Original Article

Urinary Tract Infection in Idiopathic Nephrotic Syndrome in Children: Clinical Profile, Etiological Organisms and Antibiotic Sensitivity Patterns

Rezoana Najnin[1], M Azizul Hossain[2], Ishrat Jahan[3], Hazera Akter[4], Kazi Abdul Mannan[5]

Abstract:

Background: Nephrotic syndrome is a common childhood renal disorder; the prevalence of Urinary tract infection (UTI) in these patients is high. The increased prevalence of UTI is due to immunoglobulin loss, defective T cell function, presence of ascites and relative malnutrition.Objective:To determine the clinical characteristics of UTI and its antimicrobial sensitivity pattern among the children with idiopathic nephrotic syndrome. **Methods:** A cross-sectional study which was conducted among purposively selected 54 patients with idiopathic nephrotic syndrome in the department of pediatrics from January to June 2017 at Comilla Medical College Hospital. Data were collected by performing physical examination of the children and face-to-face interview of the parents and investigation reports using a structured questionnaire. Descriptive and bivariate analysis was done using the analytic software SPSS version 21.0. Means and standard deviations were calculated for parametric variables and means were compared using Student's t-test. Nonparametric variables were expressed in proportions. Differences between frequencies were tested using Chi-square test, p-values <0.05 were considered significant. **Results:** Majority of the children was male (55.5%) hailing from a middle-class family (59.3%) with a mean age of 4.5±22 years. The prevalence of UTI among the patients was 25.9%. The clinical features associated with UTI were frequent urination (p<0.001) suprapubic tenderness (p<0.001) and dysuria (p<0.001) although a number of UTI were asymptomatic. Frequent episodes of nephrotic syndrome were associated with UTI (p<0.048) Urinalysis showed that pus cell (p=0.001) and RBC (p=00.4) were significantly associated with UTI. The common organisms isolated were E.coli (64.3%). Proteus (21.5%), Klebsiella (14.3%), Staphylococcus (7.1%) and Pseudomonas (7.1%). Majority of the common antibiotics were resistant to the organisms isolated. The highest sensitivity was for Imipenem (78.6%), Nitrofurantoin (71.4%), Cefuroxime (57 1%) and Ciprofloxacin (42.9%). **Conclusion:** There is a high prevalence of UTI in children presenting with nephrotic syndrome. Therefore, a routine urine culture should be done on patients with nephrotic syndrome and appropriate antibiotics should be used.

Key Words: UTI, Children, Nephrotic syndrome, Etiological organisms,Antibiotic sensitivity.

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Introduction:

Nephrotic syndrome is a common chronic renal disorder encountered in children and it accounts for approximately 1% of hospital admissions. In western countries, the annual incidence ranges from two to seven new cases among children under 16 years of age per 100000 total population.[1] There is a racial variation in susceptibility with a reported incidence in Asian children of 9-16/100,000.[2] The prevalence of minimal change nephrotic syndrome is higher in Indian subcontinent. Such incidence in Bangladesh is yet unknown.[2] However, It is a quite common clinical condition in our country affecting usually the young children.[3] It is more common among 2-6 years of age with male to female ratio of 2:1. Most of patient with frequent relapse are under-five children, came from rural area and belong to poor social class compared to that of infrequent relapse. Other risk factors of relapse are low serum albumin level, low serum total protein level, urinary tract infection (UTI) at initial attack.[3] Children with nephrotic syndrome are exposed to a

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variety of infectious complications that result in significant mortality and morbidity, especially in developing countries.[4] Common infections include peritonitis, cellulitis and pneumonia.[2]

UTI is one of the commonest renal diseases in childhood.[5] The prevalence of UTI is 9% and is significantly higher in girls than in boys.[4,6] Nephrotic syndrome is common childhood renal disorder, among these group of patients, the prevalence of UTI is high.[4,5,7] A hospital based study in Bangladesh showed that UTI was found in 30.8% nephrotic children and in majority cases (68.8%) they were asymptomatic.[8] The increased prevalence of UTI in patients with Nephrotic syndrome are due to immunoglobulin loss in urine,[9] defective T cell function, presence of ascites and relative malnutrition.[10] UTI has also been reported to adversely influence the response of patients with nephrotic syndrome to corticosteroids.[11] A study in Bangladesh reported that UTI at initial attack were observed to be statistically significant in case of frequent relapse group.[3]

Fever remains a more common presentation in neonates, infants and younger children, whereas older children present with classic signs of UTI.[12] Temperature >41°C and abdominal pain were significantly associated with UTI.[13] Another common symptom of UTI is dysuria.[6] Significant features associated with UTI were fever of at least 7 days duration, a peak evaluation temperature ≥ 38.3°C and a white blood cell count>10/mm3.14 Children with infection had significantly lower serum albumin and higher serum cholesterol compared to non-infected children.[1,4]

However, diagnosis remains a difficult task probably because its presentation is non-specific and similar to other common illnesses. The diagnosis of UTI in young children is important as it can be a marker for urinary tract abnormalities and, in the newborn, may be associated with bacteremia. Early diagnosis is critical to preserve renal function of the growing kidney. Delay in initiation of the antibacterial therapy is associated with an increased risk of renal scarring, hypertension, and progression to end-stage kidney disease.[16]

Antibiotic therapy which is the mainstay of treatment is dependent on a number of factors such as the predominant pathogens in the patient's age group, antibacterial sensitivity patterns in the practice area, the clinical status of the patient, the opportunity for close follow-up, and of course, cost of treatment.[16] Local resistance data is important in selecting empirical antibiotic. Children with uncomplicated UTI can be treated with oral antibiotic such as trimethoprim- sulphamethoxazole, amoxicillin clavulanic acid, 2nd genaration cephalosporin (cefuroxime, cefprozil), 3rd genaration (cefixime, cefpodoxime, ceftibuten, cefdinir), nitrofurantoin and some of the well-known parenteral agents like ampicillin and gentamycin for enterococci, Group B streptococcus and gram negative bacteria and third generation cephalosporin (ceftazidime, ceftriaxone, cefepime) are used in resistant uropathogens. If intravenous therapy chosen, single daily dosing of aminoglycosides is safe and effective. E coli were resistant to most of antibiotics and resistance to cotrimoxazol is quite high for all isolates. Ciprofloxacin as oral and amikacin as parenteral are good for first line treatment of UTI in nephrotic syndrome.[8] Now a days, flouroquinolones are developing resistance to this class of medication in Bangladesh.In nephrotic syndrome, children are prone to recurrent UTI due to decrease immunity, steroid use and disease itself. So there is chance of repeated and widespread use of common conventional antibiotics that may be risk factor for emergence of antibiotic resistance.

Methods:

It is a Cross sectional study, was conducted in the Department of Pediatrics, Comilla Medical College Hospital, Cumilla, study period was January 2017 to June2017. A total of 54children were enrolled for this study,who fulfilled the inclusion criteria. The study population consisted of Children of both sex up to 12 years of age of any income status, fulfilling the following criteria of International Study of Kidney Diseases in Children (ISKDC) for nephrotic syndrome.

- Generalized oedema
- Heavy proteinuria: Urine protein >40 mg/m^2/hour
- Hypoalbuminemia (serum albumin <25 g/L)
- Hypercholesterolemia (>250 mg/dl)

The following group of patients were excluded from the study:

- Children whose parents refused to give consent
- Children who refused to admit into the hospital
- Children who had the history of antibiotic usage within 4 weeks of admission

Informed written consent was taken from parents/guardians before enrollment.A history was taken from the child's parent and a systemic physical examination of the child was performed with the aim of making a primary diagnosis. Investigations other than urine microscopy and culture were determined by the working diagnosis.

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Age, sex, results of urine culture and in vitro antibiotic sensitivity pattern of isolated organisms were studied. Their clinical presentations with associated conditions and risk factors were noted. Urine specimens from children with nephrotic syndrome were obtained by clean catch method following careful preparation of the urethral orifices. For men, glans penis was cleaned by soap and water. For women, labia were spread open and with a gauze moistened with water , vulva was cleaned from front to back and then mid stream urine samples were collected into sterile containers and promptly transported to the laboratory within 30 minutes where the specimens were processed immediately for routine microscopy. Only samples with more than 5 pus cell per HPF were subjected for culture and amtimicorbial susceptibility testing in the laboratory of Comilla Medical College Hospital, Comilla.

After collection, data were checked for consistency and completeness and cleaned and edited. Statistical Package for Social Sciences (SPSS) version 21.0 was used to analyze the data. Data analysis was begun with descriptive analysis. Means and standard deviations were calculated for parametric variables and means were compared using Student's t-test. Non-parametric variables were expressed in proportions. Differences between frequencies were tested using X^2 test. The strength of association between variables were assessed by calculating the odds ratio (95% CI) of the prevalence in subjects with vs those without the feature under examination. p-values<0.05 were considered significant. Data were presented by tables and graphs.

Results:

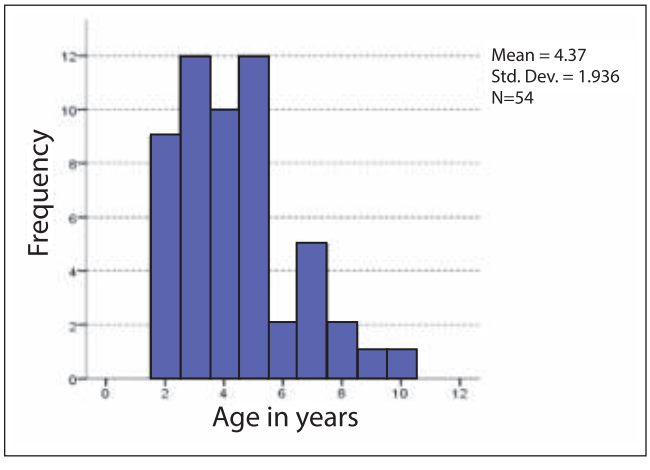

Fig. 1: Age distribution of the children (n= 54)

The age of the children ranged from 2 to 12 years with a mean of 4.4±1.9 years. The age of the majority of the children was within 2 to 5 years.

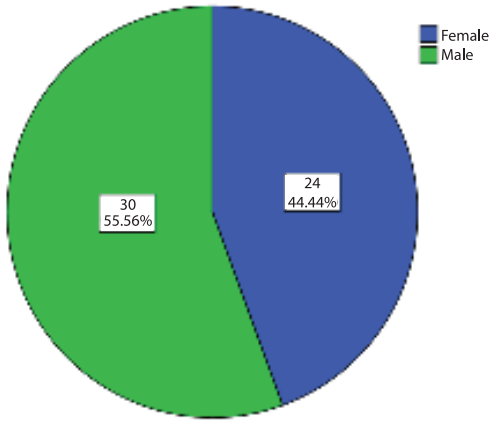

Fig. 2: Distribution of patients by sex

Out of 54, male were 30 (55.6%) and female were 24 (44.4%) and male & female ratio was 1.3: 1.

Table-I: Socio-demographic characteristics of the parents

Characteristics	Number	Percentage
Education of father		
Illiterate	3	5.6
Primary	22	40.7
Secondary	23	42.6
Higher secondary	5	9.3
Graduate or post graduate	1	1.9
Education of mother		
Illiterate	10	18.5
Primary	29	53.7
Secondary	14	25.9
Higher secondary	1	1.9
Occupation of father		
Unemployed	2	3.7
Service	10	18.5
Business	13	24.1
Day labor	8	14.8
Garments worker	4	7.4
Farmers	8	14.8
Others	9	16.7
Occupation of mother		
Housewife	35	64.8
Working mother	19	35.2
Income status		
Lower income status	22	40.7
Middle income status	32	59.3

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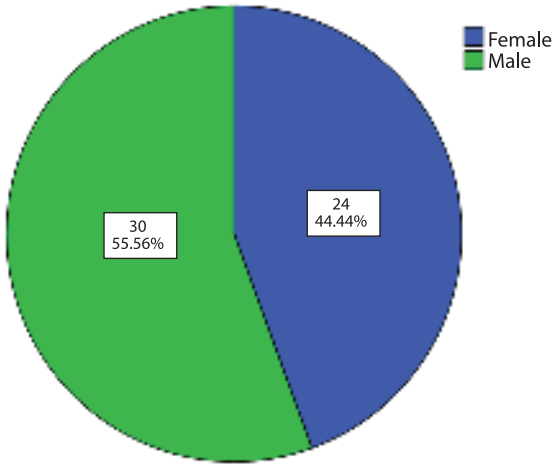

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Out of 54, male were 30 (55.6%) and female were 24 (44.4%) and male & female ratio was 1.3: 1.

Table-I: Socio-demographic characteristics of the parents

Table-I shows the parents' socioeconomic status. Here, the education level of more than three forth (79.6%) of the father is within primary or secondary level. On the other side, the education level of more than 50% of the mother is below primary level.The occupation of the mothers showing most of them are housewives (64.8%), whereas fathers are mostly (42.6%) involved in service and business.This table also illustrated about the socio-economic status of the respondents depicting, the majority (59.3%) were from middle class, on the contrary, the 40.7% were came from lower class.

Table-II: Nephrotic syndrome related factors

Factors	Number	Percentage
Type of relapse		
Infrequent relapse	49	90.7
Frequent relapse	5	9.3
Duration of symptom in this episode		
Upto 7 days	23	42.6
More than 7 days	31	57.4
History of receiving steroid therapy within 4 weeks		
Yes	1	1.9
No	53	98.1

Table-II shows that majority of the children (90.7%) had infrequent relapse I.e., episode within 0 – 2per 12 months. Majority (57.4%) of the children were having the symptoms for more than 7 days during above mentioned episodes.The table also illustrated that 98.1% children have no history of taking steroid therapy within 4 weeks.

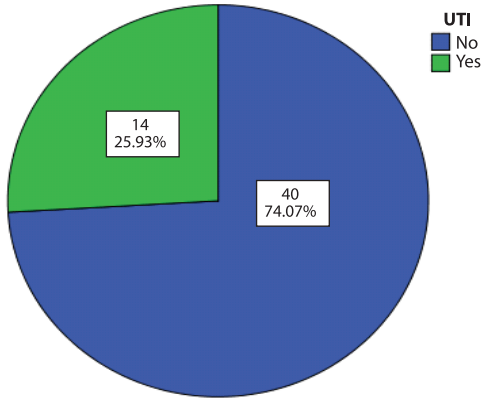

Fig. 3: Prevalence of UTI among the children with idiopathic nephrotic syndrome (n=54)

Among 54 patients of nephrotic syndrome only 14 (25.9%) children were suffering from UTI whereas 40 (74.1%) children were not diagnosed as UTI.

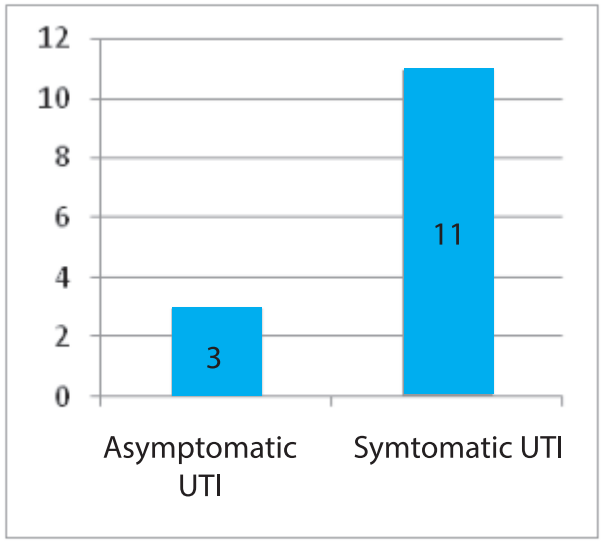

Fig. 4: Proportion of asymptomatic and symptomatic UTI(n=14)

Out of 14 patients of UTI, 11 (61.1%) were symptomatic and three (8.3%) were asymptomatic.

Table-III: Clinical features associated with UTI

Clinical features	UTI		P value*
	No N(%)	Yes N(%)	
Generalized oedema			
No	6 (85.7)	1 (14.3)	0.451
Yes	34 (72.3)	13 (27.7)	
Hematuria			
No	39 (73.6)	14 (26.4)	0.550
Yes	1 (100)	0 (0.0)	

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Anemia			
No	24 (77.4)	7 (22.6)	0.515
Yes	16 (69.6)	7 (30.4)	
Oliguria			
No	2 (66.7)	1 (33.3)	0.763
Yes	38 (74.5)	13 (25.5)	
Hypertension			
No	40 (74.1)	14 (25.9)	-
Yes	0 (0.0)	0 (0.0)	
Fever			
No	18 (78.3)	5 (21.7)	0.545
Yes	22 (71.0)	9 (29.0)	
Vomiting			
No	24 (70.6)	10 (29.4)	0.446
Yes	16 (80.0)	4 (20.0)	
Diarrhea			
No	32 (72.7)	12 (27.3)	0.636
Yes	8 (80.0)	2 (20.0)	
Abdominal pain			
No	21 (77.8)	6 (22.2)	0.535
Yes	19 (70.4)	8 (29.6)	
Suprapubic tenderness			
No	35 (94.6)	2 (5.4)	<0.001
Yes	2 (29.4)	12 (70.6)	
Renal angle tenderness			
No	37 (77.1)	11 (22.9)	0.154
Yes	3 (50.0)	3 (50.0)	
Dysuria			
No	33 (91.7)	3 (8.3)	<0.001
Yes	7 (38.9)	11 (61.1)	

***Chi square test**

Table-III describes the clinical features of the children with idiopathic nephrotic syndrome with or without UTI. The features associated with UTI were frequent urination (p<0.001). Suprapubic tenderness (p<0.001) and dysuria (p<0.001). UTI was more common among those who were suffering from frequent urination (58.8%) than those who were not (10.8%). The proportion of UTI was higher among those who had suprapubic tenderness ((50.0%) than who did not have (5.4%). UTI was more prevalent among those suffering from dysuria (61.1%) compared to those who were not (8.3%). Other clinical features i.e. generalized oedema (p=0.451), hematuria (p=0.550), anaemia (p=0.515), hypertension, fever (p=0.545), vomiting (p=0446), diarrhea (p=0.636), and renal angle tenderness (p=0.154) were not associated with UTI.

Table-IV: Factors associated with UTI inidiopathic nephrotic syndrome

Features	**UTI**		**P value***
	No N (%)	**Yes N (%)**	
Age			
Up to 3 years	14 (66.7%)	7 (33.3%)	0.588
4-5 years	17 (77.3%)	5 (22.7%)	
More than 5 years	9 (81.8%)	2 (18.2%)	
Sex			
Female	17 (70.8%)	7 (29.2)	0.627
Male	23 (76.7%)	7 (23.3)	
Type of relapse			
Infrequent relapse	38 (77.6)	11 (22.4)	0.048
Frequent relapse	2 (40.0)	3 (60.0)	
Duration of symptom in this episode			
Upto 7 days	16 (69.6)	7 (30.4)	0.515
More than 7 days	24 (77.4)	7 (22.6)	

Table-IV illustrates the factors associated with UTI in idiopathic nephrotic syndrome. The proportion of UTI decreased with increase of age of the children. It was maximum among the age group up to 3 years (33.3%), followed by 4-5 years (22.7%) and more than 5 years (18.2%). However, this association was not statistically significant (p=0.588). Female children (29.2%) were more common of developing UTI than male children (23.3%) which was not statistically significant (p=0.627). Frequent relapse (60.0%) was associated with UTI compared to infrequent relapse (22.6%, p<0.048). No association was observed between duration of symptom in this episode and UTI (p=0.515)

Table-V: Investigation findings and UTI idiopathic nephritic syndrome

Investigation findings	**Mean ± SD**		**P-value***
	UTI absent	**UTI present**	
Serum albumin (gm/dl)	1.71 ± 0.26	1.70 ± 0.21	0.899
Serum cholesterol (mg/dl)	329.57 ± 65.05	337.21 ± 62.27	0.704
Spot urine protein creatinine ratio	3.54 ±1.02	3.94 ±0.99	0.217
Urine pus cell	2.15 ±0.62	2.79± 0.42	0.001
Urine RBC	0.23 ±.42	0.64 ±0.49	0.004
Urine epithelial cell	0.95 ±0.22	1.00 ±0.00	0.403

***t-test**

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Table-V describes the differences of the blood and urine parameters in the patients of idiopathic nephrotic syndrome with and without UTI. There was no significant difference in serum albumin (p=0.899) and serum cholesterol (p=0.704). Spot urine protein creatinine ratio did not have any significant difference (p=0.217). The mean urine pus cell was significantly higher in UTI (2.79±0.42) and non-UTI (2.15±0.62). The mean urine RBC was also higher in UTI (0.64±0.49) than non-UTI (0.23±0.42). No significant difference was found in urine epithelial cells between two groups (p=0.403

Table-VI: Organisms isolated from the patients

Name of the organism	Number	Percentage
E.coli	7	50.0
E.coli and Staphylococcus aureus	1	7.1
E.coli and Pseudomonas	1	7.1
Klebsiella	2	14.3
Proteus	3	21.5
Total	**14**	**100.0**

Out of 54 patients, organism was isolated in 14 patients. Single organism of isolated from 12 patients and multiple organisms were isolated form two patients. The most common organism was E.coli (64.3%), followed by Proteus (21.5%), Klebsiella (14.3%), Staphylococcus (7.1%) and Pseudomonas (7.1%)

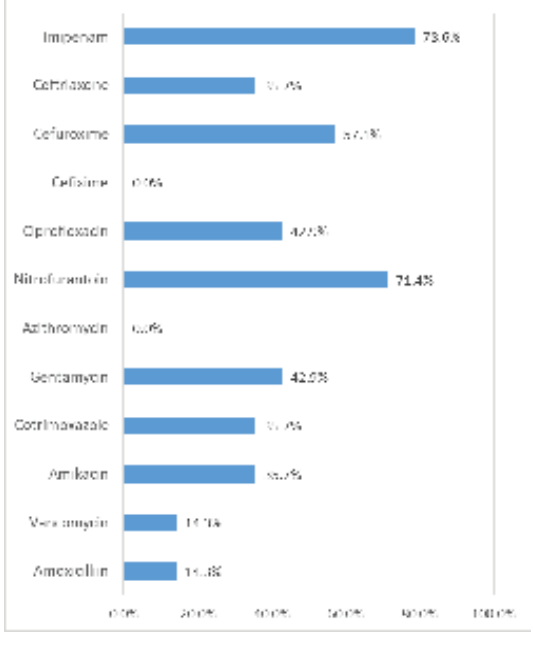

Fig. 4: Antibiotic sensitivity pattern

Antibiogram of the isolated organisms (n=14) is shown in Figure VI. The highest sensitivity was for Imipenem (78.6%), Nitrofurantoin (71.4%), Cefuroxime (57.1%), Ciprofloxacin (42.9%), Gentamicin (42.9%), Amikacin (35.7%), Cotrimoxazole (35.7%) and Ceftriaxone (35.7%). On the other hand, the lowest susceptibility was for Cefixime (0.0%), Azithromycin (0.0%), Amoxicillin (14.3%) and Vancomycin (14.3%) for all the bacteria isolated.

Discussion:

The child with idiopathic nephrotic syndrome represents an immunocompromised host and hence is susceptible to a variety of infections. This could be a result of decreased serum immunoglobulin concentrations, protein deficiency, decreased bactericidal activity of the leukocytes, immunosuppressive therapy, decreased perfusion of the spleen caused by hypovolemia and loss in the urine of a complement factor that opsonizes certain bacteria.[18] The pressure on the collecting system by edematous pyramids causes narrowing and functional obstruction to the flow of urine, further predisposing them to UTI.[19] The present study showed that 25.9% patients with nephrotic syndrome had UTI which is much higher than the prevalence of 1 to 3% reported in the general population.[20] One possible reason of higher prevalence could be this study pertained to hospitalized patients, so that mild infections such as UTI, which are usually managed on an outpatient basis, were not included or reported. The finding of the present study was almost consistent with the study of McVicaret. Al. WHO reported a prevalence of 21.0%[7] and Alwadhi et al. who reported a prevalence of 22.8%[1]. However, Gulati et al. reported a prevalence of UTI of 13.8% in nephrotic syndrome patients.[21] The high prevalence of UTI among nephrotic syndrome patients have been reported by some other studies.[5, 17] Adeleke and Asani reported a prevalence of 66.7%[5] and Ibadin and Aboodun reported a prevalence of 44.8%[17] and these are higher to the present study. Usually the prevalence of UTI is higher in girls than in boys.[4, 6] In this study the prevalence of UTI was slightly higher in female (29.2%) than in male (23.3%) which was not statistically significant. In general population, post-neonatal UTI is relatively rare in males, sex did not influence the development of UTI.[11] The immune compromise associated with nephrotic syndrome is not sex discriminatory, this may be the reason to explain the high prevalence of UTI in males in the present study which is also similar to the studies conducted in Nigeria.[5, 17]

In this study UTI was more common in case of frequent relapse nephrotic syndrome compared to infrequent relapse. There might be an association between relapse

of nephrotic syndrome and UTI. However, Mc Vicaret al. observed that these infections did not precipitate relapse.[7] On the other hand, Sonnenscheinet al. suggested that these episodes had an adverse effect on the response to therapy.[20] Another important fact was that a proportion of UTI cases were asymptomatic and UTI was detected as part of screening investigation. Thus, asymptomatic UTI might be an important and underdiagnosed cause of relapse in a child with nephrotic syndrome. Majority of UTI were asymptomatic; justifying routine urine microscopic examination and urine culture in all children presenting with an episode of nephrotic syndrome regardless of presence or absence of symptoms.Although detailed pathophysiologic investigations were not undertaken in this study, it was observed that no significant relationship of serum albumin concentrations and serum cholesterol concentrations with UTI in the patient of nephrotic syndrome. However, Gulati et al reported that the children with infectious complications had significantly lower serum albumin concentrations and high serum cholesterol concentrations than the group of nephrotic children in relapse who did not have infectious complications.[17]

The most common organism was E.coli (64.3%), followed by Proteus (21.5%), Klebsiella (14.3%), Staphylococcus(7.1%) and Pseudomonas (7.1%) in this study. Our finding of significant prevalence of UTI caused by gram-negative bacilli is consistent with previously reported data.[1,5,17] The sensitivity pattern for Imipenem is (78.6%), Nitrofurantoin (71.4%), Cefuroxime (57.1%), Ciprofloxacin (42.9%), Gentamicin (42.9%), Amikacin (35.7%), Cotrimoxazole (35.7%) Ceftriaxone (35.7%), Amoxicillin (14.3%),Vancomycin (14.3%), Cefixime (0.0%) and Azithromycin (0.0%) for all the bacteria isolated. There is an increasing trend of resistance by common bacteria to routine antibiotics, this had been noted in the region.[8,22] The common practice of self-medication, use of fake and substandard drugs and drug abuse could explain this unfortunate trend.

Conclusion:

There is a high prevalence of UTI in children presenting with idiopathic nephrotic syndrome. UTI is an important but often underdiagnosed infection in children with nephrotic syndrome due to absence of symptoms. It is therefore advocated that routine urine cultures should be carried out on patients with nephrotic syndrome and appropriate antibiotics should also be used.

Limitation of the study:

First, this study was conducted with small sample size and it was conducted in selected tertiary level hospital, hence may not represent the whole population. Secondly Sample was not randomly selected

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