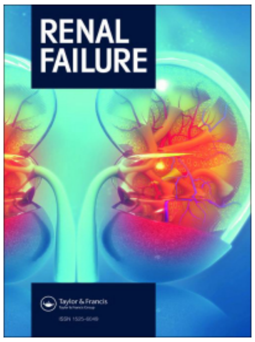

Renal Failure

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/irnf20

Acute kidney injury in hospitalized children with diphtheria in northwestern Nigeria: incidence and hospitalization outcomes

Olayinka Rasheed Ibrahim, Abdurrazzaq Alege, Michael Abel Alao & Olanrewaju Timothy Adedoyin

To cite this article: Olayinka Rasheed Ibrahim, Abdurrazzaq Alege, Michael Abel Alao & Olanrewaju Timothy Adedoyin (2025) Acute kidney injury in hospitalized children with diphtheria in northwestern Nigeria: incidence and hospitalization outcomes, Renal Failure, 47:1, 2465817, DOI: 10.1080/0886022X.2025.2465817

To link to this article: https://doi.org/10.1080/0886022X.2025.2465817

Published online: 23 Feb 2025.

RENAL FAILURE
2025, VOL. 47, NO. 1, 2465817
https://doi.org/10.1080/0886022X.2025.2465817

Taylor & Francis
Taylor & Francis Group

CLINICAL STUDY

OPEN ACCESS Check for updates

Acute kidney injury in hospitalized children with diphtheria in northwestern Nigeria: incidence and hospitalization outcomes

Olayinka Rasheed Ibrahim[a], Abdurrazzaq Alege[b], Michael Abel Alao[c] and Olanrewaju Timothy Adedoyin[d]

[a]Department of Pediatrics, Division of Clinical Medicine, University of Global Health Equity, Kigali, Rwanda; [b]Department of Pediatrics, Federal Teaching Hospital, Katsina, Nigeria; [c]Department of Pediatrics, University College Hospital, Ibadan, Nigeria; [d]Department of Pediatrics and Child Health, University of Ilorin Teaching Hospital & University of Ilorin, Ilorin, Nigeria

ABSTRACT

Background: Despite the kidney being affected by diphtheria exotoxin, the extent of acute kidney injury (AKI) and its possible impact on outcomes remain unknown. This study examined the incidence, risk factors, and outcomes of AKI in children with diphtheria.
Methods: This was a prospective cohort study of confirmed diphtheria managed from July 1, 2023, to April 30, 2024, at a health facility in Nigeria. We obtained data on clinical and laboratory features and treatments received. AKI was defined using Kidney Disease: Improving Global Outcomes (KDIGO) criteria.
Results: We included 237 children with a median [interquartile range] age of 7.0 [4–10] years. Using KDIGO, 139 (58.6%) had AKI [stage 1:88 (37.1%); stage 2: 18 (7.6%); and stage 3: 33 (13.9%)]. Variables associated with AKI included age, sore throat, inability to swallow, difficulty breathing, nasal blockade, hypoxemia, nasal discharge, pallor, abnormal chest findings, hospitalization duration, vaccination status, white blood cells, lymphocytes, platelets, serum bicarbonate, sodium and potassium, and treatments received, $p < 0.05$. On multivariable logistic regression, predictors of AKI included age ≤ 60 months [AOR 2.75, 95% CI 1.27–5.95], dexamethasone [AOR 2.57, 95% CI 1.11–4.60], oxygen therapy [4.85, 95% CI 1.24–18.99], and ibuprofen [AOR 2.74, 95CI% 1.16–6.44]. Mortality rate was 24.5% (58/237) and 33.1% (46/139) in AKI. The odds of deaths with AKI were 3.56 (95% CI 1.76–7.14).
Conclusion: There is a high incidence of AKI among children with diphtheria and increased odds of death. Factors that predicted AKI included younger age, oxygen therapy, and medications (ibuprofen and dexamethasone).

ARTICLE HISTORY
Received 28 January 2025
Revised 5 February 2025
Accepted 6 February 2025

KEYWORDS
Acute kidney injury; diphtheria; child; children; outcomes; risk factors

Introduction

Diphtheria is a reemerging infectious disease caused by *Corynebacterium diphtheriae*, with the potential for multisystemic involvement due to its exotoxin-mediated injuries affecting various organ systems in the human body [1]. Recent data in Nigeria show a significant burden of the disease with a total of 36,151 reported from Epi-week 19 [2022] to Epi-Week 35 [2024] due to multiple factors, including low vaccination coverage, low socioeconomic factors, and limited availability of antitoxin [2,3]. The huge burden of diphtheria is associated with a disproportionately poor hospitalization outcomes among admitted cases due to well-documented complications that arise from the effects of exotoxin on the cardio-respiratory systems [4,5]. While the various systems are involved, studies also show the kidney system is also involved in the complications of diphtheria though the extent of the possible impact on hospitalization outcomes remains unknown [4–6]. Possible reasons for kidney involvement include direct toxin-mediated damage to kidney tubules, causing acute tubular necrosis, and involvement of kidney interstitials, causing interstitial nephritis [7,8]. Despite kidney involvement *via* various pathogenic mechanisms, the extent of its involvement remains poorly understood, with a lack of studies that apply standard definitions to critically appraise the true burden of acute kidney injury (AKI) and outcomes among cases of diphtheria, especially in the pediatric subpopulation that bears a larger burden of the disease. Therefore, we hypothesized that the burden of AKI would be high and associated with poor hospitalization outcomes in a

CONTACT Olayinka Rasheed Ibrahim ibroplus@gmail.com, iolayinka@ughe.org Department of Pediatrics, Division of Clinical Medicine, University of Global Health Equity, Kigali, Rwanda.

cohort of children diagnosed with diphtheria. Thus, this study aimed to examine the burden of acute kidney injury and hospitalization outcomes (defined as death or discharge) among a cohort of pediatric cases of diphtheria managed at a tertiary health facility in Northwestern Nigeria.

Materials and methods

Study designs and settings

This prospective cohort study took place at a tertiary health facility in northwestern Nigeria and included children aged less than or equal to 14 years managed for diphtheria from 1st July 20234 to 30th April 2024. The tertiary health facility has a 500-bed capacity, including a dedicated 15-bed unit for highly infectious diseases, with trained and dedicated staff. The health facility serves as the main tertiary health facility for an estimated 8 million people, including children, and offers various specialty and sub-specialty health services.

Inclusion and exclusion criteria

We included cases with clinical features and laboratory confirmation of *Corynebacterium diphtheriae*. We excluded those with no clinical and laboratory evidence of diphtheria managed during the study period and those with an age greater than 14 years (upper pediatric age limit of the hospital policy).

Laboratory confirmation of the cases

Laboratory case confirmation was conducted at the Nigeria National Reference Laboratory, located at the Nigeria Center for Disease Control and Prevention (NCDC) Headquarters in Abuja, Nigeria. All patients meeting the case of definition of suspected diphtheria had throat samples taken upon admission [9]. The specimens were conveyed in Amies Charcoal Media and later grown on Tellurite blood agar at the reference laboratory. Samples exhibiting positive culture growth underwent a modified Elek test to demonstrate toxin generation by an immunoprecipitation reaction. Throat samples also underwent real-time polymerase chain reaction to identify the A and B subunits of the diphtheria toxin gene (tox).

Patients' management

All diphtheria cases were managed at an isolation ward dedicated to highly infectious diseases. The cases were managed based on the NCDC protocol for managing cases of diphtheria, including administration of diphtheria antitoxin [made available free of cost by NCDC], administration of antibiotics (intravenous or oral erythromycin, or oral azithromycin), IV dexamethasone, ibuprofen or paracetamol, intravenous fluids, oxygen therapy for those with hypoxemia (oxygen saturation less than 92%), and broad-spectrum antibiotics if there is suspicion of sepsis. Each of the cases also had laboratory workup, including complete blood counts, electrolytes, urea, and creatinine, along with throat samples collected for confirmation of diphtheria. Patients were discharged to follow-up at the clinic upon improvement in their clinical states and subsequently given the full vaccine for diphtheria based on their age (Pentavalent vaccines in children less than 5 years and tetanus-diphtheria vaccine (Td) for those 5 years and above).

Data collection

We opened a register to capture all admitted suspected and confirmed diphtheria cases in the infectious disease unit. This register included biodata, socioeconomic class, immunization history, clinical features, laboratory findings, and outcomes (death or discharge and any identified complications). The register was updated regularly.

Definition of acute kidney injury

The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) criteria were used to define the AKI and included a serum creatinine value rise of ≥ 0.3 mg/dL that occurred within 48 h or a rise of 1.5 times the baseline over seven days and further staged as 1–3 [10,11].

Ethical approval

This study was conducted in accordance with the principles of the Declaration of Helsinki. The Federal Teaching Hospital Katsina (FTHK) ethical review committee approved this study. Informed consent was obtained from the parents/guardians of the study, while children aged nine and above also gave assent to participate in the study. The data were kept with absolute confidentiality and secured on a password-protected computer.

Data analysis

The data were entered into a Microsoft Excel spreadsheet and exported to IBM-SPSS version 29 for data analysis. To define the incidence of AKI, we back-calculated the baseline serum creatinine level using a full-age spectrum formula validated in the sub-Saharan population and applied the KDIGO serum creatinine criteria with an assumed baseline estimated glomerular filtration rate (eGFR) of 120 mL/min per 1.73 m^2 [12,13]. Age was not normally distributed, was summarized as median and interquartile range, and further sub-grouped for analysis. The sex, clinical features, laboratory findings, and treatments were summarized with frequency tables and percent and further compared using Chi-square. Variables that were significant on univariate analysis ($p < 0.05$) were entered into multivariable logistic regression to identify factors that predicted acute kidney injury and hospitalization outcomes (defined as death or discharge). The results of multivariable logistic regression were presented as an adjusted odds ratios (AOR) along with a 95% confidence interval. The level of significance was set at $p < 0.05$.

Results

General characteristics

This study included 237 children with a median [interquartile range] age of 7.0 [4–10] years, and about half were aged five–ten years [122; 51.5%]. There were more females [129; 54.4%] and from the lower and middle social classes [210; 88.6%]. Of the 237 children, 151 (63.7%) did not receive any vaccinations (Table 1).

Incidence of AKI

Using the KDIGO serum criteria, 139 patients (58.6%) had acute kidney injury. Based on staging, 88 (37.1%) had stage 1, 18 (7.6%) had stage 2, and 33 (13.9%) had stage 3 (Figure 1). Of the 139 cases of AKI, 51 (36.7%) were diagnosed by day two of admission, while 88 (63.3%) were diagnosed between days 3 and 7.

Relationship between the clinical and laboratory features and acute kidney injury among hospitalized children with diphtheria

The most common clinical presentations were fever (96.6%), sore throat (92.0%), and inability to swallow (66.7%). The most common findings at presentation were cervical lymphadenopathy (100.0%), visible membranes (94.5%), and neck swelling (55.3%). There was a significant association between age, sore throat, inability to swallow, difficulty breathing,

Table 1. General characteristics of the study children.

Variables	Total $n = 237$	Male $n = 108$	Female $n = 129$	p
Age [Months]				
Median (IQR)	84.1 [48.0–120.0]	72.0 [48.0–120.0]	84.0 [48.0–120.0]	0.145[U]
≤ 12	3 (1.3)	0	3	0.402[f]
13–59	63 (26.6)	30	33	
60–120	122 (51.5)	54	68	
≥ 120	49 (20.7)	24	25	
SEC				
Lower	126 (53.2)	56	70	0.251*
Middle	84 (35.4)	43	41	
Upper	27 (11.4)	9	18	
Vaccination status				
No	151 (63.7)	66	85	0.275*
Partial	31 (13.1)	12	19	
Full	55 (23.2)	30	25	

IQR: Interquartile range; SEC: Socio-economic class; U-Mann Whitney U test; F-Fischer exact test.
*Chi-square test.

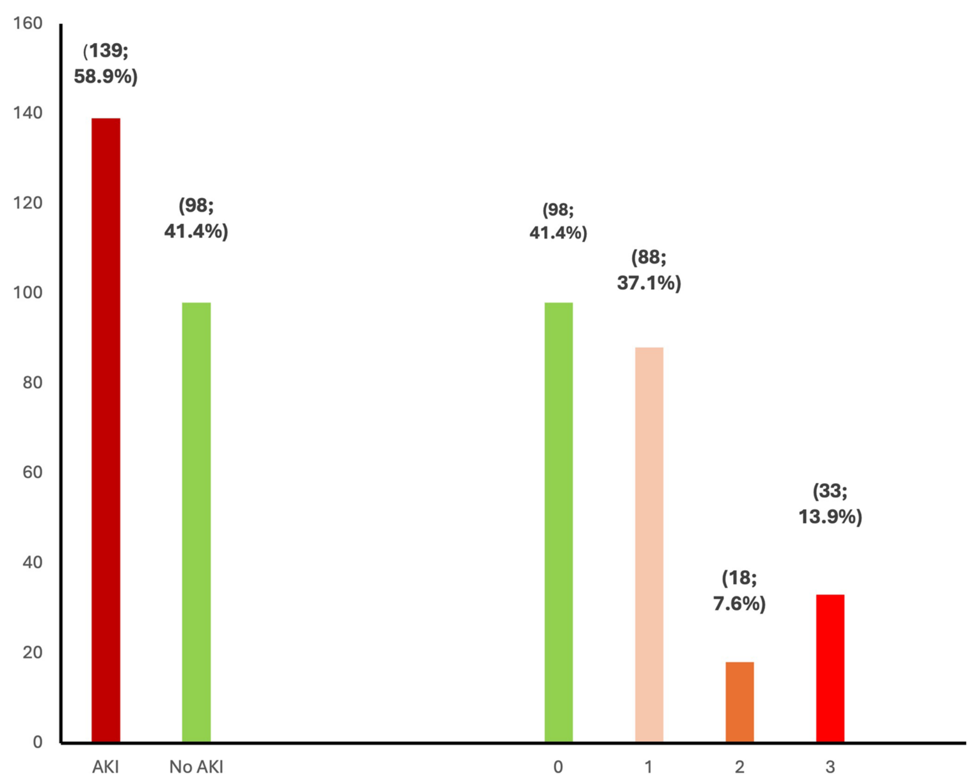

Figure 1. Incidence of AKI.

nasal blockade, hypoxemia, bloody nasal discharge, pallor, abnormal chest findings, durations of hospitalizations, vaccination status, and occurrence of acute kidney injury (<0.05) (Table 2) . Among the laboratory findings (tests obtained at presentation), white blood cells, lymphocytes, platelets, serum bicarbonate levels, serum sodium levels, and serum potassium levels were associated with acute kidney injury ($p < 0.05$) (Table 2).

Relationship between treatments received and acute kidney injury among the children hospitalized with diphtheria

Among the treatments received by the hospitalized children, oral macrolides, intravenous dexamethasone, ibuprofen, and oxygen therapy were associated with the occurrence of acute kidney injury (Table 3).

Table 2. Relationship between clinical and laboratory features and acute kidney injury among children hospitalized with diphtheria.

Variables	*n* = 237 (%)	Stage 0 *n* = 98 (%)	Stage 1 *n* = 88 (%)	Stage 2 *n* = 18 (%)	Stage 3 *n* = 33 (%)	P value
< 60 months	66 (27.8)	19 (19.4)	17 (19.3)	14 (77.8)	16 (48.5)	<0.001
Male	108 (45.6)	49 (50.0)	43 (48.9)	8 (44.4)	8 (24.2)	0.065
SEC						
Upper	27 (11.4)	14 (14.3)	10 (11.4)	0 (0.0)	3 (9.1)	0.316
Middle	84 (35.4)	38 (38.8)	31 (35.2)	4 (22.2)	11 (33.3)	
lower	126 (53.2)	46 (46.9)	47 (53.4)	14 (77.8)	19 (57.6)	
Fever	229 (96.6)	93 (94.9)	86 (97.7)	18 (100.0)	32 (97.0)	0.601
Sore throat	218 (92.0)	90 (91.8)	85 (96.6)	12 (66.7)	31 (93.9)	<0.001
Inability to swallo	158 (66.7)	63 (64.3)	50 (56.8)	13 (72.2)	32 (97.0)	<0.001
Difficulty breathing	57 (24.1)	19 (19.4)	15 (17.0)	5 (27.8)	18 (54.5)	<0.001
Nasal blockade	24 (10.1)	6 (6.1)	7 (8.0)	3 (16.7)	8 (24.2)	0.017
History of Contact	132 (55.7)	52 (53.1)	48 (54.5)	10 (55.6)	22 (66.7)	0.587
Hypoxemia*	38 (16.0)	10 (10.2)	9 (10.20	5 (27.8)	14 (42.4)	<0.001
Neck swelling	131 (55.3)	48 (49.0)	50 (56.8)	9 (50.0)	24 (72.7)	0.115
Visible membrane	224 (94.5)	94 (95.9)	81 (92.0)	17 (94.4)	32 (97.0)	0.617
Exudates	28 (11.8)	11 (11.2)	10 (11.4)	3 (16.7)	4 (12.1)	0.928
Tonsillar enlargement	99 (41.8)	43 (43.9)	34 (38.6)	4 (22.2)	18 (54.5)	0.134
Bloody nasal discharge	22 (9.3)	4 (4.1)	7 (8.0)	0 (0.0)	11 (33.3)	<0.001
Pallor	30 (12.7)	12 (12.2)	9 (10.2)	0 (0.0)	9 (27.3)	0.024
Resp. findings (abnormal)	43 (18.1)	16 (16.3)	11 (12.5)	6 (33.3)	10 (30.3)	0.042
LOH-Median[IQR] days	4.0 [2.5–6.0]	4.0 [3.0–6.0]	4.0 [3.0–6.0]	4.0 [2.0–6.0]	2.0 [2.0–5.5]	0.467
Immunization						
No	151 (63.7)	62 (63.3)	49 (55.7)	12 (66.7)	28 (84.8)	0.011
Partial	31 (13.1)	8 (8.2)	18 (20.5)	4 (22.2)	1 (3.0)	
Full	55 (23.2)	28 (28.6)	21 (23.9)	2 (11.1)	4 (12.1)	
Complications						
0	156 (65.8)	72 (73.50	64 (72.7)	13 (72.2)	7 (21.2)	<0.001
1	57 (24.1)	20 (20.4)	17 (19.3)	4 (22.2)	16 (48.5)	
≥ 2	24 (10.1)	6 (6.1)	7 (8.0)	1 (5.6)	10 (30.3)	
Cardiac complication	41 (17.3)	15 (15.3)	15 (17.0)	3 (16.7)	8 (24.2)	0.707
Airway obstruction	15 (6.3)	6 (6.1)	3 (3.4)	2 (11.1)	4 (12.1)	0.280
Neurologic complication	30 (12.7)	10 (10.2)	13 (14.8)	2 (11.1)	5 (15.2)	0.774
WBC > 10 X ^{9}/L	126 (53.2)	44 (44.9)	47 (53.4)	9 (50.0)	26 (78.8)	0.009
Lymphocytes >40%	105 (44.3)	52 (53.1)	35 (39.8)	9 (50.0)	9 (27.3)	0.048
Platelets <100,000/ uL	30 (12.7)	10 (10.2)	8 (9.1)	3 (16.7)	9 (27.3)	0.042
Bicarbonate ≤ 15 mEq/L.	67 (28.30	19 (19.4)	20 (22.7)	6 (33.3)	22 (66.7)	<0.001
Sodium <135 mEq/L.	84 (35.40	32 (32.7)	25 (28.4)	7 (38.9)	20 (60.6)	0.009
Potassium >4.5 mEq/L.	191 (80.6)	86 (87.8)	73 (83.0)	14 (77.8)	18 (54.5)	<0.001

SEC-socioeconomic class; LOH-Length of hospitalization; IQR-Interquartile range; Resp-respiratory; durat-duration.
*Oxygen saturation less than 92%; Cardiac complications: occurrence of myocardial dysfunctions such as myocarditis, arrhythmia, and confirmed either clinically, electrocardiogram and or echocardiogram; Neurological complications: presence of neurological manifestations including limb neuropathy, palatal paralysis, bulbar palsy and other cranial nerve palsy; Airway obstruction: life threatening comprise of airway due to narrowing from pseudomembrane and thick secretion.

Table 3. Relationship between treatments received and acute kidney injury among children hospitalized with diphtheria.

Variables (Treatments)	*n* = 237 (%)	Stage 0 *n* = 98 (%)	Stage 1 *n* = 88 (%)	Stage 2 *n* = 18 (%)	Stage 3 *n* = 33 (%)	P value
Antitoxins	194 (81.9)	79 (80.6)	75 (85.2)	14 (77.8)	26 (78.8)	0.756
IV Penicillin	92 (38.8)	33 (33.7)	33 (37.5)	7 (38.9)	19 (57.6)	0.109
IV Erythromycin	141 (59.5)	64 (65.3)	53 (60.2)	10 (55.6)	14(42.4)	0.139
Oral Macrolides*	131 (55.3)	62 (63.3)	52 (59.1)	12 (66.7)	5 (15.2)	<0.001
IV Dexamethasone	165 (69.6)	59 (60.2)	61 (69.3)	15 (83.3)	30 (90.9)	0.005
Paracetamol	204 (86.1)	81 (82.7)	78 (88.6)	17 (94.4)	28 (84.8)	0.469
Ibuprofen	43 (18.1)	13 (13.3)	26 (29.5)	2 (11.1)	2 (6.1)	0.004
IV fluids	207 (87.3)	81 (82.7)	80 (90.9)	17 (94.4)	29 (87.9)	0.285
Oxygen therapy	61 (25.7)	16 (16.3)	18 (20.5)	7 (38.9)	20 (60.6)	<0.001

*Azithromycin or Erythromycin.

Table 4. Multivariable logistic regression of factors associated with acute kidney injury in hospitalized children.

Variables	AKI $n = 139$ (%)	AOR	95% CI	P value
< 60 months	47 (33.8)	2.746	1.268, 5.945	0.010
Male	59 (42.4)	0.922	0.491, 1.731	0.800
Sore throat	128 (92.1)	1.640	0.473, 5.692	0.436
Inability to swallow	95 (68.3)	0.683	0.340, 1.372	0.285
Respiratory distress	38 (27.3)	0.650	0.193, 2.189	0.487
Nasal blockade	18 (12.9)	1.229	0.333, 4.535	0.757
Hypoxemia	28 (20.1)	1.499	0.367, 6.130	0.573
Nasal bloody discharge	18 (12.9)	3.211	0.608, 16.960	0.170
Pallor	18 (12.9)	0.608	0.195, 1.899	0.392
Chest findings (abnormal)	27 (19.4)	0.276	0.070, 1.081	0.065
Cardiac findings (abnormal)	14 (10.1)	0.657	0.190, 2.268	0.506
Length of hospitalization				
≤ 24 h	20 (14.4)	1		
25–72 h	20 (14.4)	0.577	0.140, 2.373	0.446
>72 h	99 (71.2)	0.531	0.158, 1.785	0.306
Immunization				
No vaccination	89 (64.0)	1		
Partial	23 (16.5)	2.631	0.965, 7.172	0.059
Full	27 (19.4)	0.569	0.309, 1.405	0.280
Complications				
0	84 (60.4)	1		
1	37 (26.6)	0.820	0.360, 1.869	0.637
≥ 2	18 (12.9)	2.067	0.501, 8.536	0.315
WBC > 10 X ^{9}/L	82 (59.0)	1.376	0.721, 2.624	0.333
Platelets <100,000/ uL	20 (14.4)	1.271	0.422, 3.826	0.670
Bicarbonate ≤ 15 mEq/L.	48 (34.5)	1.589	0.739, 3.417	0.236
Potassium >4.5 mEq/L.	34 (24.5)	1.770	0.745, 4.205	0.196
Lymphocytes >40%		0.546	0.283, 1.054	0.071
Sodium <135 mEq/L.	52 (37.4)	1.272	0.652, 2.480	0.481
Dexamethasone	106 (76.3)	2.257	1.108. 4.598	0.025
Oxygen therapy	45 (32.4)	4.848	1.238, 18.985	0.023
Ibuprofen	30 (21.6)	2.736	1.163, 6.436	0.021
Oral Azithromycin/ Erythromycin	69 (49.6)	0.711	0.360, 1.406	0.327

WBC: White blood cells count.

Factors associated with acute kidney injury in hospitalized children with diphtheria

After adjusting for confounders, variables that were significantly associated with the occurrence of acute kidney injury included age less than 60 months [AOR 2.746, 95% CI 1.268–5.945], dexamethasone [AOR 2.567, 95% CI 1.108–4.598], oxygen therapy [4.848, 95% CI 1.238–18.985], and ibuprofen [AOR 2.736, 95 CI 1.163–6.436] (Table 4).

Outcomes

Of the 237 children included in this study, 58 in-hospital deaths occurred, with a case fatality rate (CFR) of 24.5%. Of 139 children who developed AKI, 46 (33.1%) died. The median (interquartile range) length of hospitalization among those with AKI [4.0 (2.0 to 6.0)] was comparable to those without AKI [4.0 (3.0–6.0)] years, $p = 0.809$. The median length of hospitalization among those that died [2.0 (0.9–4.0)] was shorter than those that survived [5.0 (3.0–6.0)], $p = <0.001$. The odds of death among children with AKI was 3.545 (95% CI 1.761, 7.136); $p < 0.001$). After adjusting for confounders, variables that were associated with death included age greater or equal 60 months [AOR 25.699, 95% CI 2.205, 299.481], abnormal findings on chest examinations at presentation [AOR 93.686, 95% CI 10.286, 853.311], abnormal cardiac findings [AOR 17.796, 95% 1.779, 176.208], hypoxemia [15.824; 95% CI 2.540, 98.578], length of hospitalization less than 48 h [AOR 196.439, 95% CI 14.611, 2641.03], and occurrence of AKI (Table 5). For AKI, the odds of death increased as the stages of AKI increased [for stage 2-AOR 109.982, 95% CI 3.701, 3268.27], and stage 3 [AOR 789.553, 95% CI 16.183, 38521.140]. Out of five patients with indications for dialysis, only one had hemodialysis, and none of them survived.

Table 5. Factors that are associated with hospitalization deaths.

Variables	Total $n = 237$	Discharged $n = 179$	Deaths $n = 58$	AOR	95% CI	P
≥ 60 months	132	132 (73.7)	39 (67.2)	25.699	2.205, 299.481	0.010
Male	108	87 (80.6)	21 (19.4)	0.421	0.088, 2.010	0.278
Socio-economic class						
Upper	27	22 (81.5)	5 (18.5)	1		
Middle	84	71 (84.5)	13 (15.5)	0.602	0.013, 27.365	0.795
lower	126	86 (68.3)	40 (31.7)	0.589	0.014, 24.253	0.780
Neck swelling	131	84 (64.1)	47 (35.9)	13.111	1.988, 89.135	0.008
Bloody nasal discharge	22	9 (40.9)	13 (59.1)	5.195	0.336, 73.748	0.224
Chest findings (abnormal)	43	9 (20.9)	34 (79.1)	93.686	10.286, 853.311	<0.001
Cardiac findings (abnormal)	24	11 (45.8)	13 (54.2)	17.796	1.779, 176.208	0.014
Hypoxemia	38	7 (18.4)	31 (81.6)	15.824	2.540, 98.578	<0.003
LOH						
< 48 h	59	19 (10.6)	40 (69.0)	196.439	14.611,2641.03	<0.001
Immunization						
No vaccination	151	104 (68.9	47 (31.1)	0.455	0.082, 2.526	0.368
WBC > 10 X ^{9}/L	126	86 (68.3)	40 (31.7)	1.622	0.278, 9.938	0.578
Bicarbonate ≤ 15 mEq/L.	67	42 (62.7)	25 (37.1)	0.468	0.077, 2.836	0.408
AKI						
0	98	86 (87.8)	12 (12.2)			
1	88	73 (83.0)	15 (17.0)	4.308	0.790, 35.658	0.086
2	18	12 (66.7)	6 (33.3)	109.982	3.701, 3268.27	0.007
3	33	8 (24.2)	25 (75.8)	789.553	16.183, 38521.140	<0.001

Nagelkerke R square Rule: 0.874; LOH: Length of hospitalization.

Discussion

Diphtheria is an acute infectious disease caused by an exotoxin that mediates cellular damage in various organ systems, including the kidneys. This study comprehensively assessed kidney injury using the 2012 KDIGO criteria in a cohort of 237 cases of diphtheria managed at a health facility in northwestern Nigeria. This study showed a high incidence of AKI (59%), which far exceeds the rate of 13–35.4% reported in some studies as a component of complications associated with diphtheria [14,15]. The high incidence of AKI observed in this study is not unexpected, considering that standard AKI definitions were applied, which allows the detection of milder forms of AKI. Besides, this was a prospective cohort study compared with the other retrospective studies, and the definitions of AKI were not clear in one of the studies [15], while the study in India included only those children who required kidney replacement therapy [14]. Possible reasons for the high prevalence of AKI in this study may be due to various pathogenic mechanisms related to the effects of diphtheria exotoxin on the Kidney [7,8]. Diphtheria toxin induced tubular epithelial injury causing acute tubular necrosis, interstitial inflammation causing interstitial nephritis, and podocytes injury; all of which may have contributed to kidney dysfunctions. The implication of our findings illustrated that AKI may have been under-recognized in pediatric cases of diphtheria due to the failure to apply standard definitions with potentially missed cases. This further advocates the continuous application of standard definitions while evaluating AKI in various clinical conditions, especially infectious disease-related causes.

After adjusting for confounders, variables that predicted AKI included age less than 60 months [AOR 2.75, 95% CI 1.27 to 5.95], dexamethasone [AOR 2.6, 95% 1.11, 4.60], oxygen therapy [4.89, 95% CI 1.24, 18.99], and ibuprofen [AOR 2.74, 95 CI, 1.16, 6.44]. While we could not lay our hands on any other study that exclusively assessed AKI among cases of diphtheria to allow us to comprehensively compare our findings, these variables have been identified as critical in the development of acute kidney injury *via* various pathogenic mechanisms. For instance, the younger age group has relatively immature kidneys compared to the older age group, making them vulnerable to toxin-mediated injury and subsequent acute tubular necrosis [16]. Patients who received oxygen therapy were due to hypoxemia, which may have affected the kidney tubules as well as the kidney medulla cortex with hypoxic cortical and kidney tubular injury [17,18]. Another possibility is ischemia-reperfusion injury with the generation of abnormal oxygen free radicals when oxygen therapy are provided during the course of treatment, which may also exacerbate kidney injuries [18]. On the other hand, ibuprofen is a well-established cause of kidney injury due to afferent pre-arteriolar vasoconstriction from the inhibition of the conversion of arachidonic acid into E2 prostaglandins, prostacyclins, and thromboxanes (all of which are potent arteriolar dilatation) [19,20]. Contrary to expectations, we observed a higher incidence of AKI among patients who received dexamethasone. While this observation is unexpected, it is worth noting that a randomized control trial on the prophylactic use of high dexamethasone did not show any benefit in preventing AKI among patients who underwent cardiac surgery [21]. It is also possible that interactions between multiple risk factors for AKI (hypoxia, exotoxin-mediated injury, and ibuprofen) may also offset the expected protective effects of dexamethasone. These findings call for cautious use of dexamethasone with close monitoring of kidney function during the management of diphtheria to reduce the risk of developing or worsening AKI.

The deaths from those with AKI far exceeded the overall death among the cohort in this study, as AKI increased the odds of deaths by 3.55 (95% CI 1.76, 7.14). These findings corroborate the fact that AKI, irrespective of the clinical diagnosis, is associated with poor outcomes [21]. The poor outcomes of AKI are due to multiple factors, including metabolic disturbances, fluid overload, and distant organ impairment [21]. In addition, the risk of death increases with increasing stages of AKI, further validating the KDIGO criteria for detecting AKI as not only being able to detect but also prognosticate outcomes [21]. Thus, there is a need to monitor diphtheria cases in the pediatric subpopulation that develop AKI owing to a higher likelihood of death.

Also worthy of noting in this study are the fully vaccinated children (55) in this study that developed diphtheria, about half (27) of whom also had AKI. While literature showed that fully vaccinated may also have diphtheria, the occurrence of diphtheria in this set of children may be due to some factors: low vaccination coverage in the state [40% for the third dose of the pentavalent vaccine] and subsequent low herd immunity [22–24]. Also, waning of the protective effect of vaccines over time with the World Health Organization (WHO) recommendation of booster doses at 12–23 months, 4–7 years, and 9–15 years of age, which is at present not part of the national immunization schedule in Nigeria [3,25]. In addition, vaccine cold challenges in the country may have also affected the potency of vaccines received [3,25]. This observation calls for sustained improved vaccination coverage to achieve high herd immunity; Nigeria should consider a booster as advocated by WHO and possibly ensure optimal vaccine-related delivery strategies, including the effectiveness of the vaccine cold chain delivery system.

Study strengths and limitations

This study appears to be the first to apply the KDIGO criteria to define AKI and evaluate the hospitalization outcomes of AKI among a cohort of pediatric patients with diphtheria. In addition, we examined not only the clinical features and laboratory results but also the association with the treatments administered for the occurrence of AKI. Notwithstanding, this study has some limitations: it is a single-center study, and the findings may not be generalized outside the study population. Additionally, baseline serum creatinine was estimated among the cohort, which may have an impact on the incidence of AKI, and children who developed AKI were not followed up to allow us to evaluate the long-term impact of diphtheria on the kidney, including acute kidney disease and chronic kidney disease. Also, only one of the five children with indications for dialysis received kidney replacement therapy (hemodialysis) and may have impacted the outcomes in this study.

Conclusions

This study showed that a high incidence of AKI among pediatric patients with diphtheria is associated with increased odds of death. Factors that predicted the occurrence of AKI included younger age, need for oxygen therapy, and medications (ibuprofen and dexamethasone). We suggest the need to monitor the kidney status in pediatric diphtheria and avoid ibuprofen with cautious use of dexamethasone in the presence of AKI.

Acknowledgments

We thank the staff of the infectious disease unit that was involved in the management of the cases and the hospital for waiving all hospital costs, including the fees for the laboratory tests.

Author contributions

ORI, AA and MAA were involved in study design, literature review, data curation and analysis draft and approved the final version. OTA was involved in the study design, critical appraisal, supervision, and approved the final version.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The author(s) reported there is no funding associated with the work featured in this article.

References

[1] Sharma NC, Efstratiou A, Mokrousov I, et al. Diphtheria. Nat Rev Dis Primers. 2019;5(1):81. doi:10.1038/s41572-019-0131-y.
[2] Weekly diphtheria situation report; 2024.
[3] Abdulrasheed N, Lawal L, Mogaji AB, et al. Recurrent diphtheria outbreaks in Nigeria: a review of the underlying factors and remedies. Immunity, Inflamm Dis. 2023;11:e1096.
[4] Dash N, Verma S, Jayashree M, et al. Clinico-epidemiological profile and predictors of outcome in children with diphtheria: a study from northern India. Trop Doct. 2019;49(2):96–101. doi:10.1177/0049475518823657.
[5] Ahmed A, Singh M, Tank P, et al. Clinico-epidemiological profile and predictors of poor outcome among children during a diphtheria outbreak in Haryana. Indian Pediatr. 2023;60(4):280–284. doi:10.1007/s13312-023-2859-1.
[6] Gupta S, Jayashree M. Diphtheria: relic or relevant. J Pediatr Crit Care. 2017;4(3):85. doi:10.21304/2017.0403.00198.
[7] Prasad N, Patel MR. Infection-induced kidney diseases. Front Med. 2018;5:1–11. doi:10.3389/fmed.2018.00327.
[8] Muhammad A, Zhang Y, Huang L, et al. The diagnosis of acute interstitial nephritis caused by infection versus antibiotic-induced interstitial nephritis: a narrative review. Clin Kidney J. 2024;17:1–16.
[9] NCDC. Nigeria Centre for Disease Control and Prevention; 2023. [accessed 2024 Apr 5]. . Available from: https://ncdc.gov.ng/diseases/sitreps%0Ahttps://ncdc.gov.ng/diseases/factsheet/49.
[10] Summary of recommendation statements. Kidney Int Suppl. 2012;2:8–12.
[11] Levey AS, Eckardt K-U, Dorman NM, et al. Nomenclature for kidney function and disease: report of a Kidney Disease: improving Global Outcomes (KDIGO) Consensus Conference. Kidney Int. 2020;97(6):1117–1129. doi:10.1016/j.kint.2020.02.010.
[12] Batte A, Starr MC, Schwaderer AL, et al. Methods to estimate baseline creatinine and define acute kidney injury in lean Ugandan children with severe malaria: a prospective cohort study. BMC Nephrol. 2020;21(1):417. doi:10.1186/s12882-020-02076-1.
[13] Ibrahim OR, Afolayan FM, Alao MA, et al. Impact of methods of estimating baseline Serum Creatinine (bSCr) on the incidence and outcomes of acute kidney injury in childhood severe malaria. Egypt Pediatr Assoc Gaz. 2023;71:36.
[14] Gampa M, Karna PN, Reddy KV, et al. Study of diphtheria and its complications: a retrospective study from a tertiary care hospital. Pediatr Infect Dis. 2021;3(4):140–142. doi:10.5005/jp-journals-10081-1307.
[15] Jayashree M, Shruthi N, Singhi S. Predictors of outcome in patients with diphtheria receiving intensive care. Indian Pediatr. 2006;43(2):155–160.
[16] Parikh AC, Tullu MS. A study of acute kidney injury in a tertiary care pediatric intensive care unit. J Pediatr Intensive Care. 2021;10(4):264–270. doi:10.1055/s-0040-1716577.
[17] Honda T, Hirakawa Y, Nangaku M. The role of oxidative stress and hypoxia in renal disease. Kidney Res Clin Pract. 2019;38(4):414–426. doi:10.23876/j.krcp.19.063.
[18] Legrand M, Mik EG, Johannes T, et al. Renal hypoxia and dysoxia after reperfusion of the ischemic kidney. Mol Med. 2008;14(7–8):502–516. doi:10.2119/2008-00006.Legrand.
[19] Patzer L. Nephrotoxicity as a cause of acute kidney injury in children. Pediatr Nephrol. 2008;23(12):2159–2173. doi:10.1007/s00467-007-0721-x.
[20] Lucas GNC, Leitão ACC, Alencar RL, et al. Pathophysiological aspects of nephropathy caused by non-steroidal anti-inflammatory drugs. J Bras Nefrol. 2019;41(1):124–130. doi:10.1590/2175-8239-JBN-2018-0107.
[21] Girling BJ, Channon SW, Haines RW, et al. Acute kidney injury and adverse outcomes of critical illness: correlation or causation? Clin Kidney J. 2020;13(2):133–141. doi:10.1093/ckj/sfz158.
[22] Mohan V, Chandrasekaran V, Sistla S. Clinical profile and risk factors for mortality in children admitted with diphtheria:

an observational study. Infect Dis. 2023;55(6):431–438. doi: 10.1080/23744235.2023.2202759.

[23] Ibrahim OR, Lawal IM, Mohammed B, et al. Diphtheria outbreak during Covid-19 pandemic in Katsina, North-Western Nigeria: epidemiological characteristics and predictors of death. Niger J Basic Clin Sci. 2022;19(1):59–65. doi:10.4103/njbcs.njbcs_35_21.

[24] National Bureau of Statistics and United Nations Children's Fund. Multiple indicator cluster survey 2021, survey findings report. Abuja, Nigeria; 2022.

[25] World Health Organization. Diphtheria vaccine: WHO position paper, August 2017 – Recommendations. Vaccine. 2018;36(2):199–201. doi:10.1016/j.vaccine.2017.08.024.