

An Update Review of Therapeutic Regimens for Steroid Resistant Idiopathic Nephrotic Syndrome

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Introduction

Idiopathic nephrotic syndrome is commonly seen in childhood between three months and 16 years of age, and constitutes 90% of all causes of nephrotic syndrome in childhood. It is defined as the association of nephrotic syndrome with minimal glomerular changes or nonspecific lesions, such as segmental and focal glomerular sclerosis or diffuse mesangial proliferation without any immune complex deposition.

Steroid therapy is the first line of treatment in idiopathic nephrotic syndrome. The protocol from the International Study of Kidney Disease in Children (ISKDC) is widely adopted. The initial treatment for first onset idiopathic nephrotic syndrome with prednisone at a dose of 60 mg/m²/day in three divided doses or a maximum dose of 80 mg/day for four weeks, followed by 40 mg/m² given in three consecutive days out of seven during the following four weeks.¹ Therefore a total eight weeks of steroid therapy is most commonly used. About 90% of the children with idiopathic nephrotic syndrome respond to the steroid therapy. The remaining 10% who do not respond are labeled steroid resistant.

Prognosis

Steroid resistant nephrotic syndrome (SRNS) carries a

much poorer prognosis than the steroid sensitive variety. About 50% of SRNS patients have ended up in end stage renal failure in long term studies.²⁻⁴ Whereas 90% minimal change disease (MCD) responds to the ISKDC oral steroid regimen, only 50% of mesangial proliferative glomerulonephritis (DMP) and about 18% of focal segmental glomerulosclerosis (FSGS) will respond. FSGS is the second commonest cause of progressive glomerular disease in children that cause end-stage renal failure after congenital anomalies. Cattran et al studied 93 patients (55 adults and 38 children) with FSGS and followed for average 11 years. Those respond to the steroid therapy showed a 100% renal survival through the years. However, the renal survival in those non-responder deteriorated over years, with 73% in 5 years, 58% in 10 years, and 51% in 15 years.²

Renal biopsy is useful in children with SRNS. FSGS and DMP give a poorer renal outcome than those do with MCD. The percentage of sclerotic glomeruli may also be predictive. Those with diffuse mesangial proliferation are prone to develop end stage renal failure.⁵ The likelihood of steroid unresponsiveness is higher when the biopsy shows interstitial fibrosis.⁴ The different pathology also predicts the response to different therapeutic regimen, as MCD with steroid resistance is more likely to respond to the combination therapy of oral cyclophosphamide and steroid than the other pathologies.³ Furthermore renal histology may change with time, after the first renal biopsy which shows finding of minimal change, but repeated biopsy later will show FSGS changes.⁵ It is possible that SRNS represent a spectrum of renal disease in that MCD may progress to FSGS. Alternatively, single focal lesion in FSGS may be missed in initial biopsies which are not deep enough to include the juxtamedullary region where the FSGS lesion are usually located.

Therapeutic Regimens

Recently, different combination of drug regimen,

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including intravenous methylprednisolone, alkylating agent, and cyclosporine, have been used with varying degrees of success. Other medications like angiotensin converting enzyme inhibitors, tarcolimus, mycophenolate mofetil, non-steroidal anti-inflammatory drugs, or even plasmapheresis have also been tried, but mostly in small number of patients, so that results are difficult to assess. Most of the studies have focused on patients with FSGS. There is little data concerning effectiveness of these regimens in patients with MCD or mesangial proliferative lesions.

Alkylating Agent

Ponticelli et al⁶ studied the use of cyclophosphamide of 2.5 mg/kg/day for six months in patients with steroid resistance or frequent relapsing nephrotic syndrome, comparing the use of cyclosporine of 2.5 mg/kg/day. It showed that 66% of patients had reduction of proteinuria in the cyclophosphamide group, which is comparative to cyclosporine. Moreover the renal function is more stable in those treated with cyclophosphamide. However in this study, the criteria for effectiveness is reduction of proteinuria rather than complete remission.

Tufro-McReddie studied twenty-one patients with focal glomerulosclerosis, 19 had SRNS who were treated with 20 weeks of cyclophosphamide of 2 mg/kg/day.⁵ Eight of them (42%) achieved complete remission within the first 10 weeks, three with partial remission. After average 73 months of follow-up, 62% of them still remained in complete remission and 24% of them had end stage renal failure. It shows some encouraging result in using longer duration of cyclophosphamide in treating these steroid resistant FSGS. There is no specific side effect like hemorrhagic cystitis, bone marrow suppression during this treatment. However the probability of malignancies or gonadal toxicity have not been encountered.

A larger scale of study by Besbas et al³ was carried, in which 164 patients with SRNS was treated with cyclophosphamide of 2 mg/kg/day to 2.5 mg/kg/day in combination with prednisone 10 mg/day for 12 weeks. Thirty-four patients (20.7%) achieved complete remission, 40 (24.4%) showed partial remission. Thirty-two remained in complete remission and 21 with partial remission for at least six months. Fifteen of them had relapse during the follow-up, but seven of them (46.6%) responded to steroid therapy. Twelve (7%) progressed to chronic renal failure, most of them had FSGS on renal biopsy and 10 of them did not respond to cyclophosphamide treatment at all. On the other hand, cyclophosphamide has shown to be not beneficial in treating patients with FSGS in a controlled study by the ISKDC.⁷ Sixty patients had steroid resistant FSGS, 25 of them received prednisone of 40 mg/m² on

alternate days for 12 months, and the other 35 received cyclophosphamide of 2.5 mg/kg for 90 days in addition to the same dose of prednisone. 25% of each group had complete remission. However, it was found that the group receiving cyclophosphamide and prednisone had higher percentage of failure in terms of deteriorating renal function or onset of renal failure, as compared with the prednisone group (57% vs 36%). Therefore the ISKDC did not recommend routine use of cyclophosphamide in conjunction with oral steroids in patients with SRNS.

Chlorambucil has been tried in the group who does not respond to cyclophosphamide in Besbas's study mentioned above.³ Forty children were recruited who were treated with chlorambucil of 0.2 mg/kg/day for eight weeks. Eight of them (20%) achieved complete remission, and 5 (12.5%) had partial remission. Six out of the 27 non-responder progress to chronic renal failure. Elzouki et al⁸ treated five children, who were steroid and cyclophosphamide resistant, with chlorambucil. Four (80%) achieved remission and two relapse afterwards. No significant side effect was noticed in these studies were found. Vincristine in combination with prednisone was used to treat seven children with steroid resistant FSGS,⁹ but only two out of seven had complete remission.

Methylprednisolone or the Triple-therapy Protocol

In addition to oral prednisone and alkylating agent, intravenous methylprednisolone has been added to constitute a regimen, commonly referred to as the Triple-therapy protocol. Tune and Mendoza et al^{10,11} treated 32 SRNS children with FSGS, with this triple therapy regimen,¹⁰⁻¹⁴ consisting of intravenous methylprednisolone at a dose of 30 mg/kg thrice weekly for two weeks (total six doses), followed by once weekly for eight doses, once per two weeks for four doses, once per four weeks for eight doses, and then once per eight weeks for four more doses. Oral prednisone of dose 2 mg/kg every other day is added at the beginning of the third week to end of tenth week, with slow taper gradually afterwards.

Alkylating agent, either cyclophosphamide or chlorambucil was added in those not fully controlled by intravenous methylprednisolone and oral prednisone. The indications are: 1) no significant improvement of proteinuria by the initial six doses of intravenous methylprednisolone; 2) complete or partial response by the initial two weeks with subsequent significant increase of proteinuria at any time during the intravenous methylprednisolone regimen; 3) urine protein/creatinine ratio of ≥ 2 (which indicate nephrotic range of proteinuria) at the tenth week or later. Cyclophosphamide (2.0-2.5 mg/kg/day) or chlorambucil (0.18-0.22 mg/kg/day) was given for eight to ten weeks. If the alkylating agent was started

at the end of the first two weeks, weekly intravenous methylprednisolone was continued until the end of the alkylating agent therapy, then tapered as scheduled. If the alkylating agent was started in later time, six more doses of pulse intravenous methylprednisolone were given over two weeks, and the alkylating agent was given with weekly pulses afterwards. A second course of alkylating agent was considered if a patient showed partial or complete response to the triple therapy, which either relapsed during the treatment course or failed to achieve urine protein/creatinine ratio ≤ 1 . Those with relapse after completion of the protocol were treated as if they were new cases.

In these 32 patients, 14 had one course of alkylating agent, eight had two courses, and three had more than two courses and seven did not need at all. These patients were followed up for 0.75 to 12.5 years. Twenty-one out of 32 patients (66%) achieved complete remission in last follow up and requiring no therapy, three (9%) had mild proteinuria, two (6%) had moderate proteinuria, and six (19%) remained nephrotic. For those 11 non-responders, three out of them (27%) progressed to end stage renal failure, five (45%) had decreased creatinine clearance, and three (37%) had persistent proteinuria with normal creatinine clearance. The side effect from this regimen is limited with delayed growth in 17%, hypertension in 17% and cataracts in 22%.^{13,14} They both concluded that the triple-therapy regimen is effective in the majority of children with SRNS due to FSGS.

Sa et al¹⁵ treated five patients with SRNS from FSGS with intravenous methylprednisolone 30 mg/kg thrice weekly for two weeks, followed by weekly doses for next two months, biweekly for two months, and monthly dose for eight months. Oral prednisone 2 mg/kg alternate day started after the first two weeks of methylprednisolone and then tapered in the following six months after the discontinuation of methylprednisolone. Oral cyclophosphamide of 2 mg/kg/day was added during the 8-week period of weekly methylprednisolone therapy. Two (40%) achieved complete remission. Furthermore, the relapses became steroid sensitive.

However Waldo et al¹⁶ treated 13 children with SRNS, using intravenous pulses methylprednisolone of 20 mg/kg and chlorambucil of 0.2 mg/kg/day for eight weeks, with oral prednisone 40 mg/m² alternate day from the third to tenth week. Complete remission was observed in five out of 13 children (38%), partial remission in two (15%), and six (46%) not respond at all. It showed a less favorable outcome as compared to the study of Tune and Mendoza. Tune and Mendoza¹⁷ commented that it might be related to the difference in racial group of the patients, as there was about 60% of African-American in Waldo's study, while there was only 10% of African-American in their

study. Unfavorable outcome of FSGS with SRNS has been well reported in African-American children. The regimen in Waldo's study is more conservative.¹¹

Cyclosporine

Cyclosporine has also been widely used. A randomized double-blind study was carried out by the New York-New Jersey Pediatric Nephrology Study Group, comparing the efficacy of cyclosporine and placebo in 24 children with steroid resistant FSGS.¹⁸ The patients were randomized to receive either placebo or cyclosporine for six months. Cyclosporine is given at a dose of 3 mg/kg twice daily, which was adjusted with a target trough level of 300 to 500 ng/mL (by whole blood polyclonal radioimmunoassay method). Twelve patients received cyclosporine, and all of them achieved a diminution of proteinuria, whereas only two out of the 12 patients receiving placebo had similar improvement. However none of them achieved complete remission and all patients treated with cyclosporine had an increase in proteinuria after withdrawal of treatment.

Niaduet et al¹⁹ studied 71 children with idiopathic nephrotic syndrome in whom 23 are steroid resistant. The children received cyclosporine (6 mg/kg) in two daily doses alone or in combination with prednisone 30 mg/m²/day for one month, which tapered to alternate day for five months afterwards. Fourteen out of the 23 children received cyclosporine monotherapy, only one patient (7%) had complete remission, which persisted after treatment withdrawal. Four patients (17%) achieved partial remission and remained nephrotic after stopping cyclosporin therapy. For those 14 treated with cyclosporine and prednisone, eight (57%) had complete remission and seven of them remained in remission one year after stopping the treatment. They concluded that cyclosporine alone is less effective in steroid resistant patients, but that low dose steroid in combination with cyclosporine may enhance its efficacy in these patients.

Subsequently, Niaduet et al carried another clinical study to evaluate the efficacy of the combination therapy of prednisone and cyclosporine.²⁰ Sixty-five children with SRNS were treated with cyclosporine (150 to 200 mg/m²) daily in combination with prednisone (30 mg/m²) daily for one month and then on alternate day prednisone for five months. Twenty-seven patients (42%) achieved complete remission after the course of treatment, and four patients (6%) achieved partial remission, the other 34 patients (52%) had no response. Complete remission was noticed within the first month of treatment in half of those patients. Eight out of the 27 patients experienced relapse after stopping the therapy, but they became steroid sensitive. For those with partial remission, the response was usually transient and cessation of the treatment

resulted in increases in proteinuria. End-stage renal failure was noticed in 12 patients (35%) who showed no response to the combination therapy. Thus, cyclosporine in combination with steroid is effective in a significant proportion of patients with SRNS.

Gregory et al²¹ studied 15 patients with FSGS who were either steroid dependent or steroid resistant. Cyclosporin of dose from 5 to 10 mg/kg/day in two divided doses was given to achieve a whole blood trough level of 70 to 120 ng/mL, in addition to alternate day prednisone 2 mg/kg/day. Thirteen of them (86%) achieved complete remission and the other two had partial remission. However all of them required maintenance therapy either with cyclosporine or cyclosporine with steroid to maintain the remission.

In a Japanese study by Hino et al,²² 11 patients with SRNS were treated with cyclosporine at 2.5 to 5.0 mg/kg/day to achieve a trough level of 50 to 120 ng/mL, together with alternate day oral prednisone at 0.5 to 1 mg/kg/48hr for six months followed by a gradual taper. Seven out of 11 (64%) achieved complete remission within half to four months, but six of them experienced relapses as cyclosporine was withdrawn. One patient showed partial remission and other three had persistent nephrotic syndrome.

Hymes²³ treated 18 SRNS patients with cyclosporine (5 to 10 mg/kg/day) to achieve a whole blood trough level of 80 to 200 ng/mL, with alternate day prednisone of 0.3 to 0.5 mg/kg. Nine (50%) of them achieved complete remission and five (28%) had partial remission. These 14 patients who responded did so after two months of therapy. However, when cyclosporine was withdrawn from 11 patients, nine patients had relapse within six months. The majority of the relapses showed respond to restarting cyclosporine and prednisone, only three of them became cyclosporine resistant. End stage renal failure was noticed in two out of the four who failed in treatment initially, and two out of three who were cyclosporine resistant.

All these studies seem to favor the combination of cyclosporine and alternate day prednisone in achieving complete remission of proteinuria in steroid resistant patients, with efficacy from 50% -80%. However proteinuria usually increases as the treatment is tapered or withdrawn, although the majority did become more steroid sensitive. This suggests that cyclosporine may improve steroid sensitivity in these previously steroid resistant nephrotic patients.^{20,22}

In addition to cyclosporine and oral prednisone, Waldo et al²⁴ studied the effect of intravenous methylprednisolone. Ten patients with steroid resistant FSGS were treated with intravenous methylprednisolone of 30 mg/kg thrice weekly for two weeks, then once a week for six weeks. From the second week onwards,

alternate day oral prednisone of 2 mg/kg and cyclosporine of 6 mg/kg/day were added. After the eight weeks of methylprednisolone, oral prednisone was reduced to 1 mg/kg alternate day for five more months, then 0.5 mg/kg alternate day for six months. Cyclosporine was then reduced to 3 mg/kg/day from the eighth week onwards. Eight of the ten (80%) patients achieved complete remission, one patient had partial remission and one patient did not respond at all. The mean time to achieve remission was 3.6 weeks. Cyclosporine was withdrawn from five of the eight responders, one due to development of lymphoma. The other four patients were successfully withdrawn from cyclosporine. One patient had a subsequent relapse that responded to prednisone therapy. The addition of intravenous methylprednisolone in the initial induction phase improves the efficacy as compared to combination of cyclosporin and prednisone alone.

Cyclosporine nephrotoxicity is common and often exists without any deterioration of renal function. Histologically it usually presents as interstitial fibrosis and tubular atrophy, but rarely affects the glomeruli or arteries. Though the incidence of chronic nephrotoxicity seemed to be low in the studies,^{19,21,22,24,25} the number of patients studied were small. Repeated renal biopsies may be needed in children with SRNS on long-term cyclosporine to monitor the changes.

Other common side effects in children with SRNS on cyclosporine include gum hypertrophy and hirsutism. Hypertension and hyperkalemia, seen in patients on higher doses of cyclosporine such as those after renal transplantation, are not frequently observed in SRNS patients.

Tarcolimus (FK506)

This is an immunosuppressive agent which shares many properties of cyclosporine. It has been used as an antirejection agent in renal and liver transplantation. There is some very preliminary data on its use in SRNS. In one study, seven patients with SRNS were treated with FK506 at 0.5 mg/kg/day,²⁶ in whom cyclosporine therapy was tried in three of them but failed. Three of them (42.8%) showed complete remission whilst the other three showed partial remission. The remaining one patient did not show any response. The main side effect, like cyclosporin, is nephrotoxicity. In a serial study, McCauley et al²⁷ again used FK506 in treating seven patients with SRNS, six of them (85.7%) had reduction in proteinuria, with three had complete remission and three had partial remission. Thus there is early indication that FK506 is effective in the treatment of children with SRNS. However most of the reports contain few patients. Larger studies are needed to evaluate its efficacy and safety.

Mycophenolate Mefetil (Cellcept)

It was used to treat seven patients with SRNS,²⁸ in both idiopathic and secondary nephrotic syndrome. Prednisone can be withdrawn in all of them, and they all showed reduction in proteinuria.

Levamisole

This is a potent anthelmintic agent with immunomodulating properties, which has previously been shown to be useful in treating steroid dependent nephrotic syndrome. However in a recent study²⁹ in five patients with SRNS. Levamisole at a dose of 2.5 mg/kg/48hrs, used for 2 to 18 months, was found to be ineffective in treating children with SRNS.

Vitamin E

This has been tried in rats with experimental induced focal glomerulosclerosis.³⁰ Vitamin E enriched diet was found to be effective in reduction of proteinuria, with diminished progression of glomerulosclerosis and tubulointerstitial scarring in the rats. A clinical trial by Tahzibet al,³¹ treating 10 patients with SRNS with vitamin E of 400IU/day for 2 to 3 months. Nine of them (90%) showed reduction of proteinuria. However long term controlled study is needed to evaluate the efficacy of vitamin E in patients with SRNS.

Angiotensin-converting Enzyme Inhibitors (ACEI)

They have been shown to improve proteinuria in 50% of those with FSGS and membranoproliferative glomerulonephritis,³² which prevent the progression to end stage renal disease. Other therapy like non-steroid anti-inflammatory drug had been studied. However all these studies recruited small number of patients, it is difficult to draw any conclusion without any large number controlled study.

Plasmapheresis

It is suggested that the development of FSGS be related to circulating glomerular capillary albumin permeability factors, especially in patients with recurrent FSGS in renal transplant allografts. Plasmapheresis has been shown to reduce proteinuria, in patients with recurrent FSGS after renal transplantation.³³ However there is little data concerning the efficacy of plasmapheresis in treating FSGS in native kidney. Feld et al³⁴ treated eight adults with primary FSGS who had SRNS, treating with plasmapheresis three times a week for two weeks. Proteinuria was reduced in two patients (25%). Both patients had stable renal function on follow-up. However, four out of six who did not respond progressed to end stage renal failure. A case report by Ginsburg et al³⁵ showed reduction in proteinuria after weekly plasmapheresis in

addition to prednisone and azathioprine in a patient with primary FSGS. These reports are very preliminary and need confirmation by larger studies.

Conclusion

Steroid resistance occurs in about 10% of children with idiopathic nephrotic syndrome. It carries a poorer prognosis for developing end stage renal failure. Renal biopsy is useful in patients with steroid resistant nephrotic syndrome, as it provides information concerning the outcome and probably response to therapy. In general focal segmental glomerulosclerosis and diffuse mesangial proliferation indicate poor outcome and warrants more aggressive therapy than the current oral steroid monotherapy for minimal change disease.

Various protocols have been used for the treatment in steroid resistant nephrotic syndrome. The majority of the studies were found on patients with FSGS. Alkylating agent in combination with oral steroid therapy has met with variable response. The triple-therapy introduced by Tune and Mendoza, with the combination of intravenous methylprednisolone, oral prednisone and alkylating agent has produced the most encouraging result. 66% had complete remission with little side effect noticed. The racial factor should be considered for selection of patients, as the African-American population has a poorer response to the regimen.

Cyclosporine in combination with alternate day prednisone has also been used successfully for induction of remission in SRNS although the overall results were less impressive than the triple therapy. Besides, cyclosporine has a modulating effect to the steroid responsiveness in those with relapse. However the frequency of relapse after withdrawal of treatment is quite high, thus resulting in cyclosporine dependency. As nephrotoxicity from cyclosporine can exist without any change in renal function, renal biopsy is needed to assess this side effect in those on long-term cyclosporine treatment.

Other form of therapy including plasmapheresis, FK506, mycophenolate mofetil, angiotensin converting enzyme inhibitors, and vitamin E all have some encouraging results in reduction of proteinuria. However most of these studies or report include small number of patients, and a group of adult rather than children.

As the number of children with SRNS is generally small in the general population, multicenter cooperative trials are needed to properly assess different treatment protocols. A randomized controlled trial comparing triple therapy versus cyclosporine with oral steroids in children with SRNS is long overdue.

References

1. International Study of Kidney Disease in Children: Nephrotic syndrome in children: prediction of histopathology from clinical and laboratory characteristics at time of diagnosis. *Kid Int* 1978;13:159-65.
2. Cattran DC, Rao P. Long-term outcomes in children and adults with classic focal segmental glomerulosclerosis. *Am J Kid Dis* 1998;32:72-9.
3. Besbas N, Topaloglu R, Saatci O, Bakkaloglu A. Long-term follow-up in children with steroid-resistant nephrotic syndrome. *Clin Pediatr* 1992;31:283-8.
4. Early identification of frequent relapsers among children with minimal change nephrotic syndrome. An report of the International Study of Kidney Disease in Children. *J Pediatr* 1982;101:514-8.
5. Tufro-McReddie A, Alvarez E, Arrizurieta E, Horacio R. Focal glomerulosclerosis in children: an Argentinian experience. *Pediatr Nephrol* 1992;6:158-61.
6. Ponticelli C, Edefonti A, Chio L. Cyclosporine vs cyclophosphamide for patients with steroid-dependent and frequently relapsing idiopathic nephrotic syndrome: multicenter randomized controlled trial. *Nephrol Dial Transplant* 1993;8:1326-32.
7. Tarshish P, Tobin JN, Bernstein J, Edelmann Jr CM. Cyclophosphamide does not benefit patients with focal segmental glomerulosclerosis: a report of the International Study of Kidney Disease in Children. *Pediatr Nephrol* 1996;10:590-3.
8. Elzouli AY, Jaiswal OP. Evaluation of chlorambucil therapy in steroid dependent and cyclophosphamide resistant children with nephrosis. *Pediatr Nephrol* 1990;4:459-62.
9. Almeida MP, Almeida HA, Coelho Rosa F. Vincristine in steroid-resistant nephrotic syndrome. *Pediatr Nephrol* 1994;8:79-80.
10. Tune BM, Karpekar R, Sibley RK, Reznik VM, Griswold WR, Mendoza SA. Intravenous methylprednisolone and oral alkylating agent therapy of prednisone-resistant pediatric focal segmental glomerulosclerosis: a long term follow-up. *Clin Nephrol* 1995;43:84-8.
11. Tune BM, Lieberman E, Mendoza SA. Steroid-resistant nephrotic focal segmental glomerulosclerosis: a treatable disease. *Pediatr Nephrol* 1996;10:772-8.
12. Tune BM, Mendoza SA. Treatment of the idiopathic nephrotic syndrome: regimens and outcomes in children and adults. *J Am Soc Nephrol* 1997;8:824-32.
13. Mendoza SA, Tune BM. Management of the difficult nephrotic patient. *Pediatr Clin North Am* 1995;42: 1459-68.
14. Mendoza SA, Reznik VM, Griswold WR, Krensky AM, Yorgin PD, Tune BM. Treatment of steroid-resistant focal segmental glomerulosclerosis with pulse methylprednisolone and alkylating agent. *Pediatr Nephrol* 1990;4:303.
15. Sa GA, Mendonca E, Luis JP, Almeida M, Rosa FC. Treatment of childhood steroid-resistant nephrotic syndrome with pulse methylprednisolone and cyclophosphamide. *Pediatr Nephrol* 1996;10:250.
16. Waldo FB, Benfield MR, Kohaut EC. Methylprednisolone treatment of patients with steroid-resistant nephrotic syndrome. *Pediatr Nephrol* 1992;6:503-5.
17. Mendoza SA, Tune BM. Controlled, multi-center trials are needed in pediatric nephrology. *Pediatr Nephrol* 1992;6: 506.
18. Liberman KV, Tejani A for the New York-New Jersey Pediatric Nephrology Study Group: A randomized double-blind placebo-controlled trial of cyclosporin in steroid-resistant idiopathic focal segmental glomerulosclerosis in children. *J Am Soc Nephrol* 1996;7:56-63.
19. Niaduet P, Broyer M, Habib R. Treatment of idiopathic nephrotic syndrome with cyclosporine A in children. *Clin Nephrol* 1991;35(Suppl 1):31-6.
20. Niaduet P, The French Society of Pediatric Nephrology: Treatment of childhood steroid-resistant idiopathic nephrosis with a combination of cyclosporine and prednisone. *J Pediatr* 1994;125:981-6.
21. Gregory MJ, Smoyer WE, Sedman A, et al. Long-term cyclosporine therapy for pediatric nephrotic syndrome: a clinical and histologic analysis. *J Am Soc Nephrol* 1996;7: 543-9.
22. Hino S, Takemura T, Okada M, et al. Follow-up study of children with nephrotic syndrome treated with a long-term moderate dose of cyclosporine. *Am J Kid Dis* 1998;31:932-9.
23. Hymes LC. Steroid-resistant, cyclosporine-responsive, relapsing nephrotic syndrome. *Pediatr Nephrol* 1995;9:137-9.
24. Waldo FB, Benfield MR, Kohaut C. Therapy of focal and segmental glomerulosclerosis with methylprednisolone, cyclosporine A, and prednisone. *Pediatr Nephrol* 1998;12:397-400.
25. Sieberth HG, Classen W, Fuhs M, Ittel T, Kindler J, Mihatsch MJ. Serial kidney biopsies in patients with nephrotic syndrome treated with cyclosporine. *J Autoimmun* 1992;5(Suppl A):355-61.
26. McCauley J, Scantlebury V, Jordan GM, et al. FK506 in the management of transplant-related nephrotic syndrome and steroid-resistant nephrotic syndrome. *Transplant Proc* 1991;23:3354-6.
27. McCauley J, Shapiro R, Ellis D, Igdal H, Tzakis A, Starzl TE. Pilot study of FK506 in the management of steroid-resistant nephrotic syndrome. *Nephrol Dial Transplant* 1993;8:1286-90.
28. Briggs WA, Choi MJ, Scheel PJ Jr. Successful mycophenolate mofetil treatment of glomerular disease. *Am J Kid Dis* 1998; 31:213-7.
29. Tenbrock K, Muller-Berghaus J, Fuchshuber A, Michalk D, Querfeld U. Levamisole treatment in steroid-sensitive and steroid-resistant nephrotic syndrome. *Pediatr Nephrol* 1998; 12:459-62.
30. Trachtman H, Schwob N, Maesaka J, Valderrama. Dietary vitamin E supplementation ameliorates renal injury in chronic pyromycin aminonucleoside nephropathy. *J Am Soc Nephrol* 1995;5:1811-9.
31. Tahzib M, Gaunthier BO, Frank R, Trachtman H. Vitamin E reduces proteinuria in children with renal disease (abstract). *Ped Resear* 1998;43:314A.
32. Nosrati SM, Khwaja S, El-Shahaway M, Massry SG. Effect of angiotensin converting enzyme inhibition by perindopril on proteinuria of primary renal diseases. *Am J Nephrol* 1997;17: 511-7.
33. Mowry J, Marik J, Cohen A, Hogg R, Sahney S, Ettinger R. Treatment of recurrent focal segmental glomerulosclerosis with high-dose cyclosporine A and plasmapheresis. *Transplant Proc* 1993;25:1345-6.
34. Feld SM, Figueroa P, Savin V, et al. Plasmapheresis in the treatment of steroid-resistant focal segmental glomerulosclerosis in native kidneys. *Am J Kid Dis* 1998;32: 230-7.
35. Ginsburg DS, Dau P. Plasmapheresis in the treatment of steroid-resistant focal segmental glomerulosclerosis. *Clin Nephrol* 1997;48:282-7.