Original Article

Nephrotic Syndrome

Treatment Outcome in Childhood Steroid Resistant Nephrotic Syndrome with Different Therapeutic Regimens

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ABSTRACT

Objective: To determine the efficacy of different treatment strategies in children with steroid resistant nephrotic syndrome (SRNS) and to find the impact of histopathological lesions on the treatment outcome.

Study Design: Retrospective observational

Place and Duration of Study: This study was conducted at Paediatric Nephrology Department, the Children's Hospital and the Institute of Child Health, Multan from January, 2006 to July, 2014.

Materials and methods: Medical record of 77 patients with SRNS was reviewed. For the purpose of treatment patients were divided into two groups depending upon the initial renal function tests (RFTs). Group 1 included patients with normal RFTs. They received cyclosporine A (CsA), mycophenolate mofetil (MMF), combined CsA and MMF, and intravenous methylprednisolone (MP) pulses as step 1, 2, 3, and 4 respectively. Group 2 included patients with deranged RFTs and they were given either MMF, or MP pulses. Long-term follow up was done ranging from 1-5 years. Treatment outcome with different therapeutic regimens was determined. The role of histopathology in predicting final outcome was also evaluated.

Results: In group 1, 44/61(72%) patients achieved complete remission with successive treatment steps1-4.Two (3.4%) patients were partial responders whilst 15(24.6%) patients failed to respond to all treatment regimens. Out of the 16 patients in group 2, only 02 (12.5%) achieved remission. Patients with focal segmental glomerulosclerosis (FSGS) were least likely to respond to treatment (12/28;42.8%),followed by mesangioproliferative glomerulonephritis (MesPGN)(15/23;65.2%), and minimal change disease (MCD)(14/18;77.8%).

Conclusion: SRNS patients with normal initial RFTs are much more likely to respond to immunosuppressives than those with deranged RFTs at presentation. FSGS is more difficult lesion to treat compared with non-FSGS lesions.

Key Words: Steroid resistant nephrotic syndrome, children, renal function tests, histopathological lesions

INTRODUCTION

The nephrotic syndrome (NS) is a common renal disorder with an incidence of 90-100/million population/year in the Indian sub-continent.[1,2] It is characterized by heavy proteinuria (40mg/m^2/hour), hypoal buminemia (< 2.5G/dl), edema, and hypercholes trolemia (> 250mg/dl).[3] Nephrotic syndrome in children may be primary/idiopathic or it may be secondary to some underlying cause. Idiopathic nephrotic syndrome may be steroid sensitive (SSNS) , or steroid resistant (SRNS). Resistance to steroid therapy accounts for about 10% of idiopathic nephrotic syndrome at first presentation whilst about 1-3% of initially steroid-sensitive patients become steroid resistant subsequently, and are called late non-responders.[3] This response to steroids is the primary determinant of the final outcome of the disease, with >60% of those resistant to steroids going to develop chronic kidney disease (CKD).[4,6,7] Treatment of these SRNS patients continues to pose a therapeutic challenge with considerable variety of strategies.[7] A number of medications such as cyclosporine A (CsA), mycophenolate mofetil (MMF), cyclophosphamide (CPM), methylprednisolone (MP), and others have been used with varying results.[8-11] Recent reports have shown remission rates ranging from 20% to 70% using these drugs in SRNS.[11] The underlying histopathology usually affects the course of disease and the response to treatment.[12] Main histopathological lesions in SRNS include focal segmental glomerulosclerosis (FSGS), mesangiopro-liferative glomerulonephritis (MesPGN), and minimal change disease (MCD) and are treated with a common steroid protocol.[13] Gulati S et al[14,15] showed that following immunosuppressive therapy, patients with MCD had significantly greater remission rates compared to those with non-MCD. They concluded that kidney biopsy is of significant prognostic value in SRNS. A recent meta-analysis, however, failed to show any difference in the efficacy of immunosuppressive agents in inducing remission in SRNS children with MCD versus FSGS.[16] So, there is still controversy over the role of renal biopsy in the management of children with SRNS.[15] Recent guidelines for childhood SRNS by the Kidney Disease: Improving Global Outcome (KDIGO) state that the kidney function measured at the time of diagnosis is a predictor of the long-term risk for kidney failure.[9]

The present study was designed to determine the effectiveness of different therapeutic regimens in

children with SRNS coming to our institute. We, also, evaluated the impact of initial deranged renal function and the underlying histopathologic lesion on the final patient outcome.

MATERIALS AND METHODS

A retrospective analysis was done in 77 children with SRNS, with onset age between 1-15 years, referred to our institute over the last 8.5 years. Renal biopsy was performed in 69 patients whilst it was refused in 8 patients. Inclusion criteria were: (1) steroid resistance, either initial or late, (2) MCD, MesPGN, and FSGS on renal biopsy, and (3) follow up period $\geq$1 year. Exclusion criteria were: (1) Secondary NS, (2) membranous nephropathy (MN), mesangiocapillary glomerolonephritis (MCGN), or immunoglobulin A nephropathy (IgAN) on renal biopsy, (3) Familial SRNS, and (4) infantile or congenital onset NS.[7]

Nephrotic syndrome (NS) was defined as edema, proteinuria > 40mg/m^2/hour or spot urine protein: creatinine > 2 (mg : mg), and hypoalbuminemia < 2.5 G/dl.[1,3] Remission was defined as 3 consecutive days' nil or trace proteinuria on reagent strip (Urocolor^{TM}). Steroid resistance was defined as not achieving remission following 4 weeks' prednisolone (PDN)(60mg/m^2/day in three divided doses) plus 3 alternate day pulses of intravenous methylprednisolone (MP) (30mg/kg/dose) given over 4 hours.[3] Late non-responder were the patients who were initially steroid sensitive but became steroid resistant over the course of the disease. Partial remission was defined as the absence of edema and proteinuria + or ++ by reagent strip. Relapse was defined as 3 consecutive days' ++ proteinuria, or single +++ or ++++ proteinuria on reagent strip, with or without edema.[3] Deranged renal function at presentation was defined as serum creatinine level above the upper limit of the normal for age.[7] The estimated glomerular filtration rate (eGFR) was calculated by Schwartz formula.[5] Chronic kidney disease (CKD) was labeled when serum creatinine was persistently high for a period of 3 months or more. CKD 5 was taken when patient needed chronic regular dialysis for survival.[7]

For the purpose of treatment, SRNS patients were divided into two groups depending upon the initial RFTs in the steady state condition. Group 1 patients had normal RFTs and the Group 2 patients had deranged RFTs. Patients were subjected to sequential treatment steps. Partial responders and non-responders to a treatment regimen were put on to the next step treatment and so on. For all the group 1 patients, cyclosporin A (CsA) was used as the first line agent (step 1; S1), regardless of the biopsy report. It was given according to the recommendation of French Society of Pediatric Nephrology [8], in a dose of 150mg/m^2/day in 2 divided doses along with oral prednisolone (PDN) in a dose of 30mg/m^2/day, also in 2 divided doses. After 1 month of treatment, PDN was switched to alternate day 30mg/m^2/dose as a single morning dose after breakfast for the next 5 months; CsA was continued in the same daily dose for 6 months in the responding patients. Regular monitoring of RFTs with serum electrolytes was advised to avoid nephrotoxicity and hyperkalemia. CsA trough levels could not be done routinely due to high cost. Repeat renal biopsy was done after 1 year of treatment to look for any histopathologic evidence of nephrotoxicity. Patients not responding to this regimen (i.e CsA resistant) were the candidates for step 2 (S2) treatment with mycophenolate mofetil (MMF) in a dose of 1200mg/m^2/day in 2 divided doses along with steroids.[22-24] Patients not responding to either CsA or MMF were given a combination of CsA and MMF as step 3 (S3) treatment, while withdrawing steroids, as practiced by Nikibakhsh AA et al in Iran,[25] and novel multidrug therapy in children with CsA-resistant NS by Aizawa-Yashiro et al.[26] Patients resistant to combined CsA and MMF were, as step 4 (S4), treated with the aggressive Mendoza protocol[28] in a final attempt to achieve remission. The SRNS patients in the group 2 (with deranged RFTs) were given either MMF plus steroids or methylprednisolone (MP) intravenous pulses plus oral PDN $\pm$ CPM as proposed by Mendoza et al (Table I).

Table No.I:Mendoza Protocol for Treatment of SRNS

Weeks	Intravenous Methylprednisolone Pulse (30mg/kg)	Oral Prednisolone
1-2	3 times/week	None
3-10	Once every week	2mg/kg qod
11-18	Once every other week	With/without taper
19-50	Once every 4 weeks	Slow taper
51-82	Once every 8 weeks	Slow taper

Note: Oral cyclophosphamide (2.5mg/kg/ day)was added to the treatment regimen when there was no remission despite IV methylprednisolone and oral prednisolone, and was continued for 3 months.

All the patients were regularly followed up for a period ranging from 1-5 years, regarding clinical response, complications of the disease and the drugs, and were properly counseled at the start of treatment and during each follow up visit to maintain good compliance with treatment and follow up. Fast track hospitalization was available in case of any complications.

Data were statistically analyzed using SPSS-19. Descriptive statistics were applied to analyze the data. The quantitative variables were calculated by mean and standard deviation and qualitative variables by percentages and frequencies. Effectiveness of different treatment regimens in terms of remission, partial remission, no remission and progression to CKD, and the impact of initial status of renal function and that of

different histopathologic lesions on these outcome variables were analyzed.

RESULTS

The study group comprised of 77 patients with SRNS; 72 (93.5%) were initial steroid resistant and 5 (6.5%) were late non-responders. Gender distribution showed 49 (63.6%) males and 28 (36.4%)females with a ratio of 1.75. Age range of patients was 1-15 years with a mean of 8.11 ±3.58 years. Sixty nine (89.6%) patients underwent renal biopsy (Table 2).

Table No.2: Demography of 77 SRNS patients

Category	Number (%age)
Biopsied	69(89.6%)
Unbiopsied	08(10.4%)
Initial SR	72(93.5%)
Late SR	05(6.5%)
Males	49(63.6%)
Females	28(36.4%)
Age(Years)	
<4	22(28.6%)
4-10	31(40.2%)
>10	24(31.2%)

SR=Steroid resistant

The histopathologic subtypes revealed FSGS (n=31; 40.3%), MesPGN (n=25; 32.5%), MCD (n=21; 27.3%) in decreasing order of frequency. Eight patients (10.4%) could not be biopsied as their parents refused consent. Group 1 comprised of 61 (79.2%) patients with normal RFTs. Group 2 included 16 (20.8%) patients with deranged initial RFTs. The patients in group 1 received CsA plus PDN, MMF plus PDN, combined CsA and MMF plus PDN, and intravenous MP pulses ± oral PDN and CPM as S1,S2, S3, and S4 treatment respectively. Following S1, 31/61 patients (50.8%) achieved complete remission, 5/61 (8.2%) were partial responders, and 25/61 (41%) were non-responders. Three patients (4.9%), who were resistant to both steroids and CsA, went into remission with MMF plus steroids (S2). Six patients (9.8%) got remission with S3. After three steps of treatment, 40/61 (65.6%) children went into remission. Mendoza protocol[28] (Table 2) (S4) was effective in inducing remission in further 4/61 (06.6%) patients who did not respond to S1- S3. In group1, 02/61 (3.3%) patients were partial responders and 15/61 (24.6%) were non-responders to any immunosuppressive treatment (Table 3). These 17 (27.9%) patients in group1 went on to develop CKD.

Table.No.3: Group 1: Step wise treatment of 61 SRNS patients with normal RFTs.

Sequential Treatment Step	Drugs	Number of Patients	Complete Remission	Partial Remission	No Remission
Step 1	CsA + PDN	61 (79.2%)	31 (50.8%)	05 (8.2%)	25 (41%)
Step 2	MMF + PDN	30 (49.2%)	03 (4.9%)	07 (11.5%)	20 (32.8%)
Step 3	CsA + MMF +PDN	27 (44.3%)	06 (9.8%)	09 (14.8%)	12 (19.7%)
Step 4	IVMP + PDN ± CPM	21 (34.4%)	04 (6.6%)	02 (3.3%)	15 (24.6%)
Total: Steps 1-4		61 (100%)	44 (72%)	02 (3.3%)	15 (24.6%)

RFTs= Renal function tests, CsA= Cyclosporin A, PDN= Prednisolone, MMF= Mycophenolate mofetil, IVMPP= Intravenous methylprednisolone, CPM= Cyclophosphamide

Table No.4: Group 2: Treatment of 16 SRNS patients with impaired RFTs

Treatment Option	Drugs	Number of Patients	Complete Remission	Partial Remission	No Remission
Option 1	IVMP+PDN ±CPM	12 (75%)	02 (16.7%)	02 (16.7%)	08 (66.7%)
Option 2	MMF + PDN	04 (25%)	None	None	04 (100%)
Total		16 (100%)	02 (12.5%)	02 (12.5%)	12 (75%)

RFTs= Renal function tests, IVMPP= Intravenous methylprednisolone, PDN= Prednisolone, CPM= Cyclophosphamide, MMF= Mycophenolate mofetil

Table No.5: Impact of Histopathology on treatment outcome in SRNS patients (n=77)

Histopathological Lesion	Number of Patients	Complete Remission	Partial Remission	No Remission
FSGS	28(36.4%)	12(15.6%)	02(2.6%)	12(15.6%)
MesPGN	23(29.9%)	15(19.5%)	01(1.3%)	08(10.4%)
MCD	18(23.4%)	14(18.2%)	01(1.3%)	04(5.2%)
No biopsy done	08(10.4%)	05(6.5%)	00	03(3.9%)
Total	77(100%)	46(59.7%)	04(5.2%)	27(35.1%)

FSGS= Focal segmental glomerulosclerosis, MesPGN= Mesangioproliferative glomerulonephritis, MCD= Minimal change disease

Out of the 16 patients in group 2, 12 (75%) were given treatment trial according to the Mendoza protocol. Only 2/16 (12.5%) got complete remission; 02 (12.5%) were partial responders and 08 (66.7%) were non-responders. Four patients (25%) in this group were treated with MMF plus steroids but none achieved complete remission. Thus, 14 (83.3%) patients in this group were non-responders or partial responders (Table 4) and they ultimately developed CKD. Overall, 31/77 (40.3%) patients, in our study, progressed to different CKD stages.

To find the impact of histopathological lesions on the treatment outcome, our analysis revealed that out of the 28 children with FSGS 12 (42.9%) achieved complete remission, 02 (7.1%) were partial responders and 12 (42.9%) were resistant to all immunosuppressives. Amongst the MesPGN group 15/23 (65.2%) patients went into complete remission, 01 (4.3%) was partial responder, and 08 (34.8%) were non-responders. Out of the 18 children with MCD 14 (77.8%) got complete remission, 01 (5.5%) was partial responder, and 04 (22.2%) were non responders. Out of the eight unbiopsied patients, 04 achieved remission with CsA and PDN, 01 responded to MMF plus PDN, and 03 were unresponsive to all immunosuppressives (Table 5). Overall, 46/77 (59.7%) achieved complete remission, 04/77 (5.2%) were partial responders, and 27/77 (35.1%) patients with SRNS were resistant to all treatment trials.

DISCUSSION

Treatment of SRNS in children continues to pose a therapeutic challenge to the pediatric nephrologists. The lack of large-scale randomized controlled trials leads to a paucity of strong evidence to inform treatment decisions.[9] The treatment strategies are heterogeneous with variable efficacy and side effects' profile. Optimal strategies with least toxicity remain to be determined.[7] Without effective treatment, progression to the end-stage kidney disease is very likely. We have been treating our SRNS children employing a sequential stepwise approach using different immunosuppressive therapies. Failure to respond to any step of treatment or intolerance/toxicity to any drug was the criterion to use the next treatment step. Patients were broadly divided into 2 groups depending upon the initial RFTs because: 1) the SRNS patients who present with deranged renal function are less likely to respond to treatment, 2) calcineurin inhibitors should be avoided in these patients because of their inherent nephrotoxicity, and 3) because they are more likely to progress to kidney failure.[6,9] Group 1 SRNS patients, in our study, had normal RFTs at the time of starting treatment. CsA was used as first line (S1) treatment for these patients regardless of the histopathology. In the literature, many studies reported that CsA is beneficial to the SRNS patients. However, the risk of relapse is high after therapy withdrawal, with the risk of nephrotoxicity.[7-10] Regular monitoring of trough levels is not essential, unless there is non-response, sudden elevation of serum creatinine, or likelihood of non compliance.[1] Long-term use of low dose CsA has been reported beneficial in reducing proteinuria, with a low risk of nephrotoxicity.[20,21] Plank et al[18] reported on a randomized, controlled, multicenter trial involving initial non-responders that CsA had a significantly higher rate of response than CPM pulse therapy. We used CsA along with low dose of PDN as practiced by the French Society of Pediatric Nephrology [8] and achieved complete remission in about 51% patients. Long-term low dose (2-3mg/kg/d) of CsA was continued to maintain remission in most of these responders for 1-2 years if there was no evidence of nephrotoxicity on renal function monitoring and on repeat renal biopsy after one year of treatment. Only three patients developed deranged RFTs during CsA therapy; but on stopping CsA, further RFTs monitoring showed reversal to the normal. MMF was substituted in the patients showing any evidence of nephrotoxicity or in those who relapsed on withdrawing or tapering CsA. It was also used as S2 treatment in those patients resistant to both steroids and CsA and in combination with CsA as S3 treatment. Our three (4.9%) patients responded to S2 treatment and another six (9.8%) patients achieved complete remission with S3. The combination of CsA and MMF has a synergistic immunosuppressive effect and, as a result , may induce remission in patients with steroid- and CsA- resistant FSGS.[25] Combined CsA and MMF therapy and other multidrug therapy is being increasingly employed both in children and adults with SRNS at many centers with promising results.[25,26] MMF seems to be safe for children with SRNS in terms of side effects as well as disease control, at least in the short term. However, it is less effective in SRNS than CsA and has not been recommended as first-line agent in such patients.[9] CPM was not used alone with steroids in our patients with SRNS. Bajpai et al[19], in a prospective study, administered intravenous CPM pulses. They concluded that the efficacy of this treatment was limited in inducing sustained remission in initial non-responders. The International Study of Kidney disease in Children (ISKDC) reported no benefit of orally administered CPM and prednisone compared with prednisone alone.[27] Reported toxicity of CPM also limits its role in SRNS.[10] However, in our study, CPM was added to those SRNS patients who were given intravenous MP pulses and oral PDN according to the Mendoza protocol[28] and still did not achieve complete remissionA few studies showed efficacy of CPM in SRNS, but the frequency of side effects was high.[11]

Group 2 patients, in our study, had initial deranged RFTs. The SRNS patients who have already progressed to any stage of CKD are very less likely to achieve

remission with any treatment modality.[9] Abeyagunawardena et al[6] reported that renal impairment at presentation and extensive FSGS were independent predictors for poor outcome in children with SRNS. Paik et al[29] have also reported that initial impaired renal function and resistance to treatment were independent risk factors for poor renal outcome. Mekhali D et al[7], however, demonstrated that initial renal impairment was not a predictor of poor renal outcome. According to them, only age >10 years at onset of SRNS was an independent factor of end stage renal disease. In our study , only two patients (12.5%), out of 16 SRNS patients with deranged RFTs, responded to intravenous MP pulse therapy; rest 14 (87.5%) went on to progress to higher CKD stages. These SRNS patients also failed to respond to MMF. CsA was not employed in these already renal compromised patients due to its further risk of nephrotoxicity. Comparing group 1 and 2, about 28% patients in group 1 and 83% patients in group 2 developed progressive CKD. Overall, 59.7% patients achieved remission in our study, and 40.3% patients developed progressive CKD and were further treated by supportive CKD treatment, or dialysis as required.

Our study lacks employment of other therapeutics like chlorambucil, vincristine, and tacrolimus. Latest effective drug reported in the literature, rituximab, is not still available in our country. We hope to have prospective trials with these drugs in future.

Taking into consideration the impact of histopathology, in 69 biopsied patients, on the treatment outcome, patients with FSGS were less likely to attain remission (42.8%) compared with MCD (77.8%) and MesPGN (65.2%). FSGS with chronic sclerosing glomerulonephritis was the lesion with no response to any treatment modality, and was also associated with either initial deranged RFTs or subsequent development of progressive CKD. Literature review shows similar results in patients with collapsing FSGS.[4,6,7,29,30] MCD proved to be the most benign lesion in our SRNS patients with about 78% achieving complete remission with S1 or S2 treatment. Gulati S et al[14] also showed that prognosis in children with SRNS with MCD is much better than non-MCD. They concluded that it is difficult to differentiate clinically MCD from non-MCD and that renal biopsy is of prognostic value in these children.

CONCLUSION

We conclude that SRNS in children is a difficult disease with significant morbidity. However, remission is achievable in majority of patients with cyclosporine and other immunosuppressive agents. Combination therapy with cyclosporine and mycophenolate mofetil has encouraging results in patients unresponsive to either drug alone. However further prospective trials are needed in this regard. Deranged renal function at the outset and FSGS with chronic sclerosing glomerulonephritis carry poor prognosis.

REFERENCES

1. Bagga A, Gulati A, Gulati S, Mehta KP, Vijayakumar M. Management of steroid resistant nephrotic syndrome. Ind Pediatr 2009;46(1):35-47.
2. Meckinney PA, Feltbower RG, Brocklebank JT, Fitzpatrick MM. Time trends and ethnic patterns of childhood nephrotic syndrome in Yorkshire, UK. Pediatr Nephrol 2001;16:1040-1044.
3. Niaudet P. Lipoid nephrosis in children. Rev Prat 2003;53:2027-2032.
4. Gipson DS, Chin H, Presler TP, Jennette C, Ferris ME, Massengill S, Gibson K, Thomas DB. Differential risk of remission and ESRD in childhood FSGS. Pediatr Nephrol 2006;21:344-34926.
5. Schwartz GJ, Haycock GB, Edelmann CM Jr, Spitzer A. A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. Pediatrics 1976;58:259-263.
6. Abeyagunawardena AS, Sebire NJ, Risdon RA, et al. Predictors of long-term outcome of children with idiopathic FSGS. Pediatr Nephrol 2007; 22(2):215-221
7. Mekahli D, Liutkus A, Ranchin B et al. Long-term outcome of idiopathic steroid resistant nephrotic syndrome: a multicenter study. Pediatr Nephrol 2009;24:1525-15327.
8. Nauidet P. Treatment of childhood nephrotic syndrome with a combination of cyclosporine and prednisone. French Society of Pediatric Nephrology. Kidney Int 1997;125:981-86.
9. Lombel RM, Hodson E, Gipson D. Treatment of steroid -resistant nephrotic syndrome in children-new guidelines from KDIGO. Pediatr Nephrol 2012; DOI 10.1007/s00467-012-2304-8.
10. 10.Hafeez F, Ahmad TM, Anwar S. Efficacy of steroids, cyclosporin, and cyclophosphamide in steroid resistant idiopathic nephrotic syndrome. JCPSP 2005;15(6):329-332.
11. Hodson EM, Habashy D, Craig JC. Intervention for idiopathic steroid resistant nephrotic syndrome in children. Cochrane Database Syst Rev 2006;(2): CD003594.
12. Kari JA, Halawani M, Mokhtar G, Jalalah SM, Anshasi W. Pattern of steroid resistant nephrotic syndrome in children living in the kingdom of Saudi Arabia. Saudi J Kidney Dis Transpl 2009;20(5):854-857.
13. Gulati S, Kher V, Sharma RK, Gupta A. Steroid response pattern in Indian children with nephrotic syndrome. Acta Pediatr Scand 1994;83:530-533.
14. Gulati S, Sengupta D, Sharma RK, Sharma A, Gupta RK, Singh U, et al. Steroid resistant

nephrotic syndrome: Role of histopathology. Ind Pediatr 2006;43(10):55-60.
15. Gulati S, Sharma AP, Sharma RK, Gupta RK. Do current recommendations of kidney biopsy in nephrotic syndrome need modifications? Pediatr Nephrol 2002;7:404-408.
16. Habashy D, Hodson EM, Craig JC. Interventions for steroid-resistant nephrotic syndrome: A systematic review. Pediatr Nephrol 2003;18: 906-912.
17. Del Rio M, Kaskel F. Evaluation and management of steroid-unresponsive nephrotic syndrome. Pediatrics 2008;20:151-156.
18. Plank C, Kalb V, Hinkes B, Hildebrandt F, Gefeller O, Rascher W. Cyclosporine A is superior to cyclophosphamide in patients with steroid resistant nephrotic syndrome- a randomized controlled multicenter trial by the Arbeitsgemeinschaft fur Padiatrische Nephrologie. Pediatr Nephrol 2008;23:1483-149317.
19. Bajpai A, Bagga A, Hari P, Dinda A, Srivastava RN. Intravenous cyclophosphamide in steroid-resistant nephrotic syndrome, Peditr Nephrol 2003;18:351-356.
20. Hamasaki Y, Yoshikawa N, Hattori S, et al. Cyclosporine and steroid therapy in children with steroid-resistant nephrotic syndrome: Japanese Group of Renal disease. Pediatr Nephrol 2009;24(11):2177-2185.
21. El-Hussieni A, El-Basuony F, Mehmoud I, Sheashaa H, et al. Long-term side effects of cyclosporine in children with idiopathic nephrotic syndrome. Nephrol Dial Transplant 2005;20:2433-2438.
22. Barletta GM, Smoyer WE, Bunchman TE, Flynn JT, Kershaw DB. Use of mycophenolate mofetil in steroid -dependant and-resistant nephrotic syndrome. Pediatr Nephrol 2003;18:833-83726.
23. Bayazit AK, Noyan A, Cengiz N, Anarat A. Mycophenolate mofetil in children with multidrug-resistant nephrotic syndrome. Clin Nephrol 2004;61:25-29.
24. Li Z, Duan C, He J, Wu T, Xun M, Zhang Y, Yin Y. Mycophenolate mofetil therapy for children with steroid-resistant nephrotic syndrome. Pediatr Nephrol 2010;25:883-88819.
25. Nikibakhsh AA, Mehmoodzadeh H, Karamyyar M,et al. Treatment of steroid and cyclosporine-resistant idiopathic nephrotic syndrome in children. Int J Nephrol 2011; 2011:930965
26. Aizawa-Yashiro T, Tsuruga K, Wantanabe S, Oki E, Tanaka H. Novel multidrug therapy for children with cyclosporine-resistant or-intolerant nephrotic syndrome. Pediatr Nephrol 2011;26(8):1255-1261.
27. Tarshish P, Tobin JN, Bernstein J, Edlemann CM. Cyclophosphamide does not benefit patients with focal segmental glomerulosclerosis. A report from the International Study of Kidney Disease in Children. Pediatr Nephrol 1996;8:1-3.
28. Mendoza SA, Reznik VM, Griswold WR, Krensky AM, Yorgin PD, Tune BM. Treatment of steroid-resistant focal segmental glomerulosclerosis with pulse methylprednisoslone and alkylating agents. pediatr Nephrol 1990;4(4):303-307.
29. Paik KH, Lee BH, Cho HY, Kang HG, Ha IS, Cheong HI, et al. Primary focal segmental glomerular sclerosis in children: clinical course and prognosis. Pediatr Nephrol 2007;22:389-395.
30. Gipson DS, Gibson K, Gipson PE, Watkins S, Moxey-Mims M. Therapeutic approach to FSGS in children. Pediatr Nephrol 2007;22(1):28-36.

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