

**DRUG USE PATTERN AND ASSESSMENT OF ADVERSE DRUG REACTIONS IN THE
MANAGEMENT OF NEPHROTIC SYNDROME IN PAEDIATRICS**Priya Nair S.*¹, Jayakrishnan S. S.¹ and Susan Uthup²¹Department of Hospital & Clinical Pharmacy, College of Pharmaceutical Sciences, Govt. Medical College, Thiruvananthapuram, Kerala, India.²Department of Paediatric Nephrology, SAT Hospital, Govt. Medical College, Thiruvananthapuram, Kerala, India.***Corresponding Author: Priya Nair S.**

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ABSTRACT

Nephrotic syndrome is a common chronic disorder, characterized by alterations of permselectivity at the glomerular capillary wall, resulting in its inability to restrict the urinary loss of protein. The objective of the study was to find out the drug use pattern and assessment of adverse drug reaction during the management of Nephrotic syndrome in paediatrics. It was a six months prospective observational study conducted in the tertiary care setting, with 81 patients along with their caretakers attending the Paediatric Nephrology Clinic, Department of Paediatrics, SAT hospital, Govt. Medical College, Thiruvananthapuram, Kerala, India. Patients who meet the inclusion criteria are included in the study. The prescription of the patients were collected and data regarding the physician's clinical assessment of patients, laboratory results, drug prescribed, details of patients with adverse effects, treatment taken and recovery status were entered in the prepared proforma. The study data reveals that, majority of the patient population were in the age group between 5 to 10 years and showed male predominance. Mean age of onset of Nephrotic syndrome in the study population was found to be 4.1 ± 3.2 years. In the study group most of the patients were steroid responsive, steroid dependent, followed by steroid resistant. The compliance rate was found to be very high. The non-compliance reported was due to ignorance and adverse effects. The most common ADR with prednisolone was found to be increased appetite followed by behavioural and mood change. Stunting, cushing's syndrome, osteoporosis and cataract were the other adverse effects. The most commonly occurring ADR with levamisole was extreme fatigue, followed by muscle weakness, memory loss and vasculitic rashes. Cyclophosphamide is effective among late responders and frequent relapsers. The study concluded that Childhood Nephrotic syndrome has a relatively favourable long-term prognosis. ADRs contribute significantly to patient's morbidity and mortality and are a significant public health concern.

KEYWORDS: Adherence, Adverse drug reactions, Drug use pattern, Nephrotic syndrome, Paediatrics.**INTRODUCTION**

Nephrotic syndrome is a common chronic disorder, characterized by alterations of permselectivity at the glomerular capillary wall, resulting in its inability to restrict the urinary loss of protein. Nephrotic range proteinuria is defined as proteinuria exceeding 1000 mg/m² per day or spot (random) urinary protein-to creatinine ratio exceeding 2 mg/kg.

Nephrotic syndrome (NS) is defined by massive continued losses of urinary proteins, resulting in hypoalbuminemia and edema. These are associated with complications such as increased susceptibility to infections, thromboembolism, altered lipid and carbohydrate metabolism and losses in binding proteins in the urine.^[2]

Paediatrics is the field of practice where the pharmacist's care is needed. Nephrotic syndrome now being a

common disease among children opens a wide variety of opportunities to pharmacist to display their knowledge and consistency. Nephrotic syndrome needs relative attention from pharmacist regarding its treatment and adverse effects of drug. Hence, pharmacist can play an important role in assessing the safe and economic use of drugs and in parent counseling.

The present study focuses on the management of Nephrotic syndrome in paediatrics, which evaluates the use of medicines, its adverse effects, socio-economic profile and demographic profile of the patients.

METHODOLOGY**Objectives****Primary objective**

- To study the drug use pattern and assessment of adverse drug reaction during the management of Nephrotic syndrome in paediatrics.

Study Setting: Tertiary care setting, Paediatric Nephrology Clinic, Department of Paediatrics, SAT hospital, Medical College, Thiruvananthapuram.

Study Population: Children from 1 to 12 years of age diagnosed with Nephrotic Syndrome attending Paediatric Nephrology clinic.

Sample Size: 81 patients along with their caretakers attending the Paediatric Nephrology clinic.

Study Design: Prospective observational study.

Study Duration: Six months.

Inclusion Criteria

- Patients with definite diagnosis of Nephrotic Syndrome.
- Patients in the age group of 1- 12 years.

Exclusion Criteria

- Patients less than 1 year of age.
- Patients attending the Nephrology clinic with disease other than Nephrotic Syndrome.
- Patients with advanced renal failure.

Study Procedure: Patients attending the Nephrology clinic who meet the inclusion criteria were included in the study. Since the study is on children, parents were given a brief introduction regarding the study and confidentiality of the data. Informed consent was obtained from all parents. The prescription of the patient were collected and data regarding the physician’s clinical assessment of patients, laboratory results and drug prescribed was recorded in the prepared proforma. A list of adverse effects to be reviewed during the study period was made. All patients were evaluated for any adverse drug reaction. Details of patients with adverse effects including date of onset of reaction, treatment taken and recovery status were entered in proforma. The patients with adverse effects were followed up, and were contacted through phone or at their address if they fail to turn up for follow up.

Instruments Used

- Modified Kuppusswamy Scale and prepared valid proforma.

RESULTS

Table: 1 Distribution of patients according to age.

Age	Count	Percent
<=5	29	35.8
5 – 10	33	40.7
>10	19	23.5
Mean ± SD	7.6 ± 3.8	

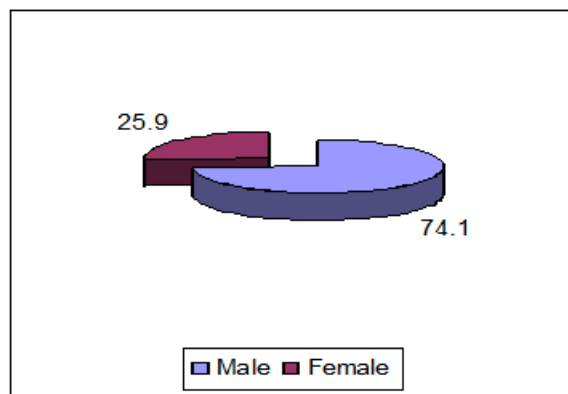


Figure 1: Distribution of the patients according to gender.

Table 2: Distribution of patients according to family history.

Family history	Count	Percent
Diabetes	5	31.3
Hypertension	3	18.8
Asthma	5	31.3
Nephritis	1	6.3
Infectious disease	1	6.3

Table 3: Distribution of patients according to socio-economic status.

Socio economic status	Count	Percent
Class I (upper)	3	3.7
Class II (upper middle)	14	17.3
Class III (lower middle)	31	38.3
Class IV (upper lower)	33	40.7

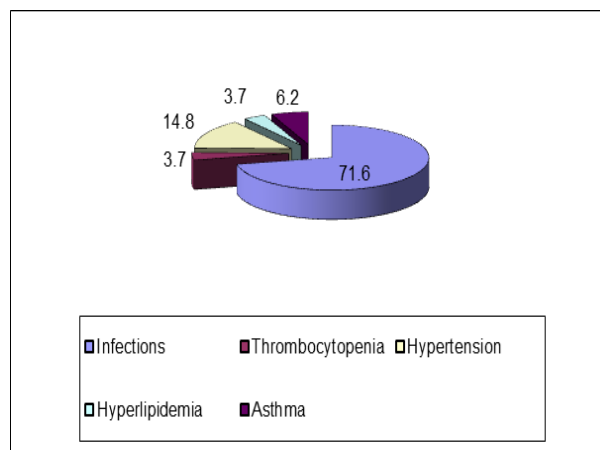


Figure 2: Distribution of patients based on comorbidity.

Table 4: Distribution of patients according to duration of steroid therapy.

Duration in years	Count	Percent
<=1	26	32.1
1 - 5	38	46.9
>5	17	21.0
Mean ± SD	3.3 ± 2.9	

Table 5: Distribution of patients according to the type of response.

Type of response	Count	Percent
Steroid responsive infrequent relapsing	12	14.8
Steroid responsive Nephrotic syndrome	22	27.2
Steroid dependent Nephrotic syndrome	18	22.2
Steroid resistant Nephrotic syndrome	9	11.1
Steroid sensitive Nephrotic syndrome	4	4.9
Steroid responsive frequent relapsing	16	19.8

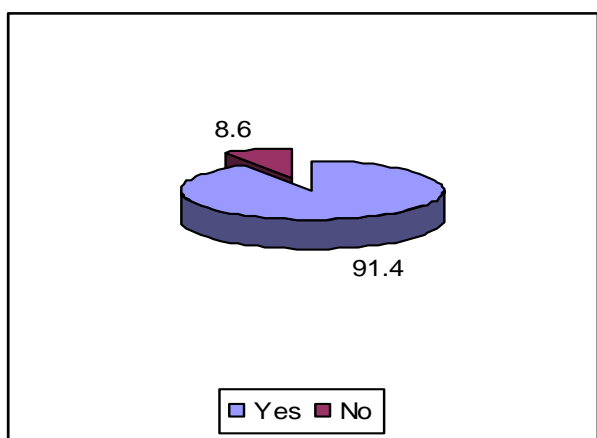


Figure 3: Distribution of patients according to compliance.

Table 6: Distribution of patients based on drug use in specific therapy.

Specific drugs	Count	Percent
Prednisolone	77	95.1
Cyclophosphamide	16	19.8
Tacrolimus	7	8.6
Levamisole	12	14.8
Cyclosporin	8	9.9

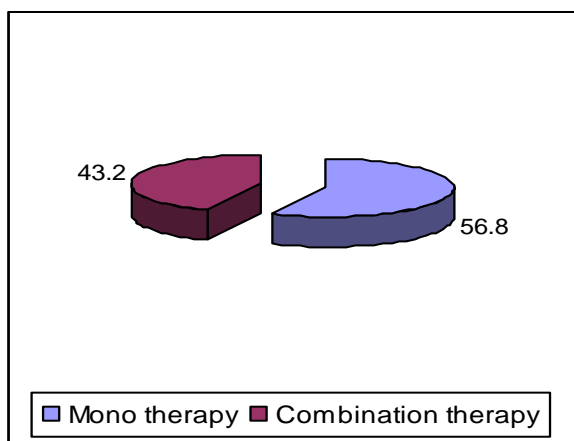


Figure 4: Monotherapy Vs Combination therapy.

Table 7: Pattern of drug used simultaneously with specific therapy.

Simultaneous therapy	Count	Percent
Antiulcer	60	74.1
Antihypertensives	25	30.9
Antibiotics	23	28.4
Diuretics	13	16.0
Lipid lowering	4	4.9

Table 8: Distribution of ADRs caused by Prednisolone.

ADR	Count	Percent
Cushing's syndrome	24	32.4
Behavioural & mood changes	31	41.9
Increased appetite	41	55.4
Stunted growth	30	40.5
Osteoporosis	16	21.6
Cataract	6	8.1

Table 9: Distribution of patients based on the number of ADRs caused by Prednisolone.

No of ADR	Count	Percent
0	3	3.9
1	22	28.6
2	31	40.3
3	20	26.0
4	1	1.3

Table 10: Distribution of ADRs caused by Cyclophosphamide.

ADR	Count	Percent
Bone marrow depression	11	68.8
Increased risk of infection	4	25.0
Poor wound healing	6	37.5
Gastrointestinal disturbances	7	43.8

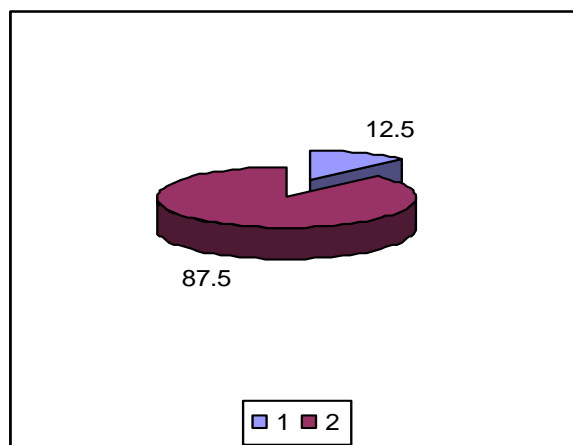


Figure 5: Distribution of patients based on the number of ADRs caused by Cyclophosphamide

Table 11: Distribution of ADRs caused by Levimasole.

ADR	Count	Percent
Abdominal pain	7	58.3
Muscle weakness	3	25.0
Memory loss	3	25.0
Extreme fatigue	6	50.0
Vasculitic rash	2	16.7

Table 12: Distribution of patients based on the number of ADRs caused by Levimasole.

No of ADR	Count	Percent
1	3	25.0
2	9	75.0

Table 13: Distribution of ADRs caused by Cyclosporin.

ADR	Count	Percent
Muscle cramps	1	12.5
Hypertension	3	37.5
Gum hyperplasia	2	25.0
Hirsutism	4	50.0
Constipation	3	37.5

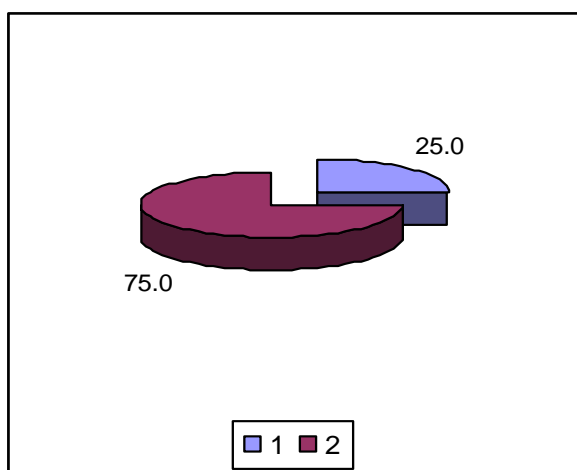


Figure 6: Distribution of patients according to the number of ADRs caused by Cyclosporin.

Table 14: Distribution of ADRs caused by Tacrolimus.

ADR	Count	Percent
Headache	6	85.7
Nausea& diarrhoea	5	71.4
Mood change	2	28.6

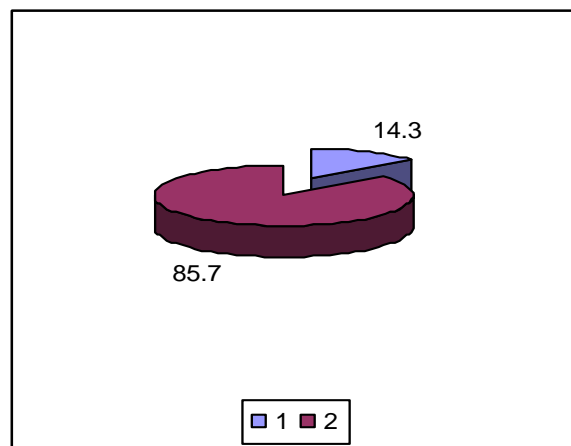


Figure 7: Distribution of patients based on number of ADRs of Tacrolimus.

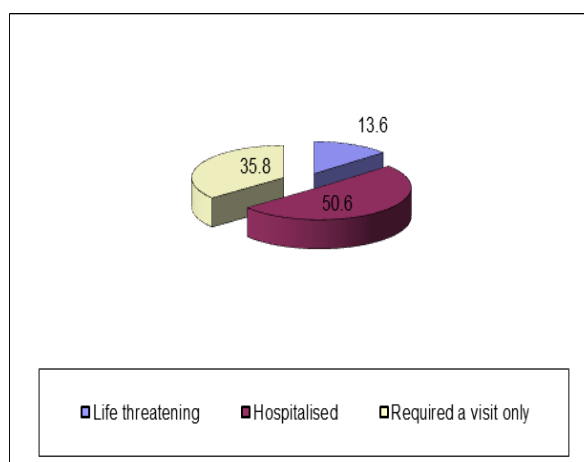


Figure 8: Distribution of patients based on severity of ADRs.

Table 15: Distribution of patients based on outcome of ADR.

Outcome of ADR	Count	Percent
Recovered	39	48.1
Not yet recovered	29	35.8
Unknown	13	16.0

DISCUSSION

Patient Demographic Data

Majority of patients in this study were in the age group between 5 to 10 years. The average age of the patients was 7.6 ± 2.6 years. The demographic data showed that there is a prevalence of Paediatric Nephrotic syndrome higher in male (74.1%) than in female (25.9%). This observation agrees with the fact that NS is common in male. Upon analyzing the age of onset of the disease majority of patients fall under the age group of 1- 5 years (64.2%) followed by 5- 10 years (22.2%). The average age of onset was found to be 4.1 ± 3.2 years. The study correlates with the fact that the age of onset of NS is greater in 2-7 age groups. *Kabuki N et al.*^[46] The present study shows that maximum patients had onset at the age of 1-5 years. According to *Kabuki N et al*, these patients

are prone to develop frequent relapses and take greater time of remission. Out of the 81 patients, 16 patients had relevant family history out of which 5 patients (31.3%) each had family history of diabetes and asthma, 3 patients (18.8%) had family history of hypertension and 1 (6.3%) each had nephritis and infectious disease. On assessing the socioeconomic status it was found that, majority of the patients (40.7%) belong to class IV (upper lower), followed by class III (lower middle) (38.3%). The low socio-economic status of the patient was a major problem in the prognosis of the disease. Most of the patient's parents deny doing renal biopsy due to its high cost and this also affected the compliance rate. Nephrotic syndrome is always accompanied by other disease manifestations. 71.6% patients had complaints of infections followed by 14.8% patients with hypertension, 3.7% each had hyperlipidemia and thrombocytopenia and 6.2% patients had asthma. A study conducted by **Moorani K N^[53]** et al on spectrum of infection in Indian children concluded that acute respiratory tract infection, and skin infections are the most common followed by UTI and peritonitis. Majority of the infections were associated with active disease.^[53] Mean duration of treatment among the study population was 3.3 ± 2.9 years. In the study group most of the patients (27.2%) were steroid responsive, steroid dependent (22.2%), followed by steroid resistant (11.1%). Steroid dependents had attained remission with steroid initially but gradually became dependent. 9 cases of steroid resistant patients were recorded who were treated with second line alkylating agents and immunomodulators. Among the selected patients, 74 (91.4%) reported very good compliance to the treatment. Only 8 patients (8.6%) reported non-compliance. The major cause of non-compliance was the adverse effects of drugs and some parents due to their ignorance to stop the medicine by themselves when the child is in remission.

Pattern of Drug Use

In our study group 95.1% of patients were prescribed steroids. Second line drugs include Cyclophosphamide (19.8%), Levimasole (14.8%), Cyclosporin (9.9%), Tacrolimus (8.6%). Since most of the patients were steroid responsive, Prednisolone was the most prescribed drug. Other drugs such as Levimasole, Cyclophosphamide, cyclosporine and Tacrolimus were prescribed for patients with frequent relapses, steroid dependent and resistant Nephrotic syndrome. In our study population 4 patients were not on specific therapy. Out of which 3 were 'not on drugs' and 1 was on supportive therapy, which included antibiotics for infections.

Depending upon the extent of proteinuria the dose of steroid varies. The relapse dose starts from 2mg/kg once daily depending on the age and clinical profile of the patients. Once daily dose was continued till the patient achieved remission and consequently alternate-day dose ranging from 1.5mg/kg is given for next 4 weeks then tapered and stopped. Frequently relapsing patients were

kept in minimum maintenance dose for 3-6 month after achieving remission.

Frequent relapsers and steroid dependent were more often treated with levimasole along with steroids. Second line drugs are added because once daily dose is necessary for the patient to be in remission in such patients, or the alternate day dose should be maintained to 5-10 mg for longer period since the decrease in dose causes immediate recurrence of the disease.

Dr T J Beattie et al^[58] conducted a study on Levimasole for steroid dependent NS and found out Levimasole is effective in maintaining a steroid free remission in this condition and has few side effects.^[58]

In our study population 16 patients were given Cyclophosphamide, out of which 6 who were dependent patients were administered Cyclophosphamide pulse infusion. Its efficacy is compared to the results obtained with oral Cyclophosphamide based on historical comparisons with previous studies.^[59]

Eight patients were given cyclosporine therapy, out of which 3 were frequent relapsers and others were steroid resistant. Cyclosporine was given at a dose of 5mg/kg/day and continued for 2-3 years.

Phadke K, et al^[60] analysed the use of cyclosporine in Nephrotic syndrome. The study concluded that in steroid dependent or resistant children with normal renal functions, Cs A therapy may be considered as one of the possible therapeutic options. The result suggested that the longer duration of Cs A therapy may possibly be indicated in those cases.

56.8% of the patients were prescribed with Prednisolone only and the remaining 43.2% patients were prescribed with second line drugs along with Prednisolone. The combination therapy includes the use of Levimasole, Cyclophosphamide, Tacrolimus and Cyclosporine for steroid dependent and resistant patients.

Since Nephrotic syndrome is associated with complications, supportive therapy is beneficial as adjuvant therapy. Antiulcers (74.1%) were more frequently prescribed antihypertensives (30.9%), antibiotics (28.4%), diuretics (16%) and lipid lowering agents (4.9%) respectively.

In our study group majority of the patients were prescribed anti ulcers. Ranitidine (85%) at a dose of 75-150 mg/day was the most frequently prescribed anti ulcer followed by Pantoprazole (15%) at a dose of 20-40mg.

Most commonly prescribed antihypertensive was Losartan (14.8%) at a dose of 25mg/day followed by Enalapril (13.6%) at a dose of 5-10mg/day and combination of Amlodipine with Nifedipine (7.4%) at adose of 5-10mg/day.

Cephalosporins were the most commonly used antibiotics (47.8%), mostly third and fourth generation Cephalosporins were used, followed by combination of Amoxicillin with Clavulanic acid (39.1%) at a dose of 375-625 mg/day and Azithromycin (13%) at a dose of 250-500 mg/day.

Diuretics were used in combination with serum albumin or independently. It is typically given as supportive therapy prior to steroid treatment. The combination of Frusemide and Spirinolactone (76.9%) at a dose of 10:50mg/day were frequently prescribed, followed by frusemide (23.1%) at a dose of 20-40mg/day. The use of diuretics along with albumin is still under dispute. Some studies reveal the benefits of the combination while certain studies oppose the use of the combination.

Hyperlipidemia is treated rarely with lipid lowering agents because the symptoms decrease according to remission. Only patients with persistent high cholesterol levels are treated. In the study group Atorvastatin was given to 4 patients at a dose of 10-40mg/day with persistent hypercholesterolemia.

Various drugs were co-prescribed in Nephrotic patients. Some patients had attacks of asthma, and were prescribed Salbutamol (19.8%) and 14.8% patients were prescribed Paracetamol. Vitamin D (6.2%) along with calcium (12.3%) can decrease the predictable side effects of steroids like thinning of skin, bone deformities. Multivitamins (12.3%), cough syrup (3.7%), antiepileptics (12%), warfarin (12%) were the other drugs prescribed.

Adverse Drug Reactions

Out of the 77 patients who used Prednisolone, the commonly reported ADR was increased appetite 55.4%. The next commonly seen ADR was behavioural and mood change 41.9% but none of the patients required psychological intervention. Stunting (40.5%) another side effect of steroid was also noted. The height of the patients was noted at the beginning of the study and also at the end of the study period and the difference was noted. Side effects interfered with the compliance of the therapy with some patients especially moon face and Cushing's syndrome (32.4%). Osteoporosis (21.6%) and Cataract (8.1%) was also seen. The observation from the study suggested that paediatricians should be aware of the potential risk of developing steroid related complications especially in case of ocular complication and bone disease.

Out of the 16 patients who used Cyclophosphamide, the most commonly faced ADR was bone marrow depression (68.8%) which led to anemia in many patients, followed by GI disturbances (43.8%), poor wound healing (37.5%) and increased risk of infections (25%). From the 12 patients who used Levamisole, 58.3% patients experienced abdominal pain, 50% patients had extreme fatigue, 25% patients felt muscle

weakness and memory loss each, and 16.7% patients had vasculitic rash.

Among the 8 patients who used cyclosporine, 50% patients had hirsutism which was a major issue of concern among the parents of female patients, 37.5% each had constipation & hypertension, 25% had gum hyperplasia and 12.5% had muscle cramps. Out of the 7 patients who used Tacrolimus, 85.7% patients had headache, 71.4% had nausea and diarrhoea and 28.6% patients had mood change.

The total ADRs reported in the present study, majority of the cases- 41 patients (50.6%) required hospitalization. Only 11 cases (13.6%) were life threatening adverse effects. 29 cases were minor reactions, which required a hospital visit only. Among the reported ADRs 39 patients (48.1%) recovered. The outcome of 13 cases (16%) was unknown and 29 patients were not yet recovered.

SUMMARY

The study data reveals that majority of the patient population were in the age group between 5 to 10 years and shows male predominance. Mean age of onset of Nephrotic syndrome in the study population was found to be 4.1 ± 3.2 years. Majority of the patients approaching this government set up belong to low economic class, with preliminary education. Infection was the major co-morbidity reported. Hypertension, Hyperlipidemia and Asthma also prevails. Mean duration of treatment among the study population was 3.3 ± 2.9 years.

In the study group most of the patients were steroid responsive, steroid dependent, followed by steroid resistant. The compliance rate was found to be very high. The non-compliance reported was due to ignorance and adverse effects.

Most of the patients were treated with Prednisolone. The most common ADR with prednisolone was found to be increased appetite followed by behavioural and mood change. Stunting, Cushing's syndrome, osteoporosis and cataract were the other adverse effects. Frequent relapsers and steroid dependent were more often treated with levamisole along with steroids. The most commonly occurring ADR with levamisole was extreme fatigue, followed by muscle weakness, memory loss and vasculitic rashes. Cyclophosphamide is effective among late responders and frequent relapsers. Bone marrow depression which led to anemia was found to be the major adverse effect, followed by GI disturbances, poor wound healing and increased risk of infection were among the other adverse effects. Cyclosporine is used in cases of MCNS who have not been benefited significantly from Levamisole or Cyclophosphamide and continue to relapse. Hirsutism was a major issue of concern among the parents of female patients followed by constipation & hypertension, gum hyperplasia and

muscle cramps. Tacrolimus was also used in combination with prednisolone and ADRs reported were only minor events of headache, nausea and diarrhoea. Most of the patients were on monotherapy compared to combination therapy. The drugs used simultaneously with specific therapy were antiulcers, antihypertensives, antibiotics, lipid lowering agents and diuretics. Other drugs used were mainly multivitamins, cough syrups, paracetamol, antiasthmatics, calcium with vitamin D.

CONCLUSION

Childhood Nephrotic syndrome has a relatively favourable long-term prognosis. However, the risks of treatment, potential of disease progression, and frequency of relapse must be considered when selecting a therapy. The search for the optimal agent for treating Nephrotic syndrome and preventing its relapse continues. Further studies are needed to identify the most effective and least toxic therapeutic regimens for inducing and maintaining remission in children with this disorder. ADRs contribute significantly to a patient's morbidity and mortality and are significant public health concern.

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