Treatment of the nephrotic syndrome associated with primary glomerulonephritis

The term nephrotic syndrome (NS) refers to a condition characterized by heavy proteinuria, hypoalbuminemia, edema and hyperlipidemia. The NS is often seen when the urinary protein excretion exceeds 3.5 g/day and is almost invariably present when proteinuria is greater than 5 g/day. In the NS there may be a constellation of biochemical and clinical abnormalities that can predispose to disabling and even fatal complications, such as infections, bone disease, arterial or venous thrombosis, cardiovascular disease, etc. In addition, the onset of NS is a marker for bad outcome for most glomerular diseases.

The NS may be caused by a large variety of renal diseases. In this paper, however, we will limit ourselves to reviewing the treatment for those cases of NS associated with primary glomerulonephritis.

Immunomodulating therapy

Some immunomodulating agents, such as corticosteroids, cytotoxic drugs and cyclosporin, may induce remission of proteinuria and protect renal function in at least some subgroups of primary glomerulonephritis. Unfortunately, all these agents have a low therapeutic index. Thus, in deciding whether, how, and when to use immunomodulating drugs, the nephrologist should be aware of their potential side effects, of the results that may be obtained in the different subgroups of glomerulonephritis, and of the possible strategies for maximizing their therapeutic index.

Minimal change disease

Minimal change disease (MCD) accounts for more than 80% of cases of NS in children, but may also occur in adulthood and in the elderly. Clinically, MCD is characterized by a pure, often severe NS. Proteinuria may persist for many years and eventually disappears. The renal prognosis is excellent, except for a few patients who develop focal and segmental glomerular sclerosis with possible progression to renal failure. However, a few children may die from complications related to the NS or its treatment. The prognosis seems to be worse in adults [1], and even more in patients who are older than 60 years [2], with several patients dying from infection, oligoanuria, thrombotic or cardiovascular complications.

According to Brodehl [3] the three main objectives in treating MCD are: (1) to induce remission of the NS as soon as possible in order to prevent the severe complications related to the nephrotic state; (2) to prevent the relapses of NS; and (3) to avoid iatrogenic side effects in a disease which can run a long relapsing course.

Corticosteroids are the drug of choice for the initial treatment of MCD. Proteinuria disappears in more than 90% of children during an eight week course of prednisone, given at a dose of 60 mg/m^2/day for four weeks, followed by 40 mg/m^2/48 hr for four other weeks [4]. In about half of the patients, remission occurs within one week and most of the other children remit within four weeks. Unfortunately, many patients have relapses of NS after remission. The rate of relapses seems to be influenced by the duration of the initial treatment. About 80% of children relapse within one year when prednisone is given for four weeks, 60% relapse after an eight week treatment and only 36% relapse when prednisone is given for 12 weeks [3]. Adults are usually treated with an initial attack dose of prednisone of 1 mg/kg/day. Only 50 to 60% of them become free of proteinuria within eight weeks. However, if corticosteroid therapy is given up to 28 weeks, complete remission may be obtained in 80% of patients [2]. As for children, the duration of initial treatment influences the risk of relapse. A controlled study showed that adults treated with prednisone for two to three months had more relapses than those given alternate-day prednisone for one year. As a consequence, the cumulative dosage of steroids was greater for the patients given short-term prednisone [5]. According to these data, to reduce the risk of relapse the initial treatment should be prolonged. It is also advisable to taper off prednisone gradually, not abruptly, in order to avoid a rebound effect which may cause exposure to relapses. In children we suggest starting with 60 mg/m^2/day of prednisone until disappearance of proteinuria for three consecutive days. Then the patient may be switched to alternate day prednisone, 40 mg/m^2/48 hr for at least 12 weeks, with subsequent tapering off of prednisone by 5 to 10 mg/m^2/48 hr every month. Most children respond within four weeks, but the response may be delayed in a few patients. Thus we prolong prednisone administration for 8 to 12 weeks before considering a child as steroid-resistant. We treat adults with prednisone, 1 mg/kg/day, either until remission or for at least six weeks if there is no complete response. After that, the patient is switched to alternate day prednisone, starting with 1.6 mg/kg/48 hr, and reducing the dose by 0.2 to 0.4 mg/kg/48 hr every month. Since some few adults enter remission after several weeks, we give prednisone at decreasing doses for four to six months before considering an adult as a non-responder. It is preferable to give prednisone in a single morning dose, between 7 and 9 a.m., in order to reduce the side effects. Of course, this schedule should be tailored for individual patients. Prednisone is stopped earlier if an intercurrent infection or any steroid-related complication occurs. For the elderly patient who may have contraindications for high-dose prednisone, the initial treatment may consist of cyclophosphamide (2 mg/kg/day) or chlorambucil (0.15 mg/kg/day) for 8 to 12 weeks.

After remission from the initial episode of NS some 20 to 30%

Table 1. Comparison of the main side effects of cyclophosphamide and chlorambucil

Agranulocytosis
  It is dose-related. At equivalent doses, the risk is similar for the two agents. Rare if the daily doses do not exceed 2 mg/kg/day for cyclophosphamide or 0.15 mg/kg/day for chlorambucil.
Gonadal toxicity
  The risk of azoospermia is greater for chlorambucil. Irreversible azoospermia may develop after a cumulative dosage of more than 10 mg/kg for chlorambucil [17] or of 300 mg/kg for cyclophosphamide [18].
Bladder toxicity
  The excretion in the urine of acrolein, a metabolite of cyclophosphamide, can lead to hemorrhagic cystitis, bladder fibrosis and even cancer. A forced diuresis may reduce the risk of bladder toxicity. This complication does not develop with chlorambucil.
Mutagenicity and oncogenicity
  In patients with connective tissue diseases cyclophosphamide induces more chromosome damage than chlorambucil [19]. Both alkylating agents can expose to an increased risk of cancer, particularly lymphoma and acute leukemia. The risk is mainly related to their cumulative dosage. In patients with non-malignant disease who developed malignancy, the mean dosage of cyclophosphamide was more than 80 g [20]—about 3 mg/kg/day for 380 days in a patient weighting 70 kg—the mean cumulative dosage of chlorambucil was 7 g [21]—about 0.2 mg/kg/day for 500 days for a patient of 70 kg.

Table 2. Recommendations for the use of CsA in patients with primary glomerulonephritis

Do not give CsA to patients with established renal insufficiency, severe hypertension and/or tubulointerstitial lesions in the renal biopsy;
The starting dose of CsA should not exceed 5 mg/kg per day for adults or 100–150 mg/m^2 per day for children;
If no response is observed within 3 months, CsA should be stopped (probably ineffective);
Plasma creatinine, blood pressure and blood CsA should be monitored (compliance, bioavailability, drug interference);
The dose of CsA should be reduced if plasma creatinine rises by more than 30% over the basal value;
Nephrotoxic drugs should be avoided;
Interactions of drugs which might interfere with CsA metabolism should be taken into account;
The maintenance dose should be the lowest effective one;
After 2 years CsA may be tapered off gradually to see whether the patient remains in remission

of patients remain without proteinuria. A similar proportion of patients, with variations depending on the type and duration of the initial therapy, has fewer than two relapses every six months. The relapse is usually as steroid-responsive as the first episode of NS. Unlike the first attack, however, the intensity and the duration of treatment do not influence the subsequent rate of relapses [6]. Spontaneous remission may occur but it is impossible to predict which patient will remit spontaneously and which will not. Some authorities suggest starting treatment early [3]; others, however, prefer to wait 7 to 10 days to avoid a useless corticosteroid administration to those patients who will remit spontaneously. The standard treatment consists of 60 mg/m^2/day (up to a maximum of 80 mg/day) for children and of 1 mg/kg/day for adults. This dosage is given until the urine is protein-free for three consecutive days. Then prednisone may be given every other day for four weeks, at a dose of 40 mg/m^2/48 hr for children and of 0.75 mg/kg/48 hr for adults. The maximum duration of prednisone administration for patients who do not respond early should be similar to that of the first episode.

Patients with two or more relapses within six months after the first episode or three or more relapses within 12 months are called frequent relapsers. Patients who relapse within 14 days after stopping the steroid or when the dosage is reduced are called steroid-dependent. Treatment of these patients is difficult since prolonged corticosteroid therapy may produce side effects, such as hypertension, psychiatric disorders, osteoporosis, obesity, diabetes, cushingoid features, infections, growth retardation, etc. Cyclophosphamide or chlorambucil can significantly reduce the rate of relapses in these patients. The results of cytotoxic therapy clearly depend on the duration of treatment. Barratt et al [7] compared the effects of two weeks and eight weeks of cyclophosphamide in steroid-sensitive patients with relapsing NS and concluded that the longer-term therapy was far more effective. Rance, Arbus and Balfe [8] reported a 27% rate of remission at one year for children given cyclophosphamide for fewer than six

weeks, while 66% of patients were still in remission when treatment was extended for 12 weeks. On the other hand, while too short a therapy is of little benefit, prolonged administration of alkylating agents can increase the risk of severe side effects. To prevent any major side effects in MCD, many clinicians now administer cyclophosphamide or chlorambucil for not more than eight weeks. With this duration of therapy, almost 70% of frequent relapsers maintain remission with time, but most steroid-dependent patients relapse soon after the treatment is stopped [9]. However, if cyclophosphamide is given at a dose of 2 mg/kg/day for 12 weeks instead of 8 weeks, about 2/3 of steroid-dependent children remain in remission after two years [10]. This cumulative dose is below the estimated threshold of risk for azoospermia (Table 1). Cyclosporin A (CsA) is another alternative to steroids. Most steroid-dependent patients can be maintained in remission with CsA, which is usually started after remission has been induced with steroids [11–13]. After the drug is stopped, early relapses occur in many but not in all patients [11]. These relapses seem to be less likely to occur if CsA is given long term and if it is tapered off gradually. The safety and tolerability of CsA in idiopathic NS was investigated in 661 patients enrolled in 10 studies [14]. Hypertrichosis (18%), gum hyperplasia (16%), gastrointestinal symptoms (11%) and hypertension (9%) were the most frequent non-renal side effects. Out of 225 patients with MCD treated with CsA, three developed end-stage renal failure. All of them were steroid- and CsA-resistant, suggesting that the unfavorable evolution was caused by an underlying focal and segmental glomerular sclerosis rather than being a nephrotoxic effect of CsA. In the other patients the mean levels of serum creatinine at the last follow-up did not differ significantly from basal values. It can be argued, however, that serum creatinine is not the most appropriate measurement to monitor renal function in patients given a potentially nephrotoxic drug. As a matter of fact, CsA may induce histological lesions even in patients with perfectly normal kidneys. Cases of interstitial fibrosis have been reported in patients given CsA because of non renal autoimmune diseases [15]. In MCD, Niaudet et al [13] took control renal biopsies from 43 children, 2 to 19 months after the initiation of CsA. In 13, extension of tubulointerstitial lesions was seen in spite of the fact that impaired creatinine clearance was detected in only one. Thus, some caution is needed when using CsA (Table 2).

In summary, there is no standard treatment for patients with frequent relapses or with steroid dependency. We suggest the
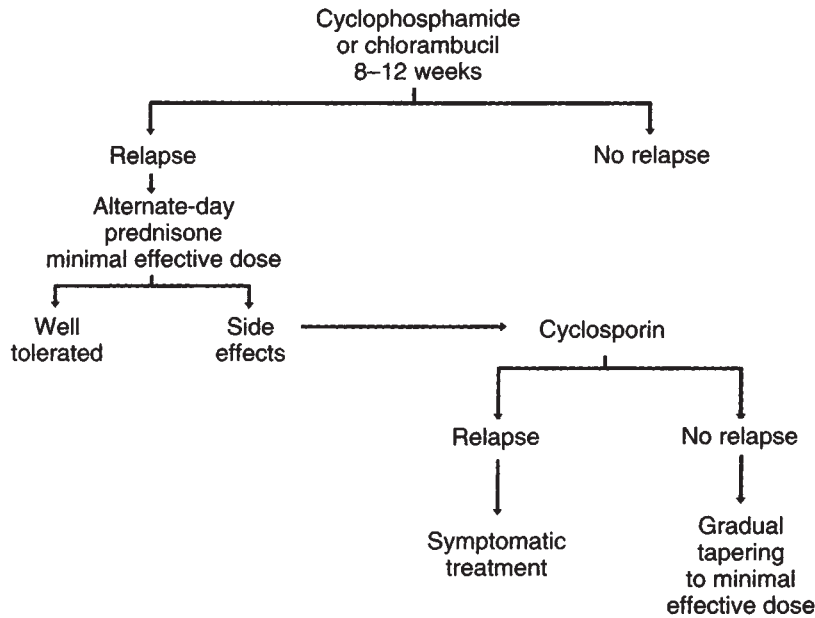
Fig. 1. *Suggested therapeutic approach for patients with minimal change disease either frequently relapsing or steroid-dependent.*

following algorithm (Fig. 1). Since cyclophosphamide or chlorambucil may obtain stable remission in a good number of cases, it is worthwhile to give first a short course of one of these agents (8 weeks to frequent relapsers, 12 weeks to steroid-dependent patients). Cyclophosphamide, at a dose of 2 mg/kg/day, is less gonadotoxic and may be preferred for children and for young adults. Chlorambucil, which is perhaps more efficacious [16] and is less toxic to the bladder, may be used for the other patients, at a dose of 0.15 mg/Kg/day (Table 1). If the NS relapses, the patients should not be treated again with alkylating agents, since their toxicity is cumulative. Usually these patients respond well to steroids. Among the various possible schedules, alternate-day prednisone is the most widely used and may be given safely for several months. Should any signs of hypercorticism appear, the steroid may be stopped and replaced by CsA. If the patient remains in remission, CsA may be reduced after 6 to 12 months by 25% every two months, to determine the minimal effective dose. Several investigators continue CsA therapy for years. We prefer to gradually stop CsA after two years. If the patient relapses, we treat her/him again with steroids for 6 to 12 months and then again with CsA for one to two years, in order to prevent the potential toxicity of prolonged administration of either drug.

Some 10% of patients with a histological diagnosis of MCD do not respond to the standard regimens with steroids. Most of them, sooner or later, show picture of focal and segmental glomerular sclerosis in renal biopsies and should be treated accordingly.

Focal and segmental glomerular sclerosis

Focal and segmental glomerular sclerosis (FSGS) is a heterogeneous clinicopathological entity which may complicate several diseases or morbid conditions. In its idiopathic form, FSGS is usually associated with the NS. Most nephrotic patients tend to progress to end-stage renal failure within 10 years after the clinical onset. The renal outcome of FSGS is similar in children and in adults, although children may sometimes show a better response to therapy. The presence of tubulointerstitial lesions at renal

biopsy is a marker of a bad renal prognosis, while the prognostic role of glomerular lesions, such as hilar lesions, mesangial proliferation and collapsing glomeruli is still under discussion.

There are not controlled prospective trials with the use of corticosteroids or cytotoxic agents in this disease. The available literature is mostly based on retrospective studies, and it is possible that some papers reporting negative results have not been published. The general impression is that only a small minority of patients with FSGS and NS achieve complete remission of proteinuria with a short course of high-dose prednisone. On the basis of this poor response, many clinicians are reluctant to treat patients with FSGS. However in a retrospective survey of the literature Schena and Cameron [22] reported that more than 40% of patients given corticosteroids and/or cytotoxic drugs versus none of untreated patients entered complete or partial remission. Moreover, 37% of treated patients versus 25% of untreated patients maintained normal renal function at the end of follow-ups of various lengths. Some studies have reported good results with prolonged therapies. A French study reported that 69% of nephrotic patients had complete remission after 6 to 12 months of prednisone [23]. Pei et al [24] reported that 40% of nephrotic patients treated with prednisone for at least six months attained complete remission. At 12 years, 96% of responders still had stable renal function while all the non-responding or non-treated patients had some degree of renal insufficiency. Mendoza et al [25] treated 23 children with intravenous methylprednisolone pulses plus oral prednisone, 2 mg/kg/48 hr for 78 weeks. When no response was obtained, cytotoxic agents were added. After a mean follow-up of 55 months, 18 patients were without NS and only one had progressed to renal failure. In spite of the very aggressive approach side effects were relatively mild in that particular series. We reviewed the outcome for 59 patients with FSGS and NS treated either with prolonged steroid treatment (27 patients) or with long-term immunosuppressive therapy (13 patients) or with corticosteroid and cytotoxic agents, alternated every other month, for six months (19 patients). After a mean follow-up of 75 months,
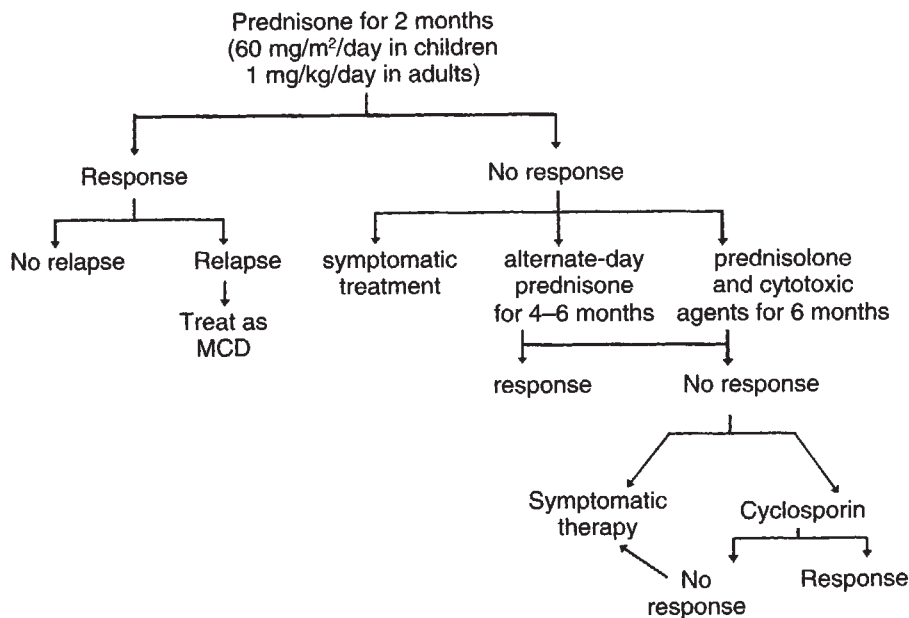
Fig. 2. *Treatment of focal and segmental glomerular sclerosis with nephrotic syndrome.* Therapeutic options in patients who do not respond to first 8-week prednisone treatment.

31 patients (52%) were in complete remission, 4 were in partial remission, 6 were still nephrotic and 16 had progressed to renal failure. Patients who responded did so after a median period of five months. There were no differences in the rates of response for the three groups of treatment, but more than 50% of patients given steroids alone versus fewer than 20% of patients treated with immunosuppressive agents relapsed after remission. Fewer than 3% of patients who had initially responded to therapy developed renal failure within 10 years versus 65% of non-responders [26].

CsA is also being used to treat FSGS. A review of the literature showed that some 40% of patients may be maintained without NS under CsA [27]. It is unclear, however, whether CsA impairs or protects renal function in FSGS. Some studies reported worsening of histological lesions in several patients treated with CsA [12, 13], but it is difficult to know whether renal lesions became aggravated because of the progression of FSGS or because of CsA-related nephrotoxicity. In an Italian controlled trial [28], patients with NS who did not respond to steroids were randomly assigned to symptomatic therapy or to be given CsA (5 mg/kg/day for adults and 6 mg/kg/day for children) for six months, then tapered off by 25% every two months until complete discontinuation. In the first year, 32% of CsA-treated patients entered complete remission and another 27% had partial remission, while only 16% of untreated controls had partial remission of NS. The mean levels of creatinine clearance for the two groups did not differ.

We think that for nephrotic patients with FSGS the first approach should consist of high-dose prednisone (60 mg/m²/day for children, 1 mg/kg/day for adults) for two months in order to recognize the few responders. For those patients, the subsequent treatment may be similar to that of MCD, including the management of possible relapses. What to do with non-responders is controversial. Many clinicians are against treatment but the available data indicate that a more prolonged treatment may obtain remission of NS and maintain renal function stable in at least 50% of patients. We are, therefore, in favor of a further

therapeutical trial for patients who do not respond to the two-month prednisone treatment, provided that they do not present particular contraindications to therapy. We suggest the following algorithm (Fig. 2). Unless steroid toxicity develops, after the first two months prednisone may be continued every other day in tapering doses for another four to six months. Alternatively, a therapeutic protocol alternating corticosteroids with a cytotoxic agent for six months may be used, similar to the one we use for membranous nephropathy [29]. With such a schedule we obtained 10 complete remissions in 19 patients with FSGS and NS [26]. If NS persists, in spite of either treatment, we switch the patient to CsA, unless renal function and/or blood pressure are abnormal or unless interstitial fibrosis is present at renal biopsy. If no remission is observed within three months, that patient will be unlikely to respond later and CsA should be stopped. For patients who respond, we gradually taper CsA after some months in order to identify the minimal effective dosage. After one to two years of treatment, a renal biopsy is considered to rule out histological lesions caused by CsA.

Membranous nephropathy

Membranous nephropathy (MN) is the most frequent cause of NS in adults. Its eventual outcome is not easily predictable. Some nephrotic patients maintain normal renal function and may even have spontaneous remission of NS, while 30 to 50% progress to end-stage renal failure within 10 years from clinical onset. The persistence of heavy proteinuria [30] and/or the presence of tubulointerstitial lesions [29] in the initial renal biopsy are the factors more often associated with a progressive deterioration of renal function. On the other hand, patients who attain a complete remission of proteinuria generally have excellent renal prognosis even in the long-term [31].

There are conflicting results for the use of corticosteroids in MN. An American study reported better chances of remission of NS and better preservation of renal function for nephrotic patients randomly assigned to prednisone, 125 mg/m²/48 hr for
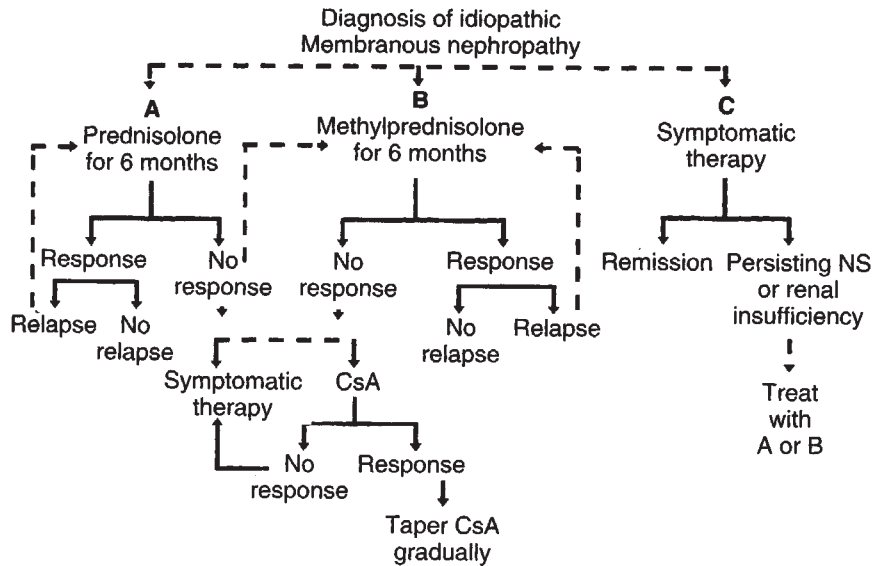
Fig. 3. *Treatment of membranous nephropathy with nephrotic syndrome.* Dotted lines indicate the different possible options.

two months, than for untreated controls [32]. These results, however, were not confirmed by an English controlled trial where the same regimen was tested in a larger number of patients followed for at least three years [33]. In a Canadian study nephrotic and non-nephrotic patients with MN were randomly assigned to supportive treatment or to prednisone, 40 mg/m^2/48 hr, for six months [34]. No difference between the two groups could be seen in either the rate of remission or the mean creatinine clearance. Controlled trials with cytotoxic agents also gave conflicting results although generally showing a favorable effect on proteinuria [35–37]. Unfortunately, however, these studies were performed on too small numbers of patients. A combination of corticosteroids with a cytotoxic agent was assessed in an Italian controlled trial [29]. Patients with MN and NS were randomly assigned to supportive therapy or to methylprednisolone (1 g for 3 days intravenously, then 0.4 mg/kg day orally for 1 month) alternated every other month with chlorambucil (0.2 mg/kg/day for 1 month) for six months. There were more remissions of NS in patients given the combined treatment (81% vs. 33%), and these often occurred after the end of the therapeutic course. After a median follow-up of five years, there were more treated patients still without NS (67% vs. 23%). The mean slope of the reciprocal of plasma creatinine was also significantly better for the treated than for the untreated group. In another Italian study, patients with MN and NS were randomly assigned to either combined treatment with methylprednisolone and chlorambucil for six months, as in the previous trial, or to methylprednisolone alone given for six months (1 g intravenously for 3 days at month 1, 3, 5 and 0.4 mg/kg/48 hr orally for 6 months) at the same cumulative dosage as in the other arm [38]. After a mean follow-up of 54 months, 64% of the patients given combined therapy versus 38% of patients given corticosteroids alone were without NS. No significant difference between the two groups was seen in the mean reciprocal of plasma creatinine up to four years. In both studies, fewer than 10% of patients had to stop combined treatment because of side effects. No disquieting late morbidity has been seen up to now in patients given chlorambucil.

In summary, there is some evidence that MN may be treatable,

but how to manage patients with NS is still controversial. Some physicians think that MN naturally has a favorable course and give only symptomatic treatment [39]; others are concerned of the potential toxicity and prefer to use corticosteroids alone [40]; still others use a combined regimen with corticosteroids and an alkylating agent [29]. To better define the possible evolutions with these different attitudes, Piccoli et al [41] recently evaluated the results of the two Italian trials previously mentioned by decision analysis. Assuming triple probabilities and costs for methylprednisolone plus chlorambucil complications compared to methylprednisolone, with no risk for supportive therapy, referring to an average 40-year-old patient, and using the quality-adjusted life expectancy year as the utility scale, they found that with methylprednisolone plus chlorambucil the difference in expected quality-adjusted life expectancy was 7.2 years compared to supportive treatment, and 2.6 years compared to methylprednisolone. To offset the longer survival obtained with methylprednisolone plus chlorambucil versus methylprednisolone, all patients treated with methylprednisolone plus chlorambucil should undergo either fatal (5% vs. 0.3% with methylprednisolone) or non-fatal complications (95% vs. 15% with methylprednisolone). This threshold denotes a great stability of the inequality in the expected quality-adjusted life expectancy. Consequently these data seem to support choosing a treatment with methylprednisolone or with methylprednisolone plus chlorambucil if one considers their side effects a suitable trade-off for a five or seven quality-adjusted life expectancy years respectively longer survival. Only an absurd increase in death rate with methylprednisolone plus chlorambucil could offset the difference. On the basis of the available data we suggest the following algorithm for nephrotic patients with normal renal function (Fig. 3). According to the clinical conditions of the patient and the conviction of the physician, one can start with either symptomatic therapy, or corticosteroids alone or methylprednisolone and chlorambucil. In case of remission no further treatment is given. Untreated patients with persisting NS or with progressive renal dysfunction may be offered either a six month treatment with corticosteroids or with methylprednisolone and

chlorambucil. For patients who relapse, the response to retreatment (either with steroids alone or combined with chlorambucil) is similar to that observed after the first course. For patients with severe NS who do not respond to either treatment, a trial with CsA may be done. Rostoker et al [42] reported that 4 of 15 nephrotic patients with MN treated with CsA entered complete remission and another 7 had partial remission. NS relapsed only in 3 of 9 patients in whom CsA was stopped.

When to start treatment is also a matter of debate. Some clinicians suggest waiting at least one to two years after clinical onset of NS in order to avoid treatment of those patients who might remit spontaneously. Others even wait until renal insufficiency develops. We prefer to start treatment early, for several reasons: (i) an effective therapy prevents the possible complications of NS; (ii) the probability of response is better for patients who do not yet have advanced glomerular or tubulointerstitial lesions; (iii) therapy is better tolerated by patients with normal renal function; and (iv) patients with an already established renal insufficiency may fail to respond to therapy or their response may be incomplete.

What to do for patients with declining renal function? First, all efforts should be made to recognize and appropriately treat any possible superimposed complication, such as venous thrombosis (echocolordoppler, cavography), interstitial nephritis (drug history, eosinophilia, eosinophiluria, rash, fever, renal biopsy), extracapillary glomerulonephritis (nephritic sediment, rapid deterioration in renal function, renal biopsy). What type of treatment may be used in patients with progressive renal failure? Short et al [40] reported some improvement of renal function with the use of high dose intravenous steroid pulses followed by alternate-day prednisone. Good results have been reported after one to two years of azathioprine or cyclophosphamide associated with low-dose prednisone [43–45] or a six month course with methylprednisolone and chlorambucil [46]. Two small controlled trials in patients with renal insufficiency are available. Falk et al [47] did not find differences between patients randomly assigned to be given intravenous pulses of cyclophosphamide every month for six months or alternate-day prednisone for two months. Reichert, Koene and Wetzels [48] found a significantly better kidney survival in patients assigned to receive methylprednisolone and chlorambucil for six months than in those given monthly intravenous pulses of cyclophosphamide for six months. When compared to other schedules with cytotoxic drugs, the six month treatment with steroids and chlorambucil has the advantage of giving a cytotoxic agent for only three months. We are therefore in favor of such a treatment in patients with renal insufficiency. We suggest however, that the dosage of chlorambucil should not exceed 0.1 mg/kg/day, since the side effects are increased in patients with renal insufficiency.

IgA mesangial nephritis

This disease is probably the most common form of glomerulonephritis. It occurs at any age but it is more common in the second and the third decade. IgA mesangial nephritis (IgAN) usually runs a slowly progressive course, with development of end-stage renal failure within 20 years in about 20 to 50% of patients [49]. Heavy proteinuria, extended glomerular sclerosis and diffuse interstitial fibrosis are usually associated with a poor renal outcome.

NS is uncommon in IgA nephritis and is usually associated with a poor prognosis. However, some few patients with NS, who show no or minimal glomerular changes in the renal biopsy, generally respond well to corticosteroids and have a fair outcome [50, 51]. For the other nephrotic patients, the biopsy usually shows moderate to severe mesangial proliferation often associated with advanced chronic lesions or focal glomerulosclerosis. Might immunomodulating therapy alter the course of the disease in these cases? Some retrospective studies reported good results with corticosteroids. However, in a randomized trial there were no differences in the final creatinine clearance between nephrotic patients assigned to symptomatic therapy and those given prednisone for four months. A good proteinuria response was seen only in steroid-treated patients with mild mesangial proliferation [51]. In another controlled trial, patients were assigned to CsA or supportive therapy [52]. CsA reduced the amount of proteinuria but caused a more rapid decline of renal function than in the untreated patients. Schena, Montenegro and Scivittaro [49] performed a meta-analysis of eight studies involving 196 IgAN patients. Patients with heavy proteinuria, whether or not associated with the NS, benefitted from the administration of corticosteroids and/or cytotoxic drugs, as 67% of treated patients had complete or partial remission of proteinuria versus 34% of untreated patients. Moreover 36% of treated patients progressed to renal failure versus 59% of the untreated patients. These data support active treatment for patients with heavy proteinuria, who are those at higher risk for developing renal failure. Unfortunately, the treatments considered in the meta-analysis were quite variable, so that it is difficult to ascertain which is the best therapy for these patients. Recently, Rostoker et al [53] reported a significant reduction of proteinuria and a stopping in decline of renal function in 11 adults with severe IgA nephropathy treated with high-dose immunoglobulins for three months.

In summary, patients with IgAN and NS with pictures of MCD in the renal biopsy usually respond well to steroids and should be managed like those having MCD (see above). There are no definite data in favor of a specific treatment for the other cases of NS, so that the choice between abstensionism and intervention is optional. Should one decide to try therapy, we would suggest a six-month course with alternate-day prednisone (1 mg/kg/48 hr), which is usually well tolerated. A special group of patients shows rapid impairment of renal function and superimposed extracapillary GN is found at biopsy. For these patients, who are destined to develop end-stage renal failure within a short time, we feel that an aggressive treatment is justified. Three to five daily intravenous methylprednisolone pulses (1 g each) followed by oral prednisone (1 mg/kg/day for 1 to 2 months, then gradually tapered off over 6 to 12 months) and cyclophosphamide (2 mg/kg/day for 2 to 4 months) may obtain partial recovery of renal function for some patients. For the more resistant cases, methylprednisolone pulses may be repeated if the clinical condition of the patient allows it. Unfortunately, it is not unusual for slowly progressive renal insufficiency to develop after an initial improvement of renal function.

Membranoproliferative glomerulonephritis

Idiopathic membranoproliferative glomerulonephritis (MPGN) is an infrequent cause of glomerular disease in both children and adults. The disease can affect patients at any age, but it usually occurs in ages of between 8 and 30 years. MPGN can be divided into types I, II, III on the basis of different patterns in light microscopy, immunofluorescence and electron microscopy, but

the prognoses and courses of these different types are similar. The renal prognosis is usually bad for patients with renal insufficiency and/or NS at presentation. More than 50% of patients with NS progress to end-stage renal failure within 10 years after clinical onset [54]. In general the disease is more severe in adults.

As for other glomerulonephritides, treatment is controversial. For many years the group of McEnery, McAdams and West [55] have been emphasizing the beneficial role of prolonged high-dose alternate-day prednisone (2 to 2.5 mg/kg/48 hr) in MPGN. They reported renal survival of 90% at nine years for 45 children with MPGN treated for several years with such a regimen. In spite of the prolonged administration, steroids were well tolerated by most patients. However, their results were less exciting for the 15 patients with overt NS at presentation. End-stage renal failure developed in four of them within five years, and another child became uremic after eight years [55]. A controlled study with a similar regimen organized for the International Study of Kidney Disease in Children concluded that alternate-day steroid therapy may actually slow the rate of progression of type I MPGN, but long-term treatment was associated with severe hypertension and seizures in several patients [56]. Other non-controlled studies reported good results with indomethacin plus low-dose cyclophosphamide or with mixtures of cytotoxic, anticoagulant and antiplatelet agents. However, in a randomized trial there were no differences in the mean proteinuria and in the decline of renal function between 27 patients treated for 18 months with cyclophosphamide, coumadin and dipyridamole and 32 controls [57]. In another controlled study, Donadio and Offord [54] reported that in patients with type I MPGN a combination of aspirin (975 mg/day) and dipyridamole (225 mg/day) lowered the rate of renal failure up to four years, but analysis at 10 years showed no difference in renal survival between treated (49%) and untreated patients (41%).

In summary, the treatment of MPGN remains elusive. Symptomatic therapy and a good control of arterial hypertension are cornerstones of importance. These measures can provide a 10 year patient survival, similar to that expected for the general population [54]. In the case of the nephrotic patient who usually has a bad renal prognosis, a course of steroids may be tried. In such a case the earlier the treatment the better the results [55]. We suggest a treatment with alternate-day prednisone at a dose of 2.0 mg/kg/48 hr for two months, with gradual decrease in the following period. If no response is observed within four to six months, the steroid should be stopped. If there is considerable reduction of proteinuria the steroid may be continued at the minimal effective dose. Some patients with MPGN may show a rapidly progressive decline in renal function, sometimes triggered by an infection of by a drug exposure. A renal biopsy should be obtained for these cases. In the presence of an extracapillary glomerulonephritis or of a superimposed interstitial nephritis, an aggressive treatment with intravenous high-dose methylprednisolone pulses, oral prednisone and cyclophosphamide may obtain a substantial recovery of renal function in several patients.

Supportive therapy

The management of nephrotic patients must take into consideration not only the specific pharmacological approach to the underlying glomerular disease, but also the supportive measures aimed at preventing and treating the clinical sequelae of massive proteinuria. This supportive therapy is of most importance for those patients who do not respond to immunomodulating agents and are therefore exposed to the complications of prolonged NS.

Dietetic measures

The intake of sodium should be restricted to around 2 g per day to reduce the positive sodium balance. From a practical point of view, it is generally sufficient to recommend not adding salt to the diet. Severe salt restriction is necessary only for patients who respond poorly to diuretics. In the past a high protein intake was prescribed to compensate for the urinary protein loss. This, however, increases glomerular permeability to macromolecules, which results in a further increase in proteinuria while the protein balance remains negative and low serum albumin levels persist [58]. On the other hand, studies with the low-protein diets have given conflicting results. Reduced urinary albumin excretion and increased serum albumin levels have been reported by some investigators [59], while others did not find any reduction in proteinuria, at least in MN [60]. As we await the results of long-term trials we feel reasonable to abandon the prescription of a high protein diet in NS while recommending a diet containing about 1 g/kg/day of protein. A lipid-lowering diet (less than 200 mg per day of cholesterol, total fat less than 30% of total calories, and polyunsaturated fatty acids about 10% of total calories) is usually prescribed for patients with hypercholesterolemia. However, individual responses to this diet are difficult, if not impossible, to predict, ranging from minimal to 15 to 20% decreases in low-density lipoprotein cholesterol levels. Moreover, the stricter the regimen the worse the compliance, especially in the long-term. Therefore it is difficult to handle the nephrotic hyperlipidemia by diet alone. Recently, a vegetarian diet based on soy and supplemented with essential amino acids has been shown to be more effective in reducing hyperlipidemia than the traditional lipid lowering diet. Some decrease in proteinuria was also observed [61]. However no data are available about the long-term compliance, efficacy and tolerance of such a diet.

Edema

Edema which does not respond to restriction of the dietary sodium intake often requires diuretic therapy. The first step may consist of administration of a thiazide agent, preferably in combination with a potassium-sparing drug, such as amiloride, triamterene or spironolactone. Many patients, however, particularly those with anasarca, volume overload, or pulmonary congestion do not respond to thiazides. Loop diuretics such as furosemide, ethacrinic acid or bumetamide are needed for these cases. Among these agents, furosemide is the most widely used because of its good tolerance even at very high doses. Furosemide may be given, either intravenously or by mouth, at doses ranging from 25 to 2,000 mg per day, according to the severity of edema and the response to therapy. Since binding of the drug to tubular fluid albumin can impair the response, high doses of furosemide are often needed to overcome the blunting effect of this binding [62]. In patients refractory to loop diuretics as monotherapy, combination with diuretics acting at different levels than furosemide, such as hydrochlorothiazide (25 to 50 mg per day) or metolazone (2.5 to 10 mg per day), may maximize the diuretic response. During diuretic treatment, the patients must be monitored to detect possible complications, such as hypokalemia, metabolic alkalosis or severe intravascular depletion.

Hypoalbuminemia and proteinuria

Administration of i.v. albumin to nephrotic patients is an expensive procedure and increases renal albumin clearance with only a small transient increase in the plasma albumin concentration. Albumin infusion may be justified only for cases with severe symptomatic plasma volume depletion with hypotension.

Some drugs may reduce the urinary loss of proteins. Inhibitors of angiotensin converting enzyme (ACE) can have important antiproteinuric effect. Although blood pressure lowering and postglomerular vasodilation theoretically might contribute to the antiproteinuric effect of ACE inhibitors, the effect is more probably related to changes in glomerular permeability to macromolecules [63]. The antiproteinuric effect of ACE inhibitors depend on the dose, the duration of treatment and the sodium intake. Heeg et al [64] reported that 5 mg of lisinopril decreased proteinuria by 27%, while 10 mg of lisinopril reduced proteinuria by up to 63%. In most patients, important and stable reduction of proteinuria occurred only after several weeks. The best antiproteinuric effect was observed with a dietary sodium intake of 50 to 100 mEq/day, and it was completely abolished when the salt intake was 200 mEq/day. Treatment with ACE inhibitors is usually well tolerated but some patients may develop anemia, hypotension or dry cough. In rare cases there is impairment of renal function, more often in patients with renal artery stenosis. In practice, to maximize the antiproteinuric effect of ACE inhibitors the patient should first be told to follow a low-salt intake diet. The ACE inhibitor should be started at low doses to test the tolerance. Doses should be increased progressively to the maximum tolerated dosage. Treatment should be prolonged for several weeks before assessing its effectiveness.

Non-steroidal antiinflammatory drugs (NSAIDs) may reduce proteinuria by 50% or more [64–66]. This effect can be attributed to a reduction of glomerular capillary permeability to protein, to a decrease in intraglomerular capillary pressure, and/or to a reduction of the filtration surface area. In the majority of patients, the effect is rapid (within 1 week) and reverses after cessation of treatment. Indomethacin (150 mg/day) and meclofenamate (200 to 300 mg/day) are the two agents used most frequently. Unfortunately, NSAIDs are not easy to handle in renal patients. These agents can cause hyperkalemia and in sodium-retaining states such as NS they can further aggravate sodium retention, reduce the response to diuretics and impair arterial hypertension. Most importantly NSAIDs may cause hemodynamically-mediated acute renal failure, acute interstitial nephritis or chronic renal damage. Thus, careful monitoring of renal function is mandatory during treatment of nephrotic patients. NSAIDs should not be given if the creatinine clearance is lower than 50 ml/min.

Recently, a six-week treatment with high-dose n-3 polyunsaturated fatty acids was shown to be able to reduce proteinuria by about 30% without important side effects [67].

Hyperlipidemia

For many patients with NS, diet is not sufficient to correct hyperlipidemia. Various lipid-lowering drugs such, as probucol, nicotinic acid, resins, fibric acid derivates and, more recently, hydroxymethylglutaryl coenzyme A (HGM CoA) reductase inhibitors, have been used in NS. Probucol is not very effective, and may reduce not only LDL but also HDL lipoproteins. Nicotinic acid may effectively reduce all circulating atherogenic lipoproteins

levels. However, in its rapid-release formulation it causes unpleasant cutaneous vasodilation; flushing is a minor consideration with the slow-release formulation but gastric irritation and hepatotoxicity are frequent, even at moderate doses. Resins are unpleasant to take, frequently cause abdominal symptoms and may interfere with the absorption of fat-soluble vitamins and of other drugs. Fibric acid derivates, such as clofibrate, bezafibrate and gemfibrozil, are more effective in lowering triglycerides (which may be normal in NS) than cholesterol. In nephrotic patients clofibrate may induce rhabdomyolysis and acute renal failure [68]. Moreover, these agents may expose to the risk of myopathy and of gallstones.

At present, HMG-CoA inhibitors, such as lovastatin, pravastatin and simvastatin, are considered as the drugs of choice for treating the hyperlipidemia of NS. These agents inhibit the rate-limiting enzyme in cholesterol biosynthesis. In nephrotic patients, HMG-CoA inhibitors produce significant decreases in serum cholesterol (36%), low density lipoproteins (43%) and apolipoprotein B (30%) levels [69, 70]. Triglycerides may also be decreased. Although these alterations in lipoprotein composition appear to be favorable, the strickingly elevated levels of atherogenic lipoprotein(a) were not influenced by HMG-CoA inhibitors [71]. Treatment with HGM CoA inhibitors is generally well tolerated by nephrotic patients. There may be a mild and transient increase in serum transaminase during the first months of therapy. Myositis and myalgia are rare, but it is wise to check creatine phosphokinase regularly.

Hypercoagulability

Thromboembolism is a serious and common complication of the NS. Anticoagulant drugs can reduce the risk of thrombosis but since they carry a substantial risk of major hemorrhagic complications, their use is generally restricted to some situations at increased risk for thrombosis such as prolonged bed rest, surgery, episodes of dehydration, or during the administration of intravenous high-dose corticosteroids. Recently, however, decision analysis studies showed that the benefits of prophylactic anticoagulation outweigh the risk at least in nephrotic patients with MN, who are particularly exposed to the risk of intravascular thrombosis [72, 73]. When to stop the treatment is still unclear. Since the risk of thrombosis remains elevated until NS persists, anticoagulation may theoretically be continued until remission or even lifelong. Such a prolonged anticoagulation is imperative for those patients who had two or more episodes of thrombosis or a single life-threatening episode.

CLAUDIO PONTICELLI AND PATRIZIA PASSERINI
Milano, Italy

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