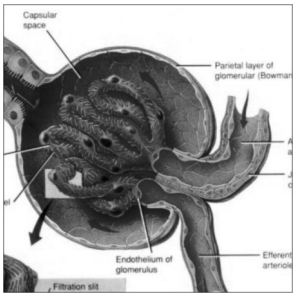
ORIGINAL
(CLINICAL PRACTICE ARTICLE)
PROF-815

NEPHROTIC SYNDROME



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ABSTRACT... drazam9@hotmail.com **Objective:** (1) To find out relapse rate in our nephrotic patients. (2) To assess the frequency of steroid dependent and steroid resistant nephrotic syndrome case. (3) To find out diagnostic value of single sample urine protein and creatinine ratio. (4) To study the complications of therapy **Design:** Prospective, cohort, open clinical study. **Setting:** Pediatrics Medicine Department Nishtar Hospital, Multan through outdoor or emergency. **Period:** From June 1997 to May 1998. **Material and methods:** Complaint of peri-orbital or generalized edema, haematuria, oliguria, azotemia, hypertension and proteinuria on urine examination. **Results:** 4050 patients were admitted during study period, only 50 patients were diagnosed nephrotic syndrome. Incidence was 1 in 8 (0.8%), male to female ratio was nearly 2:1, and generalized edema was major clinical presentation. Most of the patients had normal renal function and had no hypertension. Maximum 39(78%) patients had responded to steroids within 4 weeks of therapy, 47 (94%) patients responded to steroids but only 20(40%) remained in remission, other 21(42%) patients showed relapse, 3(6%) were steroid resistant and 6(12%) were steroid dependent. Out of 4(8%), 3(6%) patients gave response to cyclophosamide. Cushingoid features, elevated blood pressure, abdominal discomfort were common complications to steroids. Single voided urine sample protein to creatinine ratio had equal significance as had 24 hours urinary protein in diagnosis of nephrotic syndrome in children. Prognosis of this disease is good despite the recurrence that takes place and the prolonged duration of treatment. **Conclusion:** We can currently depend on single morning voided urinary protein to creatinine ratio as compared to 24 hours urinary protein, to save the time and money. Along with low dose steroid, liberal intake of fluids before and during cyclophosphamide therapy can reduce the risk of haemorrhagic cystitis.

INTRODUCTION

The nephrotic syndrome is symptom complex, usually involving children between ages of 2-10 years. Males are more commonly affected than females 2.4:1. This disease process, which affects 2 children per 100,000 annually, is characterized by proteinuria sufficiently severe to result in hypoalbuminemia, edema and hyperlipidemia. There may or may not be evidence of haematuria, reduced renal functions or mild hypertension[1].

It is most common chronic renal disease of childhood[2] and the most common type of idiopathic, among whom about 84.5% have minimal change lesion in kidneys[3]. Most children achieve a complete remission when treated with oral prednisolone, however, even most responsive patient are likely to relapse. But some children have complicated patterns of response.

PURPOSE OF STUDY

1. To find out the relapse rate in our nephrotic patients.
2. To assess the frequency of steroid dependent and steroid resistant nephrotic syndrome cases.
3. To find out the diagnostic value of single sample urine protein and creatinine ratio.
4. To study the complications of therapy.

MATERIAL AND METHODS

This was a prospective cohort, open clinical study. The study population was all the children presenting in paediatric medicine department, Nishtar Hospital, Multan through outdoor or emergency during the period of June 1997 to June 1998 with complaint of peri-orbital or generalized swelling, haematuria, oliguria, azotemia, hypertension and proteinuria on urine examination.

The criteria for subject selection was that all the children less than 12 years of age from any sex and from any area included and they could be from any socio-economic class. But should fulfill the nephrotic syndrome, clinical and laboratory criteria.

The exclusion criteria was any patient who did not fulfill the nephrotic syndrome clinical and laboratory landmark.

The sampling for cases was stratified random sampling and then suspected nephrotic patients were confirmed by laboratory test. The research instrument was a specific proforma. According to the international study of kidney disease in children the following definition was used.

A detailed history of the presenting complaints was inquired including age at onset and duration of symptoms, facial or generalized edema, hematuria or oliguria. Sex and social status, area of residence, immunization or viral infection e.g. measles, chickenpox was also asked. History of fever, vomiting, lethargy, diarrhoea was taken. Number of remission and relapses was also inquired. Family history of renal disease and previous medications especially steroids, diuretics and antibiotics was also discussed. General history includes weight and height of the patient, vital signs, edema, pallor and any complication of disease or drugs like peritonitis, renal failure, oliguria, Cushing face and hirsutism etc.

Apart from the routine investigations i.e. Haemoglobin (Hb), Total Leukocyte Count (TLC), Differential Leukocyte Count (DLC), erythrocyte sedimentation rate, Chest X-ray, routine urine examination especially for protein and red blood cells. A 24 hours urinary proteins and single urine sample (once voided) for protein to creatinine ratio was done to exclude other proteinuria causes.

RESULTS

A total of 50 patients of the nephrotic syndrome were admitted to the pediatric medicine Unit-II, Nishtar Hospital, Multan during June 1997 to May 1998. This comprises nearly 1.23% of total admission of pediatric medicine unit-II during this period. Out of these 30 patients, 32(64%) were male and 18(36%) female.

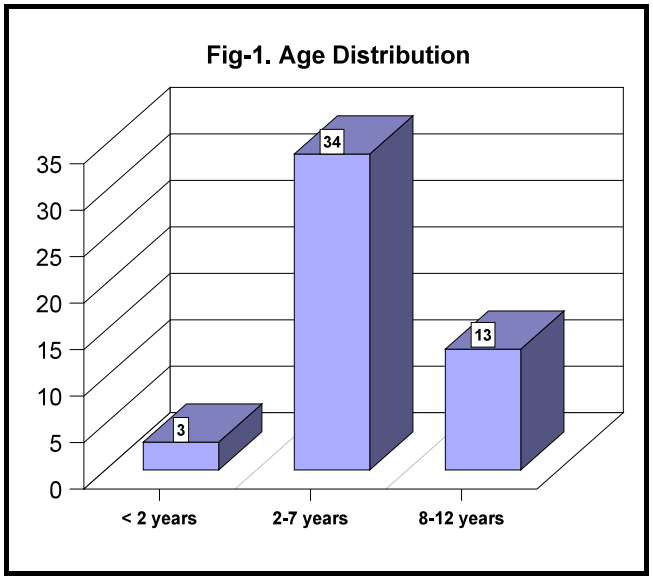
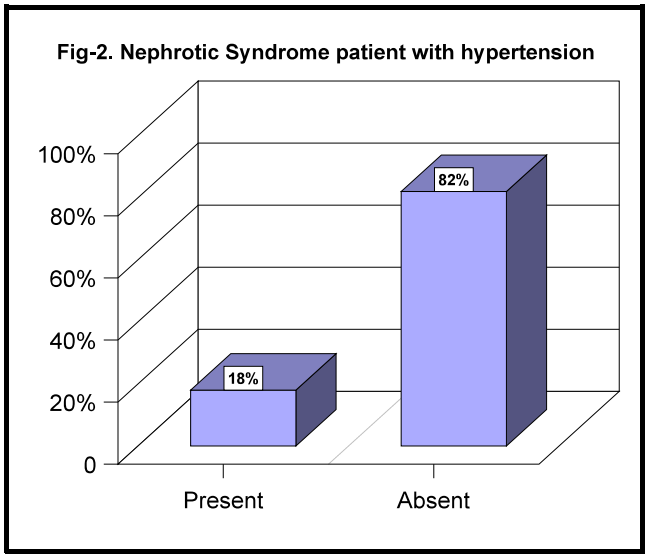


Figure-1 shows that 3(6%) were below two years,

34(68%) patients were between 2-7 years and remaining 13(26%) were between 8-12 years. Mean age was between 2-7 years.

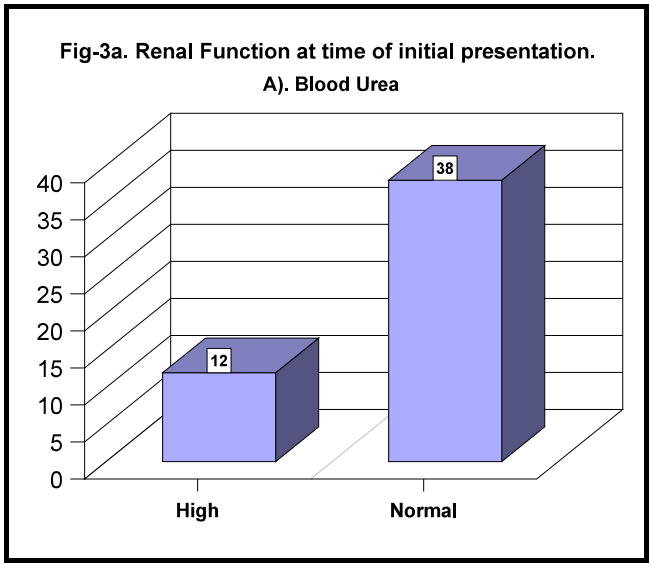
Table-I Clinical Presentation of Nephrotic Syndrome

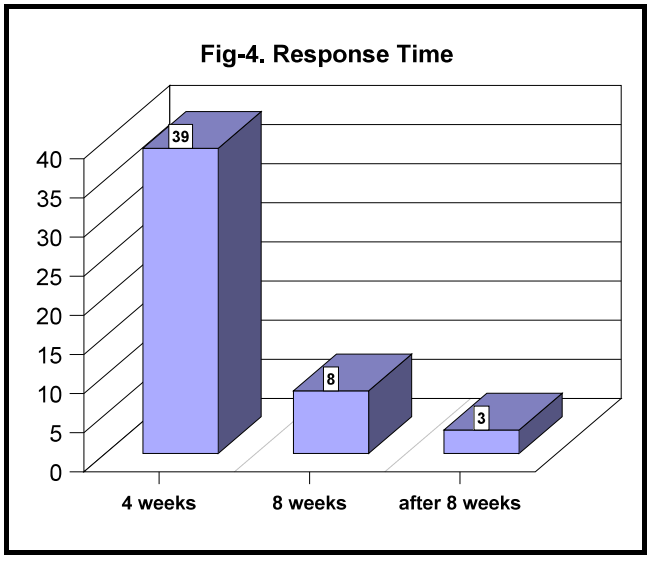
Presentation	No. of cases	%age
Edema		
Peri-orbital	40	80.0
Generalized	48	96.0
Scrotal	06	12.0
Fever	05	10.0
Abdominal tenderness	08	16.0
Oliguria	20	40.0
Hematuria		
Gross	10	02.0
Microscopic	04	08.0
Azotemia	04	08.0
Thrombosis	-	-



All patients of nephrotic syndrome had edema. Out of 50 patients, 48(96%) had generalized edema, 40(80%) had peri-orbital and 6(12%) had scrotal edema. Five patients (10%) had complaint of fever and 8(16%) presented with abdominal tenderness. 20(40%) had oliguria and 5 (10%) showed hematuria. 4(8%) patients had azotemia. None of the patients had thrombosis. It shows that major clinical presentation of nephrotic syndrome was edema especially generalized edema (Table-I).

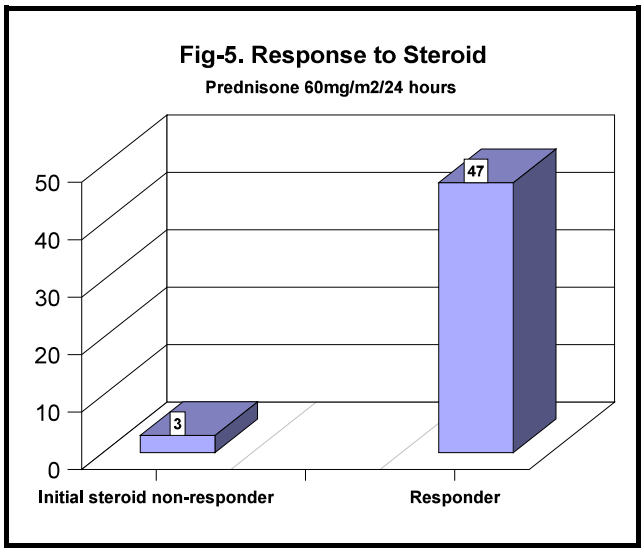
Hypertension was present in 9(18%) patients. It means in childhood nephrotic syndrome, hypertension was not common as shown in Fig-2.

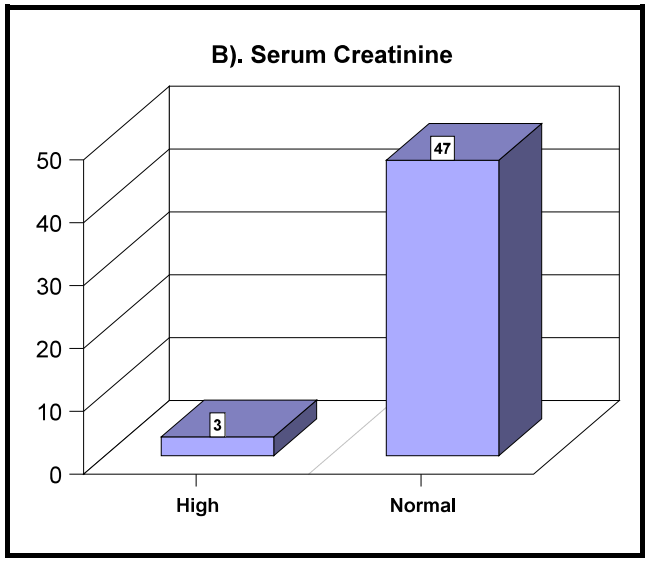




Twelve patients showed high blood urea and 3(6%) showed high serum creatinine. It means most of nephrotic patients had normal renal function at the time

of presentation (Fig-3 & 4).



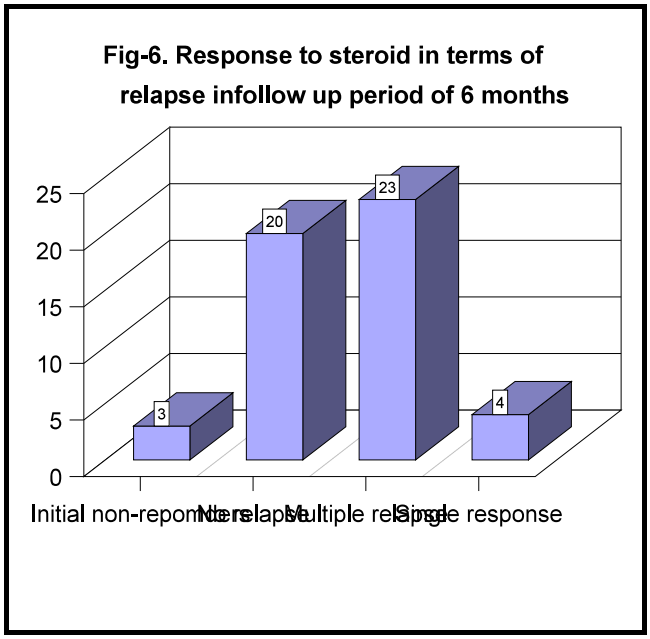


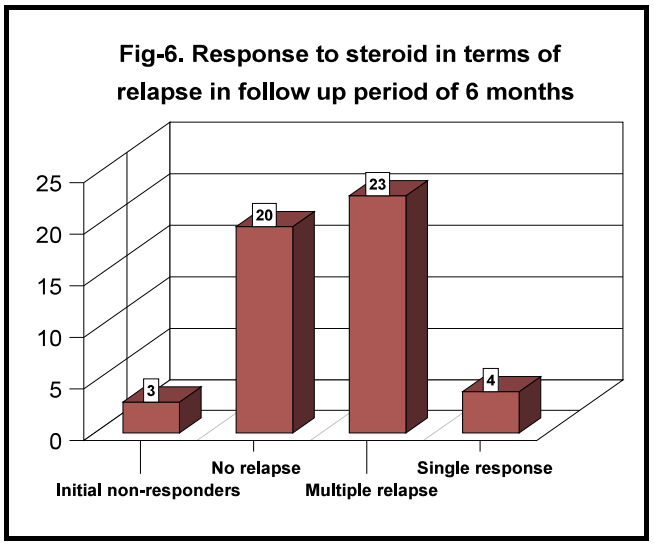
Out of 50 patients, 39(78%) showed response in first 4 weeks, 8(16%) showed response in next 4 weeks. After 8 weeks there was no response. It means maximum patients showed response to steroids in first 4 weeks and not response occurred after total 8 weeks of steroids therapy (Fig-5).

Out of 50 patients, 47(94%) were steroid responder (Fig-6).

Table-II Incidence of Steroid Dependent and Resistence Patient

	No. of cases	%age
Steroid resistance	03	06.0
Steroid responder		
Remission	20	40.0
Relapsing	21	42.0
Dependent	06	12.0
Total	50	100.0





Out of 50 patients 3(6%) were steroid resistant, 6(12%) were steroid dependent and 21(42%) showed relapsing course and only 20(40%) remained in remission as shown in table-II.

Three (6%) patients were initial responders, 20(40%) showed complete remission, 23(46%) had multiple relapses and 4(8%) patients showed single relapse (Table-III).

Table-III Incidence and Types of Steroid Toxicity Observed in Nephrotic Patients in Follow up Period of 6 Months

	No. of cases	%ge
Cushingoid	48	96.0
Elevated blood pressure	24	48.0
Infections	08	16.0
Gastrointestinal discomfort	10	20.0
Total	50	100.0

Table-IV Features of Nephrotic Patients who were put on Cyclophosphamide

Age at onset	%age	Hyper tension	Haematuria	Initial steroid response
1 Yr	4 Yrs	Positive	Negative	Yes
2 Yrs	9 Yrs	Positive	Negative	Yes
3 Yrs	6 Yrs	Positive	Negative	Yes
4 Yrs	6 Yrs	Positive	Negative	Yes
8 Yrs	10 Yrs	Positive	Negative	Yes

Out of total 50 patients, 48(96%) developed cushingoid features, 24(48%) developed elevated blood pressure, 8(16%) patient got infections, 10(20%) developed abdominal discomfort and only 6 (12%) showed growth suppression (Table-IV).

Five patients were out on cyclophosphamide therapy. Results are shown in Table-V.

Cyclophosphamide was given to five patients, one patient who was steroid resistant showed no response, other four patients showed response in terms of remission (Table-VI)

Table-V Response to Cyclophosphamide in Terms of Remission

Status	No. of pts	Response
Steroid resistant	1	Negative
Late steroid resistant	1	Positive
Steroid dependent frequent relapsing	3	Positive

Table-VI Comparison Between 24 Hours Urinary Protein and Single Voided Morning Urinary Protein-creatinine Ratio

	No. of cases	%age
24 Hours Urinary Protein		
< 960 mg/m^2/24 hours	-	-
>960 mg/m^2/24 hours	50	100.0
Total	50	100.0
Single Voided Morning Urinary Protein - Creatinine Ratio		
Ratio less than 3:1	-	-
Ratio more than 3:1	50	100.0
Total	50	100.0

Nephrotic range 24 hours urinary protein was considered more than 960 mg and nephrotic range urinary single voided protein-creatinine ratio was considered more than 3. As table-VI showed that single voided protein to creatinine ratio was equally informative as 24 hours urinary protein.

DISCUSSION

The nephrotic syndrome is still most frequent glomerular disease of childhood. In this study, the incidence in hospital admitted patients was 1 in 81 and the males were affected nearly two times of the females. The male constituted 64% and female 36%. The male to female

ratio was 1.7:1, which is slightly different from male to female ratio reported in literature i.e.2:1[4,5].

About 68% of the patients presented between the ages of 2-7 years. Only 26% presented between the ages of 8-12 years and there were less than 6% presenting below the age of 2 years. In this study maximum age incidence was around the 5th birthday, which is comparable to other studies[1,6,7]. There was no family tendency to develop nephrotic syndrome as found in present study. None of study cases had any other member of family having the disease, which is different from what is reported in the literature[8].

In present study, generalized edema, periorbital and scrotal edema were main clinical features. At time of presentation 96% had generalized edema, 80% presented with periorbital edema which were more marked on morning and less at evening and only 12% had scrotal edema along with generalized anasarca. Not a single case had isolated scrotal edema at the time of presentation. Although it had been reported[9] that nephrotic patient can develop spontaneous scrotal rupture secondary to tense ascites which impose venous as well as lymphatic return but no patient in present study had this complication.

10% of patients in this study presented with fever. Two patients (4%) had pharyngitis and mild tonsillar enlargement and one patient had a chest infection and one patient had primary peritonitis[10]. It is reported in literature that the peritonitis could be presenting complaint. Literature also shows that nephrotic patients are more prone to infection[11,12]. This is particularly true of pneuomococcal infection, before antibiotic era the pneumonococcal peritonitis was lethal complication.

In two patients (4%), it was first attack of nephrotic syndrome and infection had not precipitated the previously occurring nephrotic syndrome. Other three patients (6%) were known nephrotic patients who went into relapse after being in remission. No organism was isolated from these cases, but in literature[10] it is noted that in primary peritonitis, 4% cases had streptococcus pneumonia and 3% had gram-negative organism.

Abdominal tenderness was present in 8(16%) patients. Except one patient who had primary peritonitis, rest of the patients had no proved abdominal infection or other cause except ascites, which may be wrongly interpreted by patient as abdominal tenderness. This is due to hypovolemia and circulatory collapse, since fluid shifts from intravascular to extravascular space[13,14]. Oliguria was found in 20(40%) patients and anuria in 2(4%) patients. These findings were not associated with marked abnormalities of renal functions. Although the blood urea was raised in 24% of patients but the serum creatinine was high only in 4% patients, which in fact is more sensitive indicator of impaired renal status. The reason for oliguria or anuria and very high urea could be pre-renal. It is very unlikely that it resulted from any structural abnormalities because once we rehydrate the patient and give loop diuretic they started passing urine adequately. in this present study no patient presented to us or had any features of thrombotic complication during one year study. The incidence of thromboembolic complications in children with severe nephrotic syndrome is very high[15,16].

Hypertension was noted in 18%. It is consistent with literature[1]. The land mark for diastolic blood pressure was more than 90 mm Hg. Other 82% patients were normotensive. Only small percentage of children with minimal change disease have hematuria or hypertension[17]. These abnormalities when present are invariably transient in children with minimal disease. Hematuria was found in 5(10%) patients in this study. Out of 5 patients, one patient had gross hematuria which later on changed to microscopic hematuria. Rest of the patients had microscopic hematuria (Red cells field). White et al[18] have reported same number of patient as in this study. But in some studies high incidence of hypertension (42%) and microscopic hematuria (60%) is noted[5]. It may be due to different epidemiological and clinico-pathological characteristics of childhood nephrotic syndrome.

The patient who had turned out to be steroid resistant in this study also initially had hematuria and high blood pressure. Thus we can predict the steroid response on the basis of these atypical features of nephrotic

syndrome. The blood urea was high in 24% of patients in this study. it was due to decrease glomerular filtration rate caused by hypovolemia. But this test virtually has no diagnostic significance. 6% patients have high creatinine in this study.

Two types of long term interrupted steroid regimens have been proposed for treatment of children with minimal change nephrotic syndrome. One standard intermittent regimen which involve doses of 60 mg/m^2/24 hours in three or four divided doses for four weeks followed by the prednisone in doses of 40 mg/m^2/24 hours for three out of seven days. This intermittent treatment was reported to be effective and tolerable even in courses lasting a year or more. Many clinicians later adopted it and it was considered as standard therapy by the international study of kidney disease in children. The alternative day regimen was originally used in dermatology and internal medicine for controlling allergic diseases. Soyka and Saxena introduced it for treatment of nephrotic syndrome. It has shown that the alternate day regimen was superior to standard intermittent regimen in terms of relapse.

In present study 94% of patients showed response to steroid, 78% of patients went into remission in four weeks time and 16% of patients showed remission after 8 weeks. 6% of patients did not go into remission after 8 weeks. In literature maximum remission is also in first four weeks[12,19]. All non-responsive patients in this study had microscopic haematuria, hypertension and abnormal renal functions.

The follow period was six months at least. During six months of follow up period, out of 94% who had gone to remission, 40% had no further relapses, 8% had single relapse, 46% had multiple relapse and 6% were non-responder. Drumond[20] has shown about similar changes. Other studies have nearly similar results[17,21]. In this study complete remission was high as compared to literature, which is 16-20%[19].

Amongst the 46% multiple relapses, 12% of patients became steroid dependent. This alone remission responsiveness is comparable with European studies[22,23,24]. During the six months follow up period, 96% of study patients developed cushingoid features, 48% of patients developed elevated blood pressure more than 90 mm Hg diastolic. 16% of patients got infections, 20% of study patients had abdominal discomfort and 12% patients showed growth retardation. Catch up growth occurs when treatment was stopped, but it is not known about final height[25,26]. Saha[27] reported that children of nephrotic syndrome grew normally for their age before the onset of the disease and growth remained normal despite prednisone treatment.

In this study 5(10%) patients were given cyclophosphamide, except for one, all showed response in terms of disappearance of proteinuria. Two patients were completely cured in terms of response i.e. remission. But two patients were still in tapering phase of steroids and one patient who was steroid resistant showed no response. It is premature to say about results of these patients. In this study, one patient developed hematuria and one patient developed hematuria and one patient developed neutropenia. No other major side effect was noted in these children. Gonadal toxicity, the most serious complication could probably present later, the steroid therapy and liberal intake of fluid before and during cyclophsophamide therapy reduced the risk of haemorrhagic cystitis, but in spite of this one patient in this study developed hematuria. We can compare these results with other studies which have consistence results[28,29,30,31].

In present study comparison was doe between 24 hours urinary protein and single early morning voided urinary protein and creatinine ratio. This ratio correlates well with the magnitude of proteinuria in carefully collected 24 hours urinary sample. Same results were also reported in literature[32,33,34]. It shows we can certainly depend on this single morning voided urinary protein creatinine ratio and can save
the time.

CONCLUSIONS

Important features of this study are:
Incidence in the hospital admitted patients of nephrotic syndrome is 1 in 81.

Male to female ratio is 1.7:1.
68% presented between 2-7 years of age.
96% had generalized edema at time of initial presentation.
18% had hypertension. 10% had hematuria.
78% responded in 4 weeks. 94% responded to steroid.
6% were initial non-responders.
40% had no relapses, 42% had relapse and 12% were steroid dependent and 6% were steroid resistant and 46% had multiple relapse and 8% had single relapse during the follow up period or six months.
Cushingnoid features were the most frequently observed complication steroids.
Of the four patient put on cyclophosphamide, 3 showed remission and one patient continued to have proteinuria.
Neutropenia and hematuria were most commonly observed complication of the cyclophosphamide therapy.
100% patients had diagnostic value of single voided morning urinary protein cratinine ratio.

Most of nephrotic patients had normal renal functions.
We can currently depend on single morning voided urinary protein to creatinine ratio as compared to 24 hours urinary protein, to save the time and money. Along with low dose steroid, liberal intake of fluids before and during cyclophosphamide therapy can reduce the risk of haemorrhage cystitis.

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Participation ensures feeling of ownership

Shuja Tahir