Cyclosporin in idiopathic glomerular disease associated with the nephrotic syndrome : Workshop recommendations

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Management of idiopathic glomerular disease associated with nephrotic syndrome (INS) remains controversial and one of the most complex areas relates to utilization of the drug cyclosporin. This is despite its demonstrated effectiveness in several histologic types of the INS in randomized controlled trials. Cyclosporin is effective in inducing remission of proteinuria in approximately 80% of steroid-sensitive cases of minimal change disease (MCD). Cyclosporin is also effective in both the induction of remission and long-term preservation of renal function in steroid-dependent/-resistant MCD and steroid-resistant focal segmental glomerulosclerosis (FSGS). The overall response rate in FSGS is lower than in MCD, and long-term therapy ($>$12 months) may be required to both achieve remission and sustain it. Cyclosporin therapy is also of benefit in reducing proteinuria in 70–80% of patients with steroid-resistant membranous nephropathy (MGN). In MGN, the maximum benefit is often delayed compared to MCD ($>$12 weeks). Cyclosporin is generally well tolerated and safe. The major concern remains the nephrotoxicity, but with careful monitoring of the patient's renal function; minimizing the maintenance dose and utilizing repeat renal biopsy in those receiving long-term therapy, this risk can be minimized. The algorithms have been developed derived from the best evidence in the literature in each of the histologic types to help provide a guide to the integration of cyclosporin into the management of INS for the practicing nephrologist.

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Cyclosporin has been used in the treatment of idiopathic glomerular disease associated with the nephrotic syndrome (INS) in children and adults since 1985. Despite its proven efficacy, there remains a lack of coherent guidelines to aid clinicians in its use. An international workshop was convened to address this issue and to undertake a multidisciplinary, expert review of the clinical data currently available on cyclosporin therapy in INS. The aims of the workshop were (1) to examine where cyclosporin fits into the 'therapeutic armamentarium'; (2) to present a unified and integrated approach for the use of cyclosporin in the most common histologic variants of the INS, in both children and adults; and (3) to provide recommendations for monitoring of potential side-effects. The recommendations outlined are proposed only as a guide, and are intended for use in conjunction with the physician's clinical judgment.

IDIOPATHIC NEPHROTIC SYNDROME—AN OVERVIEW

Nephrotic syndrome is defined as presence of heavy proteinuria ($\geqslant$3.5 g day^{-1} in adults; $>$40 mg m^{-2} h^{-1} or $>$1.0 g m^2 day in children), hypoalbuminemia ($<$3.0 g dl^{-1} in adults; $<$2.5 g dl^{-1} in children), and edema. Hypercholesterolemia is commonly present. Although there are many known etiological agents that produce glomerular injury and the features of the nephrotic syndrome, this workshop's focus was on primary glomerular disease of idiopathic cause.

The three leading histologic variants associated with the INS are minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), and membranous nephropathy

Table 1 | Definition of terms used in idiopathic nephrotic syndrome

	Idiopathic NS definitions	
Term	Adult	Pediatric[14,15]
Relapse	Proteinuria $\geqslant 3.5\,g\,day^{-1}$ occurring after complete remission has been obtained for >1 month	Albu-stix 3+ or proteinuria $>40\,mg\,m^{-2}\,h^{-1}$ occurring on 3 days within 1 week
Frequently relapsing	2+ relapses within 6 months	2+ relapses within 6 months
Complete remission	Reduction of proteinuria to $\leqslant 0.20\,g\,day^{-1}$ and serum albumin $>35\,g\,l^{-1}$	$<4\,mg\,m^{-2}\,h^{-1}$ on at least 3 occasions within 7 days serum albumin $>35\,g\,l^{-1}$
Partial remission	Reduction of proteinuria to between $0.21\,g\,day^{-1}$ and $3.4\,g\,day^{-1}$ $\pm$ decrease in proteinuria of $\geqslant 50\%$ from baseline	Disappearance of edema. Increase in serum albumin $>35\,g\,l^{-1}$ and persisting proteinuria $>4\,mg\,m^{-2}\,h^{-1}$ or $>100\,mg\,m^{-2}\,day^{-1}$
Steroid-resistant	Persistence of proteinuria despite prednisone therapy $1\,mg\,kg^{-1}\,day^{-1} \times 4$ months	Persistence of proteinuria despite prednisone therapy $60\,mg\,m^{-2} \times 4$ weeks[a]
Steroid-dependent—NS recurs when stop or decrease treatment	Two consecutive relapses occurring during therapy or within 14 days of completing steroid therapy[16]	Two relapses of proteinuria within 14 days after stopping or during alternate day steroid therapy

NS, nephrotic syndrome.
[a]Or persistence of proteinuria despite prednisone therapy $60\,mg\,m^{-2} \times 4$ weeks and three methylprednisolone pulses.

(MGN). The relative frequencies of these histological subtypes vary considerably according to the age at presentation and ethnicity.[1,2] The causes of INS by definition remain unknown but evidence exists that a primary T-cell disorder may be responsible in MCD and FSGS. The first suggestion that increased glomerular basement membrane permeability was caused by a lymphokine was made more than 30 years ago.[3] Despite numerous studies, the identity of this 'glomerular permeability factor' remains elusive, but a host of experimental observations propose a T-cell-driven circulating factor that interferes with glomerular perm-selectivity to albumin.[4] The cause of idiopathic membranous nephropathy remains equally elusive.

The nephrotic syndrome is associated with both renal and extrarenal complications. It appears clinically that prolonged nephrotic range proteinuria leads to renal scarring and eventually renal failure although the[5] precise mechanism of how this occurs is unresolved.[6,7] In adults it has been shown that regardless of the underlying histology, patients with proteinuria $>3.8\,g\,day^{-1}$ had a 35% risk of end-stage renal disease (ESRD) within 2 years, compared to only a 4% risk for those with proteinuria $<2.0\,g\,day^{-1}$.[8] Added to the concern of chronic renal failure is the observation that hypoalbuminemia is associated with a poor prognosis in any pathologic condition: a meta-analysis evaluating hypoalbuminemia and patient outcome found that a decrease of $1.0\,g\,dl^{-1}$ in serum albumin increased the odds of morbidity by 89% and of mortality by 137%.[9] In addition, patients with nephrotic syndrome have an increased risk of thromboembolism. Data from studies in MGN found the prevalence of thrombotic complications to be 29% for renal vein thrombosis, 17–28% for pulmonary embolism, and 11% for deep vein thrombosis.[10,11] In addition, the nephrotic syndrome confers multiple risk factors for accelerated coronary heart disease, including hypercholesterolemia, hypertension, hypercoagulability, and exposure to certain atherogenic drugs such as steroids. The risk of developing coronary heart disease is four times greater in nephrotic patients than in sex- and age-matched controls.[12] Additional complications in children with nephrotic syndrome include a risk of serious infection, in particular cellulitis and spontaneous bacterial peritonitis.[13] In summary, obtaining and maintaining the lowest level of proteinuria when carefully balanced by an awareness of the risks of therapy will result in the best quality and quantity of both renal and patient survival in this group of patients. See Table 1 for definition of terms.

The duration and severity of proteinuria are known to be surrogate markers of the progression of glomerular disease. The main factor predicting the prognosis in all the histologic variants of the INS is the response of proteinuria to therapy.[1,17–19] Therefore, the objectives of treatment are threefold: (1) to lower proteinuria, (2) to reduce the frequency of relapses of nephrotic syndrome, and (3) to protect the kidney and prevent progression to renal failure.

CYCLOSPORIN—AN OVERVIEW

Cyclosporin is a peptide derived from the soil fungus *Tolypocladium inflatum gams*. Following reports of its immunosuppressive properties, first described in the early 1970s, cyclosporin was swiftly introduced as an anti-rejection agent for organ transplantation. Cyclosporin is a calcineurin inhibitor that suppresses the immune response by downregulating the transcription of various cytokine genes. The most significant of these cytokines is interleukin-2 (IL-2), which serves as the major activation factor for T-cells in numerous immunological processes. Cyclosporin inhibits cytokine production from T-helper cells (T-h$_1$ and T-h$_2$) and also has an inhibitory effect on antigen-presenting cells (Langerhans and dendritic cells), which are the main agents of T-cell stimulation. A further effect of IL-2 inhibition is a reduction in B-cell activation and subsequent antibody production. IL-2 levels are known to increase during proteinuria and to normalize during remission in adults with the INS and in children with MCD or FSGS.[20] However, this pattern of IL-2 activity is felt to be part of a more widespread disorder of cellular immunity that results in nephrotic syndrome, rather than being causal of proteinuria.[20]

Cyclosporin may also have an anti-proteinuric action through an effect on glomerular permeability. This includes an influence on perm selectivity, charge selectivity, and glomerular filtration rate (GFR), supported by data from both animal models and human studies[21–27] that demonstrate changes in proteinuria under conditions that have no known immunologic causation. Furthermore, although cyclosporin was found to reduce proteinuria, some studies have suggested that the primary glomerular disease lesions may worsen despite this reduction,[22,23,28] hence the potential need for follow-up renal biopsies during prolonged cyclosporin therapy.[22]

One of the main safety concerns of cyclosporin therapy is its potential nephrotoxicity. This is a class effect common to all calcineurin inhibitors, including tacrolimus[29] and, therefore, needs regular monitoring of cyclosporin blood concentration as well as renal function are mandatory. Two methods of measurement are available; trough blood levels (C_0 pre-dose concentration) or C_2 levels (concentration at 2 h post-dose). Trough level monitoring is common but does not necessarily reflect cyclosporin exposure as a function of drug intake. This may be better assessed by measuring the concentration of cyclosporin 2 h after drug intake (C_2).[30] The clinical benefits and target ranges for C_2 monitoring in idiopathic nephrotic syndrome patients are currently being researched and preliminary published data have been included in the relevant sections of this paper.[31] Cyclosporin can cause increased vascular resistance, resulting in reduced renal blood flow, decreased clearance of endogenous creatinine, and increased serum creatinine. Whether this is the mechanism that leads to the chronic tubular interstitial and vascular changes associated with chronic calcineurin toxicity is unclear at present. Current recommendations stipulate the reduction of cyclosporin dose if serum creatinine increases by $\geqslant 30\%$ above the patient's baseline value (even if this increase is within the normal range).[32,33] Studies from the dermatology literature and non-renal organ transplants have demonstrated that at least in the acute situation these changes are functional and promptly reversed following dose reduction or cessation of cyclosporin therapy.[34] Recent long-term studies support the contention that with care the drug can be safely used for years in children with the nephrotic syndrome and in renal transplant patients. Using annual assessments of creatinine and creatine clearance, stability of renal function has been shown for up to 20 years.[35,36] In addition, recent research suggests better monitoring tools using urinary biomarkers may soon provide more sensitive, accessible, and safer indicators of cyclosporin nephrotoxicity.[37,38]

The clinical efficacy and safety of once a day and pre-prandial administration of cyclosporin in patients with idiopathic nephrotic syndrome is currently being investigated.[31,39,40]

CYCLOSPORIN BIOAVAILABILITY AND CLINICAL OUTCOME

Cyclosporin is a 'critical-dose drug': this means that a small change in dose or plasma concentration may result in a clinically significant change in efficacy and/or toxicity. Individual drug dosing during cyclosporin therapy is necessary because cyclosporin has a formulation-dependent bioavailability and there is a wide interindividual variation in cyclosporin absorption.

The Neoral® formulation (Novartis Pharma AG, Basel, Switzerland) of cyclosporin provides improved consistency in drug delivery than the original Sandimmun formulation (Novartis Pharma AG, Basel, Switzerland). In recent years, generic manufacturers have introduced several new formulations of cyclosporin. Many of these generic formulations have shown considerable variation in pharmacokinetic parameters and in the way in which patients react to each particular drug. A patient who absorbs one cyclosporin formulation satisfactorily, for example, will not necessarily absorb another to the same degree, thus potentially either reducing efficacy or increasing toxicity. This could have important consequences if the brand of cyclosporin prescribed is swapped for another brand ('brand switching'), or if different brands are given at the same time ('partial switching' or 'brand mixing'). If this is necessary because of costs or for other reasons, a careful reassessment of the specific brand chosen must be carried out to ensure similar blood concentrations of cyclosporin are being achieved.

To address these problems, recommendations from several national bodies, including the National Kidney Foundation (USA) and the British National Formulary (UK), now state that the prescribing physician should specify the *exact brand* to be dispensed. Finally, patients should be consulted and educated about generic drug substitution, so they are aware of the potential implications and may alert clinicians if a different formulation is unintentionally obtained.

DEVELOPMENT OF TREATMENT GUIDELINES AND ALGO-RITHMS
Minimal change disease

Clinical background. Overview:[41,42] MCD is the most common cause of INS in children, accounting for more than 75% of all pediatric cases and for 90% of cases in children under 5 years of age. In adults, MCD accounts for approximately 20% of all cases of INS. The major characteristic of MCD is the nephrotic syndrome, which may be persistent or spontaneously remit and recur. The risk of ESRD in MCD is extremely low, the only exceptions are severe acute tubular necrosis associated with MCD seen in the elderly and in people with pre-existing severe hypertension.

Treatment options: Corticosteroids are the first-line treatment for MCD. Approximately 95% of children with MCD achieve urinary remission of proteinuria within 4 weeks and complete remission after an 8-week course of prednisone ($60\,\mathrm{mg\,m^{-2}\,day^{-1}}$ for four weeks followed by $40\,\mathrm{mg\,m^{-2}\,day^{-1}}$ on alternate days for 4 weeks). Increasing the duration of corticosteroid therapy to a total of 12 weeks improves the rate of sustained remission.[43] Adults with MCD generally receive lower doses of prednisone on a per kilogram basis ($1\,\mathrm{mg\,kg^{-1}\,day^{-1}}$ for 8 weeks), which may explain the

lower remission rate of only 50–60%. However, an increase in treatment duration (to >16 weeks) increases it to ~80%.[44,45] Such a prolonged course of glucocorticoids, however, entails an increased risk of steroid toxicity, including glucose intolerance, cushingoid features, infections, and hip osteonecrosis. Hip osteonecrosis is a particular risk in elderly patients and post-menopausal women.

More than half of all patients who are initially steroid responsive go on to experience relapses of their nephrotic syndrome. Those who relapse frequently (⩾two episodes within 6 months) have a greater risk of becoming steroid-dependent. Subsequent prolonged therapy with a corticosteroid is undesirable due to the potential of severe side effects (as discussed above), and thus alternative therapies are required in these patient subgroups, as well as in those who are steroid-resistant.

In children, cyclophosphamide (2.0–2.5 mg kg^{-1} day^{-1}) given for 8–12 weeks or chlorambucil (0.2 mg kg^{-1}) given for 8 weeks is usually well tolerated.[13] Children with frequently relapsing nephrotic syndrome appear to achieve longer remissions with cytotoxic agents than those with steroid dependency.[46] Cytotoxic therapy is also effective in steroid-sensitive adults; complete remission has been reported in 81% of cases and partial remission in a further 8.5%.[47] The disadvantage of cytotoxic therapy is the risk of potentially severe adverse effects, specifically gonadal toxicity and oncogenicity. In addition, since their toxicity is cumulative, repeat courses of therapy carry increased risk of these events. Mizoribine, an inhibitor of purine synthesis developed in Japan, was reported to reduce the relapse rate in children aged below 11 years, but had no significant treatment effect when children of all ages were considered.[48] Levamisole, an antihelmintic agent, has also been reported to reduce relapses in children (dose used: 2.5 mg kg^{-1} given on alternate days),[49] but did not show efficacy for more than 3 months after stopping treatment. Mycophenolic acid (MPA) has induced stable remission in children and[50] adults with frequent relapses,[51] but patient numbers were small and data from larger scale randomized controlled trials are required.

Efficacy of cyclosporin in MCD: The articles selected for inclusion here and in the FSGS and MGN sections have been classified and subsequently graded by the authors according to the level of evidence presented using the criteria described by Carruthers *et al.*[52] (Table 2).

The efficacy of cyclosporin in reducing the relapse rate in steroid-dependent MCD in pediatric patients was described almost 20 years ago.[53] This has been confirmed in many subsequent reports.

Level 1 evidence comes from the German study (APN NS study VIII)[54] (n = 104), which compared corticosteroid monotherapy with corticosteroid/cyclosporin combination therapy in children with their first manifestation of nephrotic syndrome. The treatment arms consisted of prednisone 60 mg m^{-2} day^{-1} for 6 weeks, then reduced to 40 mg m^{-2} 48 h^{-1} for a further 6 weeks, versus the combination of prednisone (as described) plus cyclosporin at 150 mg m^{-2} day^{-1}

Table 2 | Levels of evidence for rating studies and grading system for treatment recommendations[52]

Level	Definition of evidence
1	Randomized controlled trial (RCT) that demonstrated a statistically significant difference in at least one important outcome **OR** If the difference is not statistically significant, an RCT of adequate sample size to exclude a 25% difference in relative risk with 80% power, given the observed results
2	RCT that does not meet Level 1 criteria
3	Non-randomized trial with contemporaneous controls selected by some systematic method (that is, not selected by perceived suitability for one of the treatment options for individual patients) **OR** Subgroup analysis of a randomized trial
4	Before-after study or case series (of ⩾10 patients) with historical controls or controls drawn from other studies
5	Case series (of ⩾10 patients) without controls
6	Case reports (of <10 patients)

Grading	Definition of recommendation
A	Recommendation based on one or more studies at Level 1
B	Best level of evidence available was at Level 2
C	Best level of evidence available was at Level 3
D	Best level of evidence available was lower than Level 3 and included expert opinion

commenced upon remission of proteinuria and given for 8 weeks. Children receiving prednisone monotherapy had higher relapse rates during the first 12 months of follow-up than those patients receiving cyclosporin combination therapy. However, relapse rates in the two groups were virtually equal by 24 months (50 versus 51.5%, respectively). A benefit of cyclosporin combination therapy was observed in children <7 years old and with a total serum protein <44 g l^{-1} at onset of disease (normal range: 66–87 g l^{-1}).

Level 2 evidence is provided by Tejani *et al.*,[55] in a trial of 28 children with nephrotic syndrome randomized to receive either cyclosporin and low-dose prednisone or high-dose prednisone alone. Among 14 children receiving the combined therapy, 13 entered remission versus only eight of 14 receiving prednisone alone.

Level 2 evidence is also provided by a study from the French Society of Pediatric Nephrology, in which 40 children with steroid-dependent MCD were randomized to receive cyclosporin or chlorambucil.[56] Cyclosporin was given at a dose of 6 mg kg^{-1} day^{-1} for 12 weeks and then tapered off over a further 12 weeks, while chlorambucil was given at 0.2 mg kg^{-1} day^{-1} for 40 days (cumulative dose 8 mg kg^{-1}). Although good remission rates were achieved with both treatments the relapse rate was higher in children receiving cyclosporin, with relapses occurring during dose tapering and within 6 months of drug cessation. The sustained remission rate at 2 years was 5% for cyclosporin versus 45% for chlorambucil.

Ponticelli *et al.*[57] (Level 2) randomized 73 frequent relapsers or steroid-dependent patients (31 with MCD; remainder with FSGS), stratified by age into adults and

children, to either cyclophosphamide ($2.5\,mg\,kg^{-1}\,day^{-1}$) for 8 weeks or full-dose cyclosporin ($5.0\,mg\,kg^{-1}\,day^{-1}$) for 9 months, followed by a 3-month taper off the drug. At 9 months, 64% (18/28) of patients on cyclophosphamide and 74% (26/35) of patients on cyclosporin entered remission ($P =$ NS). However, after drug interruption many patients who were given cyclosporin relapsed. At 2 years, 25% of patients assigned to cyclosporin versus 63% of patients assigned to cyclophosphamide were still in remission.

The remaining evidence for cyclosporin use in MCD is Level 5. The long-term Collaborative Study of the French Society of Nephrology included 112 patients.[58] An update[59] of this study comprises 150 adult patients with nephrotic syndrome with either MCD or FSGS who had resisted conventional therapy or, in the case of MCD, were steroid-dependent or multi-relapsers. Eighty-six patients with MCD were treated with cyclosporin (Sandimmun formulation) at a dosage of $5.18 \pm 0.94\,mg/kg^{-1}\,day^{-1}$. Superior efficacy was reported in steroid-dependent patients (complete remission in 73% of cases and partial remission in 14%) compared to those who were steroid-resistant (30 and 26%, respectively). In addition, serum creatinine levels remained stable during cyclosporin treatment (pretreatment: $91 \pm 32\,\mu mol\,l^{-1}$, endpoint $98 \pm 36\,\mu mol\,l^{-1}$; $P =$ NS). El Husseini *et al.*[60] treated 117 children with idiopathic nephrotic syndrome for at least 2 years. The rate of complete remission was 82.1%, and another 5.1% entered partial remission. Steroids were stopped in 102 patients, of whom 31 relapsed. Out of 29 patients for whom cyclosporin was intentionally discontinued while in remission, 22 relapsed. Six of these patients did not respond to a second course of cyclosporin.

A sustained remission rate of 60% (24/40) was reported following 1 year of continuous cyclosporin treatment in children with steroid-dependent MCD.[61] This study also found that continuous cyclosporin therapy was more effective than interrupted therapy in preventing relapses of proteinuria (relapse rates of 56 versus 100%, respectively). In addition, treatment interruptions appeared to diminish the effectiveness of cyclosporin on reintroduction. Low-dose cyclosporin monotherapy (Sandimmun formulation, mean initial dose $2.4\,mg\,kg^{-1}\,day^{-1}$) was used in a small study of steroid-sensitive adults with MCD.[62] Eight of the 11 patients (73%) promptly entered complete remission after mean treatment duration of 44 days, and the remaining three patients achieved complete remission when cyclosporin was combined with corticosteroid pulse therapy. There were no significant changes in creatinine clearance or blood pressure during the study period. Lastly, remission occurred in five out of six (83%) children with MCD treated with cyclosporin (starting dose $6\,mg\,kg^{-1}\,day^{-1}$ given for a maximum of 6 months) in a study of refractory nephrotic syndrome[63] (see also Table 3 for a summary of study details).

Remission of proteinuria in MCD usually happened within the first 3 months of treatment and was maintained with cyclosporin; however, relapse occurred when the drug dose was reduced or stopped.[64]

The rapid recurrence of nephrotic syndrome following cessation of cyclosporin therapy led to the concept of 'cyclosporin dependency,' and the prospect of indefinite patient exposure to a potentially nephrotoxic drug.[59] A subsequent analysis of the Collaborative French study data[22] revealed that patients who escaped 'cyclosporin dependency' had a longer duration of uninterrupted treatment (27.2 ± 22 months) than those who were cyclosporin-dependent (6.75 ± 4.2 months). Gradual tapering of drug dose also seemed an additional factor characterizing patients with durable remission, suggesting that stopping treatment abruptly induced relapse in the form of a 'rebound effect.' Moreover, in adult patients whose remission still depended on cyclosporin, control of proteinuria could be maintained with a low dose of cyclosporin (on the order of $1-3\,mg\,kg^{-1}\,day^{-1}$), significantly below the usual toxic range.[22,62]

Tolerability of cyclosporin in MCD: Data from APN NS study VIII concluded that cyclosporin-associated side effects in children were mild and reversible.[54] The Collaborative French Society of Nephrology study[59] demonstrated good tolerability in adults, with only 10% of patients reporting side effects that led to stopping treatment. Furthermore, there was no increased risk of bacterial/viral infection and the risk of malignancy was considered to be virtually nil. In the study of El Husseini *et al.*,[60] hypertension occurred in 10% of patients, and 6% of patients had an increase in serum creatinine $>30\%$. Post-therapy biopsies, performed in 45 patients, showed mild stripe interstitial fibrosis and tubular atrophy in two patients (4.4%). At the last follow-up, one child had developed end-stage renal failure and two had chronic renal insufficiency. Duration of cyclosporin therapy (using Sandimmun formulation at $\sim 3\,mg\,kg^{-1}\,day^{-1}$) ($>24$ months) and duration of heavy proteinuria (>30 days) not typical of steroid-dependent MCD in children were identified as risk factors for cyclosporin-induced tubulointerstitial lesions in children with MCD.[65]

These findings,[60,65] coupled with lack of correlation between GFR and severity of histological changes,[22,66,67] suggest repeat renal biopsies in children receiving long-term (that is, >2 years) cyclosporin therapy should be considered.

Treatment guidelines and algorithm for use of cyclosporin in minimal change disease (for children). *Who to treat?* Cyclosporin is recommended for children who are steroid-dependent following multiple relapses or who have unacceptable steroid toxicity (Figure 1).

When to treat? Cyclosporin should be used in children who remain steroid-dependent despite a course of cytotoxic therapy [Grade B],[68] or where cytotoxic therapy is contraindicated and in children who develop steroid toxicity. Cyclosporin should be commenced after achieving complete remission of proteinuria with prednisone. In the rare case of steroid-resistant MCD in children defined by persistence of proteinuria beyond 28 days of prednisone treatment, cyclosporin may be considered [Grade D].

How to treat? Cyclosporin should be given at the smallest effective dose using a twice daily (b.i.d.) dosing regimen

Table 3 | Cyclosporin studies in minimal change nephropathy

Reference	Study design	Subjects	Treatment	Results
Levesl 1 and 2				
Hoyer[54]	Multicenter, randomized, controlled	n=55 Pred alone	Pred 60 mg m^{-2} day^{-1} × 6 weeks then 40 mg m^{-2} per 48 h × 6 weeks	CsA+Pred group had lower relapse rates at months +6, +12 (10 and 36% versus 31.5 and 51% for Pred alone)
	Children with first manifestation of NS	n=49 CsA+Pred	Same Pred scheme then CsA 150 mg m^{-2} day^{-1} given on remission × 8 weeks	Relapse rates for both groups similar by +24 months (51.5% CsA+Pred versus 50% Pred alone)
	Pred alone versus CsA+Pred			
Niaudet[56]	Multicenter, randomized, controlled	n=20 CsA	CsA 6 mg kg^{-1} body weight per day in two divided doses × 3 months; dose then tapered over next 3 months	CsA allowed Pred withdrawal in 18/20 patients; 17 of whom relapsed during tapering or within 6 months of drug D/C
	Children with steroid-dependent INS+signs of steroid-toxicity	n=20 Chlorambucil	Chlorambucil 0.2 mg kg^{-1} body weight per day × 40 days (C/D 8 mg kg^{-1} body weight)	Chlorambucil allowed Pred withdrawal in 16/20 patients; 10 of whom relapsed within 34 months of drug D/C
	CsA versus Chlorambucil		Pred given at 30–60 mg m^{-2} day^{-1}, then on alternate days following cessation of proteinuria	Relapse rate at 2 years 5% CsA versus 45% Chlorambucil
				CsA group: n=1 elevated serum creatinine (transient), n=1 hypertension, n=8 hypertrichosis, n=5 gum hypertrophy Chlorambucil group: no short-term toxicity, no leucopenia
Tejani[55]	Randomized, controlled	n=14 Pred alone	Pred 60 mg m^{-2} day^{-1} × 4 weeks then 40 mg m^{-2} per 48 h × 4 weeks	Remission in 13/14 from combination group versus 8/14 from Pred group (P<0.05)
	Children with onset of NS<1 year	n=14 CsA+Pred	CsA 7 mg kg^{-1} body weight per day+Pred 20 mg m^{-2} day^{-1} × 4 weeks then Pred reduced to 10 mg m^{-2} day^{-1} for next 4 weeks	No difference in duration of remission between two groups
	Pred alone versus CsA+Pred			
Ponticelli[57]	Randomized, controlled	n=18 CsA	CsA 5 mg kg^{-1} day^{-1} adults or 6 mg kg^{-1} day^{-1} children × 9 months; dose then tapered by 25% per month and discontinued at 12 months	Results data include MCD and FSGS cases
	Adults and children with steroid-dependent, frequently relapsing INS CsA versus cyclophosphamide	n=13 Cyclophosphamide	Cyclophosphamide 2.5 mg kg^{-1} day^{-1} × 8 weeks	At month 9: CR in 26/35 and PR in 5/35 CsA group versus CR in 18/28 and PR 1/28 Cyclophosphamide group; P=NS At year 2: 25% CsA group versus 68% Cyclophosphamide group in remission Tolerability to both drugs was good; CsA-related side effects were mild and reversed upon drug cessation
Level 5				
Meyrier[59]	Multicenter, uncontrolled, registry data	n=86 refractory MCD	CsA (Sandimmun formulation) 5.18±0.94 mg kg^{-1} day^{-1}	CR in 73% of cases and PR in 14% compared to those who were steroid-resistant (30 and 26%, respectively). Serum creatinine levels remained stable during CsA treatment (pretreatment: 91±32 µmol l^{-1}, endpoint 98±36 µmol l^{-1}; P=NS).
	Adults with steroid-resistant MCD			
Hulton[61]	Single-center, uncontrolled	n=40 Phase 1 (of whom 27 entered into Phase 2)	Phase 1: CsA 5 mg kg^{-1} day^{-1} given twice daily × 1 year	Phase 1: relapse rate 40% (16/40)

Table 3 | Continued

Reference	Study design	Subjects	Treatment	Results
	Children with steroid-dependent MCD		Pred also given ($\geqslant 1$ mg kg^{-1} per 48 h) as tapering dose and then stopped within first 8 weeks of CsA therapy	Phase 2: relapse rate 56% (10/18) group A versus 100% (9/9) group B
	Long-term CsA therapy		Phase 2: Continuous CsA therapy (group A; $n=18$) versus Interrupted CsA therapy (group B; $n=9$); CsA treatment duration $\geqslant 1$ year	Long-term Pred required to maintain remission in 40% (16/40)
				Serum creatinine remained stable and did not differ between groups, 13/40 (32% had hirsuitism, 8/40 (20%) had gum hypertrophy
Matsumoto[62]	Single-center, uncontrolled	$n=11$	CsA 2.4 (range: 1.5–3.1) mg kg^{-1} day^{-1} in two divided doses—given until CR of proteinuria achieved	CR in 8/11 (73%) after mean duration of 44 days (± 31 days)
	Adults with MCD			CR in remaining three patients achieved following addition of Pred
	Low-dose CsA monotherapy			Initial non-responders had higher levels of serum cholesterol
				No significant changes in serum creatinine or blood pressure
Singh[63]	Single-center, uncontrolled	$n=6$ MCD	CsA 6 mg kg^{-1} day^{-1} given until CR achieved	Response observed in 5/6 (83%)
	Children with refractory NS		Maximum treatment duration 6 months	No specific tolerability issues described for MCD cohort
	CsA in NS			

CsA, cyclosporin; C/D, cumulative dose; CR, complete remission; D/C, discontinuation; INS, idiopathic nephrotic syndrome; MCD, minimal change nephropathy; NS, nephrotic syndrome; Pred, prednisone.

[Grade B]. The dose should be started at 100 mg m^{-2} day^{-1} (given in two divided doses) and may be increased to 150 mg m^{-2} day^{-1}.

What to target? Treatment targets include complete or partial remission of proteinuria, preservation of stable GFR ($\pm 20\%$ of pretreatment level), and a C_0 cyclosporin level of 80–120 ng ml^{-1}.

When to stop treatment? There is little data in the literature that focuses on treatment duration; however, renal function and previous clinical course should serve as a guide; for example, estimation of creatinine clearance via the Cockcroft-Gault equation or other appropriate formula (Schwartz formula for children, modified MDRD formula in adults, and so on). In the steroid-resistant or -dependent cases following complete remission of proteinuria, cyclosporin should be continued for 1-2 years and then tapered gradually to lowest effective dose. Data suggest that continuous therapy is more effective than interrupted therapy in preventing relapses of proteinuria and in addition treatment interruptions appear to diminish the effectiveness of cyclosporin on reintroduction.[61]

Children continuing on long-term cyclosporin therapy should be regularly monitored, including a renal biopsy every 2-3 years to check for histological evidence of nephrotoxicity. The use of alternative drugs therapy should be considered (for example, cytotoxic agents or MPA) in children who remain steroid- and/or cyclosporin-dependent despite

long-term cyclosporin therapy. Comparative studies using these medications are underway. In children who are non-responsive to corticosteroids, cyclosporin should be given for at least 6 months before considering the treatment a failure.

Treatment of adults with MCD is essentially similar to that in children—see Figure 2 (adults).

Who to treat? Adults with MCD should initially be treated with corticosteroids for a minimum duration of 12–16 weeks. Cyclosporin is recommended for adults who are steroid- or steroid-dependent, or in a patient with steroid toxicity or in whom steroids are contraindicated (a rare but possible example of this is the pregnant woman with MCD or FSGS. High-dosage corticosteroids are hazardous to the mother and the fetus. Conversely, it has been established that cyclosporin is less harmful to the fetus and may control the nephrotic syndrome).[69]

When to treat? In adult patients experiencing multiple relapses, cyclosporin therapy should be tried after a 12-week course of cyclophosphamide has either failed or not produced a durable remission. It seems advisable to wait until the leukocyte counts have returned to normal before cyclosporin replaces cytotoxic therapy to avoid the added risks of combined/overlapping immunosuppression.

How to treat? In adults, cyclosporin should be commenced at a dose of 2 mg^{-1} kg^{-1} day^{-1} and gradually increased at 2-week intervals until remission is achieved *or* the dose is
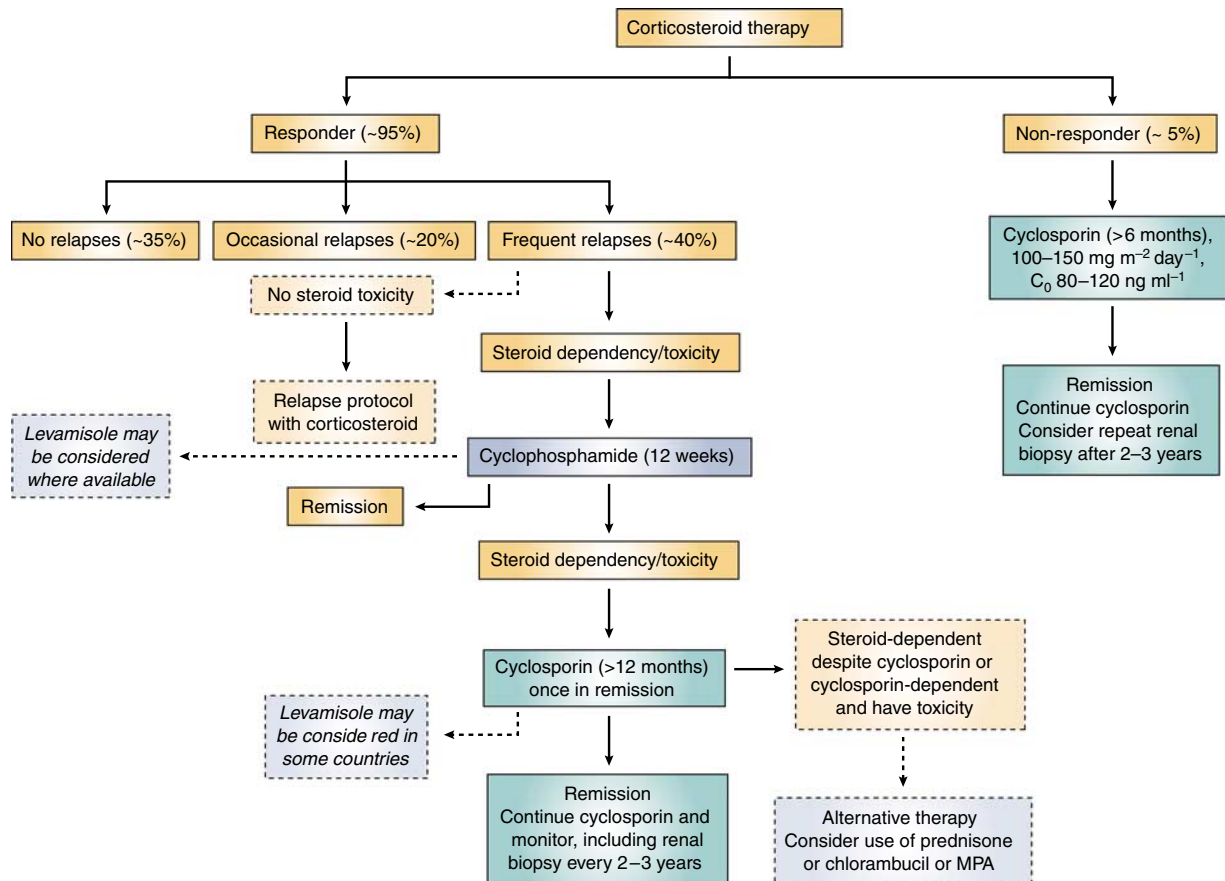
Figure 1 | Algorithm for the use of cyclosporin in the treatment of minimal change disease in children.

$5 \, \text{mg} \, \text{kg}^{-1} \, \text{day}^{-1}$ *or* toxicity occurs. Following 3 months of stable remission, the dose should be very slowly and progressively tapered to reach the minimum dosage that maintains remission. If non-nephrotic proteinuria reappears the dose of cyclosporin should be increased for one to two months until remission is achieved [Grade D]. The dose should then be tapered as before [Grade D]. It is the author's (AM) experience that in most cases remission can be sustained with cyclosporin alone, although a few cases may require low-dose prednisone for treatment of relapse despite cyclosporin treatment.

What to target? Treatment targets for adults are the same as the pediatric age group.

When to stop treatment? Following complete remission of proteinuria, cyclosporin therapy should continue for 1-2 years, during which time the dose should be tapered gradually and maintained at a minimum dose target of $\leqslant 2 \, \text{mg} \, \text{kg}^{-1} \, \text{day}^{-1}$. The acquired experience[22] indicates that in most cases of MCD the renal toxicity of cyclosporin is low, characterized by a few stripes of interstitial fibrosis. Adults continuing on long-term cyclosporin therapy should be regularly monitored, including consideration of repeat renal biopsy at 12–24 months to check for histological evidence of nephrotoxicity, especially if serum creatinine is $>30\%$ above the baseline level, and/or if the maintenance dose of cyclosporin required is $> 3.5 \, \text{mg} \, \text{kg}^{-1} \, \text{day}^{-1}$ [Grade D].

If an adult remains non-responsive to cyclosporin after 6 months of therapy, it should be stopped; a repeat renal biopsy carried out to confirm or refute the initial diagnosis. Depending on the results symptomatic treatment or alternative forms of therapy should be considered [Grade C].

FSGS (nephrotic)

Clinical background. Overview: FSGS in all age groups, accounting for 7–20% of nephrotic syndrome cases in children and a significant higher percentage in adults.[1] FSGS is observed more frequently in Afro-Caribbean patients than in Caucasians, with prevalence as high as 80% among nephrotic patients.[1] If untreated, more than 50% of patients with persistent nephrotic syndrome will progress to ESRD within 5-10 years.[1] Remission of proteinuria is the only significant predictor of renal survival in FSGS and indicates a reduced likelihood of progression to ESRD.[19] Spontaneous remission of proteinuria in FSGS is uncommon ($<6\%$ cases), emphasizing the importance of trying to achieve remission using drug treatment. Recent advances in the genetics of FSGS have altered the understanding of this group of diseases, in which the histologic picture is the common denominator rather than a specific etiological agent. Genes specific for podocyte structures or signaling have been demonstrated to be responsible for the FSGS lesion and the
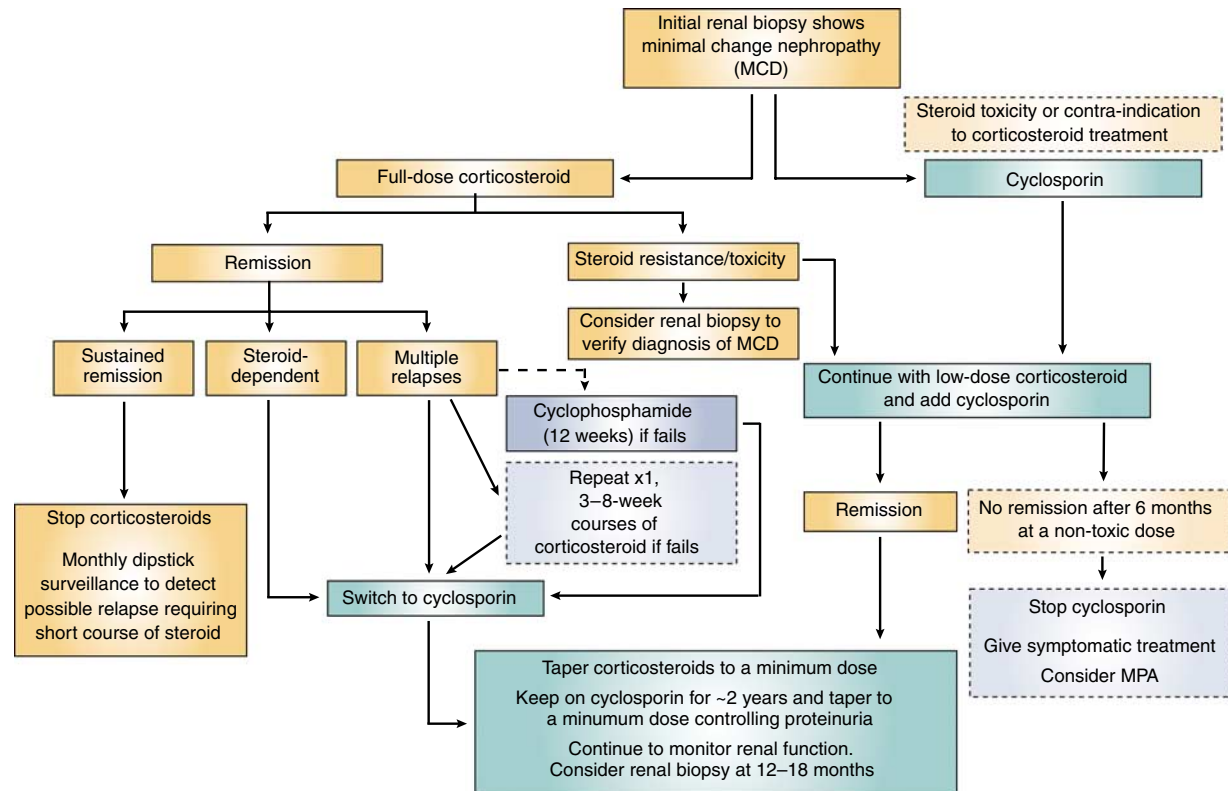
Figure 2 | Algorithm for the use of cyclosporin in the treatment of minimal change disease in adults.

proteinuria (WT1,[70] NPHS2,[71] CD2AP,[72] ACTN4,[73] and TRPC6[74,75]). The specific incidence of genetic mutations producing the FSGS lesions is unknown although it is significantly higher in children than in adults. The variability of these mutations in terms of their clinical phenotype and whether their presence negates the need for immunosuppressive therapy remain unanswered questions.[76]

Treatment options: The specific treatment of FSGS patients with the nephrotic syndrome is controversial. Very few randomized controlled trials have been made. Meta-analysis in adults, in general, shows a good response to corticosteroids alone in FSGS with complete remission rates ranging from 30 to 60% and partial remission rates in up to an additional 30%. The remaining 40–50% show no response.[77] Prolonged steroid treatment (up to 6 months) is associated with a higher complete remission rate but is accompanied by more frequent complications, and many patients, especially in the older age group, the obese, and those with other co-morbid conditions cannot tolerate long or repeated exposure to this duration of steroid treatment. The best prognostic indicator remains a complete remission of proteinuria to corticosteroid therapy,[77] although recent data also confirm the clinical importance of a partial remission on long-term outcome.[19]

Cytotoxic agents can attain good remission rates in steroid-sensitive FSGS, with complete remission in 51% of cases and partial remission in a further 23%.[78] The reasons for initiating cytotoxic agents in FSGS are similar to those for their use in steroid-sensitive MCD. However, their chance of

attaining remission in steroid-resistant FSGS is low. The most optimistic retrospective study (Levels 4 and 5), reported an overall remission rate of only 17% for complete remission and 7% for partial remission in adults and 52 and 17% for complete and partial remission in children.[79] A more pessimistic retrospective review[80] reported no benefit with cyclophosphamide (2.5 mg kg^{-1} day^{-1}).

A recent meta-analysis of randomized controlled trials in pediatric nephrotic syndrome[81] showed no significant difference in complete remission in children with FSGS treated with oral cyclophosphamide plus prednisone versus prednisone alone (one trial, $n = 53$; RR 1.01; 95% confidence interval 0.75–1.47). The general opinion is that cytotoxic agents do not increase the chances of remission in steroid-resistant FSGS but may prolong its duration.[64]

Efficacy of cyclosporin in FSGS: Level 1 evidence is presented by Cattran's study,[82] in which a 26-week regimen of cyclosporin therapy was compared with placebo in 49 adult patients with steroid-resistant FSGS; both groups received low-dose prednisone. Cyclosporin was given at 3.5 mg kg^{-1} day^{-1} in two divided doses for 26 weeks; the drug dose was tapered over the next 4 weeks and then stopped. All patients received prednisone at 0.15 mg kg^{-1} day^{-1} for 26 weeks, which was then tapered over the next 8 weeks. Patients were followed up for an average of 200 weeks. By week 26, partial or complete remission of proteinuria had occurred in 70% of the treatment group versus only 4% of the placebo group ($P < 0.001$). Relapse after stopping cyclosporin

occurred in 40% of those patients achieving remission by 52 weeks and in a further 20% by week 78, with the remainder continuing in remission to the end of the observation period. In addition, long-term renal function was significantly better preserved in the cyclosporin group; approximately 50% of the placebo group had doubled their serum creatinine level compared with only 25% in the cyclosporin group. This is an important finding in a group of patients at high risk of developing ESRD.

Further Level 1 evidence is provided by Ponticelli *et al.*[83] Cyclosporin was compared to symptomatic treatment in 44 patients (adults and children) with steroid-resistant nephrotic syndrome.[83] Only 28/44 patients had biopsy-proven FSGS; 10 adults and 4 children received cyclosporin and 9 adults and 5 children received standard therapy. The treatment group received the Sandimmun formulation of cyclosporin at $5\,mg\,kg^{-1}\,day^{-1}$ for adults and $6\,mg\,kg^{-1}\,day^{-1}$ for children in two divided doses for 6 months; the drug dose was then tapered off to 0 over the next 6 months. Eight (57%) cyclosporin-treated patients attained remission (complete or partial). Three (16%) control patients had partial remissions but incomplete details regarding their diagnoses were given (that is, FSGS and MCD cases were combined). Most remissions occurred within the first 4 weeks; however, the majority of remitters had relapsed by the end of month 12 when cyclosporin was stopped. Specific data for FSGS patients were not presented.

The German glomerulonephritis study group achieved full remission with steroids and cyclosporin in 23% of patients and partial remission in a further 38%. Additional treatment with chlorambucil was found to be ineffective in adult patients with FSGS[84] (Level 2).

A retrospective analysis of adults with FSGS demonstrated that prolonged treatment with cyclosporin (>48 months) is required to achieve complete remission in some patients[85] (Level 4).

Cyclosporin therapy ($3.0\,mg\,kg^{-1}\,day^{-1}$ given in two divided doses) significantly reduced levels of proteinuria in a 6-month randomized controlled trial of 25 children with steroid-resistant FSGS (Level 1).[86] Proteinuria decreased from 151.7 (±162.4) to 36.9 (±42.3) $mg\,kg^{-1}\,day^{-1}$ over the study period ($P<0.05$). In addition, hypercholesterolemia was found to be associated with a reduced therapeutic effect of cyclosporin. Remission occurred in 25/42 (60%) children with refractory FSGS treated with cyclosporin (starting dose $6\,mg\,kg^{-1}\,day^{-1}$ given for a maximum of 6 months) (Level 5).[63]

An overview of retrospective studies in adults and children with FSGS indicated that 40–50% of cases can be maintained in remission of proteinuria with cyclosporin.[64] Most of these patients were steroid-resistant, and a better response was observed in those who were steroid-sensitive (see also Table 4 for a summary of study details).

Tolerability of cyclosporin in FSGS: The risk of adverse effects with cyclosporin in FSGS is comparable to that reported in MCD.[58] However, concern has been expressed

regarding the potential nephrotoxicity of cyclosporin and the possible acceleration of this particular type of renal disease. The data suggest that the risk of cyclosporin nephropathy is low if guidelines are followed and patients are monitored regularly.[64] Other safety data are shown in Table 4.

Treatment guidelines and algorithm for use of cyclosporin in FSGS (nephrotic) in children. See Figure 3 for full details.

Who to treat? According to pediatric recommendations, patients usually undergo a kidney biopsy when remission cannot be achieved after 4 weeks of prednisone at $60\,mg\,m^{-2}\,day^{-1}$ (steroid resistant). In a case of a diagnosis of FSGS, cyclosporin treatment should be considered as a treatment option.

When to treat? Children with persistent nephrotic range proteinuria $>1\,g\,m^{-2}\,day^{-1}$ despite 4 weeks of daily corticosteroid therapy. (The French Pediatric Nephrology Society approach recommends three pulses of methylprednisolone before the condition is called 'steroid-resistant.'). If the corticosteroid treatment is well tolerated, a further 4 weeks of therapy should be considered prior to initiating new therapy since the response rate will increase an additional 10–20%. The emerging knowledge of different gene mutations associated with FSGS may tailor the therapeutic approach—see Figure 3.

How to use? Cyclosporin should be started at a moderate dose ($100\,mg\,m^{-2}\,day^{-1}$ given in two divided doses) and gradually increased to a maximum of $150\,mg\,m^{-2}\,day^{-1}$, depending on the effect on proteinuria (upper dose limits have not yet been defined, but an increasing risk for nephrotoxicity is expected above this dose level). Long-term treatment is usually required to obtain remission [Grade A]. All published studies show a benefit with cyclosporin therapy only if it is combined with alternate day prednisone for the first 6 months ($30\,mg\,m^{-2}$ per 48 h for 6 months or $40\,mg\,m^{-2}$ per 48 h for 2 months followed by $30\,mg\,m^{2}$ per 48 h for 2 months followed by $20\,mg\,m^{-2}$ per 48 h for 2 months).

What to target? Treatment targets include complete or partial remission of proteinuria, preservation of glomerular filtration rate ($\pm20\%$), and a cyclosporin C_0 blood level of $<150\,ng\,ml^{-1}$. Individual experience [Grade D] suggests short-term higher levels may be of benefit,[87] but further evidence for this is lacking in the literature. A small study by Mitsoni *et al.*[88] suggest that C_2 appears to be a better predictor of AUC than C_0 in children with INS; however, targets using C_2 levels have not yet been defined.

When should renal biopsy be carried out? Repeat biopsies should be carried out in a patient with rapidly declining renal function, a marked disparity between an increasing serum creatinine and decreasing proteinuria and in patients receiving cyclosporin therapy beyond 2-3 years. The presence of increasing fibrosis and tubular interstitial disease should lead to a careful review of the case. It is often difficult to differentiate between drug toxicity and the natural history of the FSGS disease and hence the decision between lowering or discontinuing medication and/or adding adjunctive therapy

Table 4 | Cyclosporin studies in focal segmental glomerulosclerosis (nephrotic)

Reference	Study design	Subjects	Treatment	Results
Levels 1 and 2				
Cattran[82]	Multicenter, randomized, controlled	n=26 CsA	CsA 3.5 mg kg^{-1} day^{-1} given in two divided doses × 26 weeks, then tapered to zero over 4 weeks	PR or CR in 70% (18/26) CsA group versus 4% (1/23) Placebo group by week 26 (P < 0.001)
	Adults with steroid-resistant FSGS	n=23 Placebo	All patients received Pred 0.15 mg kg^{-1} day^{-1} × 26 weeks, then tapered over 8 eight weeks	CsA group: Relapse occurred in 40% of remitters by week 52 and in 60% by week 78; remainder stayed in remission until end of study period (∼ week 200)
	CsA versus Placebo			50% decrease in baseline creatinine clearance observed in 25% CsA group versus 52% of Placebo group (P < 0.05)
				No significant difference in cases of hypertension between treatment groups
				CsA group: n=1 case of gastrointestinal symptoms requiring drug D/C
Ponticelli[83]	Multicenter, randomized, controlled	FSGS adults:	CsA adult dose 5 mg kg^{-1} day^{-1} or pediatric dose 6 mg kg^{-1} day^{-1} × 6 months, then tapered by 25% every 2 months until D/C	PR or CR in 57% CsA group (6/10 adults and 2/4 children) versus 16%[a] Control group (3/19[a]) (P < 0.001)
	Children and adults with steroid-resistant INS (FSGS+MCD)	n=10 CsA	Supportive therapy × 12 months; corticosteroids and immunosuppressants not permitted	CsA group: Remission occurred within first 4 weeks of treatment; 70%[a] of remitters had relapsed by month 12
	CsA versus supportive therapy	n=9 Controls		Incidence of infection and hypertension similar for both groups
		FSGS children:		CsA group: Gum hypertrophy and hypertrichosis frequent but all cases reversed upon drug D/C
		n=4 CsA		
		n=5 controls	Corticosteroid rescue therapy allowed in both groups if renal function rapidly declined	
Lieberman[86]	Multicenter, randomized, controlled	n=12 CsA	CsA 3 mg kg^{-1} day^{-1} given in two divided doses × 6 months	Reduction in proteinuria in 12/12 CsA group versus 2/12 placebo group
	Children with steroid-resistant FSGS	n=12 Placebo	Vehicle control	CsA induced significant reduction in proteinuria versus baseline (P < 0.05)
	CsA versus Placebo			
Heering[84]	Multicenter, randomized, controlled	n=34 CsA	Steroids 1.5 mg kg^{-1} day^{-1} and CsA adult dose 5mg kg^{-1} day^{-1} versus	CR and PR in 60% CsA group versus 65% Chlorambucil group (NS)
	Adults with steroid-resistant FSGS	n=23 Chlorambucil	Steroids 1.5 mg kg^{-1} day^{-1} and Chlorambucil (0.1–0.4 mg kg^{-1} day^{-1}) 6–12 weeks followed by CsA	
	CsA versus Chlorambucil followed by CsA			
Levels 4 and 5				
Singh[63]	Single-center, uncontrolled	n=42 with FSGS	CsA 6 mg kg^{-1} day^{-1} given until CR achieved	Response observed in 25/42 (60%)
	Children with refractory NS		Maximum treatment duration 6 months	Hypertension in 45% patients; gum hypertrophy, hirsutism and hypertrichosis common on higher CsA doses; no cases of infection
	CsA in NS			CsA-induced nephropathy: 'severe' lesions in 50% patients on renal biopsy (all patients treated with CsA > 12 months)
Alexopoulos[85]	Retrospective case analysis	n=33 FSGS of whom n=17 had NS	n=11 patients received Pred (1 mg kg^{-1} for at least 1 month); those with partial/ no response were also given CsA (2–3 mg kg^{-1} for average of 25 months)	64% remission with Pred alone after 6–12 months treatment
	Adults with FSGS		A further 6 patients received symptomatic therapy only	CR in 28% and PR in 54% of those requiring additional CsA (at end of follow-up; mean duration 57 months)

CsA, cyclosporin; CR, complete remission; D/C, discontinuation; FSGS, focal segmental glomerulosclerosis; INS, idiopathic nephrotic syndrome; MCD, minimal change nephropathy; NS, nephrotic syndrome; PR, partial remission; Pred, predisone.
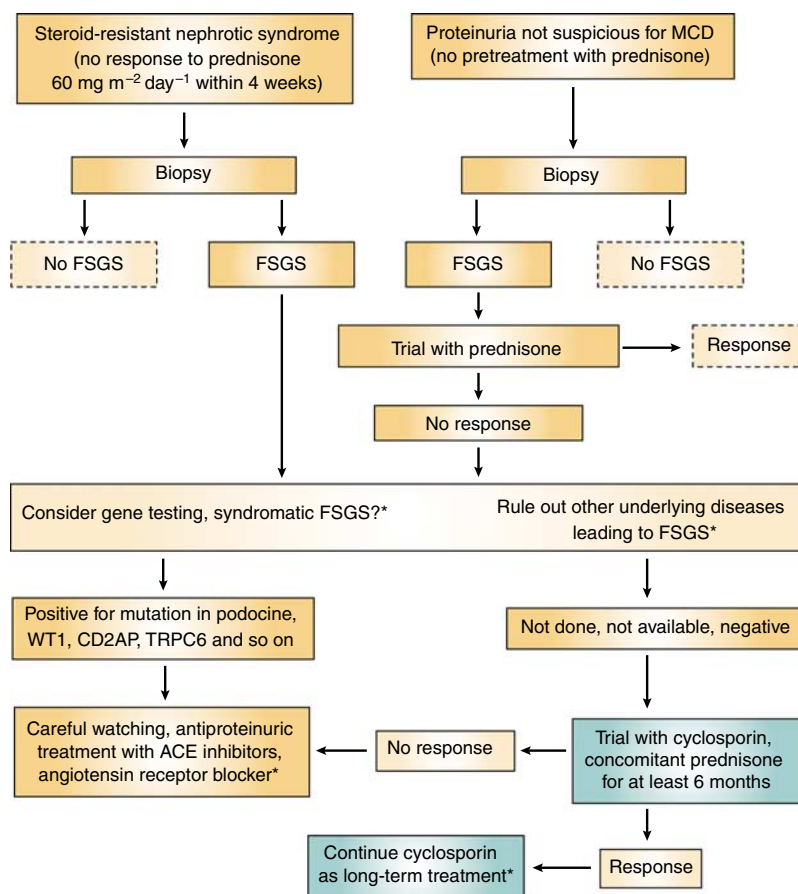[a]Data include cases of FSGS+MCD cases.

Figure 3 | Algorithm for the use of cyclosporin in the treatment of focal segmental glomerulosclerosis in children.

remains a balance between the patient's clinical course/ response or the observed histologic changes.

When to stop treatment? Renal function (GFR) serves as a guide more than renal histology. Following complete remission of proteinuria, cyclosporin should be slowly tapered (by $0.5 \, mg \, kg^{-1} \, month^{-1}$) to a minimum effective dose and then maintained for 1-2 years. Rapid deterioration of renal functional may occur even after years of continuous treatment when the cyclosporin is stopped.

If no response to cyclosporin has occurred after 6 months of treatment (a minimum would be a 50% reduction in baseline proteinuria), other symptomatic treatment should be considered.

Treatment guidelines and algorithm for use of cyclosporin in FSGS (nephrotic) in adults. *Who to treat?* Patients should initially be treated with conservative therapy to normalize blood pressure and LDL cholesterol using ACE inhibitors $\pm$ ARB therapy, diuretics, statins, and so on). Patients should also be carefully monitored for signs of any deterioration in renal function. Corticosteroid therapy ($1 \, mg \, kg^{-1} \, day^{-1}$ for 8–16 weeks) should be commenced when maximum conservative therapy fails to lower proteinuria to $<3 \, g \, day^{-1}$. Cyclosporin should be given to patients who become steroid-dependent or who are steroid-resistant [Grade A]. Cyclosporin therapy is also appropriate in

patients with steroid toxicity or in whom steroids are contraindicated (Figure 4).

When to treat? Patients with persistent proteinuria $>3 \, g \, day^{-1}$ despite corticosteroid therapy. In adults who do not achieve at least a partial remission by 8 weeks of daily prednisone and/or those who have unacceptable adverse steroid effects.

How to use? Cyclosporin should be started at low dose ($2 \, mg \, kg^{-1} \, day^{-1}$ in two divided doses) and gradually increased to a maximum of $4 \, mg \, kg^{-1} \, day^{-1}$, depending on the effect on proteinuria; the dose should not exceed $5 \, mg \, kg^{-1} \, day^{-1}$. In light of careful pharmacokinetic monitoring one could adapt the dose (see '*what to target*'). Long-term treatment is usually required to achieve the maximum benefit (>6–12 months) [Grade B].

What to target? Treatment targets include complete or partial remission of proteinuria, preservation of glomerular filtration rate ($\pm 20\%$), and a cyclosporin level— $C_0 = 125$–$175 \, ng \, ml^{-1}$ and $C_2 < 500 \, ng \, ml^{-1}$.

When to stop treatment? Renal function (GFR) serves as a guide. Following complete remission of proteinuria, cyclosporin should be slowly tapered (by $0.5 \, mg \, kg^{-1} \, month^{-1}$) to a minimum effective dose and then maintained for 1-2 years. In patients with steroid dependency, corticosteroid should also slowly be tapered to a minimum effective dose or
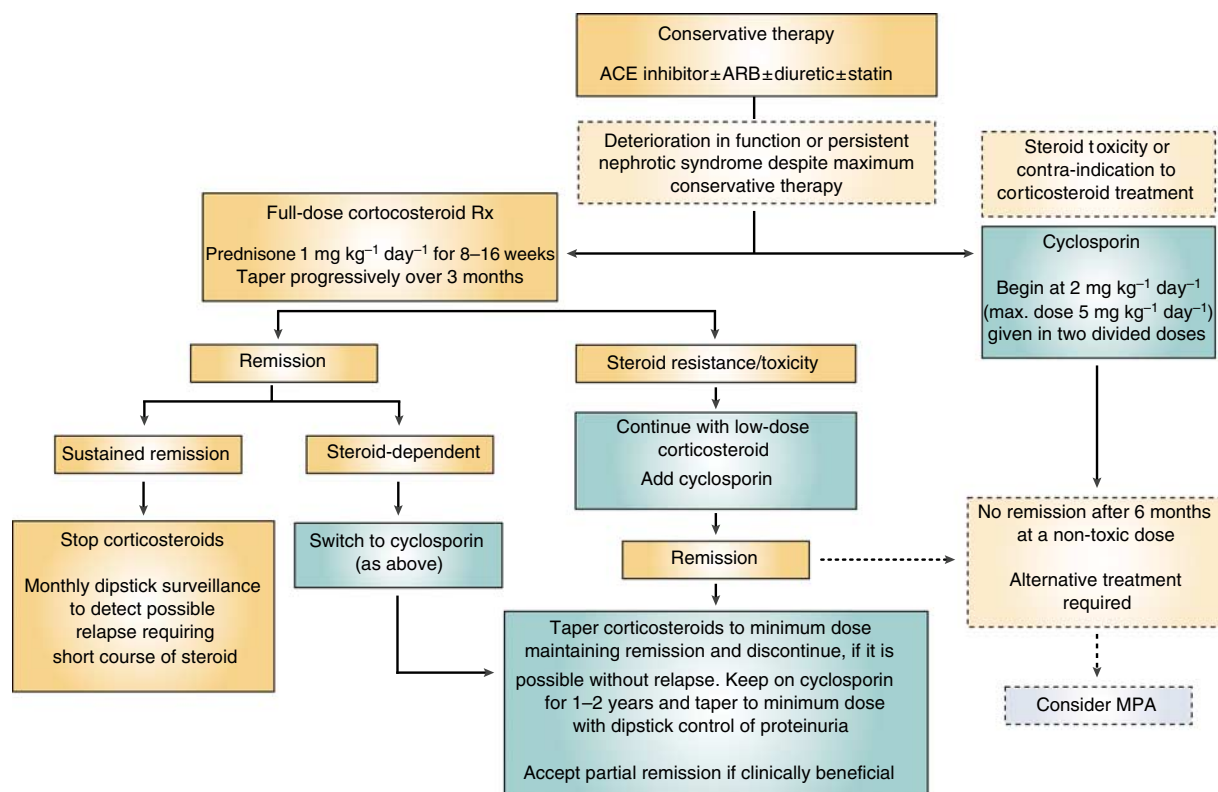
Figure 4 | Algorithm for the use of cyclosporin in the treatment of focal segmental glomerulosclerosis in adults.

discontinued, if possible before any change in cyclosporin. Patients who achieve a partial remission should be maintained on the lowest dose of cyclosporin to maintain their partial remission status with careful monitoring of the dose, cyclosporin trough level (C_0), and renal function. If no response to cyclosporin has occurred after 6 months of treatment (a minimum of 50% reduction in baseline proteinuria), other agents should be considered or added to cyclosporin (for example, cytotoxic agent or MPA).

Membranous nephropathy

Clinical background. *Overview*: Membranous nephropathy rarely occurs in children. It is, however, the most common cause of idiopathic nephrotic syndrome in adults and accounts for approximately 20–30% of adult cases. The disease is seen more frequently in men (male/female = 2–3:1) and presents most commonly between the ages of 40 and 60. The natural history of MGN is variable. Complete remission occurs spontaneously in 20–30% of cases and is more likely to occur in patients presenting with subnephrotic proteinuria and in women.[89] Approximately 20–40% of cases will have persistent proteinuria between 3 and 5 g/day[-1] and the remaining 40–50% will develop progressive renal failure.[90] Prognosis might also be influenced by racial origin since long-term outcome in the Asian population (Japanese) with MGN is significantly better than Caucasians.[91] Cattran *et al.*[17] identified risk categories for the development of chronic renal failure in MGN patients by stratifying cases according to the

severity of their proteinuria over a 6-month period; low-risk patients were those with normal serum creatinine and proteinuria consistently < 4 g day^{-1}; medium-risk patients had normal or nearly normal serum creatinine and proteinuria consistently between 4 and 8 g day^{-1}; and high-risk patients were those with abnormal and/or deteriorating serum creatinine or proteinuria $\geqslant 8$ g day^{-1}. This strategy largely avoids treatment of the patients who are most likely to spontaneously remit and/or have stable low-grade, subnephrotic proteinuria. Favorable renal outcome in MGN is associated with complete or partial remission of proteinuria.[18,92] In addition to the risk of chronic renal failure, certain extrarenal effects are more common in MGN, including accelerated vascular disease and an increased risk of thromboembolism.

Treatment options: A meta-analysis of randomized controlled trials using corticosteroid therapy as a single agent demonstrated no effect on renal survival or on the probability of remission of proteinuria.[90] A large, retrospective review from Japan did show a benefit on renal survival following a 4-week course of corticosteroids. This may reflect the influence of race on either MGN natural history or on its therapeutic responsiveness in this racial group.[91] Cycling a cytotoxic agent with a corticosteroid over a 6-month period has been shown to both reduce proteinuria and slow disease progression.[93,94] Ten-year follow-up data demonstrated a renal survival of 92% in treated patients versus 60% of untreated controls, while the probability of

remission (complete or partial) was 83% for treated patients versus only 38% for untreated patients.[93] A similar result was seen when this 6-month cycle used cyclophosphamide in place of chlorambucil. Adverse effects, real or anticipated, have somewhat limited the use of this regimen. Relapses rates when this routine was used with either of the cytotoxic agent approached 30–40% 2-3 years following discontinuation of therapy.[90,94] Mycophenolate, a relatively new immunosuppressive agent with less toxicity than cyclophosphamide is a safer alternative but the current level of evidence supporting it efficacy is still weak and relapse rates higher.[95]

Efficacy of cyclosporin in MGN: Cattran's single-blind clinical trial[96] of 51 patients with steroid-resistant MGN randomized to cyclosporin or placebo provides Level 1 evidence of its efficacy. Cyclosporin dose averaged $3.5 \, mg \, kg^{-1} \, day^{-1}$ given in two divided doses for 26 weeks; the drug dose was then tapered to 0 over the next 4 weeks. Prednisone was given to all patients at $0.15 \, mg \, kg^{-1} \, day^{-1}$ for 26 weeks and then tapered off over the next 6 weeks. Remission (complete or partial) was obtained in 75% of the treatment group versus only 22% of the placebo group by 26 weeks ($P<0.001$). By the end of the observation period (78 weeks), 39% of the treatment group had remained in remission versus 13% of the placebo group ($P<0.007$). Renal function in the two groups remained unchanged and equal throughout the trial and the follow-up period.

A study by Alexopoulos *et al.*[97] (Level 2) has shown that prolonged treatment (>12 months) with low-dose cyclosporin increases remission rates and that prolonged treatment with low-dose cyclosporin $1.4–1.5 \, mg \, kg^{-1} \, day^{-1}$ is useful in maintaining remission. Relapse occurred more frequently when the daily dose of cyclosporin was lower ($1.0–1.1 \, mg \, kg^{-1} \, day^{-1}$) or the C_0 cyclosporin levels decreased below $100 \, ng \, ml^{-1}$. Patients who relapsed had a mean C_0 cyclosporin level of $72 \pm 48 \, ng \, ml^{-1}$, compared to the mean level in non-relapsers of $194 \pm 80 \, ng \, ml^{-1}$ ($P<0.03$).

Cyclosporin has also been studied in the high risk of progression group. In a randomized controlled trial of patients with documented progressive renal insufficiency (mean creatinine was $195 \, \mu mol \, l^{-1}$) and heavy proteinuria, cyclosporin was administered at an average dose of $3.8 \, mg \, kg^{-1}$, and compared to placebo alone over a 12-month period.[98] Cyclosporin-treated patients demonstrated both significantly reduced proteinuria and a slower rate of progression as measured by rate of change in the creatinine clearance ($P=0.02$, and $P<0.02$, respectively). These positive results were sustained in more than half of the patients for up to 2 years after treatment was stopped. However, the number of patients in the study was small, there was a trend toward transient increases in creatinine noted in the cyclosporin treatment group and adverse effects were more common with treatment than in studies where the renal function was normal (Level 1).

A similar benefit was noted in an uncontrolled study of 15 individuals with steroid-resistant progressive disease, except

their relapse rate was higher[99] (Level 4). A retrospective review was reported from a large collaborative group who treated 41 patients considered high risk due to the severity of proteinuria ($>10 \, g \, day^{-1}$) and resistance to other immunosuppressive drugs.[100] Thirty-four percent achieved a complete remission after a median treatment duration of 353 days, at a mean cyclosporin dose of $3.3 \, mg \, kg^{-1} \, day^{-1}$ (Level 5).

Additional studies in MGN include cyclosporin treatment given for 3-6 months at $4–5 \, mg \, kg^{-1} \, day^{-1}$. These authors found a median reduction in proteinuria by more than 50% in 41 MGN patients.[23] The majority of remitters relapsed following drug cessation but subsequently remitted upon restarting cyclosporin (Level 5).

In another small study, eight MGN patients with refractory nephrotic syndrome received cyclosporin with the dose adjusted to achieve a C_0 (trough) level of $100 \, ng \, ml^{-1}$ for 3 months, then maintained at a C_0 of $50 \, ng \, ml$.[101] At 12 months, five out of eight patients (63%) showed complete or partial remission, and this increased to seven out of eight patients (88%) at 18 months. No changes in renal function or blood pressure occurred (Level 5).

MGN is uncommon in children with the only data suggesting a similar response as in adults but the numbers were very small (Level 6).[102]

In summary, current data indicate that cyclosporin is effective in inducing a partial or complete remission of proteinuria between 60 and 75% of MGN cases.[96,101] The time to maximum reduction of proteinuria was commonly beyond 3 months of treatment, similar to the cytotoxic/steroid regimens. (See also Table 5 for a summary of study details.)

Tolerability of cyclosporin in MGN: The risk of adverse events with cyclosporin in MGN is similar to that observed in adults with MCD or FSGS.[64] The risk of nephrotoxicity in MGN appears to be low if guidelines on cyclosporin dosing are followed.[64] In Cattran's study,[96] the incidence and severity of hypertension was increased in patients receiving cyclosporin compared to those on placebo. Additional side effects of cyclosporin (gum hyperplasia and hypertrichosis) have also been reported in this patient population.[101]

Treatment guidelines and algorithm for use of cyclosporin in membranous nephropathy. See Figure 5 for full details.

Who to treat? Patients with MGN should first be assessed with regard to their risk of progression (see above). Patients characterized as low risk may be treated only symptomatically, using ACE inhibitors and/or ARB drugs targeting a blood pressure of $\leqslant 120/75 \, mm \, Hg$. They should continue to be monitored for signs of renal function deterioration or changes in severity of proteinuria. Treatment of medium- and high-risk patients should be considered with either (i) cyclosporin ($\pm$ low-dose corticosteroids) for at least 6 months [Grade A] or (ii) cytotoxic (cyclophosomide or chlorambucil) therapy alternating monthly with corticosteroids, composed of 1 g pulses of methylprednisolone daily for the first 3 days followed by oral prednisone therapy at

Table 5 | Cyclosporin studies in membranous nephropathy

Reference	Study design	Subjects	Treatment	Results
Level 1 Cattran[96]	Multicenter, randomized, controlled	n=28 CsA	CsA 3.5 mg kg^{-1} day^{-1} given in two divided doses × 26 weeks, then tapered to zero over 4 weeks	Remission in 75% (21/28) CsA group versus 22% (5/23) Placebo group by week 26 ($P<0.001$)
	Steroid-resistant MN with NS	n=28 Placebo	All patients received Pred 0.15 mg kg^{-1} day^{-1} × 26 weeks, then tapered over 8 weeks	By week 78, remission in 39% (11/28) CsA group versus 13% (3/23) Placebo group (P=0.007)
	CsA versus Placebo			Renal function remained unchanged and equal in both groups over the test medication period
				Number of cases and severity of hypertension greater in CsA group
Cattran[98]	Randomized, controlled	n=9 CsA	CsA 3.5 mg kg^{-1} day^{-1} given in two divided doses × 12 months	CsA significantly reduced rate of renal deterioration after 12 months and this was maintained in 6/8 CsA patients over a follow-up of (mean) 21 months
	Progressive MN	n=8 Placebo	Vehicle control	CsA group: Hypertension and transient rises in serum creatinine noted
	CsA versus Placebo			
Level 2 Alexopoulos[97]	Single center, prospective trial	n=31 Pred+CsA	Initial: Pred 0.6 mg kg^{-1} day^{-1} and/or CsA 2–3 mg kg^{-1} day^{-1} in two divided doses for 12 months. Target C_0 levels 100–200 ng ml^{-1}	Initial treatment: Similar remission rates (CR+PR) in both groups (83 versus 85%, P=NS)
	Biopsy proven MGN with NS	n=20 CsA	Long-term: Pred 0.1 mg kg^{-1} day^{-1} and CsA 1.0–1.5 mg kg^{-1} day^{-1} for 26±16 months (n=26) versus CsA 1.0–1.5 mg kg^{-1} day^{-1} for 19±8 months (n=17)	Long-term: More relapses in monotherapy group (47 versus 15%, $P<0.05$) commonly in patients with $C_0<100$ ng ml^{-1}
	Prednisolone+CsA versus CsA alone Effect of low dose CsA			
Level 4 or 5 Ambalavanan[23]	Single-center, crossover	n=41 in Phases 1 and 3 (of whom 14 in Phase 2)	Phase 1: CsA 4–5 mg kg^{-1} day^{-1} given in two divided doses × 3–6 months	Phase 1: CsA lowered median proteinuria by 56% ($P<0.0001$)
	Biopsy-proven MN		Phase 2: CsA as above versus Enalapril 10–30 mg day^{-1}; both × 3 months	Phase 2: Enalapril had no effect on proteinuria
	CsA versus Enalapril		Phase 3: CsA as above (× 6 months+1 month washout) × 3 cycles	Phase 3: majority of patients relapsed during each washout period (75, 78 and 67%, respectively)
Iida[101]	Single-center, uncontrolled	n=8	CsA dose to maintain C_0 at 100 ng ml^{-1} during first 3 months, then reduced to maintain C_0 at 50 ng ml^{-1} in patients attaining PR and continued	PR or CR in 63% (5/8) after 12 months CsA therapy, rising to 88% (7/8) after 18–24 months
	Biopsy-proven MN, refractory NS		All patients received Pred 10–40 mg day^{-1} during first 3 months of CsA therapy, dose tapered thereafter	One patient with gum hyperplasia and hypertrichosis; no change in renal function or BP
	Effect of long-term, low-dose CsA			
Rostoker[99]	Single-center, uncontrolled Severe idiopathic MN with NS	n=15	CsA 4–5 mg kg^{-1} day^{-1} × 15 months (median)	PR in 7/15 and CR in 4/15 and further 4/15 had no response Responders: relapse of NS occurred in 3/9 on drug cessation; further two patients continued on CsA

Table 5 | Continued

Reference	Study design	Subjects	Treatment	Results
	Effect of long-term, low-dose CsA			Side effects were mild; hypertension (*n*=3), renal dysfunction (*n*=5)
Fritsche[100]	Retrospective case series	*n*=41	CsA average dose 3.3 mg kg^{-1} day^{-1} × median duration 353 days	CR in 14/41 (34%) after treatment period
	Biopsy-proven MN with NS		CsA treatment duration <6 months in 16/41 and >6 months in 25/41	Median treatment time to first CR was 225 days 15/41 reported ⩾1 adverse event; commonly gingival hyperplasia (*n*=4), nausea (*n*=4) and muscle cramps (*n*=4); no correlation with duration of treatment

CsA, cyclosporin; CR, complete remission; MN, membranous nephropathy; NS, nephrotic syndrome; PR, partial remission; Pred, predisone.
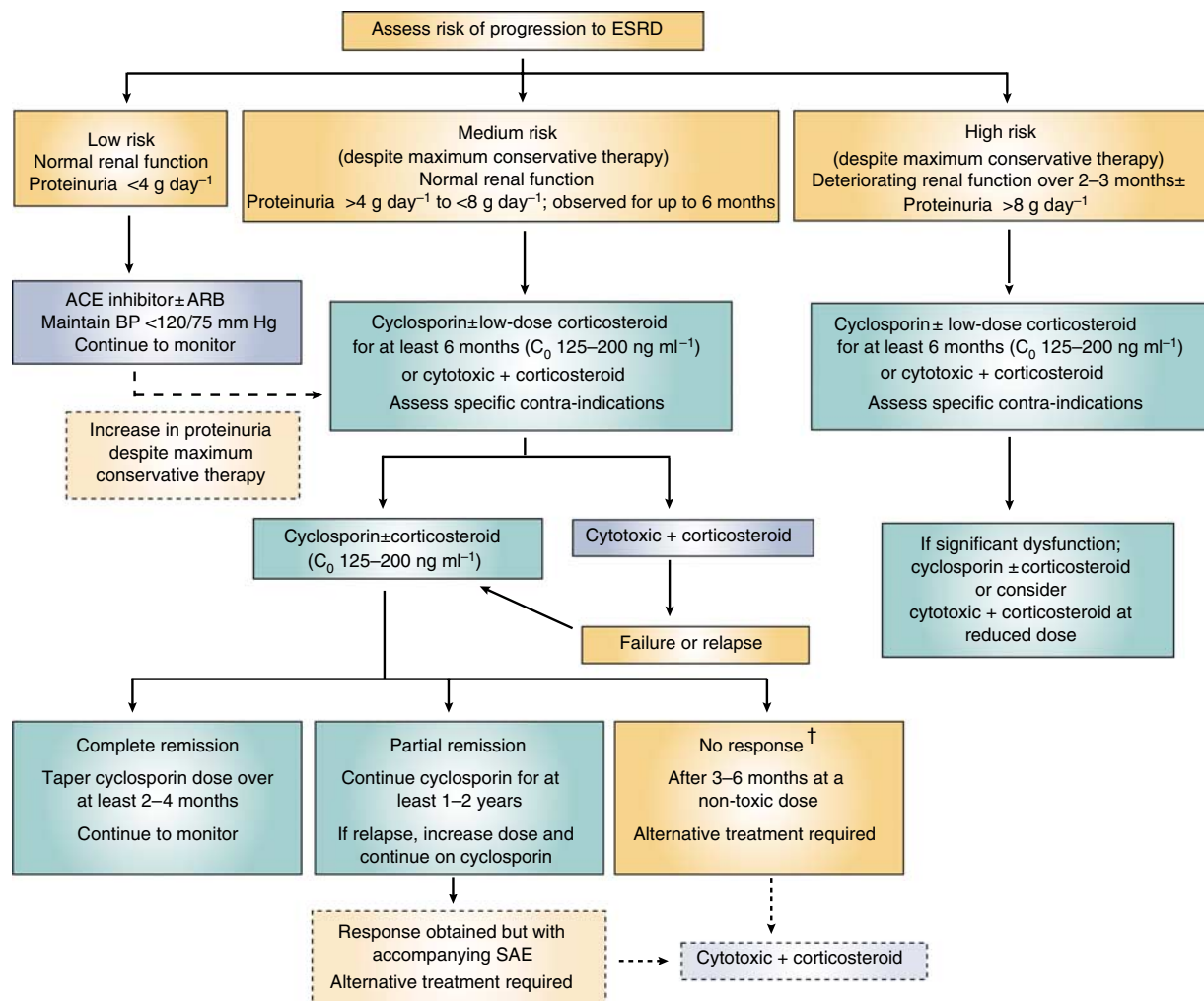
Figure 5 | Algorithm for the use of cyclosporin in the treatment of membranous nephropathy.

0.5 mg kg^{-1} over a 6-month period [Grade A]. Which of these should be the first-line treatment should be decided following assessment of the individual patient for any specific contraindications. A short course of corticosteroids alone could be considered in the patient of Asian origin but the evidence is not strong [Grade C].

When to treat? Patients with persistent nephrotic range proteinuria and/or deteriorating renal function despite maximum conservative therapy.

How to treat? Cyclosporin should be given at an initial dose of 3–4 $mg\,kg^{-1}\,day^{-1}$ with progressive reduction to the smallest effective dose (b.i.d. dosing) for at least 6 months. If proteinuria is not reduced by 50% by the end of this time frame, cyclosporin should be discontinued and an alternative therapy should be considered.

What to target? Treatment targets include complete or partial remission of proteinuria, maintenance of stable GFR ($\pm 20\%$ of pretreatment level), avoiding hypertension, and a cyclosporin level regarded as non-toxic ($C_0 = 125–175\,ng\,ml^{-1}$ and $C_2 = 400–600\,ng\,ml^{-1}$).[103]

When to stop treatment? If complete remission occurs, cyclosporin should be tapered off over 3-4 months. For partial remission, cyclosporin should be continued at full dose for an additional 1-2 years and perhaps maintained at a non-toxic level indefinitely if renal function is stable in the patient where a partial remission was difficult to achieve and/ or associated with additional morbidity and/or the patient has previously failed alternate forms of treatment, *or* alternatively cyclosporin could be slowly tapered slowly over 1-3 years and adjusted as required if proteinuria worsens during the taper.

If there is no response to cyclosporin *or* if a response occurs but with significant adverse effects, an alternative therapeutic regimen (that is, cytotoxic agent + corticosteroid) should be considered.

CONCLUSIONS

Cyclosporin is an effective treatment for the three leading histologic variants known to result in the idiopathic nephrotic syndrome of adults and children. Recent Grade A evidence supports its use after a 12-week course of cytotoxic therapy has failed in MCD and as a first-line option in MGN and FSGS either as monotherapy or in combination with corticosteroids. Cyclosporin therapy provides a sustained remission of proteinuria in a significant proportion of patients and is also effective in the long-term preservation of renal function in steroid-dependent/-resistant MCD and steroid-resistant FSGS. The side-effect profile of cyclosporin is well known and predictable. Adherence to dosing guidelines plus regular patient monitoring will minimize the risk of nephrotoxicity, the major concern of nephrologists caring for these patients.

DISCLOSURE

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