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Nephrotic syndrome in children

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Nephrotic syndrome is an important chronic disease in children, characterized by minimal change disease in the majority. Research on pathogenesis has emphasized the importance of T lymphocyte dysregulation and vascular permeability factors that might alter podocyte function and permselectivity. While mutations in genes that encode important podocyte proteins have also been identified, a hypothesis unifying available evidence on pathogenesis is yet to be proposed. Patients with nephrotic syndrome are at risk for life threatening infections and thromboembolic episodes. Long-term effects of persistent hyperlipidaemia and prolonged steroid therapy are increasingly recognized. Remission of proteinuria following corticosteroid therapy has greater prognostic value, in relation to long-term outcome, than the precise renal histology. Prospective studies show that prolonged duration of therapy for the initial episode results in sustained remission and reduced frequency of relapses. Treatment with levamisole, cyclophosphamide, cyclosporine and mycophenolate mofetil is beneficial in a variable proportion of patients with frequent relapses or steroid dependence. The management of steroid-resistant nephrotic syndrome is difficult; most patients failing to achieve remission show progressive renal damage. Calcineurin inhibitors (cyclosporine, tacrolimus) are capable of inducing remission in a significant proportion of patients, but at risk of nephrotoxicity. Reduction of proteinuria is also possible, in children, using angiotensin converting enzyme inhibitors and/or angiotensin receptor blockers. Prospective trials are necessary to identify effective and safe therapies for patients with frequent relapses, steroid dependence and resistance.

Key words Cyclosporine - levamisole - pulse therapy - steroid - resistant nephrotic syndrome

Nephrotic syndrome is a common chronic disorder, characterized by alterations of permselectivity at the glomerular capillary wall, resulting in its inability to restrict the urinary loss of protein. Nephrotic range proteinuria is defined as proteinuria exceeding 1000 mg/m^2 per day or spot (random) urinary protein-to-creatinine ratio exceeding 2 mg/mg. The proteinuria in childhood nephrotic syndrome is relatively selective, constituted primarily by albumin.

Estimates on the annual incidence of nephrotic syndrome range from 2-7 per 100,000 children, and prevalence from 12-16 per 100,000[1]. There is epidemiological evidence of a higher incidence of nephrotic syndrome in children from south Asia[2]. The condition is primary (idiopathic) in 95 per cent cases. An underlying disorder that might be identified in less than 5 per cent cases, includes systemic lupus erythematosus, Henoch Schonlein purpura,

amyloidosis and infection with HIV, parvovirus B19 and hepatitis B and C viruses[1,3,4].

More than 80 per cent patients with nephrotic syndrome show minimal change disease (MCD) characterized by normal renal histology on light microscopy. The remaining is contributed by focal segmental glomerulosclerosis (FSGS) and mesangioproliferative glomerulonephritis (MesPGN). MCD and FSGS are often considered to represent the same pathophysiological process. Membranoproliferative glomerulonephritis and membranous nephropathy are uncommon conditions in childhood (Table I)[5-7].

The age at initial presentation is useful in assessing the underlying aetiology. Nephrotic syndrome presenting in the first three months of life (congenital nephrotic syndrome) might be secondary to intrauterine infections, *e.g.*, congenital syphilis, toxoplasmosis and cytomegalovirus disease. The Finnish variety of congenital nephrotic syndrome, an autosomal recessive condition, presents commonly at this age[8]. The usual age at the onset of symptoms in patients with MCD is between 2-6 yr; 30 per cent of the adolescents also show MCD. FSGS may occur throughout childhood, though the median age is usually below 8 yr[3]. Membranoproliferative glomerulonephritis is typically seen in older children and adolescents.

Common definitions for defining the course of nephrotic syndrome are listed in Table II.

Pathogenesis

The pathogenesis of MCD is unclear, but there is a strong evidence of immune dysregulation, chiefly involving cell-mediated immunity (CMI). The tendency of nephrotic syndrome to manifest and relapse after viral infections or an atopic episode, the association with HLA antigens and Hodgkin's lymphoma, and the therapeutic response to steroids and cyclosporine A (CsA) support this view. The occurrence of prolonged remissions following measles, which downregulates CMI further endorses this hypothesis. Abnormalities

Table I. Histological lesions in idiopathic nephrotic syndrome

Glomerular lesion	Churg *et al*[5] (n=521)	White *et al*[6] (n=145)	Srivastava *et al*[7] (n=206)
Minimal change disease	76.4	77	77
Mesangial proliferative glomerulonephritis	2.3	5.5	5
Focal segmental glomerulosclerosis	6.9	7.5	5
Membranoproliferative glomerulonephritis	7.5	6	4
Membranous nephropathy	1.5	1.5	1.5
Others	5.4	2.5	7.5

Values represent percentage of all subjects

Table II. Common definitions to define the course of nephrotic syndrome

Nephrotic syndrome	Oedema; nephrotic range proteinuria (>40 mg/m²/h on timed sample, spot albumin to creatinine ratio >2 mg/mg); hypoalbuminaemia (<2.5 g/dl)
Relapse	Urinary protein excretion >40 mg/m²/h; ≥ 3+ by dipstick for 3 consecutive days
Remission	Urinary protein excretion <4 mg/m²/h; nil or trace by dipstick on spot sample for 3 consecutive days
Frequent relapses	Two or more relapses in 6 months of initial response; 4 or more relapses in any 12 month period
Steroid dependence	Occurrence of 2 consecutive relapses during steroid therapy or within 2 wk of its cessation
Steroid resistance	Failure to achieve remission after 4 wk of daily therapy with oral prednisolone at a dose of 2 mg/kg/day

Source: Ref. 3

of T cell subsets and/or function have been variably reported in a number of patients with MCD[9-11]. Most of the functional abnormalities that are described are not specific and might represent an effect (rather than a cause) of the disease[12].

Cytokine bias: Recent knowledge on functional subdivisions of the immune response has been applied to understand the pathogenesis of nephrotic syndrome. Broadly, antigen presentation to T lymphocytes results in a polarized immune response, which may be type 1 [dominated by γ-interferon, interleukin (IL) 2] or type 2 (IL4, IL10 or IL13). Type 1 cytokines predominate in cell-mediated immunity and type 2 cytokines in some aspects of humoral immunity. Type 2 cytokines are particularly associated with atopy and class switching of B cells for production of IgG4 and IgE[13].

The findings of increased plasma levels of IgE, relatively normal IgG4 (with decreased IgG1 and IgG2), and association with atopy suggest type 2 cytokine bias in subjects with MCD. Increased systemic production of representative cytokines, chiefly IL4 is also reported[14]. *In vitro* studies suggest that podocytes express receptors for IL4 and IL13[14]. Activation of these receptors, by respective cytokines, might disrupt glomerular permeability resulting in proteinuria. The clinical benefits on treatment with levamisole, which augments type 1 and downregulates type 2 cytokines also support the above hypothesis[15].

We recently examined, by immunohistochemistry renal biopsies from 30 consecutive patients with steroid-resistant nephrotic syndrome (SRNS), secondary to MCD and FSGS, for T cells expressing type 1 or type 2 cytokines. We found a significantly higher proportion of IL4 and IL10 bearing T cells compared to those expressing interferon-γ(IFN-γ) or IL2 (unpublished data). The precise mechanism/s by which the cytokine bias might affect glomerular permeability is however, not clear.

Role of permeability factor: The role of a systemic circulating factor, which might result in increased glomerular permeability, has been hypothesized in patients with MCD and FSGS. The clinical response of nephrotic syndrome to immunosuppressive medications and lack of inflammatory changes in the renal parenchyma suggest an extrarenal factor as the causative agent for proteinuria. Various vascular permeability factors have been implicated including vascular endothelial growth factor, heparanase and hemopexin[16]. Vascular endothelial growth factor is a potent permeability factor produced *in vivo* by normal glomerular podocytes, and receptors for the factor are located on glomerular endothelial and mesangial cells. However, animal and *in vitro* studies have shown conflicting findings. Heparanase is postulated to increase the permeability of glomerular capillary wall by degrading heparan sulphate glucosaminoglycans. The degradation of these anionic glycans has long been hypothesized as a cause of increased glomerular permeability to proteins. Holt *et al*[17] recently showed dysregulated heparanase synthesis in children with steroid-sensitive nephrotic syndrome. Various bioassays have helped in defining these factors, though the evidence is circumstantial and needs confirmation.

Is nephrotic syndrome a podocytopathy?: For many years the attention of researchers was focussed on the glomerular basement membrane or extraglomerular factors as being responsible for increased glomerular permeability. Recent evidence suggests that the primary defect in idiopathic nephrotic syndrome might be at the level of podocyte, the glomerular visceral epithelial cell. Injury to the podocyte can occur in many immune and non immune renal diseases. Podocyte injury or structural inherited defects are increasingly implicated in the occurrence of glomerular proteinuria. Some viruses like HIV, parvovirus B19 and simian SV40 may directly cause injury to the podocyte[4,18].

Mutations in genes encoding several podocyte proteins have been identified in children with familial nephrotic syndrome (Table III). A structurally defective podocyte or deficient basement membrane protein may result in loss of permselectivity and nephrotic range proteinuria. Such patients are less likely to respond to immunosuppressive therapy and progress to end stage renal failure[19]. The most implicated mutation involves the NPHS1 gene, encoding the protein nephrin. This transmembrane protein is present in the slit diaphragm between the podocytes (Fig. 1). Mutations in nephrin are responsible for the congenital Finnish nephrotic syndrome[8]. Abnormalities of another gene, the NPHS2 gene encoding podocin, results in recessively inherited FSGS. This mutation is also found in 10-30 per cent of sporadic onset steroid-resistant

Table III. Genetic disorders of the podocytes resulting in nephrotic syndrome

Condition	Gene (location)	Protein	Inheritance
Finnish type CNS	NPHS1 (19q13.1)	Nephrin	Recessive
FSGS	NPHS2 (1q 25-31)	Podocin	Recessive
FSGS	ACTN4 (19q13)	α-actinin 4	Dominant
Denys Drash syndrome	WT1 (11p13)	WT1 protein	Dominant
Frasier syndrome	WT1 (11p13)	WT1 protein	Dominant
Nail patella syndrome	LMX1B (9q34)	LIM-homeodomain protein	Dominant
Steroid-sensitive nephrotic syndrome	Gene located on 2p12-p13.2		Recessive

CNS, congenital nephrotic syndrome; FSGS, focal segmental glomerulosclerosis; WT1, Wilms' tumour suppressor gene

Source: Ref. 3, 8

FSGS[8,19]. The gene for autosomal dominant FSGS has been identified on chromosome 19, encoding alpha-actinin-4. Some other implicated genes are WT1 (Wilms' tumour suppressor gene), FSGS2 and LMX1B (nail patella syndrome). Mutations in WT1 are associated with Denys-Drash syndrome (characterized by male pseudohermaphroditism, nephrotic syndrome and Wilms' tumour) and Frasier syndrome (male pseudohermaphroditism, FSGS and gonadoblastomas). Steroid-sensitive nephrotic syndrome (SSNS) may rarely be familial; a locus has been mapped to chromosome 1q25, close to but distinct from the podocin gene[20]. Nephrotic syndrome with FSGS has also been reported in patients with mitochondrial cytopathies, presenting with isolated nephrotic syndrome or in association with myopathy, encephalopathy and lactic acidosis.

A hypothesis unifying the observed immunological abnormalities, increased glomerular permeability and evidence of podocyte injury is yet to be proposed. The speculation that critical podocyte proteins might be potential targets for T cell cytokines or vascular permeability factors, though attractive needs confirmation[11,16]. Availability of tests to detect genetic mutations shall enable screening of patients with SRNS for such defects in the future. The role of immunosuppressive medications in subjects with these mutations is limited.

Complications

The chief complication of nephrotic syndrome is infection, followed by thromboembolic events. Hypertension, hyperlipidaemia, features of corticosteroid toxicity and behavioural disorders are less frequent[21].

Infections: Increased predisposition to infections occurs due to loss of immunoglobulins, complement and properdin, altered T cell functions, immunosuppressive therapy and presence of oedema. Of the severe infections, peritonitis has an incidence of 2-6 per cent[1]. Other common infections are cellulitis, pneumonias and upper respiratory tract viral infections[22]. While various interventions have been used for reducing the risk of infections, proof of their efficacy is limited[23]. In a study from China, 54 patients with idiopathic nephrotic syndrome were randomized to receive standard therapy with or without intravenous (iv) immunoglobulins (dose 100-300 mg/kg/day) for 2-3 days. On follow up, the risk of nosocomial infections was lower in the intervention group as compared to controls (13.6% vs 46.8%, $P<0.05$)[24]. Another study showed that administration of a mixture of herbs (Tiaojining) with oral steroids led to early remission and lower rates of infections[25].

Varicella and pneumococcal (23-valent) vaccination is recommended for all children with nephrotic syndrome once they are in remission and

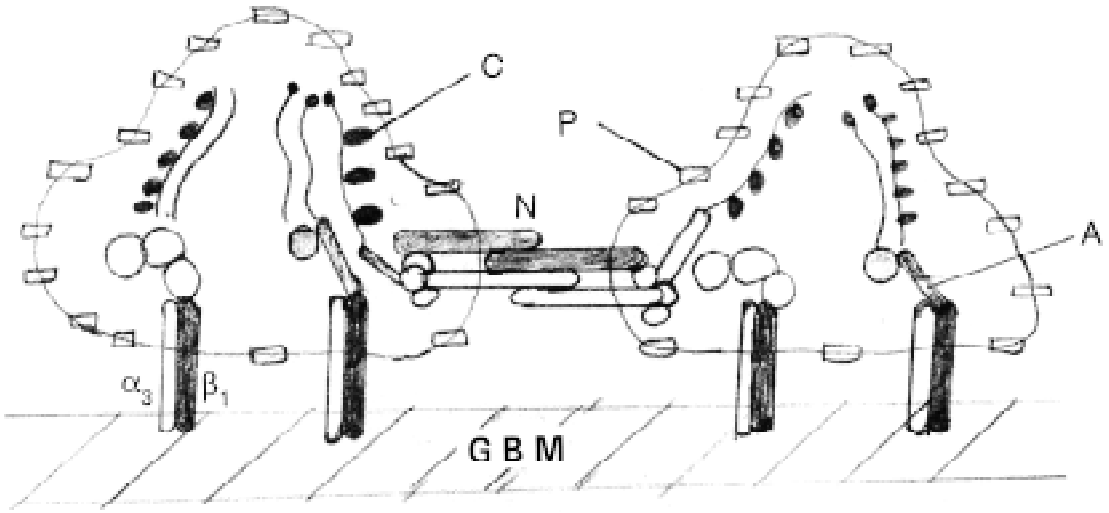

Fig. 1. Ultrastructural cross section of podocyte processes anchored to the glomerular basement membrane (GBM), through integrins (α3, β1) form the glomerular slit diaphragm (glomerular filter). The chief cellular proteins include podocin (P), nephrin (N), α-actinin 4 (A) and CD2 associated protein (C).

off steroid therapy[3,26]. Prophylactic therapy with oral penicillin V has been also used in subjects with persistent anasarca, though limited data support this practice[27].

Thromboembolism: Patients with nephrotic syndrome are at an increased risk (2-8%) for venous and arterial thrombosis, though the overall risk is lower compared to adults[28]. Additional predisposing factors including volume depletion, infections, diuretic use, venepuncture and immobilization aggravate the risk[28]. Prospective studies from our Centre suggest that almost 15 per cent of patients with nephrotic syndrome, in relapse, may show scintigraphic evidence of asymptomatic ventilation-perfusion defects, suggesting pulmonary vascular thrombosis (unpublished).

Patients with clinical and radiological evidence of thrombosis are initially treated with heparin or low molecular weight heparin. Most centres prefer the latter as it is effective and convenient to administer in 1-2 divided doses subcutaneously. Initial therapy with heparin is followed by oral warfarin for 6 months or longer. Prophylactic use of these agents for prevention of thrombosis is currently not recommended. The role of thrombolytic therapy or surgical thrombectomy is not established.

Hyperlipidaemia: Hyperlipidaemia in most patients with steroid-sensitive nephrotic syndrome is transient and does not have long-term implications[3]. However, raised blood levels of lipids may persist in patients with SRNS and potentially contribute to cardiovascular morbidity and progression of glomerulosclerosis[29]. Patients are encouraged to achieve a normal weight for height; diet should be restricted in saturated fats. While there are no clear guidelines for use of statins (HMG-CoA reductase inhibitors), short-term safety and efficacy of these agents have been demonstrated in children[30]. Simvastatin and atorvastatin decrease total and low density lipoprotein (LDL) cholesterol and triglycerides with some increase in high density lipoprotein (HDL) cholesterol.

Osteoporosis: The risk of steroid-induced osteoporosis has significant long-term implications. A prospective study from India[31] showed that 22 of 100 patients with nephrotic syndrome had features suggestive of low bone mass. Factors predictive of low bone mass were older age at onset, low calcium intake and the cumulative steroid dosage[31]. A recent study from the USA reported a high incidence of biochemical vitamin D deficiency in patients with nephrotic syndrome even during remission[32]. Leonard *et al*[33] examined the bone mineral content in 60

children with nephrotic syndrome and 195 controls, and showed that while the bone mineral content of the spine was lower in patients, the whole body mineral content when adjusted for height, age, sex, degree of maturation and race was higher than controls. They concluded that intermittent treatment with glucocorticoids in children does not significantly alter bone metabolism[33].

Based on the available evidence, it seems reasonable to provide calcium supplements to patients with frequent relapses, steroid dependence or resistance who are likely to receive long term therapy with corticosteroids.

Drug therapy

Oral corticosteroids form the cornerstone for management of most children with nephrotic syndrome. The commonly used preparations are prednisone (USA) or prednisolone (most other countries including India). Deflazacort, an oxazoline derivative of prednisolone, with equivalent anti-inflammatory and immunosuppressive activity, but fewer side effects has been used anecdotally, with satisfactory results[34]. Non availability of this preparation has limited its use for nephrotic syndrome.

Treatment of first episode: During the 1970s, the International Study for Kidney Diseases in Children (ISKDC) empirically recommended a protocol for nephrotic syndrome[35-37] that was followed, with minor modifications, over the next 25 yr. The ISKDC recommended that the initial episode be treated with prednisolone at a daily dose of 60 mg/m² for 4 wk, followed by 40 mg/m² for 3 days of the week (intermittent therapy) for another 4 wk[35-37]. Subsequently a study conducted by the Arbetsgemeinschaft fur Padiatrische Nephrologie (APN) showed that follow up therapy on alternate days was superior to intermittent prednisolone treatment[38]. Daily therapy with prednisolone may be either given, as a single morning or divided doses. A study from our Centre showed that prednisolone, as a single morning dose was as effective as divided doses for inducing remission with no higher risk of gastrointestinal adverse effects[39]. Single dose steroid therapy is convenient and likely to be associated with better drug compliance.

Patients with MCD respond quickly, more than 70 per cent achieve remission by 2 wk. The disease recurs in the majority; more than 75 per cent relapse subsequently and almost half show frequent relapses or steroid dependence. In an effort to reduce the relapse rates, there has been an emerging consensus for prolonging the duration of steroid therapy for the initial episode. The basis was the landmark APN study[40], which compared, in a randomized manner, the standard 8-wk regimen, to a longer 12-wk course (prednisolone 60mg/m² daily for 6 wk, 40 mg/m² on alternate days for 6 wk). Relapse rates were significantly lower (36 vs 62%) in patients receiving the 12-wk compared to 8-wk therapy[40]. Randomized trials from other centres including India have confirmed the benefits of prolonging the duration of initial corticosteroid therapy to 3-6 months in reducing relapse rates and proportion of patients showing frequent relapses[41,42]. One trial, however, suggested that despite its benefits, patients receiving prolonged corticosteroid treatment might be at risk of side effects[41].

A recent Cochrane meta-analysis, of randomized controlled trials, confirms that longer duration of therapy significantly reduces the risk and rate of relapses at 12 and 24 months, without increased risk of side effects[43]. The analysis concludes that the duration of steroid treatment for the initial episode should be at least three months. An increase in benefit was found for even longer duration of therapy up to 6-7 months, though this needs confirmation in further studies. It however needs to be emphasized that none of these trials was adequately powered to examine for steroid toxicity.

Trials to determine the appropriate duration of initial corticosteroid therapy are in progress, including one by the British Association of Pediatric Nephrology (http://bapn.uwcm.ac.uk). Based on current evidence and the need to reduce steroid toxicity, most specialists recommend that the initial episode be treated with prednisolone for 6 wk daily and 6-wk alternate day (total 12 wk therapy)[1,3,26,44].

Frequent relapses and steroid dependence: A majority of children with nephrotic syndrome relapse within the first 6 months of initial therapy. Almost 50-60 per cent have frequent relapses or steroid dependence.

Factors predicting frequent relapses include, age younger than 3 yr at onset, delayed time to remission (after 7-9 days) and occurrence of an early relapse (in the first 6 months after initial treatment)[45-47].

Long-term, alternate day oral prednisolone is the initial strategy for patients with steroid dependent and frequently relapsing nephrotic syndrome. Slow tapering of prednisolone is done to reach to a maintenance dose of 0.25-0.5 mg/kg on alternate days. These doses are given for prolonged periods of 9-12 months, but many still relapse, especially during intercurrent infections. Patients requiring prednisolone at doses exceeding 1 mg/kg on alternate days to maintain remission are likely to show adverse effects and should be considered for treatment with steroid sparing agents.

Levamisole, an antihelminthic drug with immunostimulatory properties, has been reported to be effective as a steroid sparing agent in a number of case series summarized in a recent review[48]. Definite evidence regarding its benefit is limited to three randomized clinical trials, which suffer from methodological limitations. Analysis of these trials shows that levamisole reduces the risk of a relapse during treatment (relative risk 0.60, 95% confidence interval 0.45–0.79)[48]. We examined the benefit of levamisole, administered at a dose of 2.5 mg/kg on alternate days, in 43 patients with steroid dependent nephrotic syndrome. The duration of therapy ranged from 6-31 months. A significant reduction in relapse rates and a moderate steroid sparing effect was observed[49]. The medication is usually well tolerated; rare side effects include leukopenia, vasculitic rash and liver toxicity[50].

Alkylating agents have been widely used for treatment of nephrotic syndrome. Therapy with oral cyclophosphamide (2-3 mg/kg/daily) and prednisolone (1 mg/kg on alternate days) for 8-12 wk induces sustained remission in 25-60 per cent patients with frequent relapses or steroid dependence at 2-5 yr follow up[51]. The results are less beneficial in subjects with steroid dependence[51,52]. Treatment with once monthly iv cyclophosphamide also seems effective, but there is no clear advantage over oral therapy[53]. Adverse effects include marrow suppression, alopecia and haemorrhagic cystitis; the risk of severe bacterial infections is 1.5 per cent[51]. The gonadal toxicity of alkylating agents is an important consideration, especially in pubertal boys. Though not usually recommended, a second 8-wk course of cyclophosphamide can be considered without reaching the threshold cumulative dose of 250 mg/kg, above which the risk of gonadal toxicity increases substantially[51]. The use of chlorambucil has been limited, in view of its toxicity, especially the risk of seizures and serious infections[3,51].

Calcineurin inhibitors [cyclosporine A (CsA) and tacrolimus] act upon intracellular binding proteins and inhibit calcium dependent signaling pathways involved in transcription of the IL2 gene. Reduced IL2 synthesis results in inhibition of T lymphocyte proliferation and attenuation of the immune response. Over the years, CsA has emerged as an important drug for treatment of patients with frequent relapses and steroid dependence. About 80-85 per cent of such patients respond to CsA[1,54]. Many patients, however, need a small dose of steroids in addition to CsA to maintain remission[55]. The dose of CsA is 4-5 mg/kg (100-150 mg/m^2) daily, which normally achieves whole blood trough levels of 150-250 ng/ml.

CsA withdrawal is usually associated with recurrence of relapse, necessitating long-term therapy extending over 1-3 yr. While prolonged treatment with CsA is being used increasingly, concerns about its nephrotoxicity mandate careful monitoring of renal functions. Patients on continuous therapy with CsA for 2-3 yr should preferably undergo renal biopsy to assess for evidence of CsA induced vasculopathy[3,55]. Experience with tacrolimus in patients with frequent relapses is limited. Potential advantages of tacrolimus include minimal cosmetic side effects and a modestly reduced risk for nephrotoxicity, hypertension and dyslipidaemia.

Mycophenolate mofetil (MMF) hydrolyzed to its active metabolite mycophenolic acid inhibits inosine monophosphate dehydrogenase, an enzyme involved in *de novo* guanosine biosynthesis. T and B lymphocytes are dependent upon *de novo* purine synthesis for their proliferation whereas other cell types can utilize salvage pathways.

Since the approval of MMF for use in subjects undergoing renal transplantation, considerable interest has arisen to explore its use in childhood nephrotic

syndrome. We examined the role of MMF in 19 children with severe steroid dependent nephrotic syndrome, who had previously not responded to therapy with levamisole and alkylating agents. Treatment with MMF, at doses of 25-30 mg/kg daily, resulted in a significant reduction in relapse rates and marked corticosteroid sparing effect. Side effects were infrequent, but cessation of therapy resulted in recurrence of relapses[56]. Similar benefits of prolonged therapy with MMF have been reported by other workers[57].

The use of cyclophosphamide, chlorambucil, levamisole and CsA in patients with frequently relapsing nephrotic syndrome is supported by systematic reviews of randomized controlled trials and evidence based guidelines[26,58]. There are however, a few controlled trials that compare the effectiveness of one agent over another, and the preferred second-line drugs. Promising results in uncontrolled trials on MMF have led to suggestions that therapy with this agent be considered before embarking on long-term treatment with potentially nephrotoxic agents like CsA. However, prospective randomized trials, with appropriate power, are necessary to compare the effectiveness and safety of MMF and CsA, before endorsing these suggestions.

An Expert Group of the Indian Pediatric Nephrology Group met in December 2000 to evolve treatment guidelines for patients with steroid sensitive nephrotic syndrome[26] (Fig. 2).

Steroid-resistant nephrotic syndrome (SRNS)

Patients with SRNS pose the most difficult therapeutic challenge. These children are at risk for complications of unremitting nephrotic syndrome and developing end stage renal disease. Medications that have been used in such patients are discussed below:

Intravenous steroids (with alkylating agents): Tune *et al*[59] first showed beneficial results of treatment in patients with SRNS using high dose iv methylprednisolone, given in a tapering schedule over 30 months[59]. Pulse corticosteroids were combined with alkylating agents (cyclophosphamide or chlorambucil) for 8-12 wk. The response rate was almost 65 per cent to this regimen. In view of significant steroid toxicity and need for multiple admissions for iv infusions, many centres have used shorter protocols, with variable benefit ranging between 10-70 per cent[3,60].

An issue of interest is regarding the choice of steroid medication for iv treatment. Methylprednisolone is expensive and not easily available, therefore a less expensive preparation, dexamethasone, has been used. Methylprednisolone and dexamethasone are synthetic steroids produced by methylation at the 6α position of prednisolone and 16α position of 9-fluoroprednisolone respectively. Compared to prednisolone, these are potent glucocorticoids with weak mineralocorticoid activity. Their efficacy in inducing remission in patients with SRNS appears to be similar[60,61]. Patients requiring high dose iv steroids may thus be treated effectively with either agent. Therapy may be associated with significant adverse effects including hypertension, arrhythmias, hypokalaemia, psychosis and severe infections.

Cyclophosphamide: Review of uncontrolled trials shows a limited role for oral cyclophosphamide plus prednisolone in inducing remission in patients with SRNS[1]. In randomized trial of the ISKDC, involving 60 patients, remission rates were similar (25%) in the steroid-only versus the steroid plus oral cyclophosphamide group[62].

Pulse cyclophosphamide (iv) administered monthly may also induce remission, though the results are variable[63-66]. A randomized trial, on 13 patients with SRNS, comparing iv and oral cyclophosphamide showed beneficial results in 100 and 25 per cent patients respectively[63]. In another report, 65 per cent of 20 patients with FSGS treated with iv pulse cyclophosphamide showed complete remission[64]. Similar therapy was however found to be less effective in a case series on patients with difficult SRNS[65]. Of the 24 patients with SRNS, who had failed previous therapy with oral and iv pulse corticosteroids, 29 per cent each achieved complete and partial remission at 6 months. On follow up at 2 yr, all subjects with partial remission had recurrence of nephrotic range proteinuria, and only 21 per cent patients were in sustained remission[65]. Patients with initial resistance and significant tubulointerstitial changes on the renal biopsy were less likely to respond to therapy.

A recent randomized trial on 49 subjects with SRNS, compared results of treatment with iv pulse

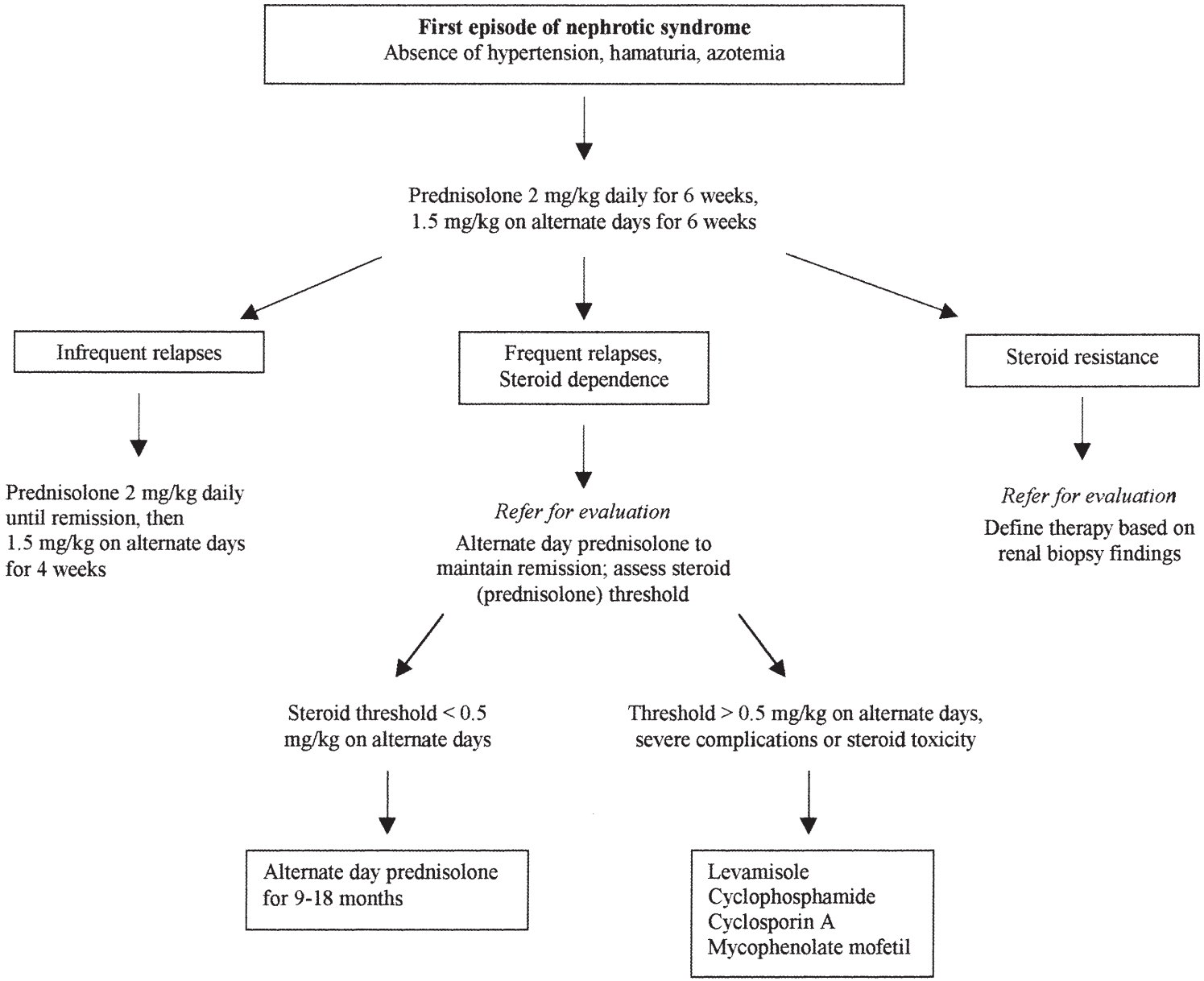

Fig. 2. Management of childhood nephrotic syndrome. A kidney biopsy is not necessary before initiating therapy in most children with nephrotic syndrome. Steroid threshold is the alternate-day prednisolone dose below which the patient is likely to relapse. Patients requiring relatively high doses of prednisolone to maintain remission, or showing features of steroid toxicity should receive treatment with steroid sparing agents. (Modified from Ref.26 with permission).

Table IV. Regimens for treatment of steroid resistant nephrotic syndrome

Drug	Dosage	Remission (%)	Side effects
Cyclophosphamide			
PO with prednisolone*[62]	2-3 mg/kg/day for 12 wk	20-30	Alopecia, marrow suppression;
iv with prednisolone**[63-66]	500-750 mg/m²/month for 6 months	40-60	haemorrhagic cystitis, nausea, vomiting (with iv therapy)
iv Pulse steroids*			
Methylprednisolone, PO cyclophosphamide and prednisolone[59]	20-30 mg/kg per pulse	10-70	Hypertension, hypokalaemia, serious infections, hyperglycaemia, arrhythmia; steroid psychosis (rare)
Dexamethasone, PO cyclophosphamide and prednisolone**[60]	4-5 mg/kg per pulse		
Cyclosporine with prednisolone*[70,72]	4-6 mg/kg/day for 2-3 yr	30-70	Nephrotoxicity, hypertension, gingival hyperplasia, hypertrichosis

*Prednisolone administered at 1 mg/kg on alternate days; dose reduced after 2-3 months
**Six alternate day pulses, then 4 fortnightly pulses and 8 monthly pulses; oral cyclophosphamide for 12 wk; tapering prednisolone over 52 wk[60]

dexamethasone and oral cyclophosphamide, to iv pulse cyclophosphamide; patients in both groups received alternate day prednisolone and daily enalapril. The rates of complete and partial remissions were similar at 6 months (47.8 versus 53.8%) in both groups[67]. The rates of serious infections were also comparable. Patients achieving partial remission showed recurrence of SRNS on follow-up, confirming instability of this response.

Vincristine: This cytotoxic agent has been used, along with alternate day prednisolone, to induce remission in patients with FSGS and MesPGN at dosage of 1.5 mg/m² iv weekly for 8 wk. The response rate from anecdotal reports varies between 20-30 per cent[68,69].

Calcineurin inhibitors: CsA has been used for the treatment of patients with SRNS for more than 2 decades. Studies have shown that the response rates to CsA alone are about 30 per cent but increase to 40-50 per cent when the drug is administered with steroids[70-71]. Children with MCD are more likely to respond compared to those with FSGS (46 versus 30%)[70]. At our Centre, CsA is the preferred agent in subjects who fail to respond to therapy with high dose steroids and/or cyclophosphamide. Of the 54 children patients treated with CsA plus alternate day prednisolone, 57.4 per cent showed complete remission and 22.2 per cent partial remission after 12 months therapy (unpublished). Remission was higher in patients with MCD (71%) compared to FSGS (47%). The common side effects of treatment were hypertrichosis (50%), gum hyperplasia (40%), hypertension, decrease in glomerular filtration rates and chronic nephrotoxicity (30%).

Children receiving CsA need monitoring of serum creatinine levels every 2-3 months; a rise of 25 per cent from the baseline requires dose reduction. Whole blood trough levels of CsA are recommended though they might not always correlate with toxicity. Studies have shown that the risk of nephrotoxicity is higher in subjects who continue to show nephrotic range proteinuria despite therapy, and prolonged use beyond 24-36 months[72]. Most experts recommend a kidney biopsy, after 2-3 yr of treatment to monitor for nephrotoxicity before deciding to continue therapy. If there is no evidence of CsA toxicity, therapy is continued and a repeat biopsy proposed after 24-30 months.

Once a decision to discontinue treatment with CsA is taken, the drug may be tapered over 6 months. Another approach involves replacement of CsA with MMF over a few months. However, a significant proportion of patients relapse after cessation of CsA therapy. Reintroduction of treatment with CsA might be necessary, and an occasional patient may show late

Table V. Summary of published trials on steroid resistant nephrotic syndrome in children

Study (yr)	N	Intervention	Response
Controlled trials:			
ISKDC (1970)[83]	31	Azathioprine and prednisolone vs prednisolone and placebo for 3 months	No remission in either group
ISKDC (1974)[84]	31	CP (PO) and prednisolone vs prednisolone for 3 months	No remission in either group
ISKDC (1996)[62]	60	CP (PO) and prednisolone vs prednisolone for 12 months	25 per cent remission in either group
Elhence *et al* (1994)[63]	13	CP (iv) and prednisolone vs CP (PO) and prednisolone	100 per cent remission in iv group; 25 per cent in PO (P = 0.02)
Ponticelli *et al* (1993)[85]	20	CsA vs supportive therapy for 6 months	40 per cent remission in CsA; 0 per cent in supportive (P <0.001)
Lieberman *et al* (1996)[86]	31	CsA vs placebo for 6 months	33.3 per cent remission in CsA; none in placebo (P <0.05)
Bagga *et al* (2004)[77]	25	Enalapril 0.6 mg/kg/day vs 0.2 mg/kg/day for 8 wk	Ua/Uc reduction. 62.9 per cent (high dose); 34.8 per cent (low dose) (P <0.01)
Mantan *et al* (2004)[67]	49	CP (iv) and prednisolone vs dexamethasone (iv), CP (PO) and prednisolone (PO)	53.8 per cent remission in CP; 47.8 per cent in dexamethasone (P=0.6)
Uncontrolled trials:			
Niaudet *et al* (1994)[87]	65	CsA, prednisolone for 6 months	41.5 per cent remission
Rennert *et al* (1999)[88]	10	CP (iv), prednisolone for 6 months	70 per cent remission
Tune *et al* (1995)[59]	32	MP (iv), CP (PO), prednisolone	60 per cent remission
Adhikari *et al* (1997)[66]	12	MP (iv), CP (PO) and prednisolone vs CP (iv), MP (iv) and prednisolone	85.7 per cent remission in MP (iv); 40 per cent in CP (iv)
Hari *et al* (2001)[60]	65	MP or dexamethasone (iv), CP (PO) and prednisolone for 52 wk	65 per cent remission
Hari *et al* (2004)[61]	81	Dexamethasone (iv) vs MP (iv) [CP (PO), prednisolone both groups]	Remission 35.1 per cent in dexamethasone; 33.1 per cent MP
Gulati & Kher (2000)[64]	20	CP (iv), prednisolone for 6 months	65 per cent remission
Bajpai *et al* (2003)[65]	24	CP (iv), prednisolone for 6 months	29 per cent remission

CP, Cyclophosphamide; CsA, cyclosporin A; MP, methylprednisolone; PO, per oral; iv, intravenous; Ua/Uc, spot urine albumin to creatinine ratio. Remission refers to complete remission

CsA resistance[73]. There are occasional reports of remission following treatment with tacrolimus in patients failing to respond to CsA[74].

The therapeutic options available for patients with SRNS are summarized in Table IV.

Angiotensin converting enzyme inhibitors (ACEI) & angiotensin receptor blockers (ARB): ACEI and ARB are increasingly being used for non specific reduction of nephrotic range proteinuria[75]. These agents reduce proteinuria by decreasing the transcapillary glomerular hydrostatic pressure and altering glomerular permeability. Apart from control of hypertension and reduction of proteinuria, ACEI decrease synthesis of transforming growth factor (TGF)-β and plasminogen activator inhibitor (PAI)-1. Both TGF-β and PAI-1 are important profibrotic cytokines promoting glomerulosclerosis. Their inhibition by blockade of the renin-angiotensin system is believed to result in decreased fibrogenesis and

resolution of sclerosis in animal models[76]. These effects of ACEI are exciting since they provide for the first time, a mechanism by which renal scarring might, in fact, be reversed[76].

The antiproteinuric effects of ACEI are both dose and time dependent. In a randomized crossover trial, a higher dose (0.6 mg/kg/day) of enalapril was more effective than standard dose (0.2 mg/kg/day) in reducing proteinuria[77]. Review of data from multiple studies in children and adults shows that administration of ACEI results in reduction of proteinuria by 40-50 per cent, without significant adverse effects[75,77].

Dual blockade of the renin-angiotensin system with simultaneous use of ACEI and ARB are reported to have a synergistic antiproteinuric effect in adults[78,79]. An ongoing trial in children comparing enalapril versus a combination of enalapril with irbesartan shall provide clearer guidelines on the use of ACEI and ARB. Currently all patients with SRNS should receive enalapril at doses of 0.2-0.3 mg/kg/day, with escalation depending on the degree of proteinuria. It is preferable that these agents be used cautiously in patients with glomerular filtration rate <30 ml/min/ 1.73 m^2.

Other therapies: A number of novel approaches are being tried for patients with SRNS. Plasmapheresis or immunoadsorption has been employed, to remove the putative "vascular permeability factor" with variable results[80]. Prolonged use of MMF is reported to reduce proteinuria, increase serum albumin and decrease cholesterol, though complete remission was not achieved[81,82].

Limited evidence based data are available on the choice of therapy for SRNS in childhood (Table V)[83-88]. The National Institutes of Health (USA) has recently initiated a prospective randomized multicentric trial to compare the effectiveness of CsA to a combination of pulse oral dexamethasone and MMF in children with FSGS. Both groups shall receive low dose alternate day prednisolone and an ACEI.

Outcome

The most important factor that determines prognosis in children with nephrotic syndrome is steroid responsiveness. While more than 70 per cent of children with steroid-sensitive nephrotic syndrome relapse and almost 50 per cent have frequent relapses or steroid dependence, their risk of progression to chronic renal failure is minimal. Studies on natural history show that 15-25 per cent patients may continue to have relapses 10-15 yr after the onset of the disease. Young age at onset and frequent relapses during childhood are associated with relapses in adulthood[89,90].

The outcome of patients with SRNS, who fail to respond to high dose steroids, cyclophosphamide and/ or CsA, is unsatisfactory. Significant proportions of patients are at risk for complications, progressive kidney disease and end stage renal failure. Almost 20-25 per cent patients with FSGS may show recurrence of the disease in allografts, with graft loss occurring in 5 per cent. The course of disease and outcome is different in patients with the genetic forms of nephrotic syndrome. Immunosuppressive medications are neither effective nor necessary, and a variable proportion show progressive kidney disease. However, the risk of recurrence of FSGS is minimal following renal transplantation in these patients.

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