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TREATMENT OF THE IDIOPATHIC NEPHROTIC SYNDROME*

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The term idiopathic nephrotic syndrome (NS) has been used either to indicate cases of NS associated with primary glomerular diseases or to replace the old definition of lipoid nephrosis. This definition, which encompasses several clinico-pathological conditions such as minimal change disease (MCD) and focal segmental glomerular sclerosis (FSGS), will be used in this paper. Although there is growing evidence that MCD and FSGS may be sustained by similar pathogenic mechanisms or may even represent different evolving stages of the same disease, at least in some cases, these two forms will be described separately, as they have different histological features, clinical presentations, outcomes and responses to therapy.

MINIMAL CHANGE DISEASE

This is typically a disease of children, but does rarely occur in adults, even in the elderly. Although a few patients found to have MCD at renal biopsy may have asymptomatic proteinuria, most patients present with full blown NS and severe oedema. The large majority of patients maintain normal renal function (creatinine clearance) during the course of the disease and a complete and stable remission of the proteinuria is usual. In a number of patients however, the final remission is reached only after many years of transient remissions and relapses. Thus, the main problem for these patients is represented by the nephrotic state which exposes them to complications such as severe oedema, susceptibility to infections, malnutrition, cardiovascular disease[1] and vascular thrombosis.[2]

NS resulting from MCD is very sensitive to treatment with corticosteroids. Although remission may occasionally be obtained with relatively moderate doses, most authorities suggest starting with aggressive initial treatment. In children the standard treatment for the first episode of NS consists of prednisolone at a dose of 60 mg/m^2/day for 4 weeks, followed by 40 mg/m^2/48 h for 4 more weeks.[3] With such a regimen, proteinuria can be expected to disappear in about 50% of children within one week, in 80–85% within 4 weeks, and in 93% within 8 weeks.[4] In a few children, however, complete remission of proteinuria occurs only after more prolonged treatment or after intravenous high-dose methylprednisolone is added.[5]

Adults are usually treated with lower doses of prednisolone, such as 1 mg/kg body weight/day. Proteinuria disappears in only 50–60% of adults within 8 weeks. However, about 80% of patients become free of proteinuria if treatment is prolonged to 16 weeks or more.[6–8] Thus, it is now clear that the concept of 'steroid-resistance', which was previously applied to patients who did not respond to high-dose prednisolone within 4–8 weeks, should be reviewed. Many adults

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and some children who were considered as steroid-resistant in the past were probably simply undertreated.

There is however a small proportion of patients with the histological appearance of MCD who do not respond even to a prolonged treatment with steroids. These patients usually show FSGS on repeated biopsy and should be treated accordingly.

After remission is obtained some 20–30% of patients do not relapse and a similar proportion only infequently. In contrast to the first episode, the intensity and duration of treatment does not influence the subsequent rate of relapses.[9] Patients with infrequent relapses are usually treated with high-dose prednisolone until remission, followed by 4 weeks of alternate-day prednisolone at a dose of 40 mg/m^2/48 h in children and of 0·75 mg/m^2/48 h in adults.[10] Spontaneous remission is also possible, particularly when relapse follows an intercurrent infection.

Unfortunately, many initial responders either become frequent relapsers (2 or more relapses within 6 months or at least 3 relapses within 12 months) or show steroid-dependency (relapse within 14 days after stopping the steroid or when the dosage is reduced). There is some evidence that the risk of relapse is greater in children given a short course of treatment for the initial attack than in those given long-term treatment. Thus, after remission has been obtained, it is advisable to prolong treatment in order to prevent further relapses. If well tolerated, low-dose prednisolone can be given every other day for 6 to 12 months. The doses of steroid should be tapered gradually to prevent relapses that may be triggered by secondary hypoadrenalism.[10]

The treatment of frequently relapsing or steroid-dependent patients is difficult. Schedules based on alternate-day prednisolone,[11] low-dose hydrocortisone[12] and intravenous high-dose methylprednisolone for inducing remission followed by low-dose prednisolone[13] can reduce iatrogenic toxicity and may allow treatment to be continued long term in some patients. However, even these therapies do not prevent relapse in all cases. Moreover, in spite of these schedules, a number of patients develop steroid-related side-effects including obesity, diabetes, osteoporosis, Cushingoid features, hypertension, infection and growth retardation in children.

Levamisole, cytotoxic agents and cyclosporine (CsA) have been suggested as potential alternative treatments to corticosteroids for patients with frequently-relapsing or steroid-dependent NS due to MCD. Levamisole is an antihelminthic drug with immuno-modulating properties. Some retrospective studies reported that this agent could reduce the risk of relapses. However, conflicting results have been obtained with controlled trials. In a British randomized study, 61 steroid-dependent children, in whom remission had been achieved with prednisolone, were randomly assigned to receive placebo or levamisole at a dose of 2·5 mg/kg/48 h. After 112 days, 4 of 30 patients given placebo versus 14 of 31 given levamisole maintained remission, the difference being significant.[14] Two other controlled trials could not find, however, any significant difference in the mean dose of prednisolone required[15] or in the median duration of remission[16] between children given placebo and those given levamisole.

Cytotoxic agents, such as cyclophosphamide and chlorambucil, can produce more lasting remission than steroids. Several factors may influence the response to these agents. Remission seems to be more stable in adults than in children. In one

study, 60% of adults given an alkylating agent were still without proteinuria after 15 years[6] while a paediatric review reported that rates of remission in children at 5 years ranged between 36 and 66%.[5] Some studies report longer remissions in frequently relapsing children treated with chlorambucil when compared with other series using cyclophosphamide.[17,18] However, a controlled trial did not find any difference in the rate of response or in the length of remission between children assigned to chlorambucil and those assigned to cyclophosphamide.[19] The duration of treatment is also important. Pennisi *et al.*[20] reported complete remission at 1 year in 92% of children given cyclophosphamide for 10–12 weeks versus 42% of children treated for 6–8 weeks. Similar results were reported by Rance *et al.*[21] Some investigators have found that the rate and duration of response to cytotoxic therapy is better in frequently relapsing than in steroid-dependent patients[19,22] but these data have not been confirmed by others.[23,24]

In spite of the efficacy of alkylating agents many clinicians are still reluctant to use these drugs in patients with MCD as they may predispose patients to leukopenia, haemorrhagic cystitis, alopecia, oncogenic effects and gonadal toxicity, testes being more vulnerable than ovaries. Therefore, the use of alkylating agents may only be justified in those patients who are at high risk of developing steroid toxicity. In our practice in order to avoid leukopenia high daily doses are not used (we suggest 2 mg/kg/day for cyclophosphamide and 0·1–0.15 mg/kg/day for chlorambucil). Cumulative doses of 200–250 mg/kg for cyclophosphamide or 10–15 mg/kg/day for chlorambucil in order to prevent azoospermia are our upper limits. With these cumulative doses, the oncogenic risk is considered minimal. Forced diuresis and/or MESNA can protect from the bladder toxicity of cyclophosphamide.

Cyclosporin (CsA) is another therapeutic option in frequently relapsing/steroid-dependent patients. A review of the literature shows that most steroid-dependent patients can be maintained in remission with CsA, which is usually started after remission has been induced with steroids.[25] After CsA is stopped an early relapse of NS usually occurs, but some patients may maintain remission, particularly if CsA dosing has been tapered gradually, after prolonged treatment.[26,27] A number of side-effects may be associated with the use of CsA. Hypertrichosis (18%), gum hyperplasia (16%), gastrointestinal symptoms (11%) and hypertension (9%) were the most frequently reported in a large retrospective study of patients with idiopathic NS.[28]

There has been much concern about the potential nephrotoxicity of CsA. In patients with non-renal autoimmune diseases a CsA-related nephropathy characterised by interstitial fibrosis and progressive renal disease can develop. This is usually preceded by a typical arteriolopathy with either nodular proteinaceous deposits in the arteriolar wall or mucinoid thickening of the intima.[29] Older age, high doses of CsA, and an increase in plasma creatinine to more than 75% over the basal values are the most important variables associated with the risk of developing irreversible CsA nephropathy.[30] The importance of the size of the dose in inducing CsA-related nephropathy is confirmed by some studies based on iterative renal biopsies in patients with MCD. Only mild nephrotoxicity was seen in adults treated with a mean dose not higher than 5·5 mg/kg/day.[27,31] In children who developed mild or moderate CsA-related histological lesions, the mean dose of CsA was 5 mg/kg/day while in patients who developed extensive interstitial fibrosis the mean dosage was 6·7 mg/kg/day.[32] On the other hand

there is evidence that CsA-related arteriolopathy, which precedes the development of interstitial fibrosis, can be reversible if CsA is stopped or given at lower doses.[33] Thus CsA can be used as an alternative to corticosteroids or cytotoxic drugs in patients with resistant disease or toxicity. However, careful monitoring is needed with the use of CsA in patients with renal diseases (Table 1).

TABLE 1

Recommendations for the use of cyclosporin (CsA) in patients with idiopathic syndrome. (Modified from 10)

CsA is contraindicated in patients with renal insufficiency, severe hypertension, and/or interstitial fibrosis at renal biopsy.
The initial dose should not exceed 4 mg/kg/day in elderly patients, 5 mg/kg/day in adults or 100–150 mg/m²/day in children.
Plasma creatinine, trough blood levels of CsA and blood pressure should be monitored during treatment.
The dose of CsA should be decreased if trough blood levels of CsA are higher than 200–250 ng/ml (monoclonal assay) and/or whenever plasma creatinine rises by more than 30% over the basal value. CsA must be stopped if plasma creatinine rises by more than 75% over the basal value.
Nephrotic drugs should be avoided.
Possible interactions of other drugs with CsA metabolism should be taken into account.
If a renal biopsy shows CsA-related arteriolopathy, the drug should be stopped or the doses decreased.
If there is no response within 3–4 months, CsA may be stopped (probably ineffective).
After 2 years CsA may be tapered off to see whether the patient remains in remission.

In summary, we suggest an aggressive and prolonged course of corticosteroids be used to treat the first episode of NS in an attempt to achieve remission and prevent relapse. Infrequent relapses can be treated with further shorter courses of corticosteroids. In frequently relapsing/steroid-dependent patients levamisole may be tried in an attempt to reduce steroid doses in responders. Although the efficacy of this drug is controversial, the tolerance is usually good which can justify its use in patients showing evidence of steroid side-effects. If levamisole is not successful, patients may be treated with continuous alternate-day prednisolone and intravenous methylprednisolone pulses during relapses. Those patients who do not tolerate corticosteroids may be given a trial with an alkylating agent for 12 weeks at cumulative doses not exceeding 250 mg/kg for cyclophosphamide or 12 mg/kg for chlorambucil. If further relapses occur, cytotoxic therapy should not be repeated, as some of the potential toxicity is cumulative. These patients can be switched to CsA, at an initial dose of 5 mg/kg/day in adults and 100–150 mg/m² in children, trying to gradually taper off the dose of CsA after one to two years (Table 2).

FOCAL SEGMENTAL GLOMERULAR SCLEROSIS

FSGS can affect both children and adults and is generally associated with NS. The prognosis may be good for the few patients with asymptomatic proteinuria but most nephrotic patients progress to end-stage renal failure within 10 years.[34] The degree of tubulo-interstitial lesions at renal biopsy is possibly the best

available predictor for progression to end-stage renal failure.[35] On the other hand, those patients who attain complete remission of proteinuria either spontaneously or after therapy usually have a fair prognosis even in the long-term.[36]

TABLE 2

Possible therapeutic steps for patients with minimal change disease

First episode. Prednisolone (60 mg/m²/day in children; 1 mg/kg/day in adults). After remission, prolong treatment with low-dose to prevent relapses.

Infrequent relapses. High-dose prednisolone until remission; then alternate days for 4 weeks.

Frequent relapses/steroid dependency. Try levamisole; if relapse, three intravenous methylprednisolone pulses (10 mg/kg) to induce remission followed by doses of prednisolone on alternate days.

If steroid toxicity develops. Stop prednisolone and give cyclophosphamide (2 mg/kg) or chlorambucil (0·1 mg/kg/day) for 12 weeks to maximal cumulative total doses of 250 mg/kg or 12 mg/kg respectively.

If early relapse occurs after cytotoxic agents cyclosporin (100 mg/m²/day in children, 5 mg/kg/day in adults). If positive response achieved, try to taper off gradually after 1–2 years.

If no response. Give symptomatic treatment.

Almost all the studies of treatment for FSGS are retrospective. Uncontrolled trials have reported that 29% of children[34] and 17% of adults[37] treated with corticosteroids entered complete remission of proteinuria. Little information is available from these studies about the evolution of renal function in these patients' long-term. Of note, the majority of patients were given corticosteroids for no more than 4–8 weeks. Better results have been obtained when patients were given more prolonged corticosteroid therapy. Pei *et al.*[38] reported that in 39% of adults and 44% of children with FSGS treated with prednisolone for at least 6 months there was complete disappearance of proteinuria. The follow-up was extended up to 12 years. The probability of maintaining normal renal function at 12 years was zero for non-responding or untreated patients while 96% of responders maintained stable renal function. Only one adult but 11 of 15 children relapsed. Banfi *et al.*[39] administered prednisolone for a mean period of 9·3 months to 27 nephrotic adults with FSGS; 20 obtained complete disappearance of proteinuria, within a mean of 6 months after starting therapy. NS relapsed in 11 patients; 7 of these achieved complete and 3 partial remission after re-treatment. After a mean follow-up of 5 years all responders but one (who relapsed and progressed to end-stage renal failure) had normal renal function. Agarwal *et al.*[40] reported complete remissions and partial remissions in 31% and 27% respectively of 38 nephrotic adults with FSGS treated with prednisolone for 6 months; one responder eventually entered end-stage renal failure. Nagai *et al.*[41] gave alternate-day prednisolone for 6 months to 7 elderly patients; 4 of them entered complete remission after 4 months treatment on average. Rydel *et al.*[42] obtained complete remission of proteinuria in 10 and partial remission in 5 of 30 nephrotic patients with FSGS treated with prednisolone for a mean period of 5·5 months. The 10-year renal survival was 100% for responders versus 39% for nonresponders and 47% for untreated nephrotics. Of interest, no clinical or histological feature could predict response in any of these studies.

The potential role for other immunosuppressive agents is even less clear. The results of retrospective studies suggest that, as with prednisolone, the longer the

treatment the higher the rate of response. However cytotoxic agents may only marginally improve the rate of remission, in comparison with corticosteroids.[43] On the other hand, the length of remission seems to be longer in patients given cyclophosphamide or chlorambucil. In our own retrospective experience, of 32 nephrotic adults with biopsy-proven FSGS treated with cytotoxic agents, after a mean follow-up of 75 months 15 were in complete remission, one had non-nephrotic proteinuria, two had NS with otherwise normal renal function, in 5 renal function had deteriorated, 8 were on dialysis and one had died. Only 18% of patients who responded to cytotoxic therapy had one or more relapses of NS.[39] Clearly these results can be criticised as they come from a retrospective uncontrolled study.

Mendoza *et al.*[44] have proposed an aggressive approach for steroid-resistant children. Their regimen consisted of intravenous high-dose methylprednisolone pulses given initially every other day, then at progressively longer intervals for more than one year; concurrently the children were also given prednisolone, 2 mg/kg/48 h. If no response was obtained, cyclophosphamide or chlorambucil was added. Their most recent analysis showed that at the end of a mean follow-up of 6 years, 21 out of 32 children treated were in complete remission, 3 were in partial remission (non-nephrotic proteinuria), 5 had reduced creatinine clearance, and 3 had progressed to end-stage renal failure.[45] However, these encouraging results were not confirmed by Waldo *et al.*[46] who gave a similar regimen to 10 children with FSGS. After 47 months, 6 patients had developed end-stage renal failure, 2 had developed renal insufficiency, and the other 2 patients were still nephrotic. However, 8 of their 10 patients were black and this may have affected the response rate, since blacks may have more severe disease than white patients.

CsA has been used both in children and in adults with FSGS. Two independent reviews of the literature found that 40% of patients could be maintained in remission from NS treated with CsA, the response being similar in children and in adults.[25,36] A retrospective analysis of the data in the files of Sandoz Pharmaceuticals showed that the combination of CsA with low-dose prednisolone could obtain complete remission in 25% and partial remission in another 29% of nephrotic patients while the responses were respectively 17% and 13% in patients treated with CsA alone (Feutren G., personal communication). This apparent benefit of CsA on proteinuria was also supported by an Italian controlled trial.[47] Nephrotic patients who had not responded to a 6-week course of high-dose prednisolone were randomly assigned to supportive therapy or to CsA (5 mg/kg/day in adults and 6 mg/kg/day in children) for six months. The CsA dose was then tapered off by 25% every two months. 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 either a partial or transient remission. The mean levels of creatinine clearance did not differ between the two groups. However, 66% of patients had a relapse in NS after CsA was stopped. Thus, while CsA may induce remission in many patients with NS, unfortunately most responders appear to relapse after CsA is stopped, so that a prolonged treatment is needed to avoid NS.

Is this approach safe? Some investigators have reported worsening of kidney lesions at repeat renal biopsy and argued against the use of CsA in patients with FSGS.[27,48,49] It is not clear however, whether the renal lesions seen on repeat

biopsy represent progression of the underlying FSGS in non-responders or represent CsA toxicity. Whatever the mechanism, the risk of severe tubulointerstitial lesions in patients treated with CsA for FSGS seems to be particularly high when there is an abnormal baseline serum creatinine, when a high proportion of glomeruli with sclerosis are seen at renal biospy, or when the initial dose of CsA is higher than 5·5 mg/kg/day.[27] On the basis of available knowledge, our practice is not to prescribe CsA to patients with abnormal renal function, severe hypertension, tubulointerstitial lesions or extensive glomerular sclerosis.

In summary, a number of clinical trials suggest that prolonged treatment with corticosteroids, cytotoxic agents, or cyclosporin may lead to either complete or a partial remission of NS in some 40–60% of patients with FSGS. Further, most responders tend to maintain normal renal function over time. These optimistic conclusions may be challenged, however, since all the studies but one have been uncontrolled, only a few have reported the results of repeated renal biopsies, and no histological or clinical criteria for identifying the possible responders could be established. As a consequence, the optimal treatment regime for FSGS is still unclear. There is general agreement that no 'specific' therapy is needed for patients with asymptomatic proteinuria. There is also consensus about using an 8-week course of high-dose prednisolone in nephrotic patients in order to recognise the few 'early responders'.

What to do with nephrotic patients who do not respond to short-treatment is controversial. Many clinicians do not give any 'specific' therapy, whereas others are quite aggressive and give prolonged steroid and/or cytotoxic treatments. Our practice is that, unless steroid toxicity develops, prednisolone be continued for another 4 to 6 months. One alternative is to give an alkylating agent for 6 months or alternate steroids and an alkylating agent every other month for 6 months, with a schedule similar to that used in membranous nephropathy,[50] in order to reduce the risk of steroid toxicity and potentially to induce a longer remission in responders. If NS persists, a trial with CsA may be offered provided that creatinine clearance and blood pressure are normal and that a recent renal biopsy does not show severe tubulointerstitial lesions. If no improvement of proteinuria is seen within 3 months of introduction, CsA should be stopped, as it is unlikely that more prolonged treatment will result in remission. In patients who respond, CsA can be continued for another 1–2 years, at the minimal effective dose. If NS reappears after stopping CsA, a renal biopsy should be repeated before deciding whether or not CsA therapy should be continued (Table 3).

TABLE 3

Possible therapeutic steps for patients with focal segmental glomerulosclerosis and nephrotic syndrome

Initial treatment. Prednisolone for 8 weeks (60 mg/m²/day in children; 1 mg/kg/day in adults).

If no response. Prednisolone on alternate days for 4–6 months or prednisolone and an alkylating agent alternated every other month for 6 months or low-dose prednisolone plus an alkylating agent for 6 months.

If no response to the above. Cyclosporin (100 mg/m²/day in children or 5 mg/kg/day in adults) to be continued for 1–2 years at the minimal effective dose. Consider renal biopsy for deciding whether or not to start and stop cyclosporin therapy. If there is no response within 3 months, symptomatic treatment only.

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ACUTE RENAL FAILURE*

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You came a long way from St Louis, but baby you still got a long way to go
St Louis Blues, 1914: W.C. Handy (1873–1958)

It is customary in a review to provide a historical perspective on the topic. Accordingly, this protocol for the treatment of acute renal failure (ARF) may be of interest—perhaps as an early precursor of a Royal Colleges' guideline.

Potassium citrate 15 grains	Senna or liquorice
Liq. Ammon. Acetatis 60 minims	Urea 30–60 g three times daily
Sp. Aetheris nitrosi 15 minims	Venesection
Aq. Chloroform ½ oz—in water, q.d.s.	5 minims tincture of digitalis

The initial recommendation is to give potassium citrate, despite the risk of inducing a hyperkalaemic cardiac arrest. This is followed by a combination of ammonia, ether and chloroform, just in case the patient is not already in uraemic coma, and some laxatives in case he does not have uraemic colitis. Urea supplementation seems at best unnecessary, and venesection would reduce oxygen delivery to the already ischaemic renal tubules. The final straw is a dose of digitalis, a drug which is very likely to accumulate in renal failure and to cause adverse effects.

If asked to date this protocol, most people would estimate the late 19th century. In fact, it is taken from Price's *Textbook of Medicine*, published in 1941.[1] This is well within living memory, and indeed this edition would have been in current use when the atomic bomb was dropped on Nagasaki in 1945. In other words, even in the nuclear age, patients with ARF might well have died as a result of their treatment rather than the disease. I do not think it is excessive to claim that we have come a long way since then. In this review, I hope to show how far we have come, and also to suggest ways in which we still have far to go.

AETIOLOGY

When studying trends in the aetiology of ARF, we are fortunate to have the meticulous records kept by Dr Anne Lambie and Professor James Robson. Table 1 compares the aetiologies of ARF for the first 20 years of the renal unit in Edinburgh (1959–1979), with the figures for 1994 from the renal unit database. As is well known, obstetric ARF has virtually disappeared, and 'surgical' or post-operative ARF, while it still occurs, is much less common.[2,3] One suspects that this reflects the identification and appropriate haemodynamic monitoring of 'high-risk' patients.

Breaking down the figures, in the medical category, the newcomers are renovascular disease—possibly being unmasked by the widespread use of ACE inhibitors; rhabdomyolysis with myoglobinuria (which is usually related to drug or alcohol abuse); and severe liver failure—many due to paracetamol poisoning[3,4]

*Based on a lecture delivered at the symposium on *Renal Medicine* held in the College on 20th September 1995.