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The treatment of minimal change nephropathy and focal segmental glomerulosclerosis

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Minimal change nephropathy (MCN) and focal segmental glomerulosclerosis (FSGS) are together responsible for almost all cases of nephrotic syndrome in children and of 25–35% in adults. This article focuses on the drug treatment of MCN and FSGS designed to cure the nephrotic syndrome. However, it is important first to remember the general aspects of management of these patients while they remain nephrotic[1].

Treatment of nephrotic syndrome

A normal protein, no added salt diet should be prescribed. Control of oedema may be accomplished with diuretics, although high doses of loop diuretics are often necessary, partly because they are highly protein bound and delivery to the kidney is reduced by hypoalbuminaemia, and partly because binding to albumin in the tubular lumen reduces their effect. The addition of thiazides, particularly metolazone, is often effective, but care must be taken to avoid hypokalaemia and hypovolaemia which may precipitate renal failure. Potassium-sparing diuretics are not very effective as diuretics, but may be useful in maintaining serum potassium. Patients with gross oedema resistant to high doses of diuretics may respond when intravenous albumin is added to their diuretic regimen. The raised serum albumin improves the delivery of loop diuretics to the kidney, although the albumin is rapidly lost in the urine. Paracentesis and haemofiltration are occasionally needed to remove fluid from refractory patients for symptomatic relief.

Other symptomatic treatment is rarely required in MCN, since the nephrotic syndrome is almost invariably relieved by corticosteroids. About 60% of patients with FSGS remain nephrotic. In such patients, angiotensin converting enzyme (ACE) inhibitors may reduce proteinuria and oedema significantly, and are especially useful when an antihypertensive effect is also necessary. Non-steroidal anti-inflammatory drugs (NSAIDs) also reduce proteinuria and act synergistically with ACE inhibitors. Although NSAIDs are useful in selected patients, care must be taken since they may also cause a marked fall in glomerular filtration rate (GFR) and diminish the effectiveness of diuretics. Severely nephrotic patients may need prophylactic anticoagulants and antibiotics. In addition, treatment of the hypercholesterolaemia in chronically nephrotic patients, with 3-hydroxy-3-methyl glutaryl co-enzyme A (HMGCoA)-reductase inhibitors should be considered to reduce the risk of long-term cardiovascular morbidity and mortality.

Minimal change nephropathy

MCN is responsible for 90% of nephrotic syndrome in children and about 20% in adults. Clinical onset is usually with abrupt onset of severe oedema. About 50% of episodes occur after an upper respiratory tract infection, but it is not known whether these are immunological triggers. The glomeruli appear normal on light microscopy, with fusion of epithelial foot processes on electron microscopy. Underlying causes of MCN should be considered before treatment is started (Table 1).

Treatment is with corticosteroids. The regimens used by nephrologists vary considerably and have not been compared in adequate controlled trials. Treatment guidelines used by the author are described here, justified where possible by published data.

Treatment of children

Children are treated with oral prednisolone 60 mg/m^2/day (or 1 mg/kg/day or 2 mg/kg alternate days) until one week after induction of urinary remission (proteinuria <300 mg/day). The corticosteroids are then reduced to 30–40 mg/m^2/day (or 60 mg/m^2 on alternate days) for 4–8 weeks after remission, depending on how quickly remission occurs (see below), with

Table 1. Secondary causes or associations of glomerulonephritis.

Minimal change	FSGS
non-steroidal anti-inflammatory drugs	IV drug abuse
haematological malignancies (especially Hodgkin's disease, occasionally other lymphomas and leukaemias)	HIV infection ('collapsing FSGS')
	malignancy
	following focal segmental glomerulonephritis
other drugs, including gold and lithium	lithium treatment
	solitary kidney
	morbid obesity

FSGS = focal segmental glomerulosclerosis.
HIV = human immunodeficiency virus.
IV = intravenous.

Key Points

TREATMENT OF NEPHROTIC SYNDROME IN GENERAL:

- Loop diuretics: large doses may be needed
- Addition of thiazides (esp. metolazone) potentiates loop diuretics – careful monitoring

Consider the need for

- 'Statins' for hyperlipidaemia
- Anticoagulants

For resistant oedema

- Albumin infusion – temporary effect but useful when stuck
- ACE inhibitors and NSAIDs reduce proteinuria but may depress GFR

MINIMAL CHANGE:

- High dose (2 mg/kg/day) prednisolone, diminishing over 4–8 weeks
- For relapse: repeat course of prednislone
- For repeated relapses: cyclosporin or levamisole
- When all else fails: cyclophosphamide 8–12 weeks

FOCAL SEGMENTAL GLOMRERULOSCLEROSIS:

- Prednisolone (1 mg/kg/day) for at least 3 months (2 in children); response in > half
- Cyclosporin effective in about half – high relapse rate on withdrawal
- Cyclophosphamide (12 weeks) may benefit steroid-relapsers
- More controlled trials needed

subsequent tapering of the dose (eg reducing by 15 mg/m^2 on alternate days every two weeks) until steroid withdrawal. The aim is to keep patients on corticosteroids for 3–4 months; this appears to be associated with a lower two-year relapse rate than if corticosteroids are given for two months or less (69% and 81% relapse, respectively)[2]. More than 90% of children respond within eight weeks (80% within 4 weeks). If proteinuria persists after four weeks' treatment, some anecdotal evidence suggests that increasing the steroid dose or giving a pulse of methylprednisolone (1 g/1.73 m^2) will increase the probability of inducing a remission. However, the possibility of non-compliance or poor absorption from an oedematous bowel should be considered; in the presence of diarrhoea, it is logical to give intravenous corticosteroids. Even in the absence of diarrhoea, I prescribe non-enteric coated formulations of prednisolone.

More than two-thirds of children relapse, nearly half more than four times, usually as, or soon after, corticosteroids are stopped or the dose reduced (the latter group are referred to as steroid-dependent (Table 2)). However, less than 5% of children with MCN enter adulthood still having relapses, although the younger the onset of the first attack the longer the duration of the disease[3]. The aim of management, therefore, is to maintain the child free of the nephrotic syndrome with the lowest possible dose of corticosteroids. The first relapse should be treated with a second induction course of corticosteroids, although a shorter course (about two weeks full-dose prednisolone daily, followed by two weeks' alternate-day treatment) may be as effective as a longer course[4]. Subsequent relapses may be treated similarly, or by tapering the prednisolone to 15 mg/m^2 on alternate days, and continuing for 12–18 months (assuming this is above the 'steroid threshold', ie the dose below which relapse occurs). Clearly, the acceptability of this approach depends on the 'steroid threshold'.

Alternatives to the use of corti-

Table 2. Minimal change nephropathy and relapse.

Children:	
30%	have only 1 attack
10–20%	relapse after several months but have < 4 relapses
40–50%	relapse frequently after cessation or on steroid dose reduction (steroid-dependent)
Adults:	
30–50%	

costeroids in relapsing MCN in children include cyclosporin, cyclophosphamide and levamisole.

Cyclosporin. Cyclosporin (up to 150 mg/m^2 or 4 mg/kg/day) is usually effective in children with both steroid-dependent and frequently relapsing nephrotic syndrome[5]. However, relapse is almost invariable within three months of stopping treatment, and there is a risk of cyclosporin nephrotoxicity. The rationale for the use of cyclosporin is the hope that it will maintain the child in remission without the need for corticosteroids until the underlying disease remits. It is important to monitor for potential toxic effects, including gingival hypertrophy, hirsutism, reduced GFR and hypertension. Many nephrologists recommend a year's course followed by tapering and stopping the drug.

Alkylating agents. The use of alkylating agents such as cyclophosphamide and chlorambucil in children with steroid-responsive disease is controversial, and their use is now less often recommended by paediatric nephrologists, first because of the potential side-effects (sterility, alopecia, haemorrhagic cystitis) and the longer-term risks of haematological and other malignancies. Although the risks are probably small even for a three-month course, they need to be balanced against the fact that MCN is usually self-limiting. Secondly, the permanent remission rate is not very high. Cyclophosphamide for eight weeks (2–2.5 mg/kg/day) is often effective, although some (but not all) studies suggest that a 12-week course is better (two-year remission rate, 60% vs 30%)[6]. Frequently relapsing children are more likely to have a permanent remission than those who are steroid-dependent. Chlorambucil (0.2 mg/kg/day) for two months appears to have a similar effect to cyclophosphamide. There are few data on second courses, which are not recommended[7]. Azathioprine has no place in the management of children with MCN[8].

Levamisole. The anti-helminthic drug, levamisole, has also been used successfully at a dose of 2.5 mg/kg on alternate days for three months[9], but most patients relapse within three months of completing the course. Nevertheless, as with cyclosporin, it may provide a relatively non-toxic alternative to corticosteroids until spontaneous remission of the condition eventually occurs.

Treatment of adults

There are even fewer good studies comparing different steroid regimes in adults with MCN, but treatment is broadly similar to that for children, with oral prednisolone at 1 mg/kg/day. Response is often delayed in comparison with children, and 25% fail to remit after 3–4 months[10] (Fig 1). The reasons for this are unclear. It has been suggested that adults are perhaps given 60 mg/day prednisolone rather than 1 mg/kg/day, or that a greater proportion of adults actually have FSGS (missed on the original biopsy), which is more steroid-resistant (see below). One week after urinary remission, the dose of prednisolone should be reduced by half for 4–6 weeks, followed by tailing off over a further 4–6 weeks aiming – as in children – for a total initial steroid course of at least four months (although this is not based on hard evidence).

Adults with MCN relapse less often than children (30–50%). Some adults develop transient non-nephrotic relapses, treatment of which, initially with a repeat course of corticosteroids, should await the development of nephrotic syndrome.

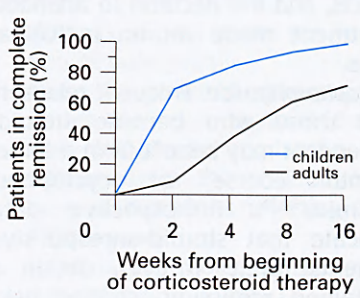
Cyclophosphamide. Frequently relapsing and steroid-dependent patients should be treated with cyclophosphamide, which induces a permanent remission more often than in children (75% and 66% at two and five years, respectively)[10]. There are no satisfactory studies comparing eight and 12 week courses in adults, but a 12-week course may be logical by extension of the paediatric experience. Remission occurs slightly more rapidly if corticosteroids are given at the same time as the cyclophosphamide.

Cyclosporin. Cyclosporin (4–6 mg/kg/day) is also effective but, as in children, relapse usually follows dose reduction or withdrawal. It is worth considering as a short- to medium-term management strategy because there is evidence that remission eventually occurs in 50–75% of patients even without treatment[10]. However, careful monitoring is required since nephrotoxicity is common after more than one year's treatment[11]. Some nephrologists prefer to try this before cyclophosphamide, especially in younger adults.

Focal segmental glomerulosclerosis

The aetiology is unknown of this relatively common type of glomerular disease which causes up to 15% of nephrotic syndrome. There is some evidence that a circulating factor may be responsible. Nephrotic syndrome

Figure 1. The cumulative response of children and adults with minimal change nephrotic syndrome to corticosteroid treatment. (*Reproduced from Ref 10 with permission of the publisher, W B Saunders Company*).



sometimes recurs within hours of renal transplantation, and serum from affected individuals can cause proteinuria in rats and alter protein permeability of glomeruli *in vitro*. The characteristic pathological features are focal and segmental glomerular scars containing IgM and C3 on immunostaining. Most cases are idiopathic, but there are several reported associations (Table 1), although in these circumstances the pathogenesis of FSGS may be different.

Traditionally, FSGS has been thought to have a poor prognosis, with a low rate of response to treatment. About 50% of patients progress to end-stage renal failure in 10 years[12] (Fig 2(a)), although only those who are nephrotic seem to be at particular risk (Fig 2(b)). It is now clear that up to 40% of patients (adults and children) respond to corticosteroids with complete remission; in the responders, the five-year actuarial renal survival exceeds 95%[13–15]. Unfortunately, there is at present no way of identifying which patients will or will not respond. The only factor, identified in retrospect in several studies, seems to be the duration of steroid treatment. For example, one study revealed that 87% and 67% of responders received 60 mg prednisolone for one and two months, respectively, with a median response time of 3.7 ± 2 months[13]. My practice is to treat nephrotic patients with FSGS with prednisolone 1 mg/kg/day for at least three months (two months in children). Responders in whom the proteinuria reduces or remits are then treated with reducing doses for about six months. The corticosteroids are tapered in non-responders and stopped within four weeks. Patients should be monitored for steroid side effects, and the decision to abandon treatment made on an individual basis.

Cyclophosphamide. Frequent relapsers and those who become steroid-dependent may benefit from a three-month course of cyclophosphamide[14,16]. Retrospective data indicate that steroid-unresponsive patients rarely, if ever, obtain a sustained remission, so the risks probably outweigh the benefits in this group[14].

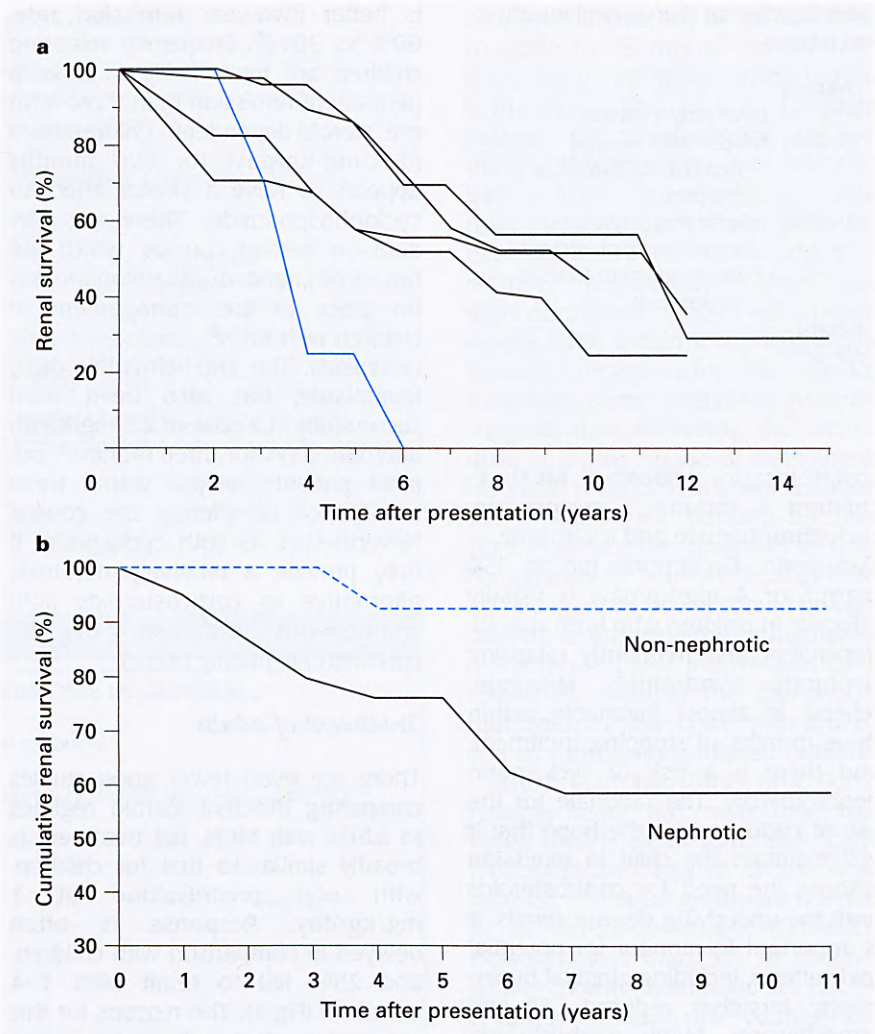


Figure 2. The renal survival of **(a)** patients with focal segmental glomerulosclerosis (FSGS) from four separate studies (total 220 patients). The blue line represents the renal survival of 10 patients with very heavy proteinuria (>14 g/day) (*composite data from Ref 12*); **(b)** 60 nephrotic and 21 non-nephrotic patients with FSGS (*data from Ref 13*). *(a) and (b) reproduced with the permission of the publisher, Blackwell Science.*

Cyclosporin. Cyclosporin is sometimes effective, especially in the steroid-dependent patients[17,18]. Although, as in MCN patients, relapse usually follows withdrawal of the drug[18], it may have a role in those with refractory nephrotic syndrome. The only published randomised controlled trial of cyclosporin included 41 patients, mostly with FSGS, but some with MCN. Treated patients received cyclosporin for six months, followed by a dose reduction of 25% every two months until withdrawal. Although 13/22 of the treated and 3/19 of the control patients had a partial or complete remission during the first year, mostly while on full-dose cyclosporin, there were many relapses following dose reduction (data beyond one year were unavailable)[19]. There have been anecdotal reports of a more sustained benefit in some patients, but further studies are necessary.

It should also be emphasised that the most important factor in slowing

the rate of renal progression in heavily proteinuric patients is extremely tight blood pressure control, as demonstrated by the modified diet in renal disease study[20].

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The polycystic kidney disease 1 (PKD-1) gene: an important clue in the study of renal cyst formation

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Solitary cysts are commonly found in normal kidneys, especially with increasing age. The hereditary renal cystic diseases, of which autosomal dominant polycystic kidney disease (ADPKD) is the most common (incidence 1 in 1,000 people), are however characterised by multiple cysts which are bilateral, often arise *in utero*, and lead to the progressive destruction of normal kidney tissue and gradual loss of renal function[1].

A major breakthrough in the study of this group of diseases came in 1985 when polycystic kidney disease 1 (PKD-1), the major gene responsible in almost 90% of patients with ADPKD, was linked to the short arm of chromosome 16 (16p)[2]. This was followed quickly by the recognition that at least 10% of ADPKD patients were not linked to chromosome 16, leading to the definition of further loci, PKD-2 (chromosome 4) and later PKD-3 (so far unlinked). Although the approximate position of PKD-1 was defined in 1985, the genomic arrangement at this locus was so complex that its precise location was not identified until 1994, by a combination of painstaking hard work and a decisive stroke of good fortune[3]. Subsequently, the PKD-1 gene and the protein it encodes, polycystin, have been the subject of intense investigation. During this period, PKD-2 has also been cloned and fully sequenced[4].

After pointing out the problems that continue to face researchers in this field, this article reviews the present state of knowledge of PKD-1 by addressing three specific questions:

1. What is known about the function of polycystin?
2. Can the marked phenotypic variability seen in individuals with PKD-1 be explained by differences in the position and type of mutations affecting the PKD-1 gene?
3. What is the molecular basis of cyst formation in PKD-1?