64	85.3
Steroid-resistant nephrotic syndrome	11	14.7
Classification		
Idiopathic nephrotic syndrome	67	89.3
Secondary*	8	10.7
Congenital/Infantile	-	-

Note: * = Sickle cell anaemia = 3, Hepatitis B = 2, Hepatitis C = 2, Systemic lupus erythematosus = 1.

The study comprised 75 children with nephrotic syndrome, ranging in age from 13 months to 18 years with the mean age of 10 ± 18 years. Table 1 describes the baseline socio-demographic characteristics of the children with NS. Most of the subjects were ≤ 5 years (37.3%). The majority were males (64, 85.3%), with a male to female ratio of 5.8:1. Steroid sensitivity was documented in

64 (85.3%). In most subjects (67, 89.3%), idiopathic NS was seen. The eight (10.7%) secondary NS comprised 3 (37.5%) with sickle cell anaemia, 2 (25%) each with viral hepatitis B and C, and 1 (12.5%) with systemic lupus erythematosus. With subjects numbering 22 and 16, the Igbos and the Fulanis constituted the majority at 29.4% and 21.3% respectively. Regarding the SES, the majority (30, 40%) were in the low SES.

Table 2. Baseline socio-demographic and laboratory risk factors of acute kidney injury in nephrotic syndrome.

Characteristics	AKI-Nephrotic syndrome (19, 25.3%)	Non-AKI Nephrotic syndrome (56, 74.7%)	X^2 OR FET	P-value	OR (95 CI)
Age groups in years					
0–5	5	23	1.820	0.402	
6–10	7	20			
≥ 11	7	13			
Gender					
Male	16	48	0.026 **	0.873	
Female	3	8			
Ethnicity					
Igbo	6	16	3.055 **	0.723	
Fulani	4	12			
Yoruba	2	10			
Bassa	2	3			
Idoma	2	2			
Others	3	13			
Socioeconomic class					
High	8	17	2.009	0.366	
Medium	6	14			
Low	5	25			
Spot urine protein/creatinine ratio (median (IQR))	525.00 (409–898)	561.00 (320–941)	528.00 α	0.961	
Serum albumin (mean ± SD)	18.9 ± 5.3	17.9 ± 4.8	0.749 β	0.456	
Serum cholesterol range (mean ± SD)	7.7 ± 4.3	6.5 ± 3.6	1.190 β	0.238	
Serum creatinine (median (IQR))	450.00 (269–490)	40.00 (25.00–54.50)	20.00 α	< 0.001	
PCV (mean ± SD)	33.7 ± 3.8	33.3 ± 4.8	0.325 β	0.746	
Age in months (mean ± SD)	109.21 ± 11.44	82.5 ±6.80	1.986 β	0.051	
Body weight in kilograms (mean ± SD)	35.6 ± 15.1	27.9 ± 11.9	2.204 β	0.031	

Note: X^2 = chi-square test, FET = Fisher's exact test, ** FET used, AKI = acute kidney injury, IQR = interquartile range, α = Mann-Whitney test, β = unpaired t test.

Table 2 compares the baseline socio-demographic and laboratory risk factors of AKI among the subjects with NS. Of the 75 subjects with NS, 19 (25.3%) were diagnosed with AKI. As per pRIFLE standardization, 19 subjects were diagnosed with AKI at presentation (Risk), but the eventual severity of AKI that the patients attained was used to describe the AKI. A majority (15, 78.9%)

progressed to Failure, 3 (15.8%) progressed to Injury and 1 (5.3%) remained at Risk from the serum peak creatinine which occurred on or before post-admission Day 7. Except for the significant difference in the higher median serum creatinine ($p < 0.001$) and higher mean baseline weights ($p = 0.031$) noted for subjects in AKI, there was no difference in other baselines socio-demographic and laboratory characteristics.

Table 3. Baseline clinical and symptomatic risk factors of acute kidney injury in nephrotic syndrome.

Characteristics	AKI-Nephrotic syndrome (19, 25.3%)	Non-AKI Nephrotic syndrome (56, 74.7%)	X^2 OR FET	P-value	OR (95 CI)
Sepsis					
Yes	16	3	46.634 **	< 0.001	0.01 (0.02–0.06)
No	3	53			
Peritonitis					
Yes	15	2	45.982 **	< 0.001	7.91 (2.15–29.15)
No	4	54			
Urinary tract infection					
Yes	13	7	22.686	< 0.001	2.55 (1.39–4.66)
No	6	49			
Malaria fever					
Yes	14	29	2.781	0.095	
No	5	27			
Nephrotoxic medications					
Yes	11^	10	11.280	0.001	1.79 (1.13–2.84)
No	8	46			
Initial response to prednisolone					
SSNS	15	49	0.829 **	0.363	
SRNS	4	7			
Secondary NS					
Yes	3	5	0.701 **	0.403	
No (Idiopathic)	16	51			
Hypertension					
Yes	12	22	3.262	0.071	
No	7	34			
Gross haematuria					
Yes	4	1	8.464 **	0.004	0.07 (0.01–0.66)
No	15	55			
Anaemia					
Yes	3	8	0.026 **	0.873	
No	16	48			
Hypoalbuminaemia					
Yes	16	48	0.361 **	0.835	
No	3	8			
Hyperchlolesterolaemia					
Yes	13	30	1.279	0.258	
No	6	26			
Microscopic haematuria					
Yes	14	32	1.637	0.201	
No	5	24			

Note: Risk = 1, Injury = 3, Failure = 15, ^ = 8 Ibuprofen, 2 gentamycin, 1 captopril, X^2 = chi-square test, FET = Fisher's exact test, ** FET used, AKI = acute kidney injury.

Table 3 depicts clinical and symptomatic features identified as risk factors of AKI among the subjects with NS. The risk of AKI did not differ among subjects by malaria fever, response to steroids, classes of NS, hypertension, anaemia, hypoalbuminaemia, hypercholesterolaemia and micro-haematuria. Infections (sepsis, peritonitis and urinary tract infections), exposure to nephrotoxic medications, and gross haematuria were features that were significantly higher among those with AKI-NS compared to non-AKI-NS. These clinical features were seen as follows; sepsis in 19 (16 among AKI, 84.2%), peritonitis in 17 (15 AKI, 78.9%), UTIs in 20 (13 AKI, 68.4%), gross haematuria in 5 (4 AKI, 21.1%) and nephrotoxic medications (NTMs) in 21 (11 AKI, 57.9%). Five (26.3%) subjects with AKI who had sepsis were also exposed to NTMs. The NTMs in the 11 subjects with AKI were Ibuprofen in 8, gentamycin in 2 and captopril in 1. Among 10 subjects who did not have AKI, the NTMs observed were vancomycin in 2, meropenem in 3, Ibuprofen in 3 and gentamycin in 2.

Regarding sepsis, NS with no sepsis at hospital admission were at significantly reduced odds of having AKI (OR = 0.01, 95% CI = 0.02–0.06, $p < 0.001$). The risk of having AKI was significantly reduced among subjects without gross haematuria (OR = 0.07, 95% CI = 0.01–0.66, $p = 0.004$). The likelihood of having AKI in NS increased by 7.9 times in the presence of peritonitis compared to not having peritonitis (OR = 7.91, 95% CI = 2.15–29.15, $p < 0.001$). Urinary tract infections in NS increased the odds of AKI by 2.55 times (OR = 2.55, 95% CI = 1.39–4.66, $p < 0.001$). Subjects who were exposed to nephrotoxic medications before presentation were almost twice as likely to have AKI compared to those who were not exposed (OR = 1.79, 95% CI = 1.13–2.84, $p = 0.001$).

Table 4 shows the outcomes in the 19 children with AKI. The serum creatinine data were available for all 17 patients at 3 months of their respective follow-up. No child with AKI achieved remission within the first 7 days of illness, but, a full renal recovery occurred in 16 (16/19, 84.2%) subjects with AKD over 3 months of follow-up. A majority (15, 78.9%) of the AKI was treated with conservative management and standard steroid therapy. Acute haemodialysis was applied in 4 (21.1%) subjects, of which, 2 (2/19, 10.5%) achieved complete resolution of AKI and 2 (2/19, 10.5%) who died from uraemia following inability to sustain renal support with haemodialysis. No mortality was recorded among those without AKI. The 16 (84.2%) children with AKD had their eGFR recovered at 3 months of follow-up, 9 had eGFR of 100–110 mL/min/1.73 m^2; 5 with eGFR of 111 to 119 mL/min/1.73 m^2; and 2 had eGFR ≥120 mL/min/1.73 m^2. Progressive decline in eGFR was noted in 1 (5.3%) subjects in CKD stage G3a (eGFR of 59 mL/min/1.73 m^2), who was also an SRNS.

Table 4. Outcomes of the 19 children with acute kidney injury.

Outcomes*	Number	Percentage
Conservative management	15	78.9
Had haemodialysis	4	21.1
Deaths	2	10.5
Full kidney recovery	16 §	84.2
Progressive chronic kidney disease	1	5.3

Note: * = not mutually exclusive, § = 9 with eGFR of 100–110 mL/min/1.73 m^2, 5 with eGFR 111 to 119 mL/min/1.73 m^2, 2 with eGFR ≥ 120 mL/min/1.73 m^2.

5. Discussions

In this study that spanned over 6 years, AKI occurred in 19 of 75 children with NS (25.3%) comprising the severe form (Failure) in 15 (78.9%) subjects, Injury in 3 (15.8%) and Risk in 1 (5.3%). The associated risk factors for AKI were sepsis, peritonitis, UTIs, gross haematuria, and the receipt of nephrotoxic medications before the presentation. Short-term mortality occurred only among 2 subjects with AKI.

As far as the authors are aware, this is the first report of AKI among Nigerian children with NS. The immediate imports of the study are that AKI is a common acute complication of NS and that AKI increases the possibility of death among Nigerian children with NS.

According to the pRIFLE criteria, the prevalence of AKI-NS at admission in this study is 25.3%. Sharma and colleagues also reported a similar 23.6% for AKI in children with NS in India [18]. However, the burden of AKI-NS varies from 0.8 to 58.6% in other studies [10,11,18,20,21,36,37]. Our prevalence of 25.3% is higher than 0.8% reported by Kilis-Pstrusinska in Poland and also higher than the 8.5–9.1% noted from the data of the Healthcare Cost and Utilization Project (HCUP)-Kids' Inpatient Database (KID) [10,21,36]. Contrariwise, Rheault et al. reported a higher 58.6% for AKI among children with NS who had AKI both at admission and during the entire hospital stay [11]. A higher incidence of 32.2% was also reported by Kim et al. in Seoul, Korea [37]. We attribute the differences in incidences of AKI to the different definitions ascribed to AKI. While standardized and sensitive pRIFLE criteria were used to define AKI in this study and those of Sharma et al. [18] and Rheault et al. [11]; Kim et al. [37] utilized the 2012 KDIGO AKI definition. However, the AKI definition was not standardized in the studies of other authors [10,20,21,36].

Whereas age and gender were not associated with the risk of AKI in this study, Sutherland et al. [36] found the highest AKI incidence was among 15–18-year-old hospitalized children. Age ≥9 years at admission were also found to be significantly related to AKI in the study of Kim et al. [37]. Again, whereas, steroid sensitivity was not found to be associated with AKI in this study and that of Kim et al. [37]; Rheault et al. [11] and Beins and colleague [38] found that Children with SRNS were more likely to develop AKI than children with SSNS. Also, hypoalbuminaemia was identified as a risk factor for AKI by some authors [18], a finding that contradicts this study. Furthermore, ethnicity was not found to be associated with AKI in this study, which contrasts the study by Rheault et al. [11] that found the non-white race to be an additional risk factor for AKI.

The possible aetiopathogenesis of AKI in NS includes acute tubular necrosis from hypovolaemia and infection, renal interstitial oedema with vascular congestion, bilateral renal vein thrombosis, acute pyelonephritis, rapid progression of the original glomerular disease, and exposure to nephrotoxic medications (NTMs) [15–18].

In this study, NS children with no sepsis were at significantly reduced odds of having AKI. In other words, the risk of AKI is less among NS without sepsis, supporting the inflammatory role of sepsis in the pathogenesis of AKI. In addition, Sutherland et al. [36] also found septicemia to be associated with AKI in their study.

Septic AKI is triggered by pathogen-associate molecular patterns from bacteria and damage-associated molecular patterns released from or exposed to damaged cells [39]. The consequent effects are glomerular and peritubular endothelial dysfunction, down-regulation of tubular reabsorption, cell-cycle arrest, regulated cell death, and destruction of damaged cell organelles [39]. We do not know the extent to which hypovolaemia from diarrhoeal disease alone contributes to the

risk of AKI as most of our subjects diagnosed with sepsis also had diarrhoea. We also cannot use neutrophil gelatinase-associated lipocalin (NGAL) to differentiate between hypovolaemia AKI and intrinsic AKI in our hospital. In any way, children with NS with underlying under-fill hypothesis tend to have some degree of hypovolaemia [17]. Nevertheless, early diagnosis of sepsis is important so that systemic and renal venous congestion, hypotension and fluid overload can be avoided in the management of septic-AKI [22,39].

NS subjects without gross haematuria are also at reduced risk of AKI in this study. Gross haematuria in NS connotes an atypical form of NS associated with glomerular inflammation, hypertension, haematuria, proteinuria and impaired kidney function [28]. The impaired kidney function itself results from tubular obstruction from heavy proteinuria [17]. Our study also supports the fact that NS with gross haematuria should be screened for AKI.

In this study, the likelihood of AKI in NS significantly increased by 7.9 times in the presence of peritonitis and by 2.55 times in those with urinary tract infections. Rheault et al. [11] found that children with infection were twice as likely to develop AKI as children without infection. Kilis-Pstrusinska et al. [20] also found the presence of infection as one of the common risk factors for acute renal failure in the course of idiopathic nephrotic syndrome. Yaseen et al. in Pakistan also identified infections including spontaneous bacterial peritonitis, acute gastroenteritis, sepsis and pneumonia to be associated with AKI in childhood NS [40]. Cavagnaro and colleagues explained that peritonitis causes AKI by worsening the intra- and extra-renal hemodynamics through elevated intra-peritoneal production of cytokines like tumour necrosis factor-α and interleukin-6 [41].

We also found that subjects who were exposed to NTMs before hospital admission were almost twice as likely to have AKI compared to those who were not exposed. Rheault et al. [11] had earlier found that NTMs, which most commonly included ACE inhibitors, calcineurin inhibitors and antibiotics, were strongly associated with the risk of AKI. The pharmacokinetics of gentamicin is altered in NS, which tends to increase their drug exposure [42]. In addition, the use of non-steroidal anti-inflammatory medication (ibuprofen) and angiotensin-converting enzyme inhibitor (captopril) decrease glomerular perfusion in the setting of hypovolaemia of NS is a good recipe for the development of AKI [37]. This may as well explain why AKI was seen among our subjects exposed to gentamicin, ibuprofen and captopril.

The only 2 deaths (2.6%) observed in the short-term in this cohort was among those with AKI (2/19, 10.5%). Rheault et al. [11] found that children with more severe stages of AKI had longer hospitalizations and experienced more mortality. Gladly, most (16/19, 84.2%) of NS with AKI recovered their full renal function as they became responsive to steroid therapy. Unfortunately, a child with AKI who was SRNS had a steady progression to a CKD Stage 3a.

6. Limitations of study

The study is limited by factors inherent in all retrospective studies. A single-centre study may also not give a general overview of AKI in Nigerian children with NS. Although sepsis, gross haematuria, UTIs and peritonitis were present at hospitalization and were significantly associated with AKI in this study, it is difficult to prove a causal relationship, as all of these features may be present as clinical features of NS that may not mean the risk of AKI. We are constrained to assume a baseline GFR of 100 mL/min/1.73 m^2 because these are children with NS coming to our hospital for the first time and we did not know their pre-morbid serum creatinine. We also do not have the

capacity to do serum levels of Ibuprofen, gentamycin and captopril to establish causal relationships with AKI. We propose a multi-centre prospective study to better understand the pathophysiology of AKI among Nigerian children with NS. While we are not unmindful of the drawbacks inherent in using serum creatinine to assess AKI in general, we also note that tubular secretion of creatinine is greatly increased by massive proteinuria of NS which then tends to greatly overestimate GFR [43]. In addition, among NS with hypervolaemia from the overfill hypothesis, serum creatinine is diluted, with a resultant overestimation of kidney function [44]. NGAL, a good biomarker that detect AKI early and which also differentiate between pre-renal AKI and intrinsic AKI is also not available in our setting.

7. Conclusions

This study indicates that AKI is common in our children with NS. This should be concerning and the need for close observation to allow for prompt diagnosis of AKI and management cannot, therefore, be over-emphasized. We found the main risk factors of AKI to include sepsis, gross haematuria, UTIs, peritonitis, and exposure to potentially nephrotoxic medications. While efforts at recognizing these risk factors of AKI among our children with NS are important, we also propose a large prospective multi-centre study to characterize the risk factors of AKI and its long-term outcomes among Nigerian children with NS.

Acknowledgements

We are grateful to the children and parents who made up the subjects of this study.

Conflict of interest

The authors declare no conflict of interest.

References

1. Niaudet P (2004) Steroid-sensitive nephrotic syndrome in children, In: Avner E.D., Harmon W.E., Neasden P. Editors, *Pediatric Nephrology*, Philadelphia: Lippincott William&Wilkin, 543–573.
2. International Study of Kidney Disease in Children (1981) Primary nephrotic syndrome in children: clinical significance of histopathologic variants of minimal change and of diffuse mesangial hypercellularity. A report of the International Study of Kidney Disease in Children. *Kidney Int* 20: 765–771. https://doi.org/10.1038/ki.1981.209
3. Olowu WA, Ademola A, Ajite AB, et al. (2017) Childhood nephrotic syndrome in tropical Africa: then and now. *Paediatr Int Child Health* 37: 259–268. https://doi.org/10.1080/20469047.2017.1374002
4. Asinobi AO, Gbadegesin RA, Adeyemo AA, et al. (1999) The predominance of membranoproliferative glomerulonephritis in childhood nephrotic syndrome in Ibadan, Nigeria. *West Afr J Med* 18: 203–206.

5. Asinobi AO, Ademola AD, Okolo CA, et al. (2015) Trends in the histopathology of childhood nephrotic syndrome in Ibadan Nigeria: preponderance of idiopathic focal segmental glomerulosclerosis. *BMC Nephrol* 16: 213. https://doi.org/10.1186/s12882-015-0208-0
6. Asinobi AO, Gbadegesin RA, Ogunkunle OO (2005) Increased steroid responsiveness of young children with nephrotic syndrome in Nigeria. *Ann Trop Paediatr* 25: 199–203. https://doi.org/10.1179/146532805X58139
7. Ladapo TA, Esezobor CI, Lesi FE (2014) High steroid sensitivity among children with nephrotic syndrome in Southwestern Nigeria. *Int J Nephrol* 2014: 350640. https://doi.org/10.1155/2014/350640
8. Asinobi AO, Ademola AD, Ogunkunle OO (2019) Steroid response in primary childhood nephrotic syndrome in a tropical african environment. *Niger J Clin Pract* 22: 790–795. https://doi.org/10.4103/njcp.njcp_206_16
9. Hodson EM, Wong SC, Willis NS, et al. (2016) Interventions for idiopathic steroid-resistant nephrotic syndrome in children. *Cochrane Database Syst Rev* 10: CD003594. https://doi.org/10.1002/14651858.CD003594.pub5
10. Rheault MN, Wei CC, Hains DS, et al. (2014) Increasing frequency of acute kidney injury amongst children hospitalized with nephrotic syndrome. *Pediatr Nephrol* 29: 139–147. https://doi.org/10.1007/s00467-013-2607-4
11. Rheault MN, Zhang L, Selewski DT, et al. (2015) AKI in Children Hospitalized with Nephrotic Syndrome. *Clin J Am Soc Nephrol* 10: 2110–2118. https://doi.org/10.2215/CJN.06620615
12. Ronco C, Bellomo R, Kellum JA (2019) Acute kidney injury. *Lancet* 394: 1949–1964. https://doi.org/10.1016/S0140-6736(19)32563-2
13. Susantitaphong P, Cruz DN, Cerda J, et al. (2013) World incidence of AKI: a meta-analysis. *Clin J Am Soc Nephrol* 8: 1482–1493. https://doi.org/10.2215/CJN.00710113
14. Olowu WA, Niang A, Osafo C, et al. (2016) Outcomes of acute kidney injury in children and adults in sub-Saharan Africa: a systematic review. *Lancet Glob Health* 4: e242–e250. https://doi.org/10.1016/S2214-109X(15)00322-8
15. Lowenstein J, Schacht RG, Baldwin DS (1981) Renal failure in minimal change nephrotic syndrome. *Am J Med* 70: 227–233. https://doi.org/10.1016/0002-9343(81)90754-3
16. Koomans HA (2000) Pathophysiology of edema and acute renal failure in idiopathic nephrotic syndrome. *Adv Nephrol Necker Hosp* 30: 41–55.
17. Menon S (2019) Acute kidney injury in nephrotic syndrome. *Front Pediatr* 6: 428. https://doi.org/10.3389/fped.2018.00428
18. Sharma M, Mahanta A, Barman AK, et al. (2018) Acute kidney injury in children with nephrotic syndrome: a single-center study. *Clin Kidney J* 11: 655–658. https://doi.org/10.1093/ckj/sfy024
19. González-Martin G, Bravo I, Vargas H, et al. (1986) Pharmacokinetics of gentamicin in children with nephrotic syndrome. *Int J Clin Pharmacol Ther Toxicol* 24: 555–558.
20. Kilis-Pstrusinska K, Zwolinska D, Musiał K (2000) Acute renal failure in children with idiopathic nephrotic syndrome. *Pol Merkur Lekarski* 8: 462–464.
21. Agency for Healthcare Research and Quality, HCUP Kids' Inpatient Database (KID): Healthcare Cost and Utilization Project (HCUP), 1997, 2000, 2003, 2006. Available from: https://www.hcupus.ahrq.gov/kidoverview.jsp.

22. Anigilaje EA, Adebayo AI, Ocheni SA (2019) Acute kidney injury in children: A study of aetiology, clinical profile and short-term outcomes at the University of Abuja Teaching Hospital, Gwagwalada, Abuja, Nigeria. *Saudi J Kidney Dis Transpl* 30: 421–439. https://doi.org/10.4103/1319-2442.256849
23. Schwartz GJ, Haycock GB, Edelmann CM Jr, et al. (1976) A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. *Pediatrics* 58: 259–263. https://doi.org/10.1542/peds.58.2.259
24. Akcan-Arikan A, Zappitelli M, Loftis LL, et al. (2007) Modified RIFLE criteria in critically ill children with acute kidney injury. *Kidney Int* 71: 1028–1035. https://doi.org/10.1038/sj.ki.5002231
25. Esezobor CI, Ladapo TA, Osinaike B, et al. (2012) Paediatric acute kidney injury in a tertiary hospital in Nigeria: prevalence, causes and mortality rate. *PLoS One* 7: e51229. https://doi.org/10.1371/journal.pone.0051229
26. Lane JC (2020) Pediatric nephrotic syndrome. *Medscape*. Available from: https://emedicine.medscape.com/article/982920-overview.
27. Anigilaje EA, Fashie AP, Ochi C (2019) Childhood nephrotic syndrome at the University of Abuja Teaching Hospital, Abuja, Nigeria: a preliminary report supports high steroid responsiveness. *Sudan J Paediatr* 19: 126–139. https://doi.org/10.24911/SJP.106-1547399573
28. Trachtman H, Sampson M, Sethna CB, et al. (2014) Childhood onset nephrotic syndrome, In: Fervenza F.C., Lin J., Sethi S., Singh A.K. Editors, *Core Concepts in Parenchymal Kidney Disease*, 1 st Ed, New York: Springer Science + Business Media, 23–31. https://doi.org/10.1007/978-1-4614-8166-9_3
29. Rees L, Brogan PA, Bockenhauer D, et al. (2012) Glomerular diseases. *Paediatric nephrology*, 2 nd Ed, Oxford, UK: Oxford University Press, 192–216. https://doi.org/10.1093/med/9780199601370.003.0084
30. Cattran DC, Feehally J, Cook HT, et al. (2012) Kidney disease: Improving global outcomes (KDIGO) glomerulonephritis work group. KDIGO clinical practice guideline for glomerulonephritis. *Kidney Int Suppl* 2: 139–274.
31. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents (2004) The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics* 114: 555–576. https://doi.org/10.1542/peds.114.2.S2.555
32. Oyedeji GA (1985) Socio-economic and cultural background of hospitalized children in Ilesa. *Niger J Paediatr* 12: 111–118.
33. Daniels R (2011) Surviving the first hours in sepsis: Getting the basics right (an intensivist's perspective). *J Antimicrob Chemother* 66: ii11–ii23. https://doi.org/10.1093/jac/dkq515
34. Robinson JL, Finlay JC, Lang ME, et al. (2014) Urinary tract infections in infants and children: Diagnosis and management. *Paediatr Child Health* 19: 315–319. https://doi.org/10.1093/pch/19.6.315
35. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int* 3: 19–62.
36. Sutherland SM, Ji J, Sheikhi FH, et al. (2013) AKI in hospitalized children: epidemiology and clinical associations in a national cohort. *Clin J Am Soc Nephrol* 8: 1661–1669. https://doi.org/10.2215/CJN.00270113

37. Kim MY, Cho MH, Kim JH, et al. (2018) Acute kidney injury in childhood-onset nephrotic syndrome: Incidence and risk factors in hospitalized patients. *Kidney Res Clin Pract* 37: 347–355. https://doi.org/10.23876/j.krcp.18.0098
38. Beins NT, Dell KM (2015) Long-term outcomes in children with steroid-resistant nephrotic syndrome treated with calcineurin inhibitors. *Front Pediatr* 3: 104. https://doi.org/10.3389/fped.2015.00104
39. Martensson J, Bellomo R (2016) Pathophysiology of septic acute kidney injury. *Contrib Nephrol* 187: 36–46. https://doi.org/10.1159/000442363
40. Yaseen A, Tresa V, Lanewala AA, et al. (2017) Acute kidney injury in idiopathic nephrotic syndrome of childhood is a major risk factor for the development of chronic kidney disease. *Ren Fail* 39: 323–327. https://doi.org/10.1080/0886022X.2016.1277743
41. Cavagnaro F, Lagomarsino E (2000) Peritonitis as a risk factor of acute renal failure in nephrotic children. *Pediatr Nephrol* 15: 248–251. https://doi.org/10.1007/s004670000415
42. González-Martin G, Bravo I, Vargas H (1986) Pharmacokinetics of gentamicin in children with nephrotic syndrome. *Int J Clin Pharmacol Ther Toxicol* 24: 555–558.
43. Carrie BJ, Golbetz HV, Michaels AS, et al. (1980) Creatinine: an inadequate filtration marker in glomerular diseases. *Am J Med* 69: 177–182. https://doi.org/10.1016/0002-9343(80)90376-9
44. Sutherland SM, Kwiatkowski DM (2017) Acute kidney injury in children. *Adv Chronic Kidney Dis* 24: 380–387. https://doi.org/10.1053/j.ackd.2017.09.007

AIMS Press