Management of Steroid Resistant Nephrotic Syndrome

INDIAN SOCIETY OF PEDIATRIC NEPHROLOGY

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Justification: There is a lack of evidence based guidelines for management of children with steroid resistant nephrotic syndrome (SRNS).

Process: Experts of the Indian Society of Pediatric Nephrology were involved in a two-stage process, the Delphi method followed by a structured face to face meeting, to formulate guidelines, based on current practices and available evidence, on management of these children. Agreement of at least 80% participants formed an opinion.

Objectives: To develop specific, realistic, evidence based criteria for management of children with idiopathic SRNS.

Recommendations: The Expert Group emphasized that while all patients with SRNS should initially be referred to a pediatric nephrologist for evaluation, the subsequent care might be collaborative involving the primary pediatrician and the nephrologist. Following the diagnosis of SRNS (lack of remission despite treatment with prednisolone at 2 mg/kg/day for 4 weeks), all patients (with initial or late resistance) should undergo a renal biopsy, before instituting specific treatment. Patients with idiopathic SRNS secondary to minimal change disease or focal segmental glomerulosclerosis should receive similar therapy. Effective regimens include treatment with calcineurin inhibitors (tacrolimus, cyclosporine), intravenous cyclophosphamide or a combination of pulse corticosteroids with oral cyclophosphamide, and tapering doses of alternate day corticosteroids. Supportive management comprises of, when indicated, therapy with angiotensin converting enzyme inhibitors and statins. It is expected that these guidelines shall enable standardization of care for patients with SRNS in the country.

Keywords: *Cyclosporine, Delphi method, Nephrotic syndrome, Tacrolimus.*

Idiopathic nephrotic syndrome, characterized by altered permselectivity of the glomerular filter, is a common chronic renal disorder in children. Most patients are steroid sensitive and respond to therapy with remission of proteinuria (steroid sensitive nephrotic syndrome). Revised Guidelines for treatment of these patients were published recently(1). Approximately 10-20% children with nephrotic syndrome, who do not respond to therapy with corticosteroids, are classified as steroid resistant (SRNS). Their management is difficult since patients are, on one hand, at risk for complications of unremitting nephrotic syndrome and progressive renal disease and on the other, the side effects of treatment with immunosuppressive medications(2).

Despite the availability of a number of agents with variable efficacy in inducing remission, the optimal treatment of patients with SRNS is unclear. A lack of controlled studies has hindered development of guidelines on treatment. In order to address the management of this condition, we used the Delphi technique to gather opinion of experts of the Indian Society of Pediatric Nephrology. This technique comprises a series of questionnaires, which are circulated among experts followed by, if necessary, a face-to-face meeting to enable consensus on issues where evidence based recommendations are lacking(3). Such an approach has been used to develop consensus on the management of juvenile arthritis and classification of childhood vasculitides(4).

OBJECTIVES

Experts of the Indian Society of Pediatric Nephrology were involved in a two-stage process to

formulate broad guidelines for the management of patients with idiopathic SRNS.

METHODS

The first stage comprised the Delphi method to generate responses *via* electronic mail. This was followed by a structured face-to-face meeting to facilitate discussion on issues related to the topic.

The Delphi method

The methodology was designed such that each step was based on the results of the previous steps (***Fig.* 1**).

Step 1. Definition of the problem

There is a lack of evidence based guidelines on management of SRNS in children.

Step 2. Formulation of a questionnaire

A local committee designed a questionnaire comprising 26 issues related to management of children with SRNS. The questionnaire was in a multiple-choice format, each choice being rated on a scale of 0 to 7. The questionnaire was circulated electronically among members of the local committee to elicit their response on its suitability.

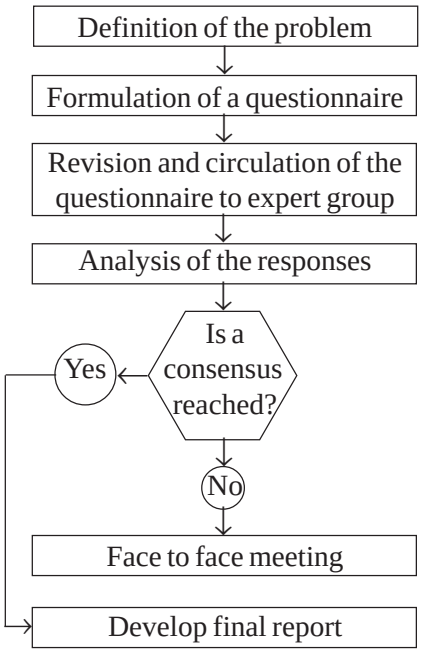

FIG 1. *Delphi method for formulating guidelines for management of steroid resistant nephrotic syndrome.*

Step 3. Revision and circulation of the questionnaire

Based on responses of the local committee, the questionnaire was revised and circulated to 33 experts across the country by electronic mail. At this stage, the participants were provided with literature on management of patients with SRNS.

Step 4. Analysis of the responses

Responses, obtained from 31 pediatric nephrologists, were collated; choices with a score of six or more in at least 80% of the responses formed an opinion. This was possible in 15 of the 26 questions circulated. An opinion was not possible in the remaining questions.

Face-to-face meeting

Experts of the Indian Society of Pediatric Nephrology (*Annexure I*) met on 16 November 2007 in Hyderabad, to review each of the issues and formulate recommendations based on opinion derived from the previous phase and current medical literature. Agreement of at least 80% participants was taken as a recommendation.

Grading recommendations

Wherever possible, treatment recommendations were graded from A to D (***Table* I**) based on the level of available evidence, as proposed by Carruthers, *et al.*(5).

RECOMMENDATIONS

In view of its rarity, complexity of treatment, progressive course and unsatisfactory outcome, all patients with SRNS should be referred to a pediatric nephrologist for evaluation. Subsequently, the care of these patients might be collaborative, between the primary pediatrician and the nephrologist.

1. Definitions

(*a*) A patient is diagnosed to have steroid resistance if there is lack of remission despite treatment with prednisolone at a dose of 2 mg/kg/day (60 mg/m^2/day) for 4 weeks. Remission is defined as

TABLE I LEVELS OF EVIDENCE FOR RATING STUDIES AND GRADING FOR TREATMENT RECOMMENDATIONS*

Level	Definition of evidence
1	Randomized controlled trial (RCT) that demonstrates a statistically significant difference in at least one important outcome, *or* if the difference is not significant, an RCT of adequate 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, *or* subgroup analysis of a RCT
4	Before-after study or case series (>10 patients) with historical controls, *or* controls drawn from other studies
5	Case series (>10 patients) without controls
6	Case reports (<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

absence of proteinuria (urine albumin nil or trace for three consecutive days by dipstick or boiling test).

(*b*) Even in patients with adverse effects related to previous steroid use, confirmation of lack of remission despite 4 weeks' treatment with daily prednisolone is necessary before making the diagnosis of SRNS.

(*c*) Similar definitions for duration of steroid therapy should be used for initial and late steroid resistance. *Initial resistance* is lack of remission at the first episode of nephrotic syndrome. Patients who are steroid sensitive initially, but show steroid resistance during a subsequent relapse have *late resistance.*

Rationale

Following treatment with daily prednisolone, 95% patients with steroid sensitive nephrotic syndrome achieve remission by the first 4 weeks and an additional 3% in additional 4 weeks(6). Prolonged courses of daily corticosteroids are associated with increased incidence of side effects. Therefore, defining SRNS as lack of remission despite 4 weeks treatment with daily prednisolone is reasonable. This definition is in conformity with that used by the Cochrane Renal Group(7). The National Institutes of Health (USA) trial on patients with steroid resistant focal segmental glomerulosclerosis (FSGS) has accepted a similar definition (*www.fsgstrial.org*). Absence of proteinuria by dipstick usually correlates with a spot urinary protein to creatinine ratio less than 0.2 mg/mg. Since systemic infections (*e.g.*, peritonitis, cellulitis, respiratory tract infections) might result in persistent proteinuria and an incorrect diagnosis of SRNS, these should be carefully excluded.

2. Renal Biopsy

(*a*) All children with SRNS, whether initial or late, should undergo a renal biopsy before instituting specific treatment.

(*b*) The histological specimen must be examined by light and immunofluorescence microscopy. Referral centers should develop facilities for electron microscopic evaluation of renal biopsy specimens.

Rationale

Despite absence of evidence based recommendations regarding the role of renal biopsy in patients with SRNS, this procedure provides important information on renal histology and outcome. Most patients with steroid sensitive nephrotic syndrome (90%) show minimal change nephrotic syndrome on renal histology. The renal histology in SRNS is different, with 30-40% patients each showing minimal change nephrotic syndrome and FSGS, and a smaller group with mesangioproliferative glomerulonephritis(8). The response to therapy is determined by renal histology; patients with minimal change nephrotic syndrome show satisfactory response to therapy, while presence of FSGS or chronic tubulointerstitial changes is associated with unsatisfactory outcomes(9). A renal

biopsy is also necessary before initiating treatment with potentially nephrotoxic agents, especially cyclosporine or tacrolimus(10).

Approximately 20% patients with SRNS show membranoproliferative glomerulonephritis, membranous nephropathy, IgA nephropathy and amyloidosis. Recognition of these conditions is important as they differ with regard to their evaluation and treatment.

Although light and immunofluorescence microscopy form the minimum requirement for evaluation of histopathology specimens, electron microscopy helps to confirm the diagnosis of minimal change nephrotic syndrome, differentiates primary from secondary FSGS, and enables diagnosis of early membranous nephropathy, membranoproliferative glomerulonephritis and Alport syndrome.

3. Mutational Analysis

(*a*) Studies for mutations of genes involved in synthesis of podocyte proteins are not routinely necessary in children with SRNS.

(*b*) Where facilities exist, mutational analysis may be offered to patients with congenital nephrotic syndrome (onset below 3 months of age), initial steroid resistance and family history of SRNS.

Rationale

Mutations in the genes encoding various podocyte proteins, including podocin (*NPHS2*) and nephrin (*NPHS1*), have been described in a variable proportion of patients with familial and sporadic SRNS(11). The likelihood of detecting a mutation is higher in patients with family history of nephrotic syndrome or its onset in infancy(12). Patients with mutations involving these genes often do not respond to immunosuppressive medications and show progressive kidney disease. In a series of patients with SRNS and homozygous or compound heterozygous mutations in *NPHS2*, none showed complete remission following treatment with cyclophosphamide or cyclosporine(13). Mutations of the gene encoding Wilms' tumor protein (*WT1*) may result in a phenotype comprising FSGS, pseudohermaphroditism and increased risk for renal or gonadal malignancies(14). Finally, while 30% patients of FSGS without mutations show a recurrence of the disease post-transplant, this is exceptionally rare in patients with mutations in the above genes(13).

In view of lack of data in Indian children, routine mutational analysis in patients with initial SRNS is not recommended. Patients with late steroid resistance have not been found to have genetic mutations(15). The utility of mutational studies prior to instituting therapy with alternative agents is also unclear.

4. Principles of Therapy

Patients with idiopathic SRNS secondary to minimal change nephrotic syndrome, FSGS and mesangioproliferative glomerulonephritis should receive similar therapy.

Rationale

Review of the literature suggests that patients with steroid resistance secondary to minimal change nephrotic syndrome are more likely to achieve remission and have a better prognosis compared to other histological types(9,16,17). However, a systematic review by the Cochrane Renal Group showed similar outcome in patients with steroid resistant minimal change nephrotic syndrome and FSGS who were treated with cyclosporine or cyclophosphamide(7). There is no clear evidence to support that patients with minimal change nephrotic syndrome and FSGS should be treated differently.

Distinction between various histological categories is also not absolute. In early stages, FSGS might be difficult to distinguish from minimal change nephrotic syndrome, depending on the adequacy of biopsy and extent of the disease. Furthermore, examination of renal histology in FSGS reveals a variety of histological subtypes, with variable response to therapy and outcome(18). Repeat biopsies might show morphological transition between minimal change nephrotic syndrome, mesangioproliferative glomerulonephritis and FSGS. Thus, these histological conditions may be found alone or in combination on

sequential biopsies in the same patient. Finally, studies in adults suggest that the chief factor predicting outcome is the response of proteinuria to therapy rather than the renal histology(19).

5. Specific Treatment

The aim of therapy is induction of remission while avoiding medication related toxicity. Treatment failure correlates with poor long-term prognosis for renal function. In view of limited studies in children with SRNS, treatment guidelines vary considerably and there is absence of consensus on therapy.

Effective regimens and their side effects are shown in ***Tables* II** and **III**. The options for treatment for patients with idiopathic SRNS include:

- Calcineurin inhibitors with tapering doses of alternate day steroids: cyclosporine (Grade A recommendation); tacrolimus (Grade D recommendation)
- Cyclophosphamide with tapering doses of alternate day steroids (Grade C recommendation)
- High dose intravenous steroids (dexamethasone, methylprednisolone) with oral cyclophosphamide and tapering alternate day steroids (Grade C recommendation)

In view of lack of consensus regarding the most appropriate therapy, the Expert Group accepts that the choice of initial treatment shall continue to depend on the preference of the physician and the cost of medications.

Rationale

There is a lack of consensus on the most appropriate first line therapy for children with SRNS, with many of the regimens extrapolated from studies in adults. The level of evidence(5) on efficacies of available regimens is summarized below.

Calcineurin inhibitors

Cyclosporine has been compared to placebo, control or supportive treatment in three randomized trials(20-22). Treatment significantly increased the proportion of patients who achieved complete remission compared with placebo or no treatment, irrespective of renal pathology [three studies, *n*=49; relative risk (RR) 0.64, 95% confidence interval (CI) 0.47, 0.88]. While no patient achieved complete remission in one study, urinary protein excretion and creatinine clearance worsened significantly in the control group (Level 2)(20). The other two trials showed significant benefit in terms of proportion of

TABLE II REGIMENS FOR TREATMENT OF IDIOPATHIC STEROID RESISTANT NEPHROTIC SYNDROME

Drug	Dosage*	Remission
Calcineurin inhibitors		
Cyclosporine and prednisolone**	4-6 mg/kg/day in two divided doses for 2-3 years	50-80%
Tacrolimus and prednisolone**	0.12-0.15 mg/kg/day in two divided doses for 2-3 years	70-85%
Cyclophosphamide		
Oral cyclophosphamide and prednisolone**	2-3 mg/kg/day for 12 weeks	25-30%
IV cyclophosphamide and prednisolone**	500-750 mg /m^2 once every month for 6 months	40-65%
Pulse corticosteroids		
IV methylprednisolone, oral cyclophosphamide and prednisolone#	20-30 mg/kg for 6 alternate day pulses; then once a week for 8 doses, fortnightly for 4 doses, once a month for 8 doses; finally bimonthly for 4 doses	40-70%
IV dexamethasone, oral cyclophosphamide and prednisolone#	4-5 mg/kg for 6 alternate day pulses; then every fortnight for 4 doses; finally once a month for 8 doses	30-50%

** Dosage refers to that of the italicized agent; ** Prednisolone dose: 1.5 mg/kg on alternate days for 4 weeks; 1.25 mg/kg next 4 weeks; 1 mg/kg for 4 months; 0.5-0.75 mg/kg for 12-18 months; # Oral cyclophosphamide for 12 weeks (weeks 3-15); tapering doses of prednisolone over 12 months*

TABLE III COMMON SIDE EFFECTS OF MEDICATIONS USED FOR TREATMENT

Drug	Common side effects
Cyclophosphamide	Alopecia, marrow suppression, vomiting, hemorrhagic cystitis, risk of systemic infections
IV methylprednisolone,	Hypertension, hypokalemia, dexamethasone, hyperglycemia, steroid psychosis, risk of systemic infections
Cyclosporine**,** Tacrolimus	Nephrotoxicity; hypertension; hypertrichosis, gingival hyperplasia and dyslipidemia*; neurotoxicity, diarrhea and hyperglycemia**
ACE inhibitors *e.g.*,	Dry cough, hyperkalemia, enalapril anemia
Statins *e.g*., atorvastatin	Headache, muscle pain, rash, raised transaminases

*Side effects frequent with *cyclosporine or **tacrolimus*

children who achieved either complete or partial remission (Level 1)(21,22). Relapse was reported in 33.3% children, who achieved partial or complete remission, by the end of 12 months' treatment(22). No data was shown on differences in efficacy in patients with initial compared to late resistance, or on long term effect on renal function.

A meta-analysis of these studies shows that treatment with cyclosporine results in a significant increase in the number of children (both minimal change nephrotic syndrome and FSGS) with complete remission compared to placebo or supportive treatment (RR 7.66, 95% CI 1.1, 55.3)(7). These data confirm the findings of multiple uncontrolled studies on the role of cyclosporine in patients with SRNS. A case series of 65 patients with initial steroid resistance showed complete remission in 46% with minimal change nephrotic syndrome and 30% with FSGS (Level 4)(23). Another retrospective report showed remission in 77% of 51 patients with FSGS treated with cyclosporine and prednisone, with or without intravenous methylprednisolone(17).

There is limited data on the efficacy of tacrolimus, which has a similar mode of action as cyclosporine (Level 5)(24). A randomized controlled trial, published in abstract form, reported similar remission rates with these agents (Level 2)(25). Tacrolimus has an advantage of a better side effect profile with less cosmetic side effects but the incidence of neurotoxicity and impaired glucose tolerance appear greater. In all published trials, the incidence of adverse effects was low, but this might be underestimated because of small patient numbers, short follow up periods and incomplete reporting.

Cyclophosphamide

Three randomized controlled trials have investigated the role of cyclophosphamide(26-28). Of these, two studies compared oral cyclophosphamide and alternate day prednisolone with prednisolone alone(26,27). There was no difference in the number of children overall (*n*=84; RR 1.01, 95% CI 0.74, 1.36) or those with FSGS (*n*=63; RR 0.82, 95% CI 0.46, 1.49) who achieved complete or partial remission following treatment with cyclophosphamide (Level 2; no benefit demonstrated). The proportion of patients with renal function deterioration (one study, *n*=60; RR 1.59, 95% CI 0.87, 2.88) or who died (RR 1.07, 95% CI 0.19 to 5.95) did not differ between the two groups. However, the mean interval between onset of treatment and time to response was shorter with cyclophosphamide plus prednisolone compared with prednisolone alone [38.4 days (range 6-80 days) versus 95.5 days (range 61-129), P<0.05]. While no statistically significant benefits of treatment were found, the number of patients studied was small and a beneficial effect of oral cyclophosphamide in SRNS cannot be excluded. Prospective studies are necessary to examine whether therapy with oral cyclophosphamide and prednisolone might be effective in a subgroup of patients with SRNS.

A study with few subjects, which compared intravenous with oral cyclophosphamide in minimal change nephrotic syndrome found that all 7 patients in the IV group had remission, compared with one of four in the latter; differences between the groups were not significant (*n*=11; RR 0.09, 95% CI 0.01, 1.39) (Level 2)(28). A number of case series have examined the role of intravenous cyclophosphamide, administered monthly for six doses along with

tapering doses of alternate day prednisolone. Review of this data suggests that therapy results in remission in 40-65% patients(29).

High dose glucocorticoids and oral cyclophosphamide

A non-randomized trial on patients with FSGS, comparing 6-months to 18-months regimen of intravenous methylprednisolone, showed remission in 60% and 85.7% patients respectively (Level 3)(30).

Multiple case series, combining intravenous corticosteroids, oral alkylating agents and prednisolone, show remission in 30-70% cases (Level 4)(31). A significant proportion of patients receiving treatment with this intensive regimen are at risk for complications, including systemic infections, hypertension and electrolyte abnormalities. In view of the risks of steroid toxicity and the need for multiple hospitalizations, extended protocols have been replaced by abbreviated regimens utilizing fewer doses of intravenous corticosteroids ***(Table* II)**.

While the commonly used agent for intravenous therapy is methylprednisolone, a prospective study comparing intravenous dexamethasone to methylprednisolone showed no difference in terms of short term efficacy or adverse effects(32). Dexamethasone and methylprednisolone showed similar respective rates of complete remission (35.1%, 95% CI 22.9, 48.9; and 33.3%, 95% CI 14.6, 46.9) (Level 3). The median time to response was similar at 10 days and the most common side effect was hypertension.

Comparative studies

Two recently published randomized controlled trials have compared the relative efficacy of the therapies, discussed above. The first study compared treatment with intravenous cyclophosphamide and oral prednisolone with oral cyclophosphamide, intravenous dexamethasone and oral prednisolone in 49 patients with SRNS(33). At 6-months, the respective rates of complete remission were comparable at 53.8% and 47.8% (Level 2). Patients in both groups showed a high risk of infections; other adverse effects included cushingoid features, hypertension, hypokalemia, vomiting and reversible alopecia.

The Arbeitsgemeinschaft fur Padiatrische Nephrologie (APN) recently reported the results of a multicenter randomized controlled trial on therapy with oral cyclosporine (150 mg/m^2/day for 48 weeks) *versus* intravenous cyclophosphamide (500 mg/m^2; seven doses over 36 weeks) in 32 patients with initial SRNS(34). While the rates of complete remission were low in both groups, significantly more patients treated with cyclosporine (7/15; 46.7%) compared with cyclophosphamide (1/17; 5.9%) had partial remission (P=0.013) (Level 1). Similar findings were described in a retrospective analysis of 37 adult patients with SRNS (histology showing minimal change nephrotic syndrome, FSGS and mesangioproliferative glomerulonephritis) who received treatment with either intravenous cyclophosphamide or cyclosporine(35). At 12 months, the efficacy of the two treatment regimens was 40% and 85.7% respectively (Level 4). A recent report published in abstract form showed significantly higher remission rates with oral tacrolimus and prednisolone as compared to pulse intravenous cyclophosphamide and prednisolone in Chinese adults with idiopathic steroid-resistant minimal change disease(36). While results from these trials suggest that calcineurin inhibitors should be considered as the first line therapy for patents with initial steroid resistance, these findings need confirmation in a larger number of patients and with extended follow up.

The number of treatment regimes in practice is a testimony to a lack of consensus in managing these heterogeneous groups of patients. Most experience is derived from case series and anecdotal reports, rather than being based on prospective randomized controlled trials. The results of treatment using intravenous cyclophosphamide are promising but require confirmation. Treatment with pulse corticosteroids, oral cyclophosphamide and prednisolone is effective in a proportion of patients, but the high incidence of adverse effects limits its overall benefits. While benefits following treatment with calcineurin inhibitors (cyclosporine or tacrolimus) with alternate day prednisolone are increasingly evidence based, there is limited data on

long term renal function. The need for prolonged treatment and risk of nephrotoxicity limit the widespread use of these agents. Finally, a proportion of patients failing to respond to a particular regimen might show remission following treatment with alternative agents.

Other agents

Other agents that have been used anecdotally are vincristine, mycophenolate mofetil(37), plasmapheresis(38) and rituximab(39).

6. Dose and Duration of Treatment

Guidelines on dose and duration of treatment with various agents are summarized in ***Table* II**.

There is a lack of guidelines on duration of treatment with calcineurin inhibitors. Most patients who respond to treatment do so within 2-3 months of initiating therapy. Therapy should therefore be considered not effective and discontinued in patients showing persistent nephrotic range proteinuria beyond 6 months. On the other hand, those showing complete or partial remission should receive treatment for 2-3 years; the dose of calcineurin inhibitors is tapered to the lowest effective dose for another 1-2 years. While there are reports on successful switching of treatment from calcineurin inhibitors to mycophenolate mofetil, the long-term benefits of such a strategy need confirmation(40). A proportion of patients who respond to treatment with cyclosporine relapse on its discontinuation; reintroduction of therapy is not always effective.

7. Monitoring Response to Therapy

Patients should be monitored initially every month, then every 3-4 months. Response to therapy is categorized as complete or partial remission of proteinuria. *Complete remission* is defined as presence of trace or negative proteinuria (by dipstick test) or spot urine protein to creatinine ratio (Up/Uc) <0.2 mg/mg. Patients are considered to be in *partial remission* if they show 1-2+ proteinuria (or Up/Uc between 0.2-2), serum albumin >2.5 g/dL and no edema. *Non-response* is defined as 3-4+ proteinuria (or Up/Uc >2), serum albumin <2.5 g/dL or edema. While the aim of treatment is achievement of complete remission, the occurrence of partial remission is satisfactory(41).

8. Choice of Calcineurin Inhibitor and Monitoring of Therapy

(*a*) The aim of treatment with calcineurin inhibitors is achievement of complete or partial remission and long-term preservation of glomerular filtration rate to within 20% of pretreatment value.

(*b*) In view of similar efficacy and less cosmetic toxicity, treatment with tacrolimus is preferred to cyclosporine, especially in girls. A factor limiting the use of tacrolimus in very small children is the non-availability of drug in liquid form.

(*c*) Blood levels of cyclosporine or tacrolimus should be routinely measured once, 2-4 weeks following initiation of therapy. Subsequent determination of levels is necessary in case of suspected drug toxicity or if the patient is receiving medications that might affect levels of these agents. Trough (12-hr) blood levels of cyclosporine should be maintained at 80-120 ng/mL and tacrolimus at 5-8 ng/mL.

(*d*) Prolonged therapy with calcineurin inhibitors might be associated with histological features of nephrotoxicity, without elevation of blood levels of serum creatinine. Renal biopsy is therefore necessary following 2-3 years of therapy to evaluate for nephrotoxicity. Examination of renal histology is also informative in patients with declining renal function (serum creatinine >50% above baseline), which persists despite reduction in dose or discontinuation of treatment with these agents.

Rationale

There is limited evidence to support the superiority of tacrolimus over cyclosporine in patients with nephrotic syndrome. Results from case series and a randomized controlled trial suggest that tacrolimus is similar in efficacy to cyclosporine but with less cosmetic side effects and decreased incidence of dyslipidemia(25). Estimation of trough blood levels is recommended for monitoring. While it is proposed

that second hour measurement of cyclosporine (C2) may be a better predictor than trough levels (Co) in patients with nephrotic syndrome, the former targets are yet to be defined(42). Trough levels of tacrolimus have been used to monitor renal transplant recipients and a similar strategy can be applied to patients with nephrotic syndrome.

In view of a lack of correlation between serum creatinine and severity of histological changes, renal biopsies are recommended in patients receiving long term (>2 years) therapy with these agents(40, 43). Histological features suggesting acute nephrotoxicity include necrosis and hyaline deposition in individual myocytes, isometric vacuolation in tubular cells, endothelial vacuolation, afferent arteriolopathy and rarely thrombotic microangiopathy(10). Chronic changes comprise nodular hyalinosis, segmental or global glomerular sclerosis or striped interstitial fibrosis and tubular atrophy. Risk factors for nephrotoxicity include prolonged duration of cyclosporine therapy (3 mg/kg/day, for more than 24 months) and persistence of heavy proteinuria beyond 30 days. The presence of increasing fibrosis should lead to a careful review, since this might be the result of calcineurin inhibitor toxicity or progression of glomerular disease. The decision to lower or discontinue medication or add adjunctive therapy is based on clinical course and histological changes.

9. Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

(*a*) All patients with SRNS should receive treatment with angiotensin converting enzyme inhibitors (*e.g.,* enalapril, ramipril), initially at low dose; later the dose may be increased based on the severity of proteinuria (Grade C recommendation).

(*b*) These agents should be avoided if the estimated GFR is <30 ml/minute/1.73 m^2.

(*c*) Angiotensin receptor blockers (*e.g.,* losartan, valsartan) may be used in patients intolerant to angiotensin converting enzyme inhibitors, or as add-on therapy to achieve better antihypertensive and antiproteinuric effect (Grade D recommendation).

Rationale

There is evidence to support the antiproteinuric and renoprotective effects of angiotensin converting enzyme inhibitors. In a controlled trial, fosinopril significantly reduced proteinuria and alleviated renal tubular damage, but did not influence blood pressure in normotensive children with SRNS (Level 3)(44). In another randomized controlled study, the antiproteinuric effect was lower with enalapril given at low dose (0.2 mg/kg/d) (median reduction 34.8%; 95% CI -7.9, 76.6) compared to high dosage (0.6 mg/kg/d) (reduction 62.9%; 95% CI 40.6, 71.6) (Level 2)(45). Although studies in adults (Level 1)(46) recommend the combined use of angiotensin receptor blockers with angiotensin converting enzyme inhibitors to potentiate the antiproteinuric effects, there is paucity of data on the efficacy and safety of combined therapy in children.

10. Lipid Profile and Use of Medications

(*a*) Lipid profile [total cholesterol, low-density lipoproteins (LDL), very low-density lipoproteins (VLDL) and triglycerides (TG)] should be done annually in patients with SRNS (Grade D recommendation).

(*b*) The indications for starting therapy are an aberration in the lipid profile, which persists despite 3-6 months of specific treatment. Patients with blood levels of total cholesterol >200 mg/dL, LDL cholesterol >130 mg/dL and triglycerides >200 mg/dL require therapy. Although evidence based guidelines are lacking for children, therapy with HMG CoA reductase inhibitors (*e.g*. atorvastatin) is recommended.

Rationale

Persistent dyslipidemia is an important risk factor for the occurrence of cardiovascular disease. In view of limited pediatric data, the above targets are in accordance with those proposed for adults. The target LDL level has been set as <130 mg/dL as suggested by the Kidney Disease Outcome Quality Initiative (KDOQI) for adolescents with chronic kidney disease(47). There is evidence that control of dyslipidemia leads to control of proteinuria and regression of renal fat deposits (Level 4)(48). Long-

term studies are necessary to assess the beneficial effects of lipid lowering on renal histology and disease progression.

COMMENTS

Guidelines on the evaluation and management of patients with steroid sensitive nephrotic syndrome were revised recently(1). The treatment of patients with SRNS continues to be challenging. The above recommendations, based on expert opinion and published evidence, are intended to provide guidelines on management for these patients.

Consensus was achieved on the definition of SRNS and role of histopathology and genetic studies in these patients. There was agreement on the need for adequate supportive therapy comprising ACE inhibitors, antihypertensive and lipid lowering agents. The need for careful clinical and biochemical monitoring was emphasized.

However, a lack of controlled trials has resulted in absence of consensus on the specific management of these patients. The number of immunosuppressive regimens proposed is an acknowledgement of the lack of satisfactory treatment for these patients. Accepting this limitation, the Expert Group proposed that this statement provide details of therapeutic options along with grade of evidence on their efficacy, to enable an informed choice regarding treatment. It was recognized that the choice of treatment in these cases would be dictated by the experience and preference of the physician and the cost of therapy.

The Group underscored the need for randomized controlled trials to compare the efficacy and safety of various treatment regimens. In view of the clinical and histological heterogeneity of the condition, these prospective trials must be appropriately stratified and adequately powered to show clinically significant differences in outcome. Studies comparing mycophenolate mofetil and dexamethasone with cyclosporin alone (www.fsgstrial.org; NCT001135811) and intravenous cyclophosphamide with tacrolimus are underway. Further refinements and standardization of care for patients with steroid resistant nephrotic syndrome is likely to occur following results from these studies.

WRITING COMMITTEE

Ashima Gulati, Arvind Bagga, Sanjeev Gulati, KP Mehta and M Vijayakumar, on behalf of the Indian Society of Pediatric Nephrology.

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ANNEXURE–I

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