28 Idiopathic Nephrotic Syndrome in Children: Clinical Aspects

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In children, the most common cause of nephrotic syndrome is idiopathic nephrotic syndrome (INS), also called nephrosis (1). INS is defined by the combination of a nephrotic syndrome (proteinuria, hypoalbuminemia, hyperlipidemia, and edema) and non-specific histological abnormalities of the kidney including minimal changes, focal and segmental glomerular sclerosis (FSGS), and diffuse mesangial proliferation. Glomeruli show a fusion of epithelial cell foot processes on electron microscopy and no significant deposits of immunoglobulins or complement on immunofluorescence.

Many authors consider minimal change disease, diffuse mesangial proliferation and FSGS as separate diseases because of differences in response to corticosteroids and subsequent clinical course. Indeed, these various pathologic features carry prognostic significance. Patients with FSGS and those with diffuse mesangial proliferation have more frequently hematuria, are often resistant to corticosteroid treatment, progress more often to renal failure and may have a recurrence of the nephrotic syndrome soon after renal transplantation. Recent data have comforted the belief that minimal change disease and FSGS are different entities. FSGS appears to be a podocyte disease (2). The notion of "podocyte dysregulation" (3, 4), the different expression of cyclin-dependent kinase inhibitors in minimal change disease and in FSGS, the role of these cell cycle disturbances leading to podocyte proliferation and maturation (5) and the identification of parvovirus B 19 in glomeruli of patients with FSGS (6, 7) are in favor of distinct entities. Moreover, Streulau et al. found TGF-β1 gene expression in 18 of 20 patients with steroid resistant FSGS and in only 3 of 14 steroid-sensitive patients (8). These data support a sequence of immunologically mediated events that contribute to progressive renal damage in children with FSGS.

In the early stages, FSGS and minimal change disease are indistinguishable (9). A significant number of patients with FSGS respond to corticosteroids, whereas some steroid resistant patients have no sclerotic changes on biopsy specimens containing adequate tissue (10, 11). Therefore, some authors believe that, although histological variants of the INS carry prognostic significance, they cannot at present be considered as separate entities (12).

The term minimal change disease has become synonymous with steroid sensitive INS although renal biopsy is usually not performed in patients who respond to steroid therapy. Indeed, in many centers, renal biopsy is recommended only for those patients who fail to respond to steroids. Consequently, renal biopsy findings in recent published series are not representative of the true incidence of various histopathological categories seen in INS. It is therefore more appropriate to classify the patients according to their response to steroid therapy. Response to steroid therapy carries a greater prognostic weight than the histological features seen on initial renal biopsy. Thus, two types of INS can be defined: steroid-responsive nephrotic syndrome, in which the proteinuria rapidly resolves and steroid-resistant nephrotic syndrome, in which steroids do not induce remission.

Epidemiology

The incidence of INS varies with age, race, and geography. The annual incidence in children in the USA and in Europe has been estimated to 1–3 per 100,000 children below age of 16 (13–15), with a cumulative prevalence of 16 per 100,000 children. Similar figures were recently reported from New Zealand (16). Geographical and/or ethnic differences are well known. In the United Kingdom for example, the incidence of INS is sixfold greater in Asian than in European children (17); this is also true for Indians (18), for Japanese and SouthWest Asians. INS is less frequent in Africa (19–21). Such differences underline the role of genetic as well as environmental factors in the pathogenesis of the disease.

Whereas INS accounts for only 25% of adult cases (22), it is by far the most common cause of nephrotic syndrome in children. Almost all nephrotic children between 1 and 6 years of age in Western countries suffer from INS. The International Study of Kidney Disease in Children found minimal change disease in 76.6% of children with primary nephrotic syndrome (13).

There is a male preponderance in children, with a male:female ratio of 2:1 (13, 23), but both sexes are similarly affected in adolescents.

The familial occurrence of INS is well known (see chapter "Genetic").

Associated Disorders

INS is, by definition, a primary disease. Nevertheless, in a number of cases, an upper respiratory tract infection, an allergic reaction, or another factor may immediately precede the development or relapse of the disease.

Many agents or conditions have been reported to be associated with INS such as infectious diseases, drugs, allergy, vaccinations, and malignancies (*Table 28-1*). The question remains whether these factors are real causes, a simple coincidences, or precipitating agents.

Table 28-1

Conditions associated with idiopathic nephrotic syndrome

Allergy
Pollen
Fungi
Cow's milk
House dust
Bee stings
Cat fur
Poison ivy
Drugs
Nonsteroidal antiinflammatory drugs
Ampicillin
Gold
Lithium
Mercury
Trimethadione
Malignancies
Hodgkin disease
Non-Hodgkin lymphoma
Colon carcinoma
Bronchogenic carcinoma
Others
Viral infection
Kimura's disease
Diabetes mellitus
Myathenia gravis
Immunization

Allergy is associated with up to 30% of cases (24–26). Among a list of anecdotal cases, the allergens reported include fungi, poison ivy, ragweed pollen, house dust, jellyfish stings, bee stings and cat fur. A food allergen may be responsible for relapses of steroid-sensitive nephrotic syndrome, such as cow's milk and egg. Laurent et al. evaluated the effect of an oligoantigenic diet given for 10–15 days to 13 patients. This diet coincided with improvement of proteinuria in nine, including complete remission in five (27).

The association between minimal change disease and malignancies mainly concerns lymphomatous disorders: Hodgkin's disease and non-Hodgkin's lymphomas (28, 29). The nephrotic syndrome may be the presenting feature of the disease. It usually disappears after successful treatment of the malignancy. Other types of neoplasia may also be associated with INS as colon carcinoma, bronchogenic, small-cell carcinoma (30).

Eosinophilic lymphoid granuloma in orientals (Kimura's disease) has also been reported in association with INS (31–33).

Several cases of minimal change disease have been reported in association with the onset of insulin-dependent diabetes mellitus. The disease is usually responsive to corticosteroids and follows a relapsing course.

Clinical and Biological Features

The disease may occur during the first year of life, but it usually starts between the ages of 2 and 7 years, with a male to female ratio of 2/1. The onset is often preceded by an upper respiratory tract infection. The disease is characterized by a sudden onset, edema being the major presenting symptom. It becomes clinically detectable when fluid retention exceeds 3–5% of body weight. Periorbital edema frequently misdiagnosed as allergy, is often the initial symptom. Edema is gravity dependent, localized to the lower extremities in the upright position, and to the dorsal part of the body in reclining position. This edema is white, soft, and pitting, keeping the marks of clothes or finger pressure. Anasarca may develop with ascites, and pleural and pericardial effusions. Although there may also be abdominal distension, dyspnoea is rare. Periorbital edema may limit eye opening and edema of the scrotum and penis, or labiae, may be seen. A rapid formation of ascites is often associated with abdominal pain and malaise: these symptoms may also be related to concomitant hypovolemia. Abdominal pain is occasionally due to a complication such as peritonitis, thrombosis or, rarely, pancreatitis. Cardiovascular shock is not unusual,

secondary to the sudden fall of plasma albumin, with abdominal pain and symptoms of peripheral circulatory failure with cold extremities and hypotension. Emergency symptomatic treatment is needed. Blood pressure is usually normal but sometimes elevated (13, 34).

The nephrotic syndrome is occasionally discovered during a routine urine analysis. Macroscopic hematuria is observed in a few cases (34). The disease may also be revealed by a complication. Peritonitis due to *Streptococcus pneumoniae* is a classical mode of onset (35). Deep-vein or arterial thromboses and pulmonary embolism may also occur during the first attack or during a relapse.

Urinalysis

Proteinuria is detected by dipstick testing 3 or 4+. Quantitative evaluation gives figures ranging from less than 1 g to more than 10 g/day. The nephrotic range proteinuria is defined as >50 mg/kg/day or 40 mg/h/m^2 but the mean value during the first days may be higher as the urinary concentration of proteins also depends on the plasma albumin concentration. In young children it may be difficult to perform 24-h urine collection and urinary protein/creatinine ratio or U albumin/U creatinine ratio in untimed urine specimens are useful. For these two indices the nephrotic range is 200–400 mg/mmol (36).

In most cases, proteinuria is highly selective, consisting of albumin and lower molecular weight proteins. The selectivity of proteinuria may be appreciated by polyacrilamide gel electrophoresis or by the evaluation of the Cameron index which is the ratio of IgG (MW 150 kDa) to transferrin (80 kDa) clearances. A favorable index would be below 0.10, or better below 0.05; a poor index is above 0.15 or 0.20. Such poor index is more often associated with FSGS. However, there is a considerable overlap in results and the test has limited value. The amount of protein excreted in the urine does not reflect the quantity of protein crossing the glomerular basement membrane since a significant amount is reabsorbed in the proximal tubule. Some children with severe steroid resistant nephrotic syndrome and tubulo-interstitial lesions have both glomerular and tubular proteinuria with an increased excretion of β-2 microglobulin, retinol binding protein and lysozyme due to an impaired protein reabsorption in the proximal tubule.

The urine sediment of patients with INS often contains fat bodies. Hyaline casts are also usually found in patients with massive proteinuria, but granular casts are not present unless there is associated acute renal failure and acute tubular necrosis. Macroscopic hematuria is rare, occurring in 3% of patients. Microscopic hematuria is present in 20% of cases and has no influence on the response to steroid therapy.

Urinary sodium excretion is low (<5 mmol/24 h), associated with sodium retention and edema. Kaliuresis is usually higher than natriuresis, but it may be reduced in oliguric patients.

Blood Chemistry

Serum proteins are markedly reduced and serum lipid usually increased. Proteinemia is below 50 g/l in 80% of patients, and below 40 g/l in 40%. Albumin concentration usually falls below 20 g/l and may be less than 10 g/l. Electrophoresis shows not only low albumin levels but also increased α-2 globulins and, to a lesser extent, β-globulins, while γ-globulins are decreased. IgG is markedly decreased, IgA slightly reduced, IgM is increased, while IgE is normal or increased. Among other proteins, fibrinogen and β-lipoproteins are increased and antithrombin III is decreased.

Hyperlipidemia is a consequence of (I) an increased hepatic synthesis of cholesterol, triglycerides and lipoproteins, (II) a decreased catabolism of lipoproteins due to a decreased activity of lipoprotein lipase which normally transforms VLDL to LDL via IDL and (III) a decreased LDL receptor activity and an increased urinary loss of HDL (37, 38). Total cholesterol and LDL cholesterol are elevated while HDL cholesterol remains unchanged or low, particularly HDL2, leading to an increased LDL/HDL cholesterol ratio (39). Patients with severe hypoalbuminemia have increased triglycerides and VLDL. Apoproteins, apo B, apo CII, apo CIII are also elevated. The levels of lipoprotein Lp(a) are elevated in nephrotic patients which further contribute to an increased risk of cardiovascular and thrombotic complications.

Serum electrolytes are usually within the normal range. A low sodium level may be related to dilution from inappropriate renal retention of water due to hypovolemia and inappropriate antidiuretic hormone secretion. The mild reduction of plasma sodium concentration is often an artifact related to hyperlipidemia. Serum potassium may be high in oliguric patients. Serum calcium is consistently low as a result of hypoproteinemia. Ionized calcium is usually normal but may be decreased due to urinary loss of 25-hydroxyvitamin D3 (40) and normal but inappropriate levels of calcitriol (41). Blood urea nitrogen and creatinine concentrations are usually within the normal range, or slightly increased in relation to a modest reduction in the glomerular filtration rate (GFR).

A few patients with FSGS and a poor subsequent outcome present with a Fanconi syndrome: glycosuria, aminoaciduria, urinary bicarbonate loss, and hypokalemia (42). A defect in urinary acidification has also been reported (43).

Hematology

Hemoglobin levels and hematocrit are increased in patients with plasma volume contraction. Anemia with microcytosis may be observed, probably related to urinary loss of siderophilin. The urinary loss of erythropoietin may also contribute to anemia (44). Thrombocytosis is common and may reach 5.10^8 or 10^9/l.

Complications

Hypovolemia

A few children are severely hypovolemic and this complication is observed typically early during a relapse (*Table 28-2*). Sepsis, diarrhea or diuretics may precipitate hypovolemia. These children often complain from abdominal pain, have low blood pressure and cold extremities. Hemoconcentration with a raised hematocrit accompanies hypovolemia.

Acute Renal Failure

Renal function is usually within normal limits at presentation. A reduction of the GFR, secondary to hypovolemia, infection or thrombosis is frequent (45, 46). A reduced GFR may be found in patients with normal effective plasma flow. Bohman et al. showed a close relationship between the degree of foot process fusion and both GFR and filtration fraction, suggesting that fusion of foot processes could lead to a reduction of glomerular filtering area and/or of permeability to water and small solutes (47). This reduction is transitory, with a rapid return to normal after remission. Van de Walle et al. found that changes in glomerular permeability may have a major role in acute renal failure (46).

Marked oliguria may occur in children (48). Oliguric renal failure may be the presenting symptom. Renal failure may be secondary to bilateral renal vein thrombosis, which is recognized by sonography or to interstitial nephritis which has been reported, especially with furosemide. Skin rash and eosinophilia are suggestive of this diagnosis.

Acute renal failure is usually reversible, often with high dose furosemide induced diuresis, especially with intravenous infusion of albumin (49). In some cases, where glomerular structure is normal on initial histology, renal failure may last for as long as a year (50) and sometimes be irreversible (51).

Table 28-2
Nephrotic hypovolemia

Clinical features	Precipitating factors
Abdominal pain	Severe relapse
Hypotension	Infection
Sluggish circulation	Diuretics
Relative polycythemia	Paracenthesis
Acute tubular necrosis	Diarrhea
Thrombosis	

Chronic Renal Failure

The main difference between responders and nonresponders is the tendency of the latter to develop end-stage renal failure, which is seen in less than 3% of responders, even in the highly-selected series. This complication occurs in 50% or more of the steroid resistant patients after a follow-up of 10 years. The only "benefit" of the decrease of GFR is the improvement of the nephrotic syndrome due to a decrease of proteinuria.

We have retrospectively analyzed in the Enfants Malades series the outcome of 181 children with steroid resistant INS who have been followed for at least 5 years. Eighty-five percent were primary nonresponders and 15% late nonresponders. Initial renal biopsy had shown minimal changes in 62 cases and FSGS in 119 cases. Renal survival rates were 65% at 5 years, 50% at 10 years and 34% at 15 years. Interestingly, the rate of progression to end stage renal failure was similar in patients with minimal changes or FSGS on initial biopsy.

The data reported in other series are difficult to compare as most of them deal with patients with FSGS. The Southwest Pediatric Nephrology Study group reported 75 children with FSGS followed for periods of 7–217 months (52). Twenty-one percent had progressed to end stage renal failure, 23% had decreased glomerular filtration rate, 37% had a persistent nephrotic syndrome and 11% were in remission. Paik et al. retrospectively analyzed 92 children with steroid resistant FSGS and found renal

survival rates at 5, 10 and 15 years of 84, 64 and 53% respectively (53). Poor pronostic factors of chronic renal failure were asymptomatic proteinuria at presentation, initial renal failure and higher proportion of glomeruli with segmental sclerosis.

Progression to end stage renal failure has been reported to be more rapid in patients of African or Hispanic descent when compared with Caucasians. Ingulli and Tejani found that among 57 African American and Hispanic children, 50% of them had reached end stage renal failure within 3 years and 95% had reached this stage after 6 years (54). In addition, among the children with INS, the proportion of those with steroid resistant FSGS tends to be more important in African American and Hispanic children.

Growth

Growth may be severely affected in children with persistent nephrotic syndrome. Depletion of hormones due to urinary losses is a possible cause of stunting. Hypothyroidism related to urinary loss of iodinated proteins has been observed and may be corrected (55). A low plasma IgF1 and IgF2 level associated with a urinary loss of the carrier proteins has also been reported (56).

Infections

Bacterial infections are frequent in nephrotic children (*Table 28-3*). Sepsis may occur at the onset of the disease. The most common infection is peritonitis, often with *Streptococcus pneumoniae* (57). Other organisms may be responsible: *E. coli*, streptococcus B, *Haemophilus influenzae* and other gram negative organisms. Apart from peritonitis, children may develop meningitis, pneumonitis and cellulitis. Several factors may explain the propensity of nephrotic children to develop bacterial infections: low IgG levels due to an impaired synthesis, urinary loss of factor B and impaired T lymphocyte function. Factor B is a cofactor of C3b of the alternative pathway of complement which has an important role in opsonization of bacteria such as *Streptococcus pneumoniae*.

Viral infections may be observed in patients receiving corticosteroids or immunosuppressive agents. Chickenpox is often observed in these young children and may be life-threatening if acyclovir is not started rapidly. Interestingly, measles infection may induce long-lasting remissions.

Thrombosis

Nephrotic patients are at risk of developing thromboembolic complications. Arterial thrombosis is less frequent (19–27%) compared to venous thrombosis (73–81%) (58, 59). Several factors contribute the increased risk of thrombosis, including hypercoagulability state, hypovolemia, immobilization and infection (*Table 28-4*). A number of hemostatic abnormalities have been described in nephrotic patients: increase in platelet aggregability, increase in fibrinogen, factors V, VII, VIII, X and XIII while the levels of anti-thrombin III, heparin cofactor, protein C, protein S, factors XI and XII are decreased, increase in the fibrinolytic system components such as tPA, PAI-1 (58). The incidence of thromboembolic complications in nephrotic children is close to 3%. However this percentage may be underestimated as shown by systematic ventilation-perfusion scans showing defects consistent with pulmonary embolism in 28% of patients with steroid dependent INS (60). Pulmonary embolism should be suspected in cases of pulmonary or cardiovascular symptoms; this may be confirmed by angiography or angioscintigraphy. Renal vein thrombosis should be suspected in cases with sudden macroscopic hematuria or acute renal failure. Doppler ultrasonography shows an increase in kidney size and the absence of blood flow in

Table 28-3

Infections in nephrotic syndrome

Clinical syndrome	Risk factors
Pneumococcal peritonitis	Low IgG
Haemophilus infection	Low factor B
Gram negative sepsis	Edematous tissue
Staphylococcus cellulitis	Impaired lymphocyte function
	Corticosteroids
	Immunosuppressive drugs

Table 28-4

Thrombosis in nephrotic syndrome

Clinical syndrome	Risk factor
Pulmonary emboli	Hypovolemia
Pulmonary artery thrombosis	Hyperviscosity
Cerebral venous thrombosis	Low anti-thrombin III
Renal vein thrombosis	High fibrinogen
Peripheral venous	Platelet hyperaggregability
Artery thrombosis	Hyperlipemia

the renal vein. Thrombosis may affect the arteries such as pulmonary arteries or other deep veins.

Renal Biopsy

Renal biopsy is usually not indicated before starting corticosteroid therapy. It is only indicated in children less than 1 year of age, when the child has macroscopic hematuria or hypertension or low C3 levels or persistent renal failure and when the child fails to respond to corticosteroid therapy. A renal biopsy may be indicated in patients who relapse before considering alternative therapy, namely anticalcineurin agents.

Light microscopy shows three morphological patterns: minimal changes, diffuse mesangial proliferation, and FSGS.

Minimal Change Nephropathy

On light microscopy, glomeruli may be normal with normal capillary walls and normal cellularity (*Fig. 28-1*). Swelling and vacuolation of epithelial cells and a slight increase in mesangial matrix are often observed. A mild mesangial hypercellularity may be noted (61) as well as scattered foci of tubular lesions and interstitial fibrosis.

Ultrastructural changes are always present, involving podocytes and mesangial stalks. Podocyte foot process fusion is generalized and constant (*Figs. 28-2* and *28-3*); its extent is closely related to the degree of proteinuria (62). Other epithelial changes consist of microvillus formation and the presence of numerous protein reabsorption droplets. The glomerular basement membranes are normal with no parietal deposits.

Figure 28-1

Minimal change disease. Glomeruli appear normal by light microscopy with no tubulointerstitial lesions.

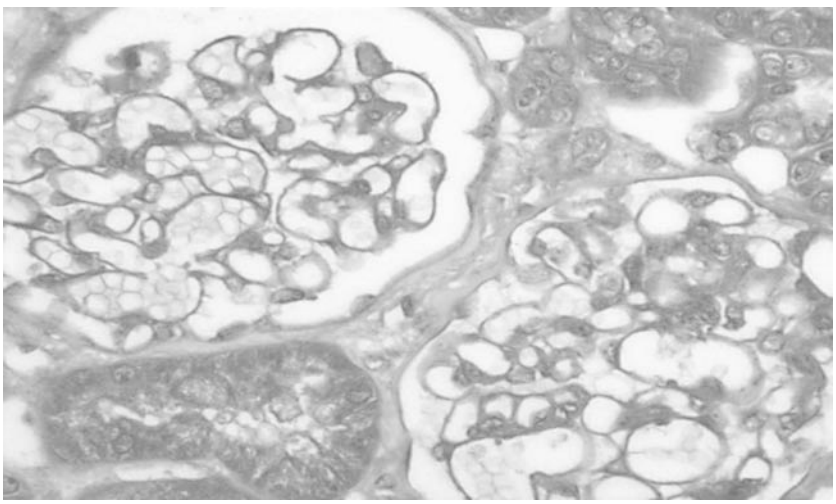
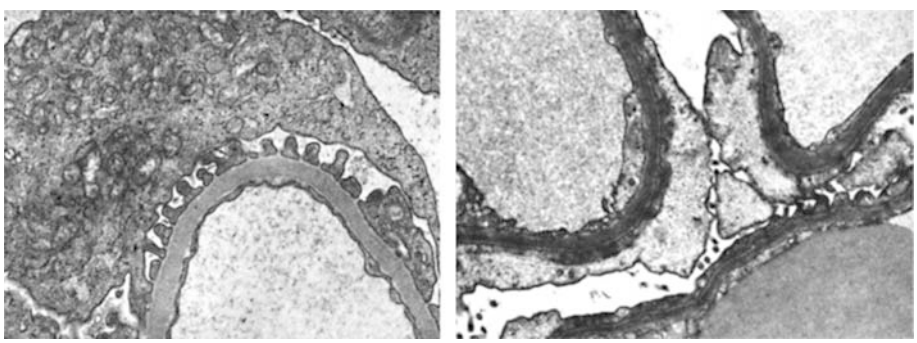


Figure 28-2

Electron microscopy. On the *left*, normal aspect with the podocyte foot processes attached to the glomerular basement membrane. On the *right*, minimal change disease with effacement of foot processes.



The endothelial cells are often swollen (63). Mesangial alterations include mesangial cell hyperactivity, increased mesangial matrix, and occasionally finely granular, osmiophilic deposits located along the internal side of the basement membrane. These ultrastructural alterations are nonspecific and are probably related to massive proteinuria.

Diffuse Mesangial Proliferation

Some patients with steroid resistant INS show a marked increase in mesangial matrix associated with hypercellularity (*Fig. 28-4*) (61, 64, 65). However, peripheral capillary walls are normal, and immunofluorescence microscopy is negative. Electron microscopy shows foot process fusion similar to the changes observed in minimal change disease. The presence of mesangial hypercellularity has been found to have prognostic significance with a higher rate of progression to renal failure (64) but these findings were not confirmed by other authors (52, 66).

Focal and Segmental Glomerular Sclerosis

The glomerular lesions affect a variable proportion of glomeruli (10, 61). The focal changes are limited to a part of the tuft, the other capillary loops showing no modification. The lesions always predominate at the corticomedullary junction (67). The segmental lesion affects a few capillary loops which stick together either at the

Figure 28-3

Scanning electron microscopy showing the normal aspect of podocytes with their foot processes on the *left* and their effacement in minimal change disease on the *right*.

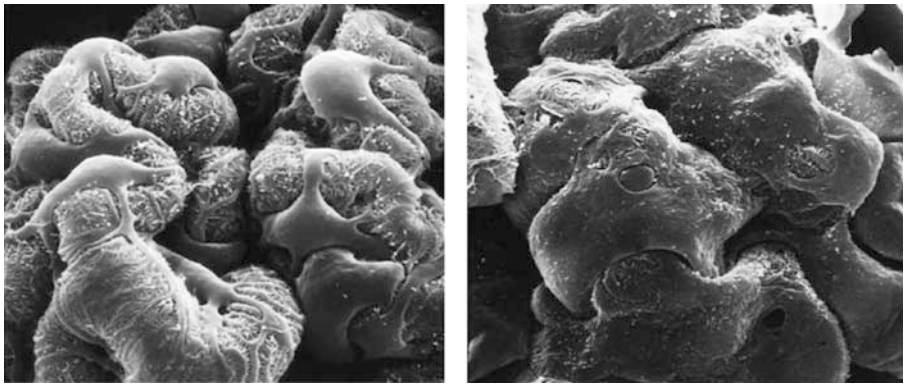
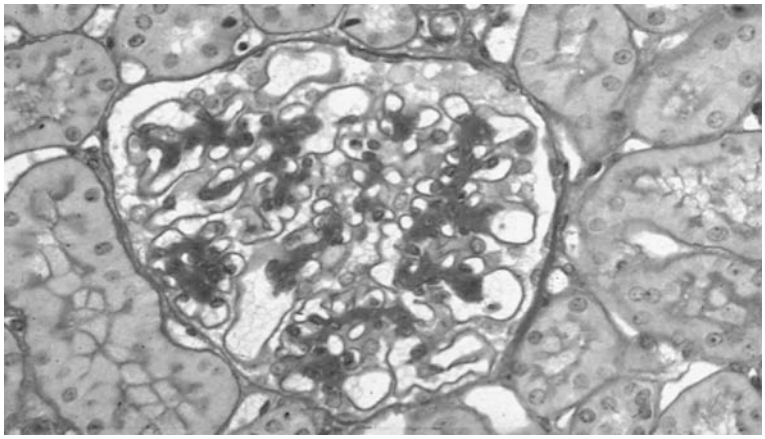


Figure 28-4

Diffuse mesangial proliferation with an increased number of mesangial cells and mesangial matrix.



hilum or at the periphery of the tuft, or at both (Fig. 28-5) (68, 69). The clinical course has been found to be more benign when the location of these sclerotic lesions is peripheral (the tip-lesion), although such findings have not been confirmed by other authors (67, 70–72). Hyaline material is often present within the sclerotic lesions. A clear "halo" zone is observed at the periphery of the sclerotic segments (Fig. 28-6). The segmental lesion has a different aspect depending on whether it affects a group of capillary loops free in Bowman's space or is adherent to Bowman's capsule. The "free" sclerotic segments are always surrounded by a "crown" of flat or hypertrophied podocytes. The podocytes form a continuous layer overlying the damaged areas of the tuft and in close apposition to the clear "halo." When the sclerotic lesion is adherent to Bowman's capsule, there is a direct synechia between the collapsed capillary loops and Bowman's basement membrane. The rest of the tuft and the nonsclerotic glomeruli show either "minimal changes" or "diffuse mesangial proliferation"

Figure 28-5

FSGS. In early stage, there is a segmental collapse of glomerular capillaries surrounded by hypertrophic podocytes containing intra-cytoplasmic vacuoles.

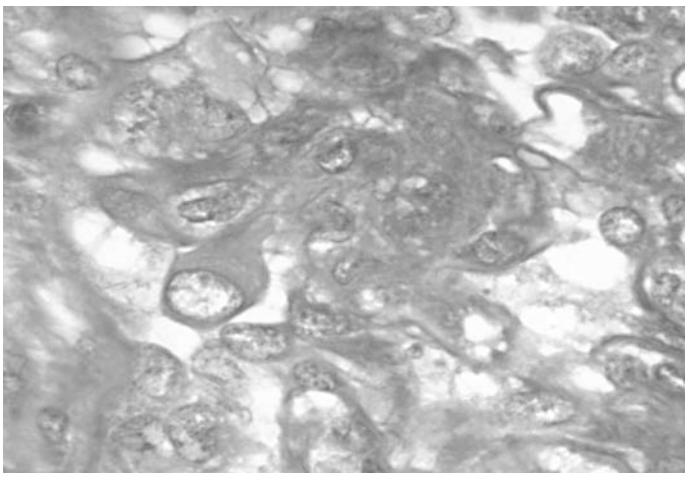
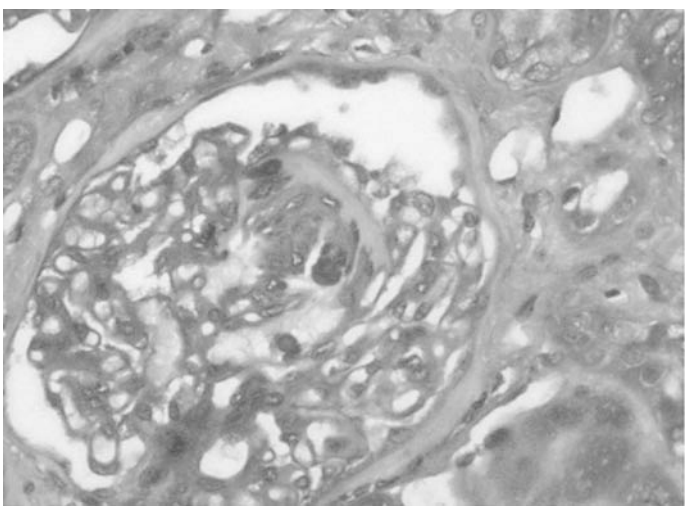


Figure 28-6

FSGS. Segmental lesion of the tuft characterized by the deposition of hyaline material at the inner side of the glomerular basement membrane with a ring of podocytes separated from the glomerular basement membrane by a clear ''halo.''



both with foot process fusion. Glomerular hypertrophy is common in FSGS, and when such hypertrophy is found in minimal change disease, it is somewhat predictive of further development to FSGS (73, 74).

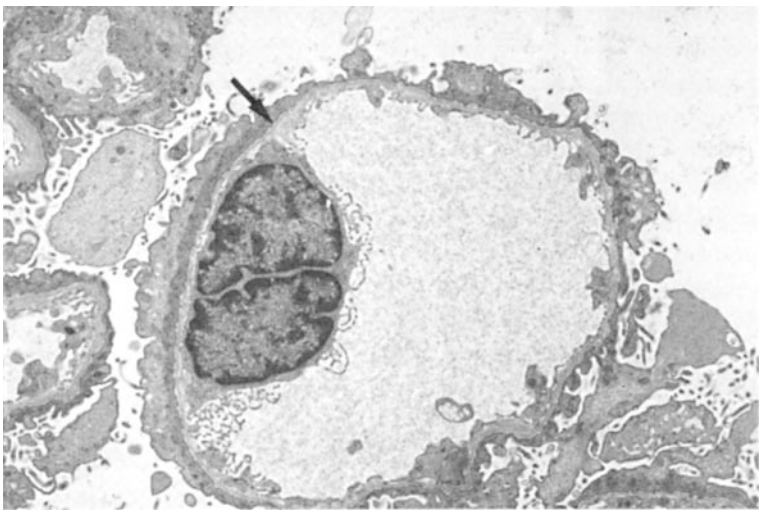
Tubular atrophy and interstitial fibrosis are often present and apparently proportional to the glomerular damage (10, 75). Focal glomerular lesions should therefore be suspected when focal tubular and interstitial changes are found associated with minimal glomerular changes. Erkan et al. found apoptosis in proximal and distal tubular cells of children with idiopathic FSGS (76). There was a correlation between the degree of proteinuria and the number of apoptotic cells. An elevated tubule cell apoptosis rate at the time of initial biopsy was found to be an independent predictor of progression to end stage renal disease.

On electron microscopy, the lesion is characterized by the presence of paramesangial and subendothelial, finely granular, osmiophilic deposits (75, 77, 78) with either disappearance or swelling of endothelial cells, and an increase in mesangial matrix material (*Fig. 28-3*). Fatty vacuoles may be seen, either in the middle of the abnormal deposit or in the cytoplasm of endothelial and mesangial cells. The peripheral synechia, located between podocytes and basement membrane, is formed by the apposition of acellular material in which thin and irregular layers of newly formed basement membranes are visible. Modifications of the podocytes consist of focal cytoplasmic degeneration, breakdown of cell membranes, and detachment of epithelial cells from basement membranes, with filling of the resulting space by cell debris and new membranes (79).

A pathologic classification of FSGS has been proposed with five histologic variants: FSGS not otherwise specified (NOS), perihilar variant, cellular variant, tip variant, and collapsing variant (80). All variants share podocyte alterations. This classification may have clinical implications in terms of response to therapy and risk of progression to renal failure. For example, glomerular tip lesions have been associated with better outcomes and collapsing variant with worse outcomes (71, 72). The glomerular tip lesion was found to be a predictor of a favorable response to therapy in a pediatric series (81). At present, this classification has no implication for treatment options.

A subgroup of patients have collapsing focal segmental glomerular sclerosis characterized by a global collapse of the glomerular capillaries with marked hypertrophy of epithelial cells (*Fig. 28-7*) (82). These patients have a severe nephrotic syndrome and rapidly progress to renal failure. The rate of response to steroids is poor. The incidence of collapsing glomerulopathy seems to have increased in the recent years. The main cause of secondary collapsing glomerulopathy is HIV associated nephropathy (83). Many authors consider that "collapsing glomerulopathy" is a distinct form of FSGS which may be "idiopathic," also observed in patients with recurrent nephrotic syndrome after renal transplantation, associated with HIV, parvovirus B19 infection or CMV infection (84, 85). Idiopathic

Figure 28-7
Collapsing glomerulopathy.



collapsing glomerulopathy predominates in blacks and has a poor prognosis (86).

FSGS is characterized by important changes in the podocytes, with major cell cycle derangement (3, 4). The normal mature podocyte does not divide and does not express proliferative markers such as PCNA and Ki-67. The podocyte express several cell surface proteins such as WT-1, C3b receptor, glomerular epithelial protein-1 (GLEPP-1), podocalyxin, synaptopodin and vimentin. The first stages of FSGS are characterized by the loss of the cell surface proteins (de-differentiation) and the expression of macrophage markers and cytokeratin (trans-differentiation). Proliferations markers (PCNA and Ki-67) are expressed, indicating a mitotic activity. This "podocyte dysregulation" is accompanied by podocyte detachment from the glomerular basement membrane.

FSGS is an irreversible scarring process in the glomeruli, as shown by the analysis of repeat biopsies (77, 78, 87). Studies in experimental animals (88) as well as in nephrotic patients have shown that proteinuria precedes the development of focal sclerotic lesions. The same sequence was reported in patients with recurrence of the disease after transplantation. Within weeks following recurrence of proteinuria podocytes observed by electron microscopy appear swollen and vacuolated. The podocytes exhibit strong mitotic activity, with multinucleation and expression of the PCNA and Ki-67 proliferation markers.

FSGS is not a specific histopathological lesion: similar alterations may be seen in persistent idiopathic proteinuria, heroin-associated nephropathy and, independently, in association with HIV infection, Alport's syndrome, hypertension, pyelonephritis, and obesity. It has also been reported in renal hypoplasia with oligomeganephronia, after partial nephrectomy and in other conditions with a reduction in nephron number, including reflux nephropathy or obstructive uropathy.

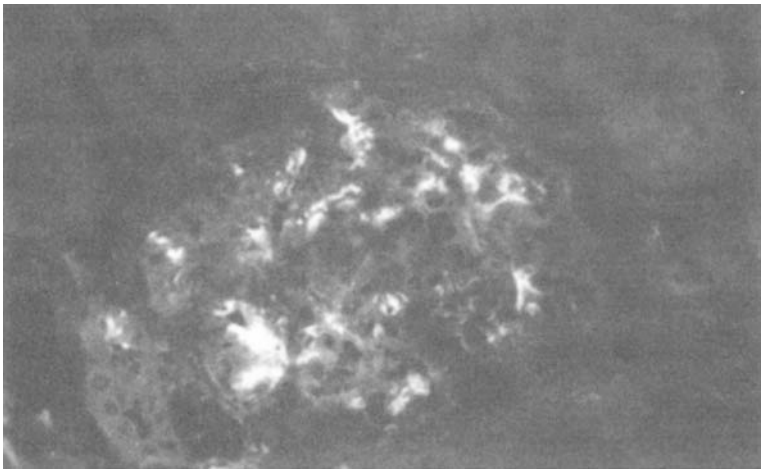
IgM Associated Nephropathy

Immunofluorescence microscopy is usually negative (89, 90). However, mesangial deposits of IgM, IgG, C3 and more rarely IgA have been reported. The most commonly found is IgM (*Fig. 28-8*) and Cohen et al. found that patients with IgM deposits in the mesangium had a poor response to corticosteroids (91). Other studies did not confirm these findings. Habib et al. reported on immunofluorescence studies in a series of 222 children with INS (92). Although IgM was the immunoglobulin most frequently present in the glomeruli (54 of 222), there was no correlation between IgM deposits, the initial response to steroid therapy or the final outcome. IgM deposits have also been described in association with diffuse mesangial proliferation and with FSGS.

A number of patients with INS display mesangial deposits of IgA. They are classified by some as IgA nephropathy. Others consider that mesangial IgA in patients with nephrotic syndrome and minimal changes, that is, without cellular proliferation is coincidental (92–94). This applies to INS associated with mesangial IgA deposits and explains a rapid response to steroids, which would not be the case in true IgA nephropathy.

Figure 28-8

INS with minimal changes. Diffuse mesangial deposits of immunoglobulin M.



Relationship Between the Different Histological Patterns

Repeat renal biopsies in patients with INS have shown morphological transition between the three main histological patterns. Some patients with clear evidence of minimal changes on initial biopsy have FSGS on a second biopsy. A high proportion of these patients are steroid-resistant. Tejani found that FSGS lesions had developed in 60% of 48 patients with steroid resistant minimal change disease, in association with aggravation of symptoms (95). The progression to sclerosis may occur from minimal change or from mesangial proliferation (64, 96). Conversely, some patients who show diffuse mesangial proliferation, whether or not associated with focal sclerosis on initial biopsy, may loose hypercellularity with time and show minimal change or FSGS on repeat biopsy (52).

In conclusion it may be considered that, at least in children, minimal change disease, FSGS, and diffuse mesangial proliferation represent histological variations of INS which may be found alone or in any combination on sequential biopsies in the same patient.

Clinicopathologic Correlations

The relative frequencies of the three histologic patterns differ in steroid sensitive and steroid resistant patients. A report of the International Study of Kidney Disease in Children showed that among 354 patients with INS who had an initial response to prednisone, 95.5% had minimal change disease, 3% had FSGS and 1.5% had diffuse mesangial proliferation (97). Conversely, among 55 patients who had failed to respond to prednisone, 45.5% had minimal change disease, 47.5% had FSGS and 7% had diffuse mesangial proliferation. This study also analyzed the numbers of responders and nonresponders within each histologic category. Among the 363 patients with minimal changes, 91.8% were responders and 6.9% nonresponders whereas among the 37 patients with FSGS, 29.7% responded to prednisone and 70.3% did not. Waldherr et al. found that only 2 out of 36 patients with diffuse mesangial proliferation responded to corticosteroids (64). An increase in steroid resistance has recently been reported in patients with FSGS (98).

Pathophysiology

Mechanisms of Proteinuria

In normal individuals, the clearance of albumin is about 1% of that of neutral proteins with similar molecular weight, 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 glomerular basement membrane is responsible for the charge selectivity of filtration. The anionic (negative) charges of the glomerular basement membrane repulse the negatively charged albumin molecules, whose isoelectric point is 4.6.

The mechanism of proteinuria in the absence of histological alterations on light microscopy has suggested an electrochemical disorder of the GBM. Indeed it was shown that the glomerular K_f is diminished despite increased permeability to serum albumin. Using polyvinylpyrrolidone (99) or dextrans (100) with Einstein–Stokes radii between 2.0 and 4.8 nm as test macromolecules, the pore-size of the GBM was shown to be reduced contrasting with massive albuminuria. This suggested a loss of glomerular negative charges. Kitano et al., using polyethylamine as a cationic probe, reported a decrease in the anionic charges of the GBM in minimal change disease (101). Carrie et al. studied renal biopsy sections stained by colloidal iron and showed that its glomerular uptake was markedly reduced (100). A reduced sialic acid content in the GBM, as sialic acid residues may be responsible for glomerular negative charges (102).

Van den Born et al. produced a mouse monoclonal antibody to partially purified heparan sulfate proteoglycan isolated from rat glomeruli (103). By indirect immunofluorescence, the monoclonal antibody bound to the GBM on rat kidney sections. By electron microscopy a diffuse staining of the GBM was observed. After intravenous injection, the monoclonal antibody was localized along the GBM with a granular staining, and 1 day later in the mesangium with a concomitant decrease in staining along the GBM. By electron microscopy, 1 h after injection, the antibody was bound mainly to the inner side of the GBM. Intravenous injection of this antibody in rats resulted in selective proteinuria. This model shows that neutralization of heparan sulfate anionic charges may contribute to albuminuria.

Levin et al. and Boulton-Jones et al. presented data indicating that loss of negative charges was not restricted to the glomeruli but was also found on erythrocyte and platelet membranes, as shown by reduced binding of Alcian blue, a cathionic dye (104, 105). A cathionic protein is found in the plasma and the urine of patients in relapse.

The Immune System in Steroid-Responsive INS

In 1974, Shalhoub postulated that INS might be secondary to a disorder of T-lymphocyte function (106). He hypothesized that the expansion of a T-lymphocyte clone might results in the production of a lymphokine, which increases the permeability of the glomerular filtration barrier to proteins. The arguments supporting this hypothesis were the response of the disease to corticosteroids and to alkylating agents, the remission occurring in association with measles, which depresses cell-mediated immunity, the susceptibility of patients to pneumococcal infections and the occurrence of minimal change nephrotic syndrome in patients with Hodgkin's disease. There are other arguments for the role of a circulating permeability factor produced by mononuclear cells in the pathogenesis of the disease (107–109). The immediate recurrence of proteinuria after renal transplantation in some patients (110), the disappearance within few weeks of proteinuria when a kidney from a patient with MCD has been transplanted in a patient without nephrotic syndrome (111), the development of transient neonatal proteinuria and hypoalbuminemia in two children born to a woman with steroid resistant FSGS that disappeared within 2 and 3 weeks respectively (112), the onset of proteinuria in rats following the injection of serum taken from patients with recurrence after renal transplantation (113). The Buffalo/Mna strain of rats spontaneously develops proteinuria with FSGS at 2 months of age. Le Berre et al. found that the nephrotic syndrome recurs when Buffalo/Mna rats receive a kidney from a healthy LEW.1W rat (114). Conversely, proteinuria and renal lesions regress when kidneys from a Buffalo/Mna rat are transplanted into normal LEW.1W rats. Although recurrence of proteinuria is not immediate after transplantation, this model may be helpful to clarify the pathogenesis of the disease and the mechanisms of recurrence after transplantation in man. However, this putative factor has not yet been identified, and it is currently unclear whether INS may be caused by several different factors, and whether this or these factors are identical in MCD and FSGS (115).

Lagrue et al. first described the vascular permeability factor (VPF), a lymphokine found in the supernatant of concanavalin A-activated lymphocytes from patients with MCD which enhances vascular permeability when injected intradermally in the guinea pig (116). Heslan et al. showed that VPF was produced by T lymphocytes and was distinct from interleukin-2 (117, 118). Maruyama et al. showed that cyclosporine at concentrations ranging from 100 to 250 ng/ml was able to suppress the in vitro production of VPF by mononuclear cells from patients with MCD (119). VPF was also found in other diseases such as IgA nephropathy. Tanaka et al. found that the supernatants of concanavalin A-activated lymphocytes from patients with MCD or FSGS induced a marked proteinuria when injected in the renal artery of rats together with a reduction of the anionic charges of the GBM (120). Koyama et al. described a glomerular permeability factor (GPF) in the supernatant of T cell hybridoma derived from the fusion between peripheral T lymphocytes of a patient with MCD and a T cell line, CCRF-HSB2 (121). The GPF was identified by the ability of the supernatant to induce a proteinuria when injected intravenously in the rat. In addition, rats injected with the supernatants show a partial fusion of foot processes of glomerular epithelial cells and no immune deposits. GPF is different from the other known lymphokines. Its molecular weight is between 60 and 160 kDa.

Savin et al. found in some patients with FSGS the presence of a serum factor which increases the albumin permeability of isolated rat glomeruli. The presence of the factor was strongly predictive of the recurrence of proteinuria after renal transplantation (109). A vascular permeability factor, which induces proteinuria when injected into the renal artery of rats, was found in the serum from a transplanted patient who had recurrence of the nephrotic syndrome (113), but many similar attempts to isolate such a factor have failed. Dantal et al. treated patients who had recurrent nephrotic syndrome with plasma protein-A adsorption (122). The administration to rats of material eluted from the protein A columns increased urinary albumin excretion. The active fraction had a molecular weight below 100,000 Da. The factor or factors that may be responsible for recurrent nephrotic syndrome after transplantation seem to be bound to an immunoglobulin (123).

Proteomic analysis of the fractionated serum from children with FSGS identified ten proteins that maintain increased glomerular permeability to albumin including: fibulin, clusterin (apo J), vitronectin, albumin isoforms, γ chain of fibrinogen, and mannan-binding lectin-associated serine protease (124).

Several lymphokines may play a pathogenic role (*Table 28-5*) (125). Increased interleukin-2 levels have been found in lymphocyte culture supernatants from patients with INS and interleukin-2 can induce proteinuria and a reduction of the anionic sites of the GBM when injected into the rat kidney (126). A nephrotic syndrome has been described in several patients treated with

Table 28-5

The role of lymphokines in idiopathic nephritic syndrome (reviewed in (133))

	IL-1	IL-2	IL-2R	INF-γ	IL-4	IL-6	IL-8	IL-10	IL-12	IL-13	IL-18	TNF-α	TGF-β	VPGF
Cytokine levels in serum of INS patients in relapse	N (134–136)	N (136–138) ↑ (135)	N (137, 139) ↑ (135, 140–142)	N (136, 138) ↑ (135, 137)	N (137, 138) ↓ (135)		N (143) ↑ (137, 144) ↓ 2 (135)	N (135, 138)				N (135, 136, 138) ↑ (134)		
Cytokine levels in serum of INS patients in remission	N (134, 135)	N (135, 137, 138)	N (135, 137, 139, 140, 142, 145)	N (135, 138) ↑ 4 (137)	N (135, 138) ↑ 4 (137)		N (135, 138, 144)	N (135, 138)				N (134, 135, 138)		
Cytokine levels in culture supernatants		N (136, 146) ↑ (137, 139, 147) ↓ (148, 149)	↑ (139) ↓ (142)	N (136, 137, 150) ↑ (139) ↓ (149, 150)	N (149, 151) ↑ (137, 139, 151, 152)	N (134)	N (137)	↑ (139, 149) ↓ (153)	↑ (154)		N (150) ↑ (155)	↑ (134, 136, 139, 156)		
Cytokine levels in culture supernatants from INS patients in remission		N (137, 139, 146) ↑ (149) ↓ (148)	N (139, 142)	N (137, 139, 150) ↓ (149)	N (137, 139) ↓ (149)	N (134)	N (137)	N (139, 153) ↓ (149)	N (150, 154)			N (134, 156) ↑ (139)		
Cytokine mRNA expression in INS patients in relapse		N (127) ↑ (138)		N (127, 138)	N (127, 138) ↑ (151)		↑ (151, 157)	↑ (138)		↑ (127)		N (138, 157) ↑ (134)	N (157)	N (157)
Cytokine mRNA expression in INS patients in remission		N (127, 138)		N (127, 138)	N (127, 138)		N (151, 157)	N (138)		N (127)		N (134, 138, 157)	N (157)	N (157)

Table 28-5 (Continued)

	IL-1	IL-2	IL-2R	INF-γ	IL-4	IL-6	IL-8	IL-10	IL-12	IL-13	IL-18	TNF-α	TGF-β	VPGF
Intracellular cytokine production in INS patients in relapse		↑ (158)		N (158–160)	N (159, 160) ↓ (158)	↓ (158)				↑ (127, 159)				
Intracellular cytokine production in INS patients in remission		N (158)		N (158–160)	N (158–160)	↓ (158)				N (127, 159)				

recombinant IL-2 and alpha-interferon. However, Heslan showed that the complete removal of IL-2 from concentrated supernatants by immunoadsorption experiments did not affect the VPF activity. More convincing is the upregulated IL-13 gene expression in both CD4+ and CD8+ T cells in children with steroid-sensitive INS during relapse (127). IL-13 is one of the cytokines secreted by T helper 2 (Th2) T cells, and it has been shown that activated T cell activation early evolves toward Th2 phenotype in minimal change disease (128). In addition, genetic polymorphisms in the *IL-13* gene correlate with long-term outcome of minimal change disease (129). Indeed, the frequency of the AAT haplotype was higher in children with persistent relapses after 5 years from onset, whereas the haplotype GCC was associated with long-term remission. Receptors for IL-13 have been found in podocytes, with direct effects of IL-13 on podocytes and their signaling pathways (130). The IL-13 promoter contains two NFkB responsive elements and high and sustained plasma levels of NFkB have been detected during relapse (131), suggesting a potential role of this pathway in INS. NFkB is down-regulated by IkBa. Sahali et al. demonstrated low levels of IkBa and down-regulation of its mRNA during relapse (131). This may lead to an explanation of the additive effects of steroids and cyclosporine treatment in INS since steroids are thought to induce a transactivation of the IkBa gene while cyclosporine blocks the degradation of the active form of IkBa (132).

The type of cell producing the circulating factor also remains unclear. Sellier-Leclerc et al. developed a humanized mouse model of INS by injecting CD34(+) stem cells or CD34(−) peripheral blood mononuclear cells from affected patients into immunocompromised NOD/SCID mice (161). Only the injection of CD34(+) stem cells induced albuminuria and effacement of podocyte foot processes. These data suggest that the cells involved in the pathogenesis of INS are more likely to be immature differentiating cells rather than mature peripheral T cells.

It was hypothesized that the increased glomerular permeability to albumin may be caused not only by the production of permeability factors but also by the lack of their inhibitors such as apolipoproteins. Sharma et al. showed in several vertebrate species that normal human serum prevents the increased permeability to albumin induced by FSGS serum (162). Inhibitors of the plasma factors may be lost in urine in patients with INS, and their presence in urine has been documented. Urine from patients but not normal urine can block the increased albumin permeability induced by serum from patients with INS in isolated rat glomeruli (163). Candiao et al. demonstrated that components of high-density lipoproteins prevent glomerular albumin permeability induced by serum from patients with FSGS (164). Decreased plasma levels and glomerular expression of clusterin (ApoJ) was demonstrated in FSGS; this suggests a possible role of this protein as the inhibitor of plasma PF (165). In conclusion, the potential of FSGS serum to increase glomerular albumin permeability may result from an imbalance between permeability factors and their natural inhibitors.

Treatment

Symptomatic Treatment

Diet

Dietary therapy should include a protein intake of around 130–140% of the recommended daily allowance according to statural age. Salt restriction is advised for the prevention and the treatment of edema. A very low salt diet is only necessary in cases of massive edema. Fluid restriction is recommended for moderate to severe hyponatremia (plasma sodium concentration less than 125 meq/l). A reduction of saturated fat is recommended. Carbohydrates should be given preferentially as starch or

dextrin-maltose, avoiding sucrose which increases lipid abnormalities.

Hypovolemia

Hypovolemia occurs as a consequence of rapid loss of protein, and is sometimes aggravated by the use of diuretics. This complication needs emergency treatment by rapid infusion of plasma (20 ml/kg) or albumin 20% (1 g/kg) administrated with control of heart rate, respiratory rate and blood pressure.

Diuretics

Diuretics should only be used in cases of severe edema, after hypovolemia has been corrected. Furosemide is administered at a dose of 1–2 mg/kg. If not effective, spironolactone (5–10 mg/kg) or amiloride (0.2–0.5 mg/kg) may be prescribed if the plasma creatinine concentration is normal (166). Patients with severe edema may be treated with furosemide or, if necessary, furosemide plus albumin to increase the rate of diuretic delivery to the kidney. This approach is immediately effective but not long-lasting. Moreover, respiratory distress with congestive heart failure have been observed in some patients (167).

Refractory edema with serious effusions may require drainage of ascites and/or pleural effusions. Immersion of the body up to the neck in a bath may be helpful in these cases (168).

Thromboemboli

Nephrotic patients with severe hypoalbuminemia are at risk for thromboembolic complications. Prevention of this complication includes mobilization, avoidance of hemoconcentration due to hypovolemia and early treatment of sepsis or volume depletion. Prophylactic warfarin therapy may be given to high risk patients with a plasma albumin concentration below 20 g/l, a fibrinogen level over 6 g/l, or an antithrombin III level below 70% of normal. Patients at risk may also be treated with low-dose aspirin and dipyridamole.

Heparin is given initially if thrombi do occur, alone or with thrombolytic agents. The heparin dose necessary to obtain a therapeutic effect is often greater than normal due to decreased the antithrombin III level.

Antihypertensive Drugs

Any arterial hypertension has to be carefully controlled, using preferably a β-blocker or a calcium channel blocker during acute episodes. In cases of permanent hypertension, an angiotensin converting enzyme inhibitor is preferred.

Infections and Immunisations

Prophylaxis of S pneumoniæ with oral penicillin is often applied in patients during the initial treatment with corticosteroids. Pneumococcal vaccine may be performed and is not associated with an increased risk of relapse (169). In cases of peritonitis, antibiotics against both S pneumoniæ and gram-negative organisms are started after peritoneal liquid sampling. Varicella is a serious disease in patients receiving immunosuppressive treatment or daily corticosteroids. Varicella immunity status should be checked in these patients. In cases of exposure, early preventive treatment by acyclovir must be instituted. Varicella vaccination is safe and effective if the child is in remission even if he is on low-dose alternate day steroids (170, 171).

Hyperlipidemia

Persistent hyperlipidemia is a risk factor for atherosclerosis and may play a role in the progression of chronic renal failure. Experience with hypolipidemic drugs in nephrotic patients is still limited but it seems that statins are effective and able to decrease hypercholesterolemia (172, 173). Although long-term side effects of these drugs are not known, it is reasonable to consider a lipid-lowering regimen in children with a persistent nephrotic syndrome (174).

Miscellaneous

Calcium metabolism may be altered by the urinary loss of 25-hydroxycholecalciferol and its carrier protein. Preventive treatment with vitamin D supplements is therefore useful but does not completely prevent bone loss (175). Thyroxine substitution may be indicated, but only in patients with documented hypothyroidism due to urinary loss of iodinated proteins.

Specific Treatment

Steroid therapy is applied in all cases of INS whatever the histopathology, even in patients with FSGS. The majority of patients are steroid-responsive (*Table 28-6*). Urine protein profile (proteome) may in the future help to predict the response to steroid therapy (176). Steroid responders may relapse, but the majority still responds to steroids over the subsequent course. Only 1–3% of patients initially steroid-sensitive subsequently become steroid-resistant and are defined as "late non-responders" (177).

Initial Treatment

Although steroid therapy is often started immediately following the diagnosis of nephrotic syndrome, it should be stressed that spontaneous remission occurs in 5% of cases within 1 or 2 weeks. Therefore, initiation of steroid therapy may be delayed for a few days (178). Some of these early spontaneous remissions are definitive. Infection must be treated before starting steroids, not only to prevent the risk of overwhelming sepsis during treatment, but also because occult infection may be responsible for steroid resistance (17).

Steroid therapy is started when the diagnosis of INS is most likely in a child older than 1 year and younger than 11 years of age, without hypertension, gross hematuria or extra-renal symptoms and normal complement levels. In some cases, the treatment is started after a renal biopsy has been performed. Prednisone remains the reference drug. Prednisolone has the advantage of being soluble in water, making treatment easier in young children, but it may fail to induce remission in some patients who respond quickly to the same dosage of prednisone. The differences in intestinal absorption and drug interactions, for instance with aluminum gels, may explain lesser efficacy in some children.

The ISKDC regimen consists of prednisone, 60 mg/m^2/day with a maximum of 80 mg/day, in divided doses for 4 weeks followed by 40 mg/m^2/day with a maximum of 60 mg/day in divided doses, on three consecutive days per week for 4 weeks (97). The Arbeitsgemeinschaft für pädiatrische Nephrologie showed that an alternate day regimen (40 mg/m^2 every other day for 4 weeks) resulted in a significantly lower number of patients with relapses and fewer relapses per patient (179). It also showed that on alternate days prednisone could be given in a single dose rather than in divided doses.

A response occurs in most cases within 10–15 days (median 11 days) (*Table 28-6*). According to the International Study of Kidney Disease in Children, approximately 90% of responders enter in remission within 4 weeks after starting steroids whereas less than 10% go into remission after 2–4 more weeks of a daily regimen (97). A few more patients go into remission after 8–12 weeks of daily steroids (13, 15), but prolongation of daily steroid treatment beyond 4 or 5 weeks increases the risk of side-effects. An alternative for patients who are not in remission after 4 weeks is to administer three to four pulses of methylprednisolone (1 g/1.73 m^2). This additional regimen seems to be associated with fewer side effects than prolongation of daily high-dose steroids and probably produces remission more rapidly in the few patients who would have entered into remission during the second month of daily therapy (180).

The duration of initial steroid therapy influences the risk of relapse.

The APN compared a standard regimen of 4-week daily prednisone and 4 weeks of alternate day prednisone with a longer initial course of 6 weeks of daily prednisone at a dose of 60 mg/m^2/day followed by 6 weeks alternate day

Table 28-6

Definitions

Nephrotic syndrome: proteinuria >40 mg/h/m^2 or >50 mg/kg/day or protein/creatinin ratio >0.2 g/mmol (>2 g/g) and hypoalbuminemia <25 g/l with or without edema
Remission: proteinuria <4 mg/h/m^2 or 0-trace on Albustix for 3 consecutive days
Steroid responsive: complete remission achieved with steroid therapy
Steroid resistant: failure to achieve remission following 4 week' prednisone 60 mg/m^2 followed by 3 methylprednisolone pulses
Relapse: proteinuria > >40 mg/h/m^2 or >50 mg/kg/day or Albustix +++ for 3 consecutive days after having been in remission
Frequent relapser: 2 or more relapses within 6 months of initial response or 4 or more relapses within a period of 1 year
Steroid dependence: 2 consecutive relapses during corticosteroid therapy or within 14 days after cessation of therapy
Early nonresponder: steroid resistance during the first episode
Late nonresponder: steroid resistance in a patient who had previously responded to corticosteroid therapy

prednisone at a dose of 40 mg/m^2/day (179). The subsequent relapse rate within 12 months following discontinuation of therapy was lower with the prolonged course of therapy compared to the standard course (36 vs. 61%).

Following an 8-week steroid regimen, 50–70% of children experience relapses. Several controlled studies have compared the 8-week regimen with longer duration of steroid regimen (3–7 months) including 4–8 weeks of daily prednisone followed by alternate day prednisone (181–185). With a follow-up of 2 years, a significant reduction of 25–30% in the relapse rate was observed with a prednisone regimen of 3 months or more.

The number of children with frequent relapses is also decreased with a longer course of prednisone. A longer duration is more important than the cumulative dose of prednisone in reducing the risk of relapse. This relative risk decreases by 0.133 (13%) for every additional month of treatment up to 7 months (97). There are no data showing that treating for more than 7 months is beneficial. However, an alternate-day regimen over a year did not reduce the rate of relapse compared to a 5-month alternate day regimen (186, 187). Although the studies were not designed to analyze the side effects of glucocorticoids, the authors did not report increased toxicity with longer duration of treatment.

A slow tapering phase to avoid adrenal suppression may maintain long-term remission as a study showed that moderate to severe adrenal suppression was associated with an increased risk of relapse (188). Some authors have suggested a possible prevention by low-dose maintenance hydrocortisone (189, 190). Another study also concluded that adrenocortical suppression increases the risk of relapse in children on long-term alternate day steroid therapy (191).

Increasing initial immunosuppression by adding cyclosporine to steroid therapy does not change the 2-year relapse rate (192).

Treatment of Relapses

About 30% of children experience only one attack and are definitively cured after a single course of steroids. Persistent remission for 18–24 months after stopping treatment is likely to reflect definitive cure, and the risk of later relapses is low. Ten to 20% of patients relapse several months after stopping treatment and are most often cured after three or four episodes, which respond to a standard course of steroid therapy. The remaining 50–60% experience relapses as soon as steroid therapy is stopped or when dosage is decreased. In some cases, exacerbation of proteinuria is only transient, and spontaneous remissions are observed (193). The risk of relapse is greater in children aged less than 5 years at onset and in males. These steroid dependent patients often raise difficult therapeutic problems.

Steroid-dependent patients may be treated with repeated courses of prednisone, 60 mg/m^2/day, continued 3 days after the urine has become protein free, followed by alternate day prednisone, 40 mg/m^2, for 4 weeks as proposed by the International Study of Kidney Disease in Children (97). Another option consists of treating relapses with daily prednisone, 40–60 mg/m^2, until proteinuria has disappeared for 4–5 days. Thereafter, prednisone is switched to alternate days and the dosage is tapered to 15–20 mg/m^2 every other day, according to the steroid threshold, that is, the dosage at which the relapse has occurred. Treatment is then continued for 12–18 months. The first approach allows better definition in terms of number of relapses but is associated with more relapses. The latter regimen is associated with less steroid side effects as the cumulative dosage is lower. Prolonged courses of alternate day steroid therapy are often well tolerated by young children and growth velocity is not affected. However, prednisone dosage must be as low as possible in order to reduce the side effects. In adolescents, steroid therapy is often accompanied by decreased growth velocity.

A controlled trial has shown that deflazacort reduces the risk of relapse in comparison with equivalent doses of prednisone, without additional side effects (194). Unfortunately, deflazacort is not available in many countries.

The role of upper respiratory tract infections in exacerbating nephrotic syndrome has been highlighted in all series: 71% of relapses were preceded by such an event in a prospective study, although only 45% of respiratory infections were followed by an exacerbation of proteinuria (195). The risk of relapse is decreased during upper respiratory tract infections when steroid therapy is given daily for 5–7 days rather than on alternate days (196, 197).

Steroid Side Effects

Side effects of prolonged steroid therapy are well known and are observed in children with a steroid dependent course. Growth retardation is observed with prolonged daily steroid therapy and alternate day therapy may preserve growth (198). However, when the dose needed to maintain remission is too high, growth may be impaired (199, 200). Osteoporosis has been reported in adults who had suffered from nephrotic syndrome during childhood (201). However, a study in children and adolescent with

steroid dependent nephrotic syndrome failed to find a deleterious effect of alternate day steroid therapy on bone mineral content (202). Biyikli et al. reported that steroid treatment causes a dose dependent decrease in bone formation, as shown by the changes in osteocalcin and alkaline phosphatase levels and low 25-hydroxyvitamin D levels (203). A randomized controlled trial compared vitamin D and calcium supplements with no prophylaxis in children receiving high dose steroid therapy during a relapse. The authors found a decrease in bone mineral content in both groups but less pronounced in the treated group ($4.6 \pm 2.1\%$ vs. $13.0 \pm 4.0\%$, respectivelly; $P<0.001$) (175). Another controlled study showed that biphosphonates are effective in preventing steroid-induced osteoprosis in children receiving long-term steroid therapy (204). The other side effects include weight gain, cataracts, behavior disturbances, and hypertension.

Alternative Treatments (*Fig. 28-9*)

An alternative treatment is indicated in children who develop severe side effects of steroid therapy, in children at risk of toxicity (diabetes or during puberty), in children with severe relapses accompanied by thrombotic complications or severe hypovolemia and in those with poor compliance.

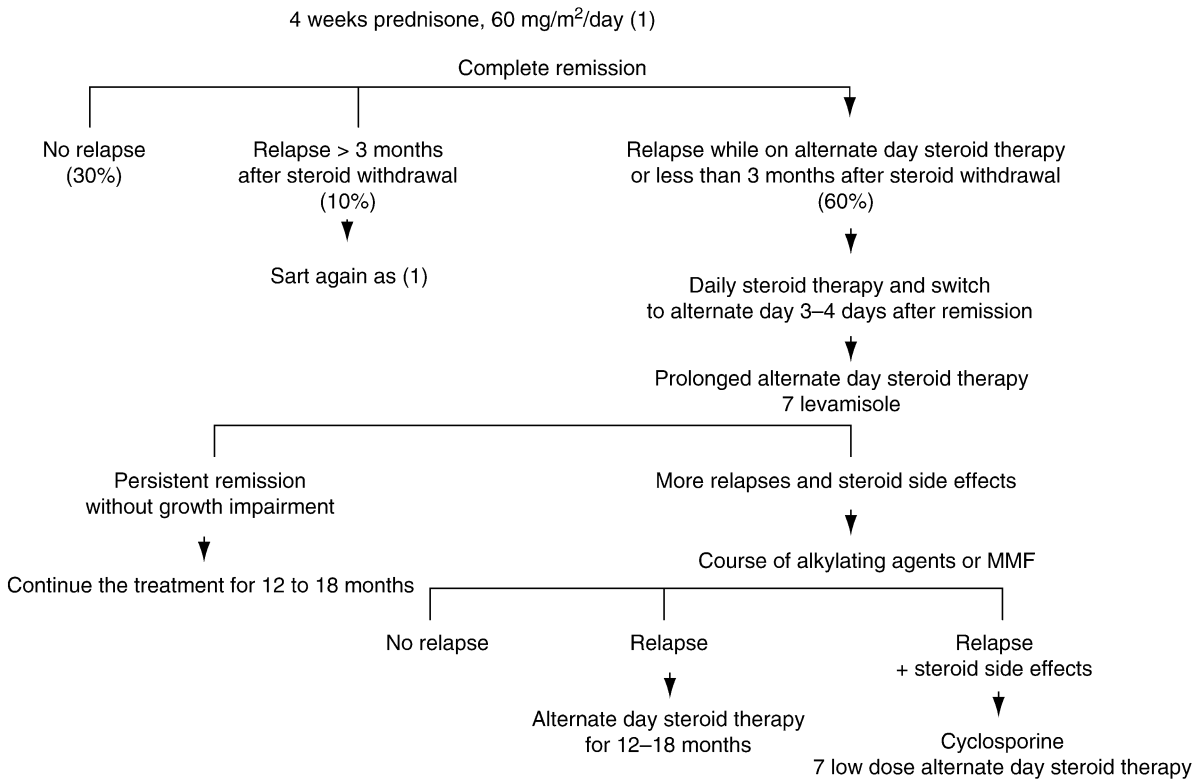
Alternative treatments include levamisole which has a steroid sparing effect, alkylating agents such as cyclophosphamide or chlorambucil, cyclosporine, mycophenolate mofetil and, more recently, rituximab.

Levamisole

The beneficial effect of levamisole was first described by Tanphaichitr et al. (205). Levamisole was subsequently reported to reduce the risk of relapse in steroid dependent patients (206–210). A significant steroid-sparing effect at a dose of 2.5 mg/kg every other day was demonstrated in a prospective controlled trial of the British Association for Paediatric Nephrology (211). Another controlled study confirmed the efficacy of levamisole for preventing relapses (212). However, the beneficial effect of levamisole is not sustained after stopping treatment.

Levamisole given for 6 months was compared with cyclophosphamide given for 8–12 weeks in a retrospective

Figure 28-9



study involving 51 children with steroid dependent nephrotic syndrome (213). The relapse rate and the cumulative dose of prednisone were reduced to the same extent with both drugs.

Levamisole is well tolerated in most children. Side effects occasionally include neutropenia, agranulocytosis, vomiting, cutaneous rash, vasculitis, neurological symptoms including insomnia, hyperactivity and seizures (214, 215). However, levamisole is not widely used due in part to the difficulty in obtaining the drug.

Alkylating Agents

Alkylating agents have been used for more than 40 years to achieve long-lasting remission.

Cyclophosphamide

The efficacy of cyclophosphamide for preventing relapses of INS was reported more than 40 years ago (216), and was proven in a prospective study by Barratt and Soothill who compared an 8-week course of cyclophosphamide to prednisone alone in children with frequent relapses (217). An International Study of Kidney Disease in Children trial found a 48% relapse rate after a mean follow-up of 22 months in children treated with a combination of cyclophosphamide and prednisone compared to a 88% relapse rate in patients on prednisone alone (218). Pennesi et al. showed that the duration of cyclophosphamide treatment had an influence on the duration of remission (219). Several other studies have addressed the relation between dose and duration of treatment and therapeutic efficacy. Treatment for 12 weeks at a daily dose of 2 mg/kg was found more effective than an 8-week course, with 67% of patients as compared to 22% remaining in remission after 2 years (220, 221). However, a randomized trial showed that prolonging the course of cyclophosphamide from 8 to 12 weeks did not further reduce the proportion of children experiencing relapses.

The duration of remission is higher when cyclophosphamide is given in association with steroids compared to cyclophosphamide given alone (218, 222, 223). Cyclophosphamide is less effective in patients with steroid dependency compared to patients with frequent relapses (224). The incidence of relapse after cyclophosphamide is significantly higher in patients with FSGS (73%) or mesangial proliferation, compared to children with minimal change (22%) (225).

More recent data show disappointing results of cyclophosphamide treatment for steroid dependent patients. Kemper et al. reported that only 6 out of 20 children had a sustained remission following a 12-week course of cyclophosphamide. In a retrospective study (226), Vester et al. reported that 24% of 106 children who had received a course of cyclophosphamide were still in remission after 10 years (227, 228). A younger age than 3 years at onset is associated with lower response rate (229).

Cyclophosphamide has also been administered as monthly boluses at 500 mg/m^2 for 6 months. Gulati et al. reported a remission rate of 38% at 5 years among the 29 steroid dependent patients (230). However, Donia et al. reported a remission rate of only 5% at 2 years in a group of 20 steroid dependent patients (231). Prasad et al. compared cyclophosphamide given orally or as boluses in 47 children (232). The remission rate 6 months after the end of treatment was higher following the cyclophosphamide boluses (73% vs. 38%) but was similar with a follow-up of 2 years.

Chlorambucil

Beneficial results have also been achieved with chlorambucil in steroid responsive INS. Grupe et al. reported on the efficacy of chlorambucil given for 2.5–12 weeks, with a relapse rate of only 13% (233). Two trials showed that chlorambucil reduces the risk of relapse at 6 and 12 months compared with placebo or prednisone alone (233, 234). Baluarte et al. obtained similar results in relapsing, steroid-responsive patients (235). Williams et al. showed that low daily doses are preferable: 91% of patients on a dose of 0.3 mg/kg and 80% of those on 3 mg/kg were still in remission 4 years later (236).

A review of 26 controlled trials and cohort studies found that the 2- and 5-year relapse rates following treatment with cyclophosphamide or chlorambucil were 72 and 36% in frequently relapsing nephrotic syndrome compared with 40 and 24% in steroid dependent nephrotic syndrome (237).

Side Effects

Cyclophosphamide toxicity includes bone marrow depression, hemorrhagic cystitis, gastrointestinal disturbances, alopecia, and infection. Leucopenia is frequently observed, but weekly hematological monitoring may limit its severity and concomitant steroids help blunt marrow depression. Hemorrhagic cystitis rarely occurs. Alopecia, which is variably pronounced, remits a few weeks after stopping treatment. Viral infections can be overwhelming if cyclophosphamide is not stopped in due time.

Long-term toxicity includes malignancy, pulmonary fibrosis, ovarian fibrosis, and sterility. Gonadal toxicity is well established and the risk of sterility is greater in boys than in girls. The cumulative threshold dose above which oligo/azoospermia may be feared is between 150

and 250 mg/kg (238–240). Azoospermia is reversible in some patients (241). In females the cumulative dose associated with sterility is greater, but not well defined. Pregnancies have been reported after treatments longer than 18 months (242).

Acute toxic effects are less frequent with chlorambucil than with cyclophosphamide. Leucopenia and thrombocytopenia may occur, and are reversible within 1–3 weeks. Severe microbial and viral infections have been reported, including malignant hepatitis and measles encephalitis.

Long-term toxic effects include the risk of developing cancer or leukemia, which has only been reported in patients who had prolonged courses of treatment. Gonadal toxicity, as with cyclophosphamide, essentially affects boys. Azoospermia is total and probably irreversible at cumulative doses above 10–20 mg/kg. No case of azoospermia was reported in patients given less than 8 mg/kg.

Cyclosporine

Cyclosporine have been shown in a number of uncontrolled studies to reduce the incidence of relapses in 75–90% of patients with steroid dependent INS (243). However, most patients experience relapses when the dosage is tapered or when cyclosporine is withdrawn. The patients thus behave with cyclosporine as they did with steroids; that is, they become cyclosporine dependent. The relapse rate usually returns to the pretreatment rate. Hulton et al. found that patients in whom cyclosporine had been discontinued and later restarted had more relapses, requiring steroids in addition to cyclosporine in order to maintain remission (244).

The effects of cyclosporine have been evaluated in two comparative trials in steroid sensitive patients. Cyclosporine at a dosage of 6 mg/kg/day for 3 months, then tapered over 3 months was compared with chlorambucil given for 2 months. At 12 months, 30% of patients who had received chlorambucil and only 5% of those who were still in remission on cyclosporine (245). A multicenter randomized controlled trial compared cyclosporine for 9 months then tapered over 3 months, with oral cyclophosphamide for 2 months (246). After 2 years, 25% of the patients (50% of adults and 20% of children) who had received cyclosporine had not relapsed, whilst 63% of those treated with cyclophosphamide (40% of adults and 68% of children) were still in remission. During the year following treatment, the relapse rate (1.8 vs. 0.7) and the steroid dosage required (109 vs. 23 mg/kg/year) were significantly higher in children who had received cyclosporine.

Tejani et al. performed a randomized controlled trial comparing low dose prednisone and cyclosporine versus high dose prednisone for 8 weeks as first line treatment in 28 children (247). Thirteen of the 14 children receiving the combined treatment went into remission compared to only 8/14 receiving prednisone alone ($p < 0.05$). The duration of remission after ending treatment was comparable in both groups. Severe hypercholesterolemia may inhibit cyclosporine efficacy and require higher dosages for similar results (248, 249).

A prospective, open multicenter trial from Japan compared the efficacy and safety of two cyclosporine regimen, a dose adjusted to maintain trough level between 60 and 80 ng/ml (group A) and a fixed dose of 2.5 mg/kg (group B) in children who had initially received cyclosporine for 6 months with a trough level of 80–100 ng/ml (250). After 2 years, the rate of sustained remission was significantly higher in group A.

Considering cyclosporine dependency, this treatment must be pursued to prevent new relapses. Indeed, cyclosporine exposes to nephrotoxicity. In case of decreased renal function, it is advisable to reduce dosage or even stop the treatment. Renal function improvement of is in favor of functional renal insufficiency or drug nephrotoxicity. Nevertheless, lesions of chronic nephrotoxicity can develop without any appreciable decline of the glomerular filtration rate (251–253). As it is often necessary to continue treatment for a long time, repeat renal biopsies are highly advisable to detect these lesions. They most often consist of tubulointerstitial injury, characterized by stripes of interstitial fibrosis containing clusters of atrophic tubules and by vascular lesions.

Other side-effects are of less concern: hypertension, hyperkalemia, hypertrichosis, gum hypertrophy, and hypomagnesemia are common but easily manageable. Cyclosporine treatment has no deleterious effect on bone mineral content (254).

Tacrolimus

In a retrospective study of ten children, it was observed that tacrolimus was not better than cyclosporine for the management of severe steroid dependent nephrotic syndrome (255). In a series of five children treated with tacrolimus, two developed insulin dependent diabetes mellitus which resolved after stopping tacrolimus therapy (256).

Azathioprine

Two controlled trials in children showed that azathioprine does not reduce significantly the number of children who relapse at 6 months compared to steroids alone or placebo (257–259).

Mycophenolate Mofetil

During the past 10 years, several reports have shown that mycophenolate mofetil (MMF) treatment may have a beneficial effect in children with steroid dependent INS

(260–272) These studies have shown that MMF allowed to decrease or stop steroid therapy in 40–75% of children. However, relapses were nearly constant after cessation of treatment. MMF was shown to have a significant cyclosporine and/or steroid sparing effect in children with cyclosporine dependent INS with a beneficial effect on renal function (263, 266). These studies confirm the efficacy and safety MMF in patients with steroid dependent nephrotic syndrome and supports its use for a longer duration than 12 months. Doses of 450–600 mg/m^2/day in two divided doses are usually given. Side effects including gastrointestinal disturbances (abdominal pain, diarrhea) and hematologic abnormalities are rare. Many authors now recommend the use of MMF rather than alkylating agents in children with steroid dependent nephrotic syndrome who suffer from side effects of steroid therapy. However, randomized trials should be performed before such recommendations can be made.

Rituximab

During the past 3 years, there have been several case reports of successful treatment of patients with severe steroid dependent nephritic syndrome (273–277). Most of the patients received 1–4 injections of rituximab at a dose of 375 mg/m^2. The duration of remission lasted 9–28 months after the treatment. The safety and efficacy of rituximab were assessed in a multicenter series of 22 patients aged 6.3–22 years with severe steroid-dependent nephrotic syndrome or steroid-resistant but cyclosporin-sensitive INS (278). Patients were treated with two to four infusions of rituximab. Seven patients were nephrotic at the time of treatment. Remission was induced in three of the seven proteinuric patients. One or more immunosuppressive treatments could be withdrawn in 19 patients (85%), with no relapse. Rituximab was effective in all patients when administered during a proteinuria-free period in association with other immunosuppressive agents. When relapses occurred, they were always associated with an increase in CD19 cell count. Adverse effects were observed in 45% of cases, but most of them were mild and transient.

Long-Term Outcome of Children with Steroid Sensitive Nephrosis

About one third of patients have only one attack and are definitively cured after the course of corticosteroids. Ten to 20% of patients experience relapses several months after stopping the treatment and a cure takes place after three or four episodes which respond to a standard course of corticosteroids. The remaining 40–50% of patients experience frequent relapses either as soon as steroid therapy is stopped (frequent relapsers) or when the dose of steroids is decreased (steroid dependent). These steroid dependent patients may have a prolonged course. However, if the patient continues to respond to steroids, the risk of progression to chronic renal failure is minimal.

Schärer and Minges found that 22% of patients had only one attack and 35% of the relapsing patients continued to relapse after 10 years (279). Trompeter et al. reported the late outcome of 152 children steroid-responsive nephrotic syndrome after a follow up of 14–19 years: 127 (83%) were in remission, four had hypertension, 10 were still relapsing, and 11 had died (280). The duration of the disease was longer in children who had started before the age of 6 years. Wynn et al. found that 15% of 132 patients had a persistent relapsing course with a mean follow-up of 27.5 years (281). Lewis et al. reported on 26 patients over the age of 20 years, of whom 5 were still relapsing in adulthood (282).

Koskimies et al. reported on the follow-up of children with INS observed in Finland from 1967 to 1976: 94 of 114 cases had responded to corticosteroids. Twenty-four percent of steroid responders had no relapse, 22% had infrequent relapses and 54% frequent relapses. More than two-thirds were in remission at time of report (283). None of these patients developed renal insufficiency and none died from the disease. Lahdenkari et al. reported a 30-year follow-up of the patients reported previously by Koskimies et al. (284). Of 104 patients, 10% had further relapses in adulthood.

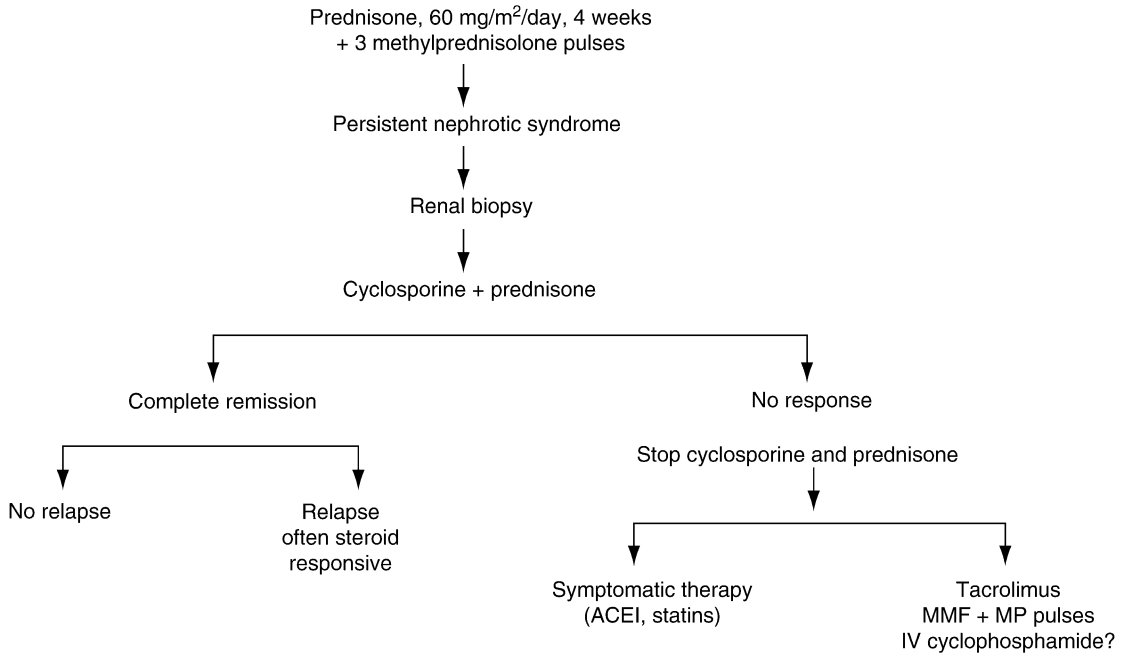
Fakhouri et al. reported on the outcome in adulthood of 102 patients born between 1970 and 1975 (201). Fourty-two percent presented at least one relapse in adulthood. A young age at onset and a high number of relapses during childhood were associated with a high risk of relapse in adulthood. Similarly, Ruth et al. in a study of 42 patients found that 14 (33%) relapsed in adulthood (285). The higher relapse rates in these two reports probably reflect patient selection with more steroid dependent cases compared to Koskimies' series.

This generally good long-term prognosis is also observed in patients with steroid-responsive focal and segmental glomerulosclerosis: the 19 children reported by Arbus et al. remained responders, and none had renal insufficiency after a mean follow-up of 10 years (286).

Treatment of Steroid Resistant INS (◉ *Fig. 28-10*)

Resistance to steroid therapy is defined by the absence of remission after 1 month of daily prednisone therapy at a dose of 60 mg/m^2/day (97). Some authors continue the

Figure 28-10



treatment for 1 or 2 weeks while others favor a series of three methylprednisolone pulses (1,000 mg/1.73 m^2) every other day (287). Indeed, the side effects of this regimen are less than those induced by an increase in the daily prednisone dose. Persistence of proteinuria 1 week after this treatment defines steroid-resistance.

Overall, the prognosis of steroid resistant idiopathic nephrotic syndrome is poor, with a high proportion of children progressing to end stage renal failure. This explains that intensive treatment regimens have been tried. The results of immunosuppressive treatments should take into account the fact that children with genetic forms of INS most often fail to respond to any therapy. However, many published trials include patients who had not been tested for mutations in the different genes involved in steroid resistant INS. Moreover, most studies are nonrandomized and include a small number of patients.

The interpretation of treatment is also complicated by the fact that some studies include patients with minimal change disease, diffuse mesangial proliferation and FSGS while other only include patients with FSGS.

Pulse Methylprenisolone

Methylprednisolone pulse therapy has been advocated for steroid resistant patients. The protocol proposed by Mendoca et al. consists of methylprednisolone (30 mg/kg intravenously), administered every other day for 2 weeks, weekly for 8 weeks, every other week for 8 weeks, monthly for 9 months, and then every other month for 6 months in association with oral prednisone and, if necessary, cyclophosphamide or chlorambucil (288). At an average of over 6 years of follow-up, 21 of 32 children were in complete remission and the 5-year incidence of end-stage renal disease was approximately 5% versus 40% in historical controls (289). Side effects included nausea during the infusion of methylprednisolone in almost all, slowed growth in four, small cataracts that did not interfere with vision in five, and infections in two. There were no cases of abdominal striae, diabetes mellitus, or aseptic necrosis of bone.

A retrospective study of 11 children with steroid resistant INS found pulse methylprednisolone therapy to be safe and effective in inducing remission (290). Similarly, Pena et al. reported that 22 out of 30 children with idiopathic steroid resistant INS entered into complete remission following methylprednisolone pulses and oral cyclophosphamide (291). Although these results are better than those seen in any other study, other reports described less favorable results. Waldo et al. found that pulse methylprednisolone pulse therapy was not effective in inducing remission in black patients (292), whilst Hari et al. in India reported a 65% response rate (293).

Alkylating Agents

Although alkylating agents have little therapeutic effect in steroid resistant patients, they are still widely used either alone or in combination with corticosteroids. Cyclophosphamide has been more often been used than chlorambucil. The rate of full or partial remission is higher in patients with partial steroid resistance, those with late steroid resistance, or those in whom initial renal biopsy has shown minimal changes, by comparison with those showing initial resistance to corticosteroids and/or FSGS. The International Study of Kidney Disease in Children recently reported on 60 children with steroid resistant FSGS who were randomly allocated to receive either prednisone 40 mg/m^2 on alternate days for 12 months (control group) or cyclophosphamide, 2.5 mg/kg BW for 3 months plus prednisone 40 mg/m^2 on alternate days for 12 months (294). Complete remissions were observed in 28% of children in the control group and in 25% of children who received cyclophosphamide. The authors concluded that there was no beneficial effect of cyclophosphamide in these patients. Geary et al. reported full or partial response to cyclophosphamide in 12 of 29 steroid-resistant patients with FSGS (295). Renal failure developed less frequently in partial responders (one of nine) than in those who did not respond at all (seven of eight). Siegel et al. observed complete remissions in six steroid-resistant patients with minimal changes, three of whom relapsed but became steroid responsive (11). Similarly, Bergstrand et al. reported that some patients with steroid-resistant nephrosis treated with cyclophosphamide had become steroid-responsive (296). Conversely, White and Glasgow observed no improvement after cyclophosphamide treatment in 15 steroid-resistant children with focal sclerosis (297). Cameron et al. reported only one responder out of 13 children with steroid-resistant nephrosis and FSGS who received cyclophosphamide (222). Similarly, Tejani et al. reported no remission with cyclophosphamide in ten steroid-resistant children (298). In a controlled trial involving 13 children with steroid resistant minimal change nephrotic syndrome, intravenous pulse cyclophosphamide was shown to be beneficial when compared to oral cyclophosphamide (299). Another report concerning five patients with steroid resistant minimal change disease found no benefit from pulse cyclophosphamide therapy (300). Rennert et al. treated ten children with steroid resistant FSGS with cyclophosphamide pulses. Only two of the five patients who were initial nonresponders went into remission whereas all five late nonresponders achieved complete remission (301). In a prospective study of 24 patients, Bajpai et al. found that therapy with intravenous cyclophosphamide had limited efficacy in patients with initial corticosteroid resistance while Sustained remission was likely to occur in patients with late resistance and those with absence of significant tubulointerstitial changes on renal histology (302).

Chlorambucil may be effective. Williams et al. treated six children who all went into remission with a follow up of 1.3–9.4 years (236). We treated 74 steroid-resistant children with chlorambucil, 0.2 mg/kg, for 2–6 months, and only 14 of them went into complete or partial remission during or shortly after the treatment.

Azathioprine

Azathioprine was considered to be ineffective in steroid-resistant patients after the report of Abramowicz et al. who found no difference between a 3-month course of azathioprine and a placebo (257). However, Cade et al. reported complete remission in 13 adult patients with steroid-resistant INS (303).

Cyclosporine

Cyclosporine has been given to steroid resistant patients and the first reports showed that only 20% of 60 steroid-resistant children achieved complete remission (304–309). A partial response was observed in 13% of cases, but it was usually transient.

The Collaborative Study of Sandimmun in Nephrotic Syndrome analyzed the data from different clinical studies, including 226 steroid resistant patients, adults and children (310). The study showed that the rate of complete remission was significantly higher when cyclosporine was given in combination with steroids: 24% compared to 14%.

The French Society of Pediatric Nephrology reported the results of a prospective trial including 65 children treated with cyclosporine, 150–200 mg/m^2, and prednisone, 30 mg/m^2/day for 1 month and on alternate days for 5 months thereafter (287). Twenty-seven patients (42%) went into complete remission and four (6%) partial remission whereas 34 (52%) failed to respond to the combined treatment. Complete remission occurred in more than half of the patients within the first 2 months of this treatment, which makes it likely that the treatment was responsible for the remission, although spontaneous remission cannot be excluded. Interestingly, eight patients who relapsed after cyclosporine treatment responded to steroid and experienced a steroid dependent course. Progression to renal failure was observed only in patients who

had not responded (12 patients) or had only a partial response (1 patient) to the combined treatment.

Ingulli et al. reported that prolonged cyclosporine treatment in children with steroid resistant FSGS reduces proteinuria and blunts the progression to end stage renal failure (311). The dose of cyclosporine (4–20 mg/kg/day) was titrated to the serum cholesterol level to achieve a remission. In this study, only 5 of the 21 treated patients (24%) progressed to ESRF compared to 42 of 54 patients from an historical group who had not received this treatment. Cattran et al. compared the effects of a 26-week regimen with cyclosporine and prednisone or prednisone alone in 49 adults with steroid resistant FSGS (312). Seventy percent patients of the treatment group versus 4% of the placebo group had a partial or complete remission. Although the rate of relapse was high, preservation of renal function was observed in a significant proportion of treated patients.

Ponticelli et al. compared cyclosporine to supportive therapy in a randomized trial (313). Seven of the 22 treated patients went into complete remission, 6 in partial remission and 9 failed to respond. Only 38% of the patients who responded had sustained remissions. In the control group, only 3 of the 19 patients achieved partial remission. Liberman and Tejani compared cyclosporine and placebo in 25 children with steroid resistant FSGS (314). All 12 patients who were treated achieved a decrease of proteinuria compared to only two in the placebo-treated patients, without a significant decrease in glomerular filtration rate in the cyclosporine treated group.

Gregory et al. treated 15 children with steroid resistant INS with an association of moderate doses of cyclosporine and prednisone. They observed a remission in 13 children after a mean duration of treatment of 2 months (315). Singh et al. reported the effect of cyclosporine in 42 children with steroid resistant FSGS (316). The mean proteinuria decreased from 7.1 g/day to 1.8 g/day while the serum albumin increased from 2.1 g/dl to 3.5 g/dl. The mean serum creatinine increased from 0.85 mg/dl to 1.26 mg/dl. Twenty five patients achieved complete remission. Ehrich et al. reported a retrospective study including 25 children with steroid resistant FSGS who received prolonged and intensified treatment with combined cyclosporine and steroids including methylprednisolone pulses. This treatment resulted in sustained remission in 84% of children with non-genetic forms of steroid resistant INS (317).

Tacrolimus

There is evidence that tacrolimus is effective in a significant proportion of patients. Loeffler et al. found tacrolimus to be effective and well-tolerated for children with steroid resistant INS, with a complete remission rate of 81% and a partial remission rate of 13% (318). Bhimma et al. treated 20 children with tacrolimus and observed a complete remission in 40% of them and a partial remission in 45% of them (319). Similarly, Gulati et al. reported the results of tacrolimus treatment in 22 children, 16 of whom achieved complete remission and 2 partial remission whereas therapy had to be stopped in 3 because of side effects (320).

Mycophenolate Mofetil

There is no convincing data for the beneficial effect of mycophenolate mofetil in these patients. Menzibal et al. treated five patients with steroid resistant INS and only one achieved complete remission (268). Mycophenolate mofetil in association with methylprednisolone pulses and angiotensine converting enzyme inhibitors was reported to significantly reduce proteinuria (321). Cattran et al. reported on a 6-month trial in 18 adults. A reduction of proteinuria was observed in eight patients but no complete remission occurred (322). A prospective trial of the NIH comparing cyclosporine and mycophenolate mofetil in combination with pulse steroids is in progress.

Sirolimus

Tumlin et al. performed a prospective, open trial with oral sirolimus given for 6 months to 21 patients with steroid resistant FSGS. Complete remission was observed in 4 patients (19%) and partial remission in 8 (38%) (323). Glomerular filtration rate in responding patients was maintained whereas it tended to decrease in nonresponders.

Rituximab

Nakayama et al. reported two patients who were successfully treated with rituximab for steroid resistant FSGS (324). Bagga et al. treated five children including three with initial resistance to steroids and two with late resistance to steroids (325). All children had received several other therapies with partial or complete response. Following 4 weekly doses of rituximab, four patients achieved complete remission and one a partial remission. Complete remission persisted in three patients. However, there are several reports of patients who failed to respond to

rituximab and it is too early to recommend such therapy in steroid resistant INS.

Non-steroidal Anti-inflammatory Drugs

These drugs may decrease proteinuria. Several authors have used indomethacin in the treatment of INS with variable results. Donker et al. found a reduction of proteinuria in patients with FSGS but with a simultaneous reduction of glomerular filtration rate (326). Velosa et al. also found a clear reduction in proteinuria in patients treated with meclofenamate (327).

The detrimental effect of non-steroidal anti-inflammatory agents on renal function is well known, and patients with renal disease seem more vulnerable (328, 329). Positive sodium balance, increased edema and risk of arterial hypertension are recognized complications. The decrease of glomerular filtration rate observed with non-steroidal anti-inflammatory drugs is usually reversible in salt-sodium depleted patients. However, irreversible renal failure has been reported with a high incidence in a prospective study in children with steroid resistant FSGS (330).

Angiotensin Converting Enzyme Inhibitors

Numerous studies in adults have demonstrated that angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) slow the rate of progression of proteinuric chronic renal disease. Captopril was reported to decrease dramatically nephrotic range proteinuria due to renovascular hypertension and secondary FSGS (331). A decrease in proteinuria, and even complete remission, have also been observed in patients with chronic glomerulopathies with or without hypertension (332). A 50% decrease of proteinuria without a concomitant decrease in glomerular filtration rate was reported in children with steroid resistant INS (333). Marked benefits with an ACE inhibitor and/or ARB therapy, plus mycophenolate were observed in nine children with steroid-resistant FSGS (321). At 6 months, mycophenolate plus angiotensin blockade resulted in a 72% decrease in proteinuria from baseline values, a benefit that was maintained for a minimum period of 24 months.

Lipid-Lowering Agents

Hyperlipidemia has been shown in experimental animals to accelerate the progression of glomerular sclerosis. Controlled trials in adult patients have shown that lipid-lowering agents can prevent the decline of renal function. No such studies have been performed in children.

Recurrence of INS in Transplanted Kidneys

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 in the graft. The overall risk of recurrence is estimated to be between 20 and 30% (334). The risk is different in children and in adult patients. Senggutuvan et al. found that 8 of 16 children had experienced recurrence compared to 3 of 27 adults (335). In children, recurrence is more frequent when the disease has started after the age of 6 years than before (336, 337). Similarly, a rapid progression of the disease to end stage renal failure seems a major factor associated with recurrence: in most series, when the duration of disease has been shorter than 3 years, the nephrotic syndrome recurs in half of the patients (336, 338). Recurrence is less frequent in African-Americans than in whites and Hispanics (339). The histopathological pattern observed on the first biopsy during the course of the disease is also an important predictive factor (335–337, 340, 341). Recurrence occurs in 50–80% of patients in whom initial biopsy showed diffuse mesangial proliferation but in only 25% of patients with minimal changes on first biopsy. Most patients who experience a recurrence in a first graft also show recurrence in a second graft (342–344). Conversely, when the graft has been lost due to rejection without recurrence, a second graft can be performed safely as recurrence is exceptional in this setting. Patients with podocine mutations or other genetic forms of INS have a very low risk of recurrence (345).

In children, recurrence of proteinuria occurs in most cases within the first hours or the first days after transplantation. A high proportion of patients with immediate recurrence show delayed graft function (344, 346). In some patients, proteinuria recurs several months later. Proteinuria is most often associated with a nephrotic syndrome. Transplant biopsy when performed early shows minimal glomerular changes with foot process fusion (347–349). Lesions of FSGS appear after several days or weeks which is a strong argument to consider these lesions as secondary rather than the cause of heavy proteinuria (348).

Graft failure occurs in about 60% of patients with recurrence versus 23% of those without recurrence

(335, 344, 350). Some patients may show good renal function for several years despite persistent nephrotic syndrome.

The beneficial role of cyclosporine in recurrent steroid resistant INS is still debated. There is no evidence that cyclosporine can prevent the recurrence of nephrotic syndrome following transplantation (351–356). Following the introduction of cyclosporine, the incidence of recurrence did not change, but graft survival was improved (351, 352, 355). In patients who have recurrent disease, high doses of cyclosporine may be effective. Mowry et al. reported on 11 children who received 12 renal transplants and who had been treated with high dose cyclosporine, plasma exchanges or a combination both (357). Remission was observed in 10 of the 12 recipients. Ingulli and Tejani reported on two children with recurrent nephrotic syndrome who both achieved remission when the dose of cyclosporine was gradually increased from 15 mg/kg/day to 27 and 35 mg/kg/day (358). A similar experience was reported by Srivastava et al. (359). In our group, seventeen children with recurrence have been treated with intravenous cyclosporine at an initial dose of 3 mg/kg/day which was afterward adapted in order to maintain whole blood levels between 250 and 350 ng/ml. In 14 of the 17 cases (82%), proteinuria completely disappeared after 20.8 $\pm$ 8.4 days (range: 12–40 days). The treatment was ineffective in the remaining three patients. Plasma exchanges were performed in four patients during the first 2 months and proteinuria regressed in three cases and persisted in one. Persistent remission was observed in 11 patients with a follow-up of 3.7 $\pm$ 3 years. Actuarial graft survival was 92 and 70% at 1 and 5 years (360). We advocate the early use of intravenous cyclosporine as a first-line treatment in recurrent INS after renal transplantation. Similarly, Raafat et al. reported that high doses of oral cyclosporine was effective in inducing long-lasting remission of recurrent nephrotic syndrome (361). There is limited experience with the use of tacrolimus (FK 506) in recurrent nephrotic syndrome after transplantation (362).

Plasma exchange has been performed in a number of patients, in some cases combined with increased immunosuppression (350, 363–368), with often partial or transient remissions. Better results are observed when the treatment is started early. Dantal et al. treated eight kidney-transplant recipients with recurrent nephrotic syndrome with plasma protein adsorption (122). The treatment consistently decreased urinary protein excretion by an average of 82% at the end of a cycle. The effect of adsorption was short-lived, with a return of proteinuria to pre-treatment levels within a maximum of 2 months.

Conclusion

Most children with INS respond to corticosteroid therapy. Although about half of them experience relapses requiring corticosteroids and several corticosteroid sparing agents, these children maintain normal renal function and the severity of the disease is mainly related to the complications of the treatments needed to maintain remission.

There is evidence to suggest that minimal changes and FSGS represent a spectrum of diseases with FSGS at the severe end (369). Indeed, it is likely that several disease entities are included in the term "steroid resistant INS." Defects in podocyte proteins have been identified in some cases and these patients do not respond to any therapy. In other patients, circulating factor(s) produced by immune cells increase the glomerular basement membrane permeability to proteins. Cyclosporine may be effective. However, more than 50% of the patients progress to end stage renal failure. Recurrence of the nephrotic syndrome occurs in 30–40% of patients after renal transplantation.

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