

# Nephrotic syndrome in children

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Proteinuria in children with idiopathic nephrotic syndrome is secondary to a loss of charge selectivity of the glomerular basement membrane. Loss of anionic charges may be secondary to a defect of heparan sulfate proteoglycans, which is also found in the congenital nephrotic syndrome, or to cationic proteins, which neutralize the anionic charges of the membrane. Reports on recurrence of nephrotic syndrome in patients with steroid-resistant idiopathic nephrotic syndrome following renal transplantation suggest that a humoral factor, possibly produced by T lymphocytes, may enhance glomerular permeability. Corticosteroids remain the basic treatment of idiopathic nephrotic syndrome. Most patients respond to steroid therapy and a high proportion of them relapse but continue to respond throughout the subsequent course of the disease. Levamisole may be effective in preventing relapses. Cyclosporine may be useful in steroid-dependent patients with signs of steroid toxicity and after a failure of a course of alkylating agent. Almost 85% of patients respond to cyclosporine, but they relapse after tapering or stopping the drug. In steroid-resistant patients, there is no study showing a clear-cut beneficial effect of alkylating agents, as the remission rate after treatment is close to the rate of spontaneous remission. Cyclosporine in association with prednisone may be effective, but the risk of nephrotoxicity seems to be higher than in steroid-dependent patients.

Current Opinion in Pediatrics 1993, 5:174-179

Idiopathic nephrotic syndrome (INS), which is the most frequent glomerular disease in children, is defined by the combination of a nephrotic syndrome and minimal change glomerular disease (MCD) with foot process fusion on electron microscopy. No deposits are seen on immunofluorescence examination. In some cases, diffuse mesangial proliferation or focal and segmental glomerular sclerosis (FSGS) may be seen, and IgM or C3 deposits may be present. Although these various morphologic features carry prognostic significance, they in no way allow distinct and specific diseases to be identified [1]. Thus, it seems preferable to think of INS as a syndrome with different clinical and histologic variants.

## Pathogenesis

### Glomerular permselectivity

The mechanisms of proteinuria in the absence of histologic alterations on light microscopy have been the

subject of numerous studies. In normal individuals, the clearance of albumin is about 1% of that of neutral proteins such as polyvinylpyrrolidone or dextran. Similarly, the clearance of neutral dextran is higher than that of anionic sulfate dextran of similar molecular weight. These data indicate that the permeability of the glomerular basement membrane (GBM) is determined not only by the size but also by the charge of the protein. It is believed that the anionic charge of the GBM is responsible for the charge selectivity of filtration. The anionic (negative) charge of the GBM repulses the negatively charged albumin molecules. Ghitescu *et al.* [2•] analyzed the renal handling of albumin with various isoelectric points. Bovine serum albumin (BSA) tagged with dinitrophenol was cationized at different isoelectric points, ranging from 6.5 to 8.5 and injected in mice. The tracer was visualized by electron microscopy using antidinitrophenol antibodies and protein A-gold particles. It was shown that anionic and neutral BSA molecules localized on the endothelial side of the GBM, whereas cationized BSA was situated in the lamina rara interna and externa. Neutral-

## Abbreviations

BSA—bovine serum albumin; FSGS—focal and segmental glomerular sclerosis; GBM—glomerular basement membrane; GPF—glomerular permeability factor; INS—idiopathic nephrotic syndrome; MCD—minimal change disease.

ization of the fixed anionic charges of the GBM with cationized BSA resulted in an increased permeability to anionic BSA.

In children with INS, the clearance of neutral macromolecules with the same molecular weight as albumin (dextran or polyvinylpyrrolidone) is reduced, indicating that the "pore" size of the barrier is smaller. Brenner *et al.* [3] have postulated that massive proteinuria in these patients is secondary to a loss of charge selectivity of filtration, which could be the result of a loss of anionic charges of the GBM or a neutralization of these anionic charges. Indeed, 10 years ago, using polyethylamine as a cationic probe, Vernier *et al.* [4] reported a decrease in the anionic charges of GBM in children with congenital nephrotic syndrome and in children with MCD.

Heparan sulfate proteoglycans, synthesized by the epithelial cells, are responsible for the anionic charges of GBM. Vermylen *et al.* [5] found a diminished GBM content of heparan sulfate in congenital nephrotic syndrome and suggested that this could be responsible for the abnormal glomerular permeability. Van den Heuvel *et al.* [6] analyzed the glucosaminoglycan content of renal basement membranes in congenital nephrotic syndrome of the Finnish type. The glucosaminoglycan content of the GBM and the tubular basement membranes from three patients with congenital nephrotic syndrome was not different from 16 normal infants. In addition, the glucosaminoglycan composition, with heparan sulfate constituting 75% of the glucosaminoglycan, was similar in the three patients and the controls. The urinary glucosaminoglycan excretion was also comparable in both groups. Indirect immunofluorescence studies on kidney biopsies using a monoclonal antibody against heparan sulfate revealed a similar staining of the glomerular and the tubular basement membranes. Jadresic *et al.* [7] found a significant increase of the urine heparan sulfate–chondroitin sulfate ratio in children with the Finnish type nephrotic syndrome, with diffuse mesangial sclerosis, or with FSGS compared with controls and to children with steroid-sensitive nephrotic syndrome. A strong correlation between heparan sulfate–chondroitin sulfate ratio and proteinuria was also found. These data suggest that the increased heparan sulfate urinary excretion is not related to a specific histologic pattern.

Van den Born *et al.* [8•] produced a mouse monoclonal antibody to partially purified heparan sulfate proteoglycan isolated from rat glomeruli. The monoclonal antibody, directed against the glucosaminoglycan side of the molecule was specific for heparan sulfate and did not react with other components of the GBM. By indirect immunofluorescence on rat kidney sections, the monoclonal antibody bound to the GBM with fine granular-to-linear staining pattern whereas by electron microscopy, a diffuse staining of the whole width of the GBM was observed. After intravenous injection, the monoclonal antibody localized immediately along the

GBM with a granular staining and 1 day later, the antibody was localized in the mesangium with a parallel decreased staining along the GBM. Precise localization of the antibody was evaluated by electron microscopy. 1 hour after intravenous injection, the antibody bound mainly to the inner side of the GBM. Intravenous injection of this antiheparan sulfate proteoglycan monoclonal antibody to rats resulted in selective proteinuria. The degree of proteinuria was dependent on the dose of monoclonal antibody injected. The proteinuria was maximal at day 1 and decreased thereafter. The quick disappearance of proteinuria may be due to the IgM isotype of the antibody whose high molecular weight prevents penetration in the GBM. This model shows that antibodies against heparan sulfate are nephritogenic and produce proteinuria when injected into the rat. Proteinuria may be secondary to a neutralization of the anionic charge of heparan sulfate.

A neutralization of the anionic charge of the GBM may occur via cationic proteins. Levin *et al.* [9] recently described a highly cationic protein in the plasma and the urine of children with steroid-responsive nephrotic syndrome. The authors postulated that this cationic factor could bind and neutralize the anionic charges of the GBM. They also suggested that such cationic proteins may arise from cells of the immune system.

### Immunologic abnormalities

Following the hypothesis of Shalhoub [10] that INS might be secondary to a disorder of T lymphocytes, a number of authors have looked for the presence of a lymphokine that could render the GBM more permeable to proteins. Peripheral blood mononuclear cells from patients with MCD cultured *in vitro* produce a vascular permeability factor, which could be responsible for massive proteinuria [11]. Heslan *et al.* [12] showed that vascular permeability factor was distinct from interleukin-2. Mayurama *et al.* [13] tested the *in vitro* effect of cyclosporine on vascular permeability factor production by T lymphocytes from patients with MCD. Cyclosporine, at concentrations ranging from 100 to 250 ng/mL, was able to suppress vascular permeability factor production. This may be relevant to the beneficial effect of cyclosporine in patients with INS.

Recently, Koyama *et al.* [14••] identified a glomerular permeability factor (GPF) in the supernatant of T-cell hybridoma derived from peripheral T lymphocytes of a patient with MCD. The hybridoma was obtained by fusion of peripheral T lymphocytes with CCRF-HSB<sub>2</sub> cells. The GPF was identified by the ability of the supernatant to induce proteinuria when injected intravenously in the rat. The supernatant containing GPF was able to enhance the concanavalin A-induced lymphocyte blastogenesis significantly. The authors showed that GPF was different from the main known lymphokines. The molecular weight of GPF was estimated to be between 60 and 160 Kd. In rats injected with the supernatants, the authors found a partial fusion of foot processes of epithelial cells of

the GBM with minor histologic changes and no immune deposit. Electron microscopy studies showed a decreased interspacing and a decreased density and diameters of injected polyethylenimine particles suggesting changes in the negative charges of the GBM induced by GPF. Tanaka *et al.* [15] tested the supernatants of peripheral blood mononuclear cells stimulated with concanavalin A for their ability to induce proteinuria when injected in the renal artery of the rats. They found that the supernatants derived from patients with MCD or FSGS induced a marked proteinuria and a reduction of the anionic charges of the GBM.

Other authors have looked for T-lymphocyte abnormalities. Mandreoli *et al.* [16] measured the soluble form of the interleukin-2 receptor in patients with MCD. They found high interleukin-2 receptor levels in the plasma and the urine during the proteinuric phase although the levels were normal during the remission. The authors postulated that soluble interleukin-2 receptor may be one of the inhibitory serum factors because a high soluble interleukin-2 receptor level was strongly correlated to the decreased response to mitogens in these patients. Fiser *et al.* [17] studied T-lymphocyte subsets by flow cytometry in children with steroid-responsive nephrotic syndrome. Patients in relapse demonstrated a significant increase in the percentage of activated T8 lymphocytes and a decrease of T4 lymphocytes. The decrease of T4 lymphocytes may be related to steroid therapy although the increase of activated T8 lymphocyte was also found in untreated patients. Altered T-lymphocyte function is also suggested by the data from Hewitt *et al.* [18], who studied the suppression of *in vitro* lymphocyte response to phytohemagglutinin induced by prednisolone. The prednisolone dose that suppresses phytohemagglutinin-induced blastogenesis was significantly higher in patients with idiopathic nephrotic syndrome. However, the response was not able to predict the steroid responsiveness.

### Mechanism of edema formation

Two theories have been proposed to account for the development of edema. According to the first theory, massive proteinuria causes hypoalbuminemia and thus a decrease in plasma osmotic pressure. The resulting hypovolemia stimulates the renin-angiotensin-aldosterone system and the sympathetic tone. As a consequence, the kidneys retain sodium and water. The second theory suggests an intrinsic defect in the tubular handling of sodium resulting in an increased reabsorption of sodium. Valentin *et al.* [19••] showed that in rats with adriamycin-induced nephrotic syndrome, the reduced natriuresis following sodium infusion is associated with renal resistance to atrial natriuretic peptide. The mechanism of resistance may be an enhanced nucleotide phosphodiesterase activity responsible for the rapid degradation of cGMP. This intrinsic defect in re-

nal sodium handling in the distal nephron may explain the sodium retention in the nephrotic syndrome.

### Prognosis

Steroid-dependent INS has a mean course of 5 to 10 years. The severity of this condition lies less in the risk of developing end-stage renal failure, which is an extremely rare outcome, than in the complications of treatment. Conversely, steroid-resistant INS may progress to end-stage renal disease. In our experience, this occurs in 50% of cases after a follow-up of 15 years.

Proximal tubular dysfunction measured by urinary excretion of retinol binding protein and  $\beta_2$ -microglobulin may predict steroid responsiveness in patients with INS [20]. Urinary excretion of these two proteins was significantly higher in steroid-resistant than in steroid-responsive patients. Patients with retinol binding protein excretion less than 1300  $\mu\text{g/g}$  creatine and  $\beta_2$ -microglobulin less than 130  $\mu\text{g/g}$  creatinine were all steroid responsive. Patients with higher levels were likely to be steroid resistant.

### Therapy

There is general agreement on the use of corticosteroids for the first attack of idiopathic nephrotic syndrome. Prednisone, at a dose of 60  $\text{mg/m}^2/\text{d}$  with a maximum of 80  $\text{mg/d}$ , is given for 1 month followed by alternate-day therapy for 1 to 3.5 months. Most children who show MCD on renal biopsy respond to corticosteroids whereas a high proportion of those with FSGS are steroid resistant. As renal biopsy is not usually performed when the patient responds to corticosteroids, MCD has become synonymous with steroid-sensitive nephrotic syndrome. However, it is more appropriate to define the patients in terms of steroid responsiveness, as 5% to 10% of steroid-resistant patients have MCD and the same proportion of steroid responsive patients have FSGS. Furthermore, therapeutic decisions and prognosis depend more on the steroid responsiveness than on the histologic category.

Of the children with INS, 85% respond to corticosteroids and 30% are cured after the first episode. Ten percent to 15% relapse several months after stopping steroid therapy, and cure takes place in most of them after two to three relapses. The other children relapse as soon as steroids are stopped or when the dosage is decreased. This constitutes the steroid-dependent INS. Such patients may be treated by repeated courses of standard treatment consisting of prednisone 60  $\text{mg/m}^2/\text{d}$  continued 3 days after the urine has become protein free, followed by alternate-day prednisone, 40  $\text{mg/m}^2$ , for 4 weeks as proposed by the International Study of Kidney Disease in Children (ISKDC). Alterna-

tively, these children may be treated with prolonged alternate-day prednisone, 15 to 30 mg/m<sup>2</sup>, according to the steroid threshold, *ie*, the dose at which the relapse occurs. This latter regimen is associated with less steroid side effects as the cumulative steroid dosage is lower.

When symptoms of steroid toxicity appear, including a decrease of growth velocity, corticosteroids should be withdrawn. In these cases, alkylating agents may be indicated. However, other drugs have been proposed. During the past 10 years, several studies have shown that levamisole, an immunostimulant drug, may have a steroid-sparing effect in steroid-responsive nephrotic syndrome with frequent relapses or steroid dependency. The British Association for Paediatric Nephrology [21•] completed a multicenter study where 61 children with frequently relapsing or steroid-dependent nephrotic syndrome were randomly allocated to receive levamisole or a placebo. Levamisole was given on alternate days at a dose of 2.5 mg/kg. Thirty-one children received levamisole whereas 30 received a placebo. Twenty patients in the first group and 18 in the second group had previously received a course of alkylating agents. Levamisole or placebo were administered for 112 days unless relapse occurred. Fourteen patients in the levamisole group and four in the placebo group were still in remission after 112 days despite prednisone withdrawal (Fig. 1). Most of them relapse within 3 months after cessation of levamisole. No episode of neutropenia or agranulocytosis was reported. This study clearly shows that levamisole may be effective in preventing relapses in patients with steroid-dependent nephrotic syndrome. Regular blood counts should be performed as the most serious side effect is neutropenia. Neutropenia was reported in only three patients among the 140 previously reported, and the neutrophil count rapidly returned to normal after discontinuation of the drug.

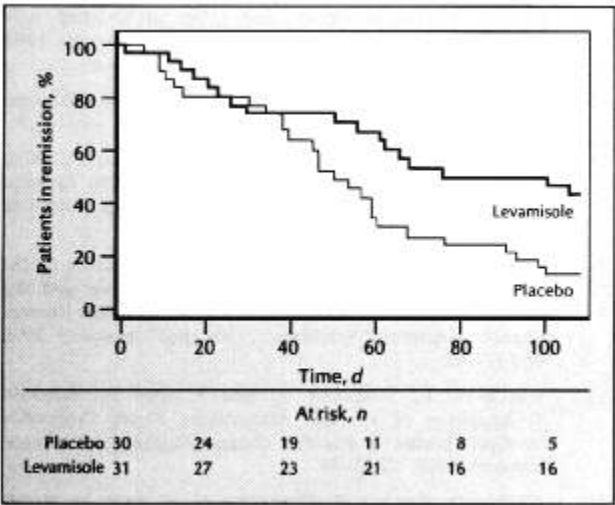


Fig. 1. Percentage of patients in remission by time to relapse in days for levamisole and placebo groups. (From British Association for Paediatric Nephrology [21•]; with permission.)

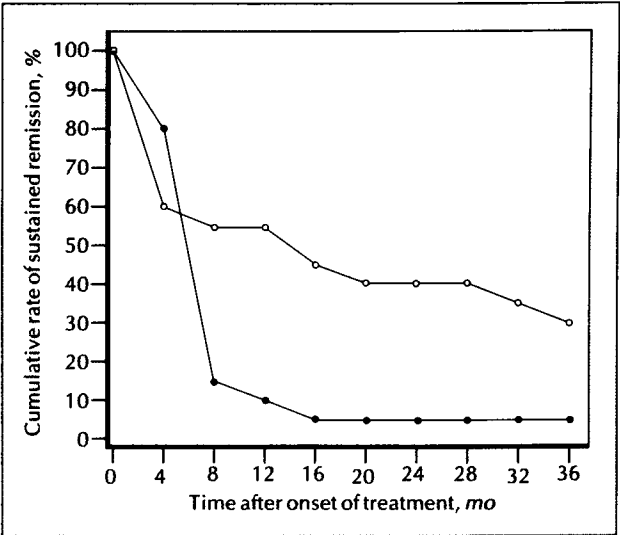


Fig. 2. Cumulative rate of sustained remission: comparison of cyclosporine (closed circles; *n* = 20) and chlorambucil (open circles; *n* = 20) treatments. (From Niaudet and The French Society of Paediatric Nephrology [23•]; with permission.)

Pruna *et al.* [22] observed a complete remission in a patient with MCD resistant to steroids and cyclosporine following a treatment with pefloxacin for severe infection. Following this case, they treated successfully two other patients, one with minimal change steroid-dependent nephrotic syndrome and the other with recurrent nephrotic syndrome following kidney transplantation. The patients received pefloxacin, 400 mg daily, for 1 month and both have remained with proteinuria less than 1 g/d 2 to 3 months after cessation of treatment.

Cyclosporine has been shown to be effective in approximately 80% of patients with steroid dependency. The French Society for Paediatric Nephrology [23•] conducted a randomized controlled trial comparing the efficacy of chlorambucil at a cumulative dose of 8 mg/kg or cyclosporine in inducing sustained remissions. Of the 20 patients treated with cyclosporine, four relapsed before prednisone withdrawal, seven relapsed at cyclosporine tapering, and eight after cyclosporine discontinuation. Of the 20 patients treated with chlorambucil, 14 relapsed but six were still in remission 27 to 49 months after the end of the treatment (Fig. 2). The authors believe that children with steroid dependency should be treated with alkylating agents at a nongonadotoxic dose before resorting to cyclosporine. Niaudet *et al.* [24] treated 71 children with INS, 45 with steroid dependency, and 23 with steroid resistance. Cyclosporine was effective in 80% of steroid-dependent children, but most relapsed at discontinuation of treatment. Cyclosporine alone was effective in only 7% of steroid-resistant patients, but 8 out of 14 patients who received cyclosporine in association with prednisone achieved complete remission.

## Transplantation

The major problem of patients with INS who progress to end-stage renal failure and who undergo renal transplantation is the risk of recurrence of the nephrotic syndrome on the graft. The overall risk of recurrence is estimated to be around 25%. The risk is different in children and in adult patients. Sengutuvan *et al.* [25] found that 8 of 16 children had experienced recurrence compared with 3 of 27 adults. In children, recurrence is more frequent when the disease has started after the age of 6 years than before. Similarly, a rapid progression of the disease to end-stage renal failure seems to be a major factor associated with recurrence as in most series, when the duration of disease has been shorter than 3 years, the nephrotic syndrome recurs in half of the patients. The histopathologic pattern observed on the first biopsy during the course of the disease is also an important predictive factor. Recurrence occurs in 50% to 80% of patients in whom initial biopsy has shown diffuse mesangial proliferation but in only 25% of patients with MCD on first biopsy. Graft failure occurs in about 60% of patients with recurrence versus 23% of those without recurrence. Some patients may show good renal function for several years despite persistent nephrotic syndrome.

Stephanian *et al.* [26•] have studied the outcome of patients with FSGS who had lost their first graft and were retransplanted. Among 14 patients, eight had lost the first transplant from recurrent disease and six from rejection. The six patients who had lost their first transplant from rejection did not experience recurrence of the disease on the second graft. Three of the eight patients who had lost their first graft rapidly from recurrence experienced recurrent disease on subsequent allografts. Five patients had prolonged survival of their first graft despite recurrence and two of them lost their second graft from recurrence, whereas one patient had recurrence with a functioning graft and two had functioning grafts without recurrence 5 months and 9 years after transplantation. From these data it can be concluded that, in the absence of recurrence of the nephrotic syndrome on the first graft, a second graft will be free of recurrence. In case of rapid recurrence and loss of the first graft, the risk of recurrence is high, but a proportion of the patients may have excellent second-graft survival.

Artero *et al.* [27] reviewed the outcome of renal transplantation patients who initially had FSGS. Recurrence occurred in 32% of 78 allografts. Patients who had progressed rapidly to renal failure recurred more frequently. Five of the seven patients who had lost their first graft from recurrence also lost their second graft from recurrence. Ten of 25 grafts with recurrence were lost from recurrence. There were no differences in the rate of recurrence in patients receiving cyclosporine and in patients receiving conventional therapy. Plasmapheresis induced a remission in three out of five patients.

## References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- Of special interest
- Of outstanding interest

1. HABIB R, CHURG J: **Minimal Change Disease, Mesangial Proliferation Glomerulonephritis and Focal Sclerosis: Individual Entities or a Spectrum.** In *Nephrology*. Edited by Robinson RR. New York: Springer-Verlag; 1984:634–644.
2. GHITESCU L, DESJARDINS M, BENDAYAN M: **Immunocytochemical Study of Glomerular Permeability to Anionic, Neutral and Cationic Albumins.** *Kidney Int* 1992, 42:25–32.
- An approach that allows a quantitative investigation, at the ultrastructural level, of the charge selectivity of the GBM. The authors have studied the renal handling of albumins of various isoelectric points.
3. BRENNER BM, HOSTETTER TH, HUMES MD: **Molecular Basis of Proteinuria of Glomerular Origin.** *N Engl J Med* 1978, 278:826–833.
4. VERNIER RL, KLEIN DJ, SISSON SP, MAHAN JD, OEGEMA TR, BROWN DM: **Heparan Sulfate-Rich Anionic Sites in the Human Glomerular Basement Membrane.** *N Engl J Med* 1983, 309:1001–1009.
5. VERMYLEN C, LEVIN M, MOSSMAN J, BARRATT TM: **Glomerular and Urinary Heparan Sulfate in Congenital Nephrotic Syndrome.** *Pediatr Nephrol* 1989, 3:122–129.
6. VAN DEN HEUVEL LPWJ, VAN DEN BORN J, JALANKO H, SCHRODER CH, VEERKAMP JH, ASSMANN KJM, BERDEN JHM, HOLMBERG J, RAPOLA J, MONNENS LAH: **The Glycosaminoglycan Content of Renal Basement Membranes in the Congenital Nephrotic Syndrome of the Finnish Type.** *Pediatr Nephrol* 1992, 6:10–15.
7. JADRESIC LP, FILLER G, BARRATT TM: **Urine Glycosaminoglycans in Congenital and Acquired Nephrotic Syndrome.** *Kidney Int* 1991, 40:280–284.
8. VAN DEN BORN J, VAN DEN HEUVEL LPWJ, BAKKER MAH, VEERKAMP JH, ASSMANN KJM, BERDEN JHM: **A Monoclonal Antibody against GBM Heparan Sulfate Induces an Acute Selective Proteinuria in Rats.** *Kidney Int* 1992, 41:115–123.
- The authors describe the production and characterization of a monoclonal antibody against heparan sulfate. After intravenous administration in rats, the antibody binds transiently to the GBM with a concomitant development of a selective proteinuria.
9. LEVIN M, GASCOINE P, TURNER MW, BARRATT TM: **A Highly Cationic Protein in Plasma and Urine of Children with Steroid Responsive Nephrotic Syndrome.** *Kidney Int* 1989, 36:867–877.
10. SHALHOUB RJ: **Pathogenesis of Lipoid Nephrosis: a Disorder of T-Cell Function.** *Lancet* 1974, 2:556–559.
11. LAGRUE G, XHENEUMONT S, BRANELLEC A, HIRBEC C, WEIL B: **Vascular Permeability Factor Elaborated from Lymphocytes. I. Demonstration in Patients with Nephrotic Syndrome.** *Biomedicine* 1975, 23:37–40.
12. HESLAN JM, BRANELLEC AI, PILATTE Y, LANG P, LAGRUE G: **Differentiation between Vascular Permeability Factor and IL-2 in Lymphocyte Supernatants from Patients with Minimal-Change Nephrotic Syndrome.** *Clin Exp Immunol* 1991, 86:157–162.
13. MAYURAMA K, TOMIZAWA S, SEKI Y, ARAI H, KUROUTE T: **Inhibition of Vascular Permeability Factor Production by Cyclosporine in Minimal Change Nephrotic Syndrome.** *Nephron* 1992, 62:27–30.
14. KOYAMA A, FUJISAKI M, KOBAYASHI M, IGARASHI M, NARITA M: **A Glomerular Permeability Factor Produced by Human T Cell Hybridoma.** *Kidney Int* 1991, 40:453–460.
- The authors describe a vascular permeability factor produced by a T-cell hybridoma derived from a patient with minimal change

nephrotic syndrome. This factor induces proteinuria when injected in rats.

15. TANAKA R, YOSHIKAWA N, NAKAMURA H, ITO H: **Infusion of Peripheral Blood Mononuclear Cell Products from Nephrotic Children Increases Albuminuria in Rats.** *Nephron* 1992, 60:35–41.
  16. MANDREOLI M, BELTRANDI E, CASADEI-MALDINI M, MANCINI R, ZUCHELLI A, ZUCHELLI P: **Lymphocyte Release of Soluble IL-2 Receptors in Patients with Minimal Change Nephropathy.** *Clin Nephrol* 1992, 37:177–182.
  17. FISER RT, ARNOLD WC, CHARLTON RK, STEELE RW, CHILDRESS SH, SHIRKEY B: **T-Lymphocyte Subsets in Nephrotic Syndrome.** *Kidney Int* 1991, 40:913–916.
  18. HEWITT IK, HOUSE AK, POTTER JM, KINNAR BF: **Altered in Vitro Lymphocyte Response in Childhood Nephrotic Syndrome.** *Pediatr Nephrol* 1992, 6:464–466.
  19. VALENTIN JP, QIU C, MULDOWNNEY WP, YING WZ, GARDNER DG, HUMPHREYS MH: **Cellular Basis of Blunted Volume Expansion Natriuresis in Experimental Nephrotic Syndrome.** *J Clin Invest* 1992, 90:1302–1312.
- In adriamycin nephrosis, an abnormality in cGMP metabolism may account, at least in part, for the blunted volume expansion natriuresis and resistance to infused atrial natriuretic peptide. Resistance to atrial natriuretic peptide may be related to an enhanced cGMP-phosphodiesterase activity.
20. SESSO R, SANTOS AP, NISHIDA SK, KLAG MJ, CARVALHAES JT, AJZEN H, RAMOS OL, PEREIRA AB: **Prediction of Steroid Responsiveness in the Idiopathic Nephrotic Syndrome Using Urinary Retinol-Binding Protein and Beta<sub>2</sub>-Microglobulin.** *Ann Intern Med* 1992, 116:905–909.
  21. BRITISH ASSOCIATION FOR PAEDIATRIC NEPHROLOGY: **Levamisole for Corticosteroid-Dependent Nephrotic Syndrome in Childhood.** *Lancet* 1991, 337:1555–1557.

A randomized, double-blind, placebo-controlled trial showing a beneficial effect of levamisole in steroid-responsive patients with frequent relapses.

22. PRUNA A, AKPOSSO K, BEDROSSIAN J, METIVER F, SALTIEL C, IDATTE JM, NOCHY D, DRUET P: **Pefloxacin as First-Line Treatment in Nephrotic Syndrome.** *Lancet* 1992, 340:728–729.
  23. NIAUDET P, THE FRENCH SOCIETY OF PAEDIATRIC NEPHROLOGY: **Comparison of Cyclosporin and Chlorambucil in the Treatment of Steroid-Dependent Idiopathic Nephrotic Syndrome: a Multicenter Randomized Controlled Trial.** *Pediatr Nephrol* 1992, 6:1–3.
- A randomized controlled trial showing an actuarial remission rate at 2 years of 45% after a course of chlorambucil compared with only 5% after a 3-month course of cyclosporine.
24. NIAUDET P, BROYER M, HABIB R: **Treatment of Idiopathic Nephrotic Syndrome with Cyclosporin A in Children.** *Clin Nephrol* 1991, 35:S31–S35.
  25. SENGUTUVAN P, CAMERON JS, HARTLEY RB: **Recurrence of Focal Segmental Glomerulosclerosis in Transplanted Kidneys: Analysis of Incidence and Risk Factors in 59 Allografts.** *Pediatr Nephrol* 1990, 4:21–28.
  26. STEPHANIAN E, MATAS AJ, MAUER SM, CHAVERS B, NEVINS T, KASHTAN C, SUTHERLAND DER, GORES P, NAJARIAN JS: **Recurrence of Disease in Patients Retransplanted for Focal Segmental Glomerulosclerosis.** *Transplantation* 1992, 53:755–757.
- Describes the course of patients with focal segmental glomerulosclerosis who were retransplanted after losing their primary graft to either rejection or recurrent disease.
27. ARTERO M, BLAVA C, AMEND W, TOMLANOVICH S, VINCENTI F: **Recurrent Focal Glomerulosclerosis: Natural History and Response to Therapy.** *Am J Med* 1992, 92:375–383.

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