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Pattern of Infection among Children with Nephrotic Syndrome in a Tertiary Level Hospital

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Abstract **Original Research Article**

Background: Patients with nephrotic syndrome are susceptible to numerous bacterial, viral, and fungal infections. To design preventive measures, it is vital to identify the various types of infections, their causative organisms, and sensitivity patterns in the local settings. ***Methods:*** From January 2012 to July 2014, this descriptive cross-sectional study was conducted in the Pediatric department of Sir Salimullah Medical College, Mitford Hospital, Dhaka. Children younger than 12 years admitted with nephrotic syndrome were screened for infection. Laboratory analysis with culture and sensitivity of urine, blood, CSF, and peritoneal fluids was performed to identify and analyze the causative organisms. ***Results:*** The most prevalent age range for the 90 admitted children with nephrotic syndrome was 2-5 years, and the male to female ratio was 0.95:1. 73% of the children had their initial attack of nephrotic syndrome, while 27% had recurrence. During admission, 38% of patients had various infections, and 57% of these infections occurred in children aged 2 to 5 years. Urinary tract infection (UTI), peritonitis, septicemia, and pneumonia were the most prevalent illnesses (incidence, 46%, 26%, 11%, and 9%, respectively). Escherichia coli, Proteus sp., and Streptococcus sp., commonly caused urinary tract infections, peritonitis, septicemia, and pneumonia. Organisms for UTI, peritonitis and pneumonia were sensitive to ciprofloxacin, azithromycin, and ceftriaxone, respectively. ***Conclusion:*** Infection should be ruled out carefully in every case of nephrotic syndrome during management in the hospital. Escherichia coli is the dominant causative agent for UTI. After sending relevant body fluids for culture sensitivity, ciprofloxacin for a suspected UTI, and azithromycin for peritonitis can be started immediately.

Keywords: Nephrotic synderome, Infection, Causative organisms, Antimicrobial sensitivity and resistance.

INTRODUCTION

Nephrotic syndrome is one of the most prevalent chronic and potentially fatal childhood illnesses.[1] In western countries, the nephrotic syndrome affects between 2 and 7 instances per 10,000 population under the age of 16, accounting for around 1% of hospital admissions [1, 2]. However, Asians have a higher annual incidence of nephrotic syndrome than Caucasians [2]. In 2011, the incidence of nephrotic syndrome was 6.61 percent higher in South Asians than in Europeans [3].

Infection is one of the most frequent complications of nephrotic syndrome, which may cause a poor response to steroid therapy, induce relapse, increases unplanned hospitalizations, and accounts for significant mortality [4-8]. In developing countries such as Bangladesh and India, the infection rate among children with nephrotic syndrome is as high as 38-83% [8].

Children with nephrotic syndrome are especially vulnerable to infection due to their immunocompromised state during the disease [1, 9].

The host becomes immunocompromised for a wide range of reasons, including tissue edema, urinary complement, and immunoglobulin loss, as well as side effects of corticosteroids and cytotoxic therapy [2, 4, 10, 11]. Increased susceptibility to infection necessitates early identification and treatment in order to minimize morbidity and mortality [1, 12].

Common infections associated with nephrotic syndrome in children include acute upper and lower respiratory tract infections including pneumonia, urinary tract infections (UTIs), sepsis, skin infections including impetigo and cellulitis, acute watery diarrhea, spontaneous bacterial peritonitis, and others [1, 2, 4, 8, 13, 14]. The infection rate and type of infection, on the other hand, vary significantly among patients from different geographic regions around the world [1].

The introduction of corticosteroids and antibiotics in the treatment of nephrotic syndrome has resulted in a decrease in mortality [1, 4, 8]. However, infection increases the likelihood of frequent relapses and steroid dependency, resulting in frequent hospitalizations, poor patient outcomes, and an increased strain on the healthcare system [1, 4, 7, 15, 16]. On the other hand, severe infectious complications associated with nephrotic syndrome, such as peritonitis and pneumonia, continue to result in a 1.5% infection-related mortality, especially in developing countries [1, 2, 4, 8, 10, 17].

Although studies on infection patterns in children with nephrotic syndrome have been conducted in Bangladesh, there is a scarcity of data on the sensitivity pattern to microorganisms, which varies over time [1, 12, 18]. It is critical to keep doctors updated about the current infection pattern in children with nephrotic syndrome in the local settings. Additionally, it is essential to identify pathogen trends and their sensitivity patterns to develop preventive strategies [12, 16].

The purpose of this study was to examine the hematological and biochemical parameters associated with infection in hospitalized children with nephrotic syndrome and to identify the causative organisms and their sensitivity patterns for these infections.

MATERIALS AND METHODS

This descriptive cross-sectional study was conducted at the Department of Paediatrics, Sir Salimullah Medical College (SSMC), and Mitford Hospital, Dhaka, from January 2012 to July 2014.

All children aged 2-12 years who fulfilled the criteria of the Study of Kidney Disease in Children (ISKDC) definition for nephrotic syndrome [19] with or without infection, including all relapse cases admitted in the Paediatrics Ward of SSMC and Mitford Hospital, Dhaka during the study period were included. Children with acute or chronic renal failure or with urogenital anomalies were excluded.

During this period, 105 children were eligible for the study, but 15 of them either did not consent to participate in the study or were absconded from the hospital. Therefore, a total of 90 children were included in the study. A detailed demographic and clinical history with a careful physical examination was done by the principal investigator. The information was recorded in a data collection sheet.

Urine routine microscopic examination (urine RME), serum creatinine, serum albumin, serum cholesterol, and 24-hour urinary total protein (UTP) was estimated for all the cases. Screening for infections was done in children with clinically suspected symptoms and signs of infection. To search for the focus of infection, one or more of the following investigations were done in addition to the routine investigations, including complete blood count, peritoneal fluid examination, Blood and Urine culture and sensitivity, culture of throat and skin swab, Mantoux test, and X-Ray chest. All the children with nephrotic syndrome were treated as per-standard treatment guidelines.

After collection, data were checked meticulously, then entered and analyzed using SPSS (Statistical Package for Social Science, IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). Proportions were compared with the Chi-square test or Fisher's Exact test where appropriate. When comparing baseline patient characteristics, a p-value <0.05 was considered significant. Descriptive statistics were presented with frequency and percentages.

The study was approved by the 'Ethical Review Committee' and Internal Review Board of Sir Salimullah Medical College, Dhaka. Informed written consent was taken from the parent or guardian of the study participants.

RESULTS

A total of 90 children were included in this study. Table I shows the socio-demographic and clinical characteristics of the study population (N=90). Among 90 study cases, 60% of cases were in the 2-5 year age group, and the rest were in the 5-12 year age group. The ratio of males and females was 0.95:1. Two-thirds of the patients came from rural areas. Most of the children (63%) were from middle socio-economic status. Among 90 studied cases, 73% of children were admitted due to an initial attack of nephrotic syndrome, and in the rest of the cases, 27% were due to relapse.

Table I: **Socio-demographic and clinical characteristics of the study population**

Characteristics	Number	Percentage (%)
Age group		
2-5 year	54	60
>5-12 year	36	40
Sex		
Male	44	49
Female	46	51
Residence		
Rural	60	67
Semi urban/ Urban	30	23
Socio-economic status		
Low	24	27
Middle	66	63
No. of family members		
≤4	71	79
≥5	19	21
Admission		
Initial attack	66	73
Relapse	24	27

Figure 1 illustrates the types of infection among the studied children (n= 90). 38% of children had culture-positive body fluids and skin swab specimens. Urinary tract infection (UTI) dominates with the highest percentage at 18% and is followed by peritonitis in 10% of cases. Septicemia prevailed in 4% of cases. Pneumonia, pharyngotonsillitis and cellulitis were found in 3.3%, 2%, and 1% of cases respectively.

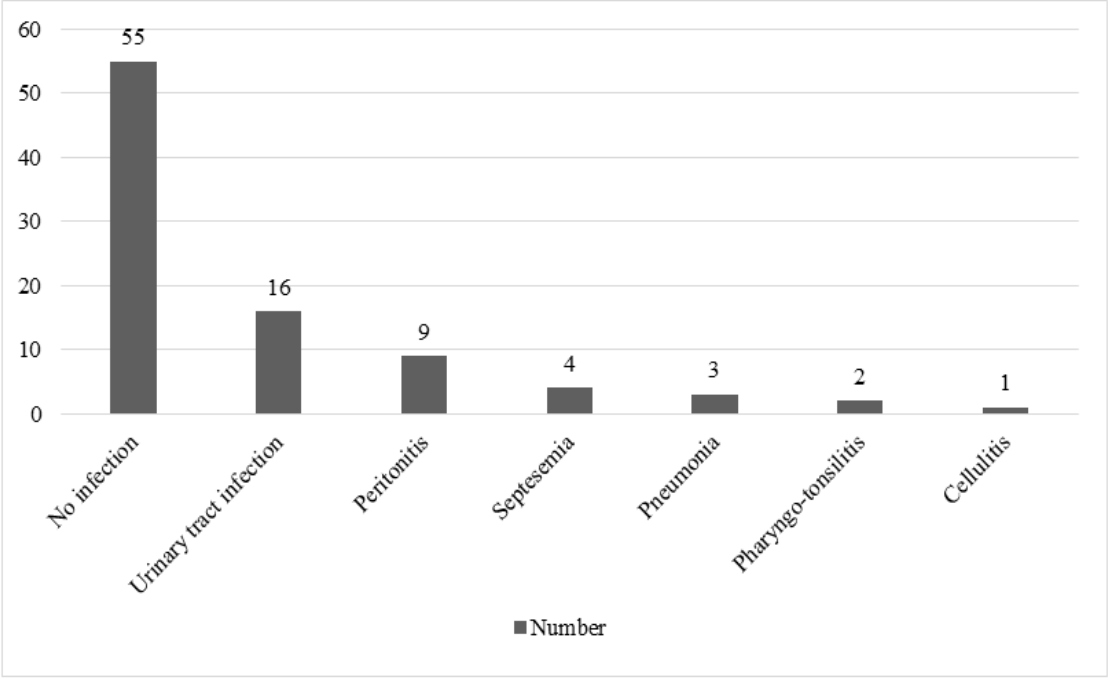

Figure 1: Frequency of infections among nephrotic syndrome

Table II shows the distribution of various laboratory values among children with nephrotic syndrome, with and without infections. Comparing infection and non-infection cases, children with infection has higher Erythrocyte Sedimentation Rate (ESR) (40% vs. 51%), white blood cell (WBC) counts (51% vs. 47%), and neutrophil count (91% vs 29%), but lower rate of haematuria (20% vs 27%), pus cells (40% vs 60%) and lymphocytes (43% vs 46%). However, only the high neutrophil count was significantly higher (p-value <0.001) in infected cases compared with non-infected cases. In addition, there was no significant difference in the mean value of serum albumin, serum cholesterol, serum total protein, and serum creatinine in children with infection or without infection.

Table II: Distribution of studied children according to laboratory investigations with or without infection

Characteristics	With Infection (n=35) n(%) or, Mean±SD	Without Infection (n=65) n(%) or, Mean±SD	P value*
High ESR (n=42)	14 (40%)	28 (51%)	0.388
High WBC (n=46)	17 (51%)	29 (47%)	0.829
High neutrophil (n=46)	32(91%)	14(29%)	<0.001
Haematuria (n=22)	7 (20%)	15 (27%)	0.464
Presence of pus cells (n=47)	14 (40%)	33 (60%)	0.084
Low lymphocyte	15 (43%)	30 (46%)	0.387
Serum albumin (gm/dl)	1.9 ± 0.2	1.9 ± 0.2	0.6
Serum cholesterol (mg/dl)	366 ± 84	401 ±82	0.06
Serum total Protein (gm/dl)	4.2 ± 0.6	4 ± 0.6	0.19
Serum creatinine (mg/dl)	0.7 ± 0.2	0.8 ± 0.2	0.06

*p-value was calculated using the Chi-square test

Figure 2 revealed the organisms among infectious cases. Out of the total 35 isolates, 34.3% were *Escherichia coli*, and 25.7% were *Proteus* species. *Klebsiella* species and *Streptococcus pneumoniae* along with other *Streptococcus* species were found in 17.1% and 20.0% cases, respectively. *Haemophilus influenzae* was found in only 2.9% of cases.

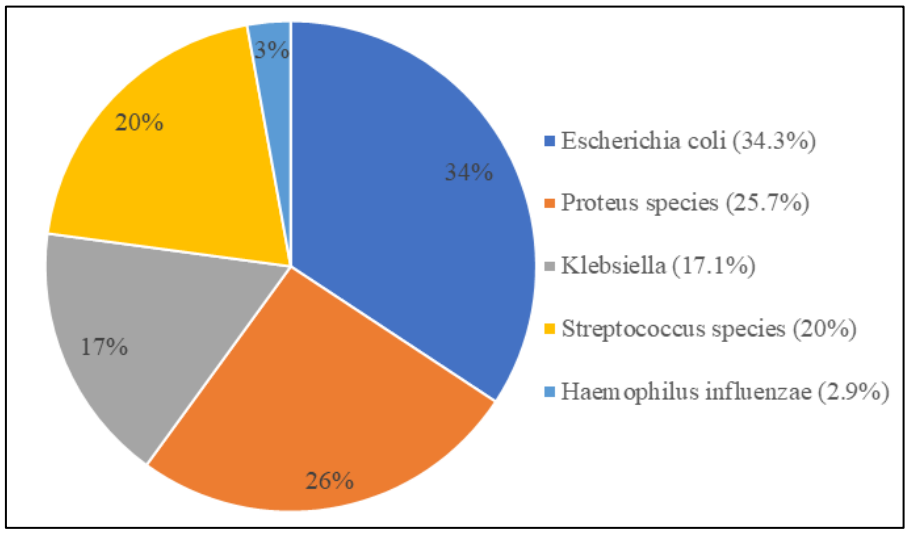

Figure 2: Distribution of studied children by types of organisms causing infection (n =35)

Table III summarizes identified organisms by infection type and sample source. UTIs were most commonly caused by *Escherichia coli* (37%), followed by *Proteus sp*. and *Klebsiella* species. Peritonitis was dominated by *Escherichia coli* (44.4%), *Proteus sp.* (33.4%), and *Streptococcus pneumoniae* (22.2%). In septicemic patients, *Streptococcus pneumoniae* was detected in 50% of cases, followed by *Escherichia coli* (25%) and *Klebsiella sp*. (25%). *Escherichia coli*, *Proteus sp*., and *Haemophilus influenzae* were isolated from each of the 3 pneumonia cases. *Streptococcus pneumoniae* was the sole organism (100%) isolated from pharyngotonsillitis throat swabs. In cellulitis, *Streptococcus sp*. (100%) was isolated from the skin swab.

All the strains of *Escherichia coli* were sensitive to azithromycin, cephradine, ceftriaxone, and amikacin but resistant to trimethoprim-sulfamethoxazole, ceftazidime, amoxicillin-clavulanic acid. *Proteus* species isolated from urine were sensitive to ciprofloxacin, nitrofurantoin, chloramphenicol, and azithromycin. In addition, *Proteus* species isolated from peritoneal fluid were sensitive to ceftriaxone. *Proteus* species were resistant to trimethoprim-sulfamethoxazole and ceftazidime. *Streptococcus sp*. was sensitive to chloramphenicol, ceftriaxone, cefuroxime, ampicillin, ciprofloxacin, azithromycin, cephradine, and ceftriaxone. They were resistant to erythromycin, bacitracin, and gentamycin. *Klebsiella sp*. isolated from urine was sensitive to ciprofloxacin, nitrofurantoin, and cephradine. *Klebsiella sp*. isolated from blood was tested for amikacin instead of nitrofurantoin and was sensitive. *Klebsiella sp*. isolated from blood was resistant to nalidixic acid, amoxicillin-clavulanic acid, chloramphenicol, and tetracycline. *Haemophilus influenzae* was sensitive to azithromycin,

cephradine, and ceftriaxone and resistant to cefuroxime, nalidixic acid, and chloramphenicol.

Table III: **Sensitivity pattern of isolated pathogens according to types of infection and body fluid and skin scraping**

Types of Infection	**Body fluid**	**Organisms isolated**	**Number (%)**	**Antibiogram**	
				Sensitive to	Resistant to
UTI (n=16)	Urine	*Escherichia coli*	6 (37.5)	AZT, CPH, CFX, AMK	SXT, CFZ, AMOX-C
		Proteus sp.	5 (31.5)	CIP, NTF, CHL, AZT	SXT, CFZ,
		Klebsiella sp.	5 (31.5)	CIP, NTF, CPH	NDX, AMOX-C, CHL, TCL
Peritonitis (n=9)	Peritoneal fluid	*Escherichia coli*	4 (44.4)	AZT, CPH, CFX, AMK	SXT, CFZ, AMOX-C
		Proteus sp.	3 (33.4)	CIP, CHL, CFX, AZT	SXT, CFZ,
		Streptococcus pneumoniae	2 (22.2)	CHL, CFX, CFM, AMP, CIP, AZT, CPH.	ERY, BCT, GEN
Septicemia (n=4)	Blood	*Streptococcus pneumoniae*	2 (50)	CHL, CFX, CFM, AMP, CIP, AZT, CPH.	ERY, BCT, GEN
		Escherichia coli	1 (25)	AZT, CPH, CFX, AMK	SXT, CFZ, AMOX-C
		Klebsiella sp.	1 (25)	CIP, AMK, CPH	NDX, AMOX-C, CHL, TCL
Pneumonia (n=3)	Blood	*Escherichia coli*	1 (33.3)	AZT, CPH, CFX, AMK	SXT, CFZ, AMOX-C
		Proteus sp.	1 (33.3)	AZT, CPH, CFX, AMK	SXT, CFZ, AMOX-C
		Haemophilus influenzae	1 (33.3)	AZT, CPH, CFX	CFM, NA, CHL
Pharyngo-tonsillitis (n=2)	Throat Swab	*Streptococcus pneumoniae*	2 (100)	CHL, CFX, CFM, AMP, CIP, AZT, CPH.	ERY, BCT, GEN
Cellulitis (n=1)	Skin Swab	*Streptococcus* sp.	1 (100)	CHL, CFX, CFM, AMP, CIP, AZT, CPH.	ERY, BCT, GEN

Note: CIP: Ciprofloxacin; NTF: Nitrofurantoin; CHL: Chloramphenicol; AZT: Azithromycin; CPH: Cephradine; CFX: Ceftriaxone; CFM: Cefuroxime; AMP: Ampicillin; AMK: Amikacin; CFZ: Ceftazidime; SXT: Trimethoprim-Sulfamethoxazole; AMOX-C: Amoxicillin-Clavaulinic acid; NDX: Nalidixic acid; TCL: Tetracycline; ERY: Erythromycin; BCT: Bacitracin; GEN: Gentamicin.

DISCUSSION

Children with nephrotic syndrome have a compromised immune system, which puts them at risk of infection from various sources [6, 8, 20, 21]. In our study, 48% of the cases were male, while 52% were female, for a male-to-female ratio of 0.95:1. In previous studies by Gulati *et al.*, Ajayan *et al.*, and Begum *et al.*, it was shown that children with nephrotic syndrome were more prevalent in boys than in girls, which is inconsistent with our findings [10, 12, 22]. However, in a previous study by Hossain *et al.*, in Bangladesh did not find any male preponderance [23].

In the present study, 73% of the children experienced their initial attack of nephrotic syndrome, and 27% had a relapse. This result is comparable to that of research conducted at IPGMR (Institute of Postgraduate Medical Research, currently known as Bangabandhu Sheikh Mujib Medical University Hospital, Bangladesh) in 1982 by Hossain *et al.*, in which initial attack cases accounted for 72% [23].

Comparable to the research conducted by Gulati *et al.*, Moorani *et al.*, and others, more than one-third (38%) of the nephrotic syndrome patients in our study had infections [8, 12, 13, 16]. However, according to a study conducted by Eddy *et al.*, the rate of severe infections in Taiwan was as low as 19% [1]. This illustrates that the incidence of the nephrotic syndrome varies across geographic locations.

Regional variation in infection types is also substantial. In our study, urinary tract infections were the most prevalent, followed by peritonitis, septicemia, pneumonia, pharyngotonsillitis, and cellulitis. In different other studies done in India, Karachi, and Saudi Arabia, the most prevalent infection in children with nephrotic syndrome was upper respiratory tract infection, whereas, in Taiwan, pneumonia was the most prevalent infection [1, 5, 12, 24, 25].

The age distribution of the children studied suggested that younger children were more susceptible to infection than older children. In our study, 57% of infections in children with nephrotic syndrome occurred between the ages of 2 to 5 years, which was comparable to the proportion found in the study by Sarker *et al.*, [26]. In this study, children aged 2 to 5 years were 1.3 times more susceptible to infection than those aged 5 to 12 years. Senguttuvan *et al.*, reported that 62% of children with nephrotic syndrome were infected before six years, consistent with the present study [13].

In our study, UTI was the most common infection among children with nephrotic syndrome (45.7%). This result was comparable to those of Senguttuvan *et al.*, Gulati *et al.*, and Afroz *et al.*, [10, 13, 27]. Studies conducted in Africa by Adeleke *et al.*, and Adedoyin *et al.*, also reported a high prevalence of UTI [28, 29]. However, UTI was infrequent in the study conducted by Ajayan *et al.*, and no incidences of UTI were found in the study done by Srivastava *et al.*, [9, 12]. Geographical or socioeconomic variation in UTI prevalence is substantial, given the wide range of incidences.

Peritonitis is a life-threatening consequence of nephrotic syndrome [8]. Based on the presence of fever, abdominal tenderness, vomiting, and ascites, we suspect that peritonitis was present in 16 (18%) of our patients. The culture sensitivity test has verified the diagnosis of 9 of these cases. In our study, peritonitis was the second most prevalent infection, although, in a study by Ajayan *et al.*, it was the most common infection [12]. However, their culture-positive rate was lower, most likely because the majority of individuals were given antibiotics by their general practitioners prior to the ascitic fluid sample collection.

In this study, 11.4% of patients with fever, poor eating, vomiting, lethargy, abdominal distension, and organomegaly with a positive blood culture were diagnosed with septicemia.

In our study, only 3.3% of the cases had evidence of pneumonia. However, in an Indian study conducted by Ajayan *et al.*, the incidence of pneumonia is substantially greater (12.9%) [12]. Zhang *et al.*, and others observed that acute respiratory infection was the most prevalent infection in their studies [5, 7, 8, 16, 30]. In contrast, Eddy *et al.*, reported that pneumonia was more prevalent in children younger than 10 years of age, while UTI was most prevalent in children older than 10 years of age [1].

We have found that 2% of the cases in our study had pharyngotonsillitis. Moorani has observed that the incidence of skin infections in children with nephrotic syndrome has decreased from as high as 28% to 2% over the years [8]. In addition, just one child in our research was diagnosed with cellulitis. Recent research conducted in the neighboring country of India has also found comparable findings [2, 13]. Improved hygiene and socioeconomic status may have contributed to the decline in incidences of skin infections [8].

There were several other infections discovered in other research, such as diarrhea, enteric fever, tuberculosis, hepatitis, measles, chickenpox, herpetic infection, and meningitis, but we did not find any of the above [12, 16, 31].

Hematological parameters in our investigation revealed that children with infection had significantly higher neutrophil counts. Serum albumin, cholesterol, and creatinine had a marginal significance in our study, although earlier research has revealed that children with high serum cholesterol and low serum albumin had a considerably increased risk of infection [12, 16, 32].

Among the isolated organisms, we found that *Escherichia coli* was the most prevalent (34.3%), followed by *Proteus* sp. (25.7%). Gulati *et al.*, and Gorensek *et al.*, found similar results in their research [10, 33]. In our study, at least one isolate of *Escherichia coli* was detected in urine, peritoneal fluid, and blood samples. *Klebsiella* sp. was found in 17.1% of the isolates in the urine sample of the patient with UTI, and in the blood sample of the children with septicemia, which is comparable to the study conducted by Adeleke *et al.*, in Nigeria [28]. In India, however, Senguttuvan *et al.*, identified higher incidences (28%) of *Klebsiella* spp. Infections [13]. Twenty percent of the isolates from patients with septicemia, pharyngotonsillitis, and cellulitis in our investigation were *Streptococcus* species. In contrast, as shown in a study by Gorensek *et al.*, *Streptococcus* sp. was the most prevalent pathogen, accounting for 38% of nephrotic syndrome infections. In addition, we found only one isolate of *Haemophilus influenzae* in children with pneumonia.

Regarding the antibiogram, 17 antibiotic discs were utilized to test for sensitivity. In both UTI and peritonitis cases, *Escherichia coli* was sensitive to azithromycin. Another study by Song *et al.*, revealed that *Escherichia coli* was sensitive to amikacin and highly resistant to ampicillin and ceftriaxone [34]. In or study, ceftriaxone was found to be sensitive against both *Streptococcus* sp. isolated from UTI patients and *Haemophilus influenzae* isolated from pneumonia patients, and a similar finding was reported by Moorani *et al.*, in a separate study [7]. *Proteus* and *Klebsiella* species were sensitive to ciprofloxacin and nitrofurantoin, and the results were comparable to those of a study conducted in China by Tain *et al.*, [35].

LIMITATION

Our study was conducted in a single tertiary hospital with a small sample size, which may not reflect

the scenario of the other parts of the country. In addition, many of the children received antibiotics before they reached the hospital, which may have contributed to low culture positivity.

A multi-centered study with a larger sample size is required to establish the significant infection pattern in children with nephrotic syndrome in different age groups in various age groups.

CONCLUSION

From the present study, it can be concluded that all children with nephrotic syndrome should undergo infection screening. Urinary tract infection was the most prevalent infection among children with nephrotic syndrome, especially those younger than five years old. Children with nephrotic syndrome were predominately infected with *Escherichia coli*, which caused both UTI and peritonitis. Ciprofloxacin for suspected UTI and azithromycin for peritonitis can be started immediately in children with nephrotic syndrome after sending relevant body fluids for culture sensitivity.

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