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Pattern and short-term outcome of pediatric kidney disease at national referral hospital in Bhutan: an observational study

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ABSTRACT

Introduction: The epidemiology of kidney diseases in children can vary widely across geographic regions. The main purpose of this study was to determine the pattern and short-term outcome of kidney disease among children hospitalized at the national referral hospital in Bhutan. **Methods:** All admitted children aged one month to 12 years with kidney disease, from January to December 2018, were included in the study. Diagnostic criteria were applied to all the patients on admission to determine study eligibility and subsequent demographic and clinical data were collected using a structured interviewer administered pro forma. **Results:** A total of 128 (7.8%) children met diagnostic criteria for kidney disease among 1648 hospitalized children during the study period. The median age at presentation was 2.5 years (interquartile range 0 to 8). The commonest disease was acute kidney injury (48, 37.5%) followed by acute glomerulonephritis (37, 28.9%), urinary tract infection (37, 28.9%), congenital anomalies of kidney and urinary tract (11, 8.6%) and nephrotic syndrome (11, 8.6%). Median duration of hospital stay was 8 days (IQR 4 to 14.8). Four (3.1%) patients were referred to India for specialist care, 5 (3.9%) underwent dialysis and 28 (21.9%) died. Of the 28 patients who died, 26 (92.9%) had acute kidney injury and 2 (7.1%) had chronic kidney disease. **Conclusions:** Pediatric kidney diseases comprise a significant proportion of disease burden at the national referral hospital. Education of primary healthcare providers about the epidemiologic burden of pediatric kidney diseases is needed to reduce kidney-related morbidity and mortality.

Keywords: Acute kidney injury; Glomerulonephritis; Kidney diseases; Pediatrics; Urinary tract infection.

INTRODUCTION

Kidney diseases in children encompass any structural or functional abnormality in the renal system, and account for 1.3 to 8.9% of all pediatric hospital admissions in developing countries[1-6]. The most commonly described are acute glomerulonephritis, nephrotic syndrome and urinary tract infection[1-5]. Studies from different geographic regions have reported variable patterns of kidney diseases in children[1-4]. These variations could be related to genetic, environmental factors or the methodological differences among studies.

Early diagnosis of pediatric kidney diseases can be challenging as the presenting symptoms may be non-specific. In infants and young children, unexplained fever or poor weight gain may be the sole presenting feature of underlying renal disease[1]. Some kidney diseases in children are preventable. Complications such as end stage kidney disease can be delayed, or altogether avoided if diagnosed early and if treatment is initiated promptly[4,7]. However, these conditions if left undiagnosed or untreated, can often lead to significant morbidity and mortality both during childhood and in adulthood[7,8].

Success in the management of acute and chronic kidney disease is reported across many developed countries, largely due to the availability of advanced pediatric nephrology services, screening programs and well-developed referral networks[9]. Moreover, well-established renal registries can provide data to guide relevant stakeholders on appropriate resource planning and allocation in developed countries[5].

All pediatric renal cases in the national referral hospital are managed by general pediatricians as there are no formally trained pediatric nephrologists in Bhutan and data regarding pediatric kidney diseases are limited due to the absence of a national registry in Bhutan. To our knowledge there has been no prior studies conducted in Bhutan describing the epidemiologic burden of pediatric kidney disease. This prospective study aims to determine the pattern and short-term outcomes of incident and prevalent kidney diseases in children hospitalized at the national referral hospital in Thimphu, Bhutan.

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METHODS

This was a prospective observational study conducted over a one-year period from 1st January to 31st December 2018. The study was conducted in the general pediatric ward, pediatric intensive care unit (PICU), private cabins and surgical ward of a 350 bedded Jigme Dorji Wangchuck National Referral Hospital (JDWNRH). JDWNRH is the apex hospital in Bhutan, which serves as the referral center for two other regional referral hospitals and nearby district hospitals besides catering to the general population of the capital city. The pediatric department has 76 pediatric and neonatal inpatient beds which includes 13 intensive care beds, and is run by general pediatricians and pediatric residents. The hospital lacks some facilities for certain renal investigations like serum complement studies, SLE panels, immunochemistry, etc. for which either specimens or patients are referred outside the country. Peritoneal dialysis for acute kidney injury became available only in August 2018.

All children aged 1 month to 12 years admitted to the pediatric ward, pediatric intensive care unit (PICU), private cabins and surgical ward were assessed for kidney diseases on admission through a history and clinical examination. Relevant clinical investigations such as complete blood count, urinalysis, blood chemistry, hematological and immunological tests were utilized to confirm specific renal diseases. Imaging techniques such as X-Ray, ultrasonography, micturating cystourethrogram, intravenous urogram and computerized tomography were also employed when indicated to support a diagnosis.

All children with kidney disease on admission or who developed kidney disease during their stay in the hospital were eligible for enrollment. Children whose parents refused to consent and those above 7 years of age, who refused to assent were excluded. Children re-admitted for the same renal disease were counted only once at their first presentation. Once enrolled in the study, management of the children with renal diseases were carried out as per the prevailing guidelines of the pediatric department or as per the treating pediatrician. Participants were followed until hospital discharge.

Pediatric residents and interns posted in the pediatric ward, PICU, surgical ward and cabin were trained by the principal investigator to assess for study eligibility, obtain informed consent and assent. Relevant demographic details, clinical history, examination and clinical findings, diagnosis and outcome at discharge were collected using a structured interviewer-administered pro forma. The primary outcome assessed was whether the patients were discharged, referred out of country, or expired.

Renal diseases were classified as; acute glomerulonephritis (AGN), nephrotic syndrome (NS), Henoch schonlein purpura nephritis (HSP nephritis), lupus nephritis (SLE Nephritis), urinary tract infection (UTI), acute kidney injury (AKI), chronic kidney disease (CKD), hemolytic uremic syndrome (HUS), congenital anomalies of kidneys and urinary tract (CAKUT) and others using standard definitions as shown in Box 1.

Box 1. Operational definitions

1. Acute glomerulonephritis was defined as sudden onset of gross hematuria, with edema, hypertension, and oliguria[10].

2. Nephrotic syndrome was defined as the presence of nephrotic range proteinuria (40mg/m2/hour), hypoalbuminaemia(<2.5g/dL), edema and hyperlipidemia (cholesterol >200mg/dL)[11].

3. HSP nephritis was defined as the patients with HSP develop renal manifestations (proteinuria > 3gms/day, hematuria or red cell casts)[11].

4. SLE Nephritis was defined when there was renal involvement in SLE patients as evident by urinalysis and 24 hour urinary protein or UPCR or Renal Biopsy proven Lupus Nephritis[11].

5. UTI was defined when in a symptomatic patient with ≥5 white blood cells per high power field on a centrifuged specimen of urine with positive nitrate test or >100,000 colonies of single pathogen in a urine sample[12].

6. AKI was defined according to AKIN criteria, an increase in serum creatinine more than 150% to 200% from baseline or urine output less than 0.5 ml/kg/h for 6 hours[13].

7. CKD was defined according to National Kidney Foundation Kidney Disease Outcome Quality Initiative (NKF-KDOQI) guidelines, kidney damage lasting for more than 3 months with or without a decrease in GFR or any patient who has a GFR less than 60ml/min/1.73m2 for 3 months with or without kidney damage[14].

8. CAKUT was defined as spectrum of disorders encompassing developmental abnormalities of kidney and urinary tract involving the upper tract as well as the lower tract[15].

9.Hemolytic uremic syndrome was defined as the simultaneous occurrence of non immune haemolytic anaemia, thrombocytopenia and acute renal failure[16].

Data was cleaned for inconsistencies and was entered twice in Epidata version V3.1 and analyzed using Epidata Analysis version V2.2.2.183 (Epidata Association, Odense, Denmark). The results were expressed as means and standard deviations (SD) for normally distributed quantitative variables. For quantitative variables that were not normally distributed, medians and interquartile ranges were used to describe the data. Frequencies and percentages were used for categorical variables. The chi-square test was applied to compare the data of

proportions. A *p*-value of <0.05 was considered significant.

This study was approved by the Research Ethics Board of Health (REBH), under Ministry of Health, Thimphu, Bhutan via letter no. REBH/Approval/2017/070 dated 25th October 2017. Administrative clearance was obtained from JDWNRH administration and the Policy & Planning Division, Ministry of Health, Thimphu.

RESULTS

Out of 1648 children admitted to JDWNRH during the study period, 128 (7.8%) were diagnosed with kidney disease. No one with kidney disease was excluded from the analysis. The demographic characteristics of the children enrolled in the study are shown in Table 1.

Seventy-six (59.4%) were male with the male to female ratio of 1.46:1. The median age at presentation was 2.5 years (IQR 0 to 8 years) and the most common age group affected was children aged five years and below (*p*= 0.2945) (Table 2).
Children with kidney diseases presented with fever (71, 55.5%), nausea or vomiting (64, 50%), body swelling (62, 48.4%) and loss of appetite (59, 46.1%) (Table 3).

Upon physical examination, 63 (49.2%) of the cohort had edema, while 42 (32.8%) had hypertension and 35 (27.3%) had pallor. Forty eight children (30.5%) had AKI, followed by AGN and UTI, each accounting for 23.6%. CAKUT and NS were seen in 7% each, CKD and urolithiasis in 2.6% each. Other kidney diseases included HSP nephritis, SLE nephritis and HUS (Table 4).

Of the 48 children with AKI, 19(39.6%) were diagnosed

Table 1. Socio-demographic characteristics of 128 hospitalized children with kidney disease in the national referral hospital in 2018

	n	%
Total	**128**	**100**
Age group		
1 month-11 months	51	39.9
1 – 5 years	30	23.4
6 – 12 years	47	36.7
Gender		
Male	76	59.4
Female	52	40.6
Monthly family income (Nu)		
<10,000	30	23.5
10,000-20,000	73	57
>20,000	25	19.5
Education level of primary care giver		
None	40	31.3
NFE*	5	3.9
Primary school	17	13.3
Secondary school	43	33.6
Graduate	21	16.3
Others	2	1.6

**NFE-Non-formal education*

Table 2. Age and gender distribution among 128 hospitalized children with kidney disease in the national referral hospital in 2018

Age	Gender				Total		*p*value
	Male		Female				
	n	(%)	n	(%)	n	(%)	
1-11 months	27	(35.5)	24	(46.2)	51	(39.9)	0.2945
1-5 years	17	(22.4)	13	(25)	30	(23.4)	
6-12 years	32	(42.1)	15	(28.8)	47	(36.7)	
Total	76	(100)	52	(100)	128	(100)	
Age (median) = 2.5 years (IQR 0 to 8)							

Table 3. Symptoms at presentation of 128 hospitalized children with kidney disease in the national referral hospital in 2018

Symptoms	*n*	(%)
Fever	71	55.5
Nausea/Vomiting	64	50
Body swelling	62	48.4
Loss of appetite	59	46.1
Abdominal pain	34	26.6
Decreased urine output	33	25.8
Tea colored urine	32	25
Diarrhea	29	22.7
Headache	25	19.5
Weakness	24	18.8
Rashes	19	14.8
Weight loss	16	12.5
Sore throat	14	10.9
Dysuria	14	10.9
Joint pain	12	9.4
Frequency of urination	11	8.6
Malodorous urine	9	7
Blurring of vision	2	1.6
Urinary incontinence	2	1.6

Table 4. Types of renal diagnoses in 128 hospitalized children with kidney disease in the national referral hospital in 2018

Renal Diseases*	*n*	(%)
AKI†	48	30.5
AGN‡	37	23.6
UTI§	37	23.6
NS‖	11	7
CAKUT¶	11	7
CKD**	4	2.6
Urolithiasis	4	2.6
HSP†† Nephritis	3	1.9
SLE‡‡ Nephritis	1	0.6
HUS***	1	0.6
Total	157	100

**Some patients had more than one renal disease*
*† Acute Kidney Injury, ‡Acute Glomerulonephritis, §Urinary Tract Infection, ‖Nephrotic Syndrome ¶Congenital Anomalies of Kidney and Urinary Tract, **Chronic Kidney Disease, †† Henoch Schonlein Purpura, ‡‡Systemic Lupus Erythromatosus, ***Hemolytic Uremic Syndrome*

with stage I, two (4.2%) with stage II and 27 (56.2%) with stage III AKI according to the Acute Kidney Injury Network (AKIN) classification system. Pre-renal causes accounted for 70.8% followed by intra-renal causes (29.2%). Sepsis and systemic infections like meningoencephalitis were the most common pre-renal causes while AGN and NS were the most frequent intra-renal causes of AKI (Table 5).

Of the 37 children with UTI, 34(91.9%) had a positive urine culture while three (8.1%) had a negative urine culture. Four patients (10.8%) had recurrent UTIs. *Escherichia coli* accounted for 61.4% of the cases with positive urine culture followed by *Klebsiella pneumoniae* (22.7%). Other organisms isolated from urine were *Enterococcus* and *Enterobacter aerogenes* (4.5% each) as shown in Table 6.

In nine (24.3%) children the diagnosis of UTI was associated with other renal diseases like AGN, CAKUT, AKI and CKD.

The mean age at presentation for children with NS was 8 ±3.9 years with a male to female ratio of 1:2.7 (*p*-value 0.0234).

Of the 11 children with CAKUT, pelviureteric junction (PUJ) obstruction and hydronephrosis accounted for (3, 27.2%) each followed by vesicoureteral reflux (VUR) (2,18.2%) and cystic renal disease (2,18.2%) and ureterocele (1,9.2%). Four children had CKD out of which, three had stage 4 CKD and one had stage 5 CKD according to National Kidney Foundation Kidney Disease Outcome Quality Initiative (NKF-KDOQI). NS and CAKUT were important causes of CKD, representing 50% each.

Table 5. Types and causes of acute kidney injury among 48 children admitted to the national referral hospital in 2018

Types of AKI*	Causes	n	(%)
Pre-renal			
	Sepsis	15	31.2
	Meningoencephalitis	9	18.8
	CHD/CCF†	6	12.5
	Pneumonia	1	2.1
	AGE‡	2	4.1
	Brain surgery	1	2.1
Renal			
	AGN§	8	16.7
	NS‖	3	6.2
	HSP¶ Nephritis	1	2.1
	SLE** Nephritis	1	2.1
	HUS††	1	2.1

**Acute Kidney Injury, †Congenital Heart Disease/ Congestive Cardiac Failure, ‡Acute Gastroenteritis, §Acute Glomerulonephritis, ‖Nephrotic Syndrome, ¶Henoch Schonlein Purpura, **Systemic Lupus Erythromatosus, ††Hemolytic Uremic Syndrome*

Table 6. Uropathogen isolates among 34 children with culture positive urinary tract infection admitted to the national referral hospital in 2018

Organisms	*n*	(%)
Escherichia coli	27	61.4
Klebsiella pneumoniae	10	22.7
Klebsiella oxytoca	1	2.3
Enterobacter aerogenes	2	4.5
Enterococcus	2	4.5
Citrobacter	1	2.3
Staphylococcus aureus	1	2.3
Total	44	100

Some children had recurrent urinary tract infection

Of the 128 patients with kidney disease, 96 (75%) were discharged, four (3.1%) were referred to India for further investigations and advanced management (three for renal biopsy and one for VUR surgery) and 28 (21.9%) patients succumbed. Of the 28 patients with renal diseases that died, 26 (92.9%) had AKI while two (7.1%) had CKD. The median duration of hospital stay was eight days (IQR 4 to 14.8 days). Forty-one (32%) patients required PICU care with a median PICU stay of seven days (IQR 3.5 to 9.5 days).

DISCUSSION

This study represents the first description of the epidemiologic burden and short-term outcome of kidney disease amongst children admitted to the national referral hospital in Thimphu, Bhutan.

We found that kidney disease represented 7.8% of all pediatric admissions to the National Referral Hospital, a proportion similar to studies from neighboring countries[1,17]. The proportion of kidney disease in our center was higher than those reported from African countries which ranged from 1.6 to 3.8%[4,5,18-20]. This variation could be due to differences in clinical and laboratory capacities to diagnose kidney diseases in different regions and also methodological variation related to data collection in our study. JDWNRH is a referral center with cases admitted from across all parts of Bhutan. As such we would expect higher rates of kidney diseases compared to studies reporting rates from regional or community based-hospitals. We also suspect that many forms of kidney diseases are not identified, under-diagnosed or not referred to a higher health center for further work up. Thus the true burden of kidney disease in Bhutan is likely higher than what we describe in this study.

Males (59.4%) outnumbered female children, which was similar to results reported by studies in Asia and Africa; though no particular explanation has been offered for this observation[1-4,18-22]. The most common age group affected in our study was children aged 5 years and below. This was in accordance with studies conducted in India, Bangladesh and Nepal[2,22-24].

The main presenting features of children with renal diseases were fever (55%), nausea or vomiting (50%) edema (49%), hypertension (33%) in addition to oliguria that was present in 26% of the cases. There were slight variations in the clinical presentations reported in studies from Nepal and Bangladesh[1,17,22]. This could be due to variation in the prevalence of different renal diseases with varying underlying etiologies in different geographic regions.

The commonest renal disease was AKI (30.5%) which differs from studies from Bangladesh (5.9%) and Pakistan (2.8%) where the commonest renal disease was nephrotic syndrome[1,21,22]. Our results, however were comparable to studies from Kashmir, India (32%) where AKI was the commonest kidney condition. In our study, sepsis (31.2%) was found to be the most frequent etiology of AKI followed by meningoencephalitis and AGN, similar to findings from Nepal where sepsis accounted for 40% of AKI[1]. This pattern may be explained by the prevalent nature of infectious diseases in developing countries. If identified early and managed adequately, many cases of AKI are preventable. Moreover, referral bias is likely present in our study. As the apex hospital in Bhutan, critically ill children are often referred to JDWNRH from district hospitals. Often such patients have progressed to multi-organ failure, thereby reflecting a higher incidence of AKI in our study. AKI was found to be a significant cause of mortality among renal diseases in this study which accounted for the majority (89.3%) of deaths. The commonest etiology for AKI was sepsis and its complications, in agreement with the findings from Nepal[1]. This may be attributed to the severity and the nature of infections at presentation, rapid development of systemic complications, inadequate dialysis facilities and lack of advanced acute kidney care.

The proportion of UTI in our study (23.6%) was similar to those reported from Kashmir (24%), Nepal (21.3%) and Sagamu (21.6%)[1,19,25]. In contrast lower rates had been reported from other studies in Pakistan (1.3%), Bangladesh (2%), and Ethiopia (8%)[4,21,22]. These differences could be related to variation in prevalence rates of other renal morbidities like AGN, NS, AKI and CAKUT.

Nine (24.3%) children who were diagnosed with UTI were associated with other renal diseases like AGN, CAKUT, AKI and CKD. Similarly, other studies have also reported occurrences of UTI in association with the above mentioned renal disorders[4,21,23]. E. coli (61.4%) was the commonest cause of culture-positive UTI, which was similar to many reviews of renal diseases in children from other parts of the world like Nepal, Iraq and the Kingdom of Saudi Arabia[1,3,9].

AGN and UTI were the second common cause of renal diseases in our study, each accounting for 28.9%. There was a relatively high prevalence of AGN which was similar to reports from Nepal, India and Nigeria[1,17,20]. The prevalence of AGN was relatively low in certain countries like Pakistan, Bangladesh, Iraq and the Kingdom of Saudi Arabia[3,9,21,25]. Environmental, racial and genetic factors may have a role.

We diagnosed NS in 7% of the study cohort. Many studies conducted in low-resource settings have found NS to be more frequent reason for hospital admission[1,3,4,8,20]. Regions with particularly high rates of reported NS include Dhaka (76%), North Eastern India (30.1%), Pakistan (49.3%), Nepal (26.1%) and Nigeria (22.8%)[1,5,17,21,22]. This variation in prevalence rates may be related to the local referral pattern and genetic or environmental factors. The mean age at presentation for children with NS was 8 ±3.9 years in our study, which was similar to studies from other developing countries[1,22]. In our study NS was more prevalent in female with a male to female ratio of 1:2.7. In contrast, a higher prevalence of NS was seen in males from African study[19]. However, no particular explanation has been offered for this male preponderance.

CAKUT was a less frequent diagnosis (7%) in our study. This finding was similar to those reported from Sudan[23], but higher than studies from northeastern India (3.1%) and Bangladesh (1.3%)[17,22]. In contrary, studies done in Pakistan (30.9%), Iraq (14.1%), and Ethiopia (26.8%) reported higher diagnoses[3,4,21]. These variations could be related to genetic factors or availability of facilities for early diagnosis of these disorders. Lack of screening programs for antenatal diagnosis, advanced diagnostic facilities, and lack of awareness among parents about the importance of early detection of these diseases may explain our relatively low figures.

At presentation only four children (2.6%) had CKD which is comparable to studies from Nepal and India[1,2,23,25]. A

higher figure (28.7%) was reported from Pakistan[21]. Causes of CKD in our study were NS (50%) and CAKUT (50%) similar to western and many developing countries in the region, where urologic malformations were the main causes of CKD[8,21,22,26]. In our study CKD was associated with poor outcome. This could be attributed to the lack of dedicated resources and expertise in renal replacement therapy, including transplantation for children with ESRD. Nutrition plays a significant role in CKD and poor access and availability of nutritional support in developing countries may contribute to high mortality among undernourished CKD cases.

Overall 28 children succumbed, leading to a renal related mortality rate of 21.7% which is higher than the mortality rate reported from studies conducted in Nepal (0.88 to 5%) and Nigeria (14.1%)[1,6,18]. Differences in renal mortality can be explained from various reasons including the promptness of presentation at the hospital, awareness of renal diseases, differences in the availability of diagnostic tests, the appropriateness of treatment, and access to free healthcare services.

LIMITATIONS

Most of the patients were initially screened for kidney disease by history and clinical examination. Detailed renal screening investigations were not done for all admitted children due to lack of adequate resources. Therefore, asymptomatic patients with renal disease may have been excluded. Our study sample size was small and we did not include children with known or new-onset kidney disease presenting to the outpatient department.

CONCLUSIONS

Kidney diseases remain a significant problem among hospitalized children in the national referral hospital of Bhutan. AKI was the most common renal disease associated with morbidity and mortality. Creating awareness among primary pediatric healthcare providers would help in early detection and management of treatable childhood renal conditions thus minimizing progression to end stage kidney disease and reducing mortality. Specialists with formal pediatric nephrology training and resources directed to improve renal diagnostic and therapeutic services including acute and chronic renal replacement therapy and renal transplantation is urgently needed to advance pediatric renal health in Bhutan.

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AUTHORS CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

SS: Concept, design, data collection and analysis, manuscript writing and review.

TL: Concept, design, data collection and analysis, manuscript review

TC: Concept, design, data collection and analysis, manuscript review

DAG: Concept, design, data collection and analysis, manuscript review

Author agree to be accountable for all respects of the work in ensuring that questions related to the accuracy and integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST

None

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