

Recent Concepts in Management of Nephrotic Syndrome

This is the third editorial on nephrotic syndrome in this journal in last 4 years. The previous 2 editorials were addressed to problems of frequent relapses(1) and review of literature on pathogenesis of nephrotic syndrome(2). In a recent article, analysis of 111 nephrotic children for appropriateness of therapy revealed inappropriate dosage and duration of prednisolone and cyclophosphamide therapy advised by 39.4% pediatricians, 59% internists and 80% general practitioners(3). Hence, this editorial aims to review conventional therapy and recent advances in management of nephrotic syndrome.

The main objectives in management of nephrotic syndrome are to induce quick remission to ensure freedom from edema and consequences of persistent nephrotic state such as hyperlipidemia, protein malnutrition, thromboembolic episodes, severe infections, *etc.* This is achieved by administration of oral prednisolone in a dosage of 2 mg/kg/day in 2-3 divided doses for the initial attack and is effective in ameliorating proteinuria in 93-98% of minimal change nephrotic syndrome and 75-77% of cases of idiopathic nephrotic syndrome which constitutes 90% of total nephrotic population in children. Hence, steroid responsive nephrotic syndrome and minimal change nephrotic syndrome are used interchangeably loosely.

A few minimal change nephrotic syndrome (MCNS) cases do not respond to steroids and a few steroid responders have histology other than MCNS like focal segmental glomerulosclerosis (FSGS) or membranoproliferative (MPGN) or mesangioproliferative glomerulonephritis (mesangial GN)- It is not clear whether MCNS and FSGS are two extremes of same disease with diffuse mesangial proliferative stage in between in those nephrotics who end in renal failure(4,6).

Though a single best plan is yet to be established, prednisolone therapy is the mainstay of the treatment and other drugs are used only if the patient does not respond to steroids or develops toxicity to steroids and needs alternative treatment(4-7). The second objective in those who respond to prednisolone is to prevent subsequent relapses. More than 50% of nephrotics relapse and in some series more than 40% of MCNS are frequent relapsers (more than 3 relapses in 1 year after initial response) or steroid dependent (relapse while tapering steroids or within 2 weeks of stopping). There is not a single clinical, biochemical, immunological or histological test to predict frequent relapsers, but occurrence of first relapse soon after the initial attack predicts frequent future relapses requiring multiple courses of prednisolone therapy which escalates the risk of steroid toxicity.

Recent data published by German Collaborative Study showed that when longer and more intensive course of prednisolone was administered for the initial attack (12 weeks instead of 8 weeks course of ISKDC regime), the subsequent relapse rate was reduced significantly, 18 months after stop-

ping the initial prednisolone therapy. It is obvious from this study that intensive initial treatment has a decisive influence on subsequent relapse and produced longer remission[^]). The longer course may result in higher incidence of steroid toxicity, hence the third issue of avoidance of steroid toxicity needs to be considered.

It is evident that side effects of steroids such as cushingoid appearance, hypertension, striae, osteoporosis, cataracts, growth retardation, infections and psychosocial disturbances adds to the morbidity and mortality of nephrotic syndrome. Although the Germany study showed no difference in the steroid toxicity with a 12 week course of prednisolone when compared with an 8 week course of ISKDC, a close monitoring of these patients with weekly BP, weight record and clinical evaluation for presence of covert infection is mandatory(4-7).

Regular follow up in Outpatient Department to detect relapse at early stage before edema starts (urine albumin 3+ on 3 consecutive days) is sufficient to start treatment. Recently, 24 hour urinary protein excretion is replaced by urine protein/creatinine ratio in early morning spot sample of urine. A ratio of 3.5 or more correlates with nephrotic range of proteinuria as observed in our institution (unpublished data) and confirmed by others(9,10).

The treatment of relapse should be less intensive and aimed at inducing urinary remission (protein free 3 consecutive early morning urine samples) followed by 4 weeks of alternate day prednisolone (1.5 mg/kg/48 h) as a single morning dose every other day. The intensity of treatment of relapse has no further influence on subsequent relapse rate. With this regime, at the end of 1 year of follow up, the steroid responsive

group will reveal itself as (i) frequent relapsers, (ii) steroid dependent, (iii) infrequent relapsers, or (iv) no relapse after the first attack. For this, strict definitions should be used otherwise future management cannot be planned.

The management of frequent relapses or steroid dependent nephrotic syndrome should be individualized and some of the options are as follows: (i) single low dose alternate day prednisolone treatment for 3-12 months to keep proteinuria under control; (ii) use of cytotoxic drugs like cyclophosphamide or chlorambucil for 8 weeks in frequent relapsers and for 12 weeks for steroid dependent cases keeping in mind short term and long term toxic effects on bone marrow, gonadal functions and oncogenic potentials. The cumulative dose of cyclophosphamide of 200 mg/kg and of chlorambucil of 10 mg/kg is considered safe. A single course of cytotoxic drugs when used with tapering dose of prednisolone results in long remissions of 24-30 months in 40-60% of children with MCNS. Steroid responsiveness is associated with better outcome even in the non minimal change nephrotics diagnosed by histologic criteria. Children who relapse soon after cyclophosphamide treatment pose major therapeutic problems for clinicians. Currently, two new drugs are used for their steroid sparing effects in steroid dependent/frequent relapsing/steroid and cyclophosphamide resistant nephrotic syndrome.

(i) Levamisole, a non-specific immunostimulant of T cell function in immunocompromised individuals, has been used in a multicentric double blind placebo controlled trial by the British Association for Pediatric Nephrology in 61 children with frequently relapsing and dependent corticosteroid sensitive nephrotic syndrome. The

dose used is 2.5 mg/kg on alternate day orally for 112 days along with tapering dose of prednisolone on alternate day for first 56 days of levamisole treatment. On follow up 14/31 on levamisole and 4/30 on placebo were in remission for more than 3 months and this result was statistically significant. Review of literature reveals 83 out of a total of 109 children and adults treated with levamisole showed complete or partial remission and steroid sparing effect. Hence, this study recommends levamisole in selected cases of frequent relapsing and steroid dependent steroid responsive nephrotic syndrome without severe nephrotic state, thromboembolic episodes, severe hypovolemic or shock. The side effects of this drug are minimal and cost benefit ratio favorable. Long term treatment free remissions are less with levamisole when compared to cytotoxic drugs(11,12). We have used this drug with good results in 50 frequent relapsers.

(ii) Cyclosporin A is a recent addition to the armamentarium of drugs for steroid dependent or steroid resistant nephrotic syndrome. It inhibits cell mediated immune responses by reducing production of interleukin-2 by activated T-lymphocytes. The dose recommended is 4-5 mg/kg/day for 6-12 months. It was highly effective in 87% steroid dependent nephrotic syndrome allowing cessation of prednisolone therapy, but most patients relapse while tapering Cyclosporin A. Thus, a steroid dependent patient is converted to cyclosporin dependent nephrotic syndrome. It is less effective in steroid resistant cases. Nephrotoxicity is a known side effect with cyclosporin hence serial renal biopsies and monitoring of drug levels are recommended during cyclosporin therapy(13,14). Its bioavailability is variable and cost is prohibitive for our country.

In Western countries like Germany and USA it is advocated in steroid dependent and steroid resistant nephrotic syndrome in children around pubertal age when cyclophosphamide and chlorambucil are contraindicated or in cases who do not respond to cyclophosphamide. Levamisole is not available for clinical use in many western countries. Cyclosporin A is not available or affordable in our country.

With this treatment, majority of MCNS will stop relapsing over 5-15 years, if they do not succumb to infections, steroid toxicity or unrelated conditions. Growth retardation is a major problem with prolonged steroid therapy or persistent nephrotic state.

The picture is not rosy for nephrotics with steroid resistant FSGS MPGN or diffuse mesangioproliferative GN as many relentlessly progress to end stage renal disease, hypertension or remain persistently in a nephrotic state(4-8).

In steroid non-responsive nephrotic syndrome kidney biopsy is mandatory to separate minimal lesions from non-minimal lesion nephrotic syndrome with the help of light, electron and immunofluorescent microscopy to decide about the choice of the drug and to predict long term prognosis(4-8).

It has been widely believed that hematuria, hypertension and reduced renal function at onset are bad prognostic signs and predict a lesion other than minimal change. But from ISKDC study it emerged that amongst patients with MCNS, diastolic hypertension was present in 13.5%, hematuria in 22.7% and elevated serum creatinine in 32.5%, but low C_3 levels in an occasional case. Hence if more than 2 atypical features or low serum C_3 is encountered in a nephrotic child, biopsy is indicated.

Desperate diseases are treated with desperate measures such as high dose IV pulse methylprednisolone, IV cyclophosphamide, or IV vincristin with controversial results(15,16). These new modalities of therapy should be used by pediatricians or pediatric nephrologists conversant with these modalities with a team approach as the treatment can be more hazardous than the disease.

In those patients who have not yet progressed to renal failure but exhibit nephrotic proteinuria, nephrotic syndrome or hypertension, use of ACE inhibitors, such as enalapril may be tried which reduces proteinuria, controls hypertension, reduces intraglomerular hypertension and hyperfiltration leading to glomerulosclerosis. We have used this drug in the dose of 0.15-0.3 mg/kg per day for 6-18 months in steroid resistant, cyclophosphamide resistant cases. Periodic monitoring with estimation of serum potassium, serum creatinine, blood count is necessary to evaluate the side effects(17).

Use of antiplatelet agents like dipyridamole and low dose aspirin with or without anticoagulants like warfarin can prevent progression of renal damage due to secondary mechanisms like platelet aggregation and intracapillary coagulopathy. The survival and reduction in nephrotic syndrome is better in MPGN and FSGS when these drugs are combined with cytotoxic drugs and prednisolone. In the non-minimal change nephrotic syndrome, collection of sufficient number of cases in each histopathologic category are difficult for randomized double blind controlled trials(15,16).

Clinical and chemical alterations in nephrotic syndrome are responsible for

common complications like severe life threatening infections, hypertension, hyperlipidemia and thromboembolic episodes during the course of the disease. One should look for these complications and treat them promptly to reduce the morbidity and mortality. Currently, high protein diet and repeated IV albumin infusions are thought to be responsible for hyperfiltration, so dietary protein intake to meet with requirement for growth is advised.

A small number of nephrotic children will need renal replacement therapy over a period of time. Renal transplant is not well established except in few centres in India. Transplant associated problems such as rejection, severe infections and recurrence of disease in transplanted kidney will be additional problems for future.

To conclude, the current trend in management of nephrotic syndrome is to treat the patients with intensive prednisolone therapy for the initial attack which is known to reduce the incidence of subsequent relapse in steroid responsive nephrotic syndrome. Frequent relapsers and steroid dependent should be treated with levamisole (if nephrotic state is not serious) or cyclophosphamide (if the patient is not pubertal). Cyclosporin can be used if the patient can afford 6-12 month treatment. Long remissions are induced by cytotoxic agents. Kidney biopsy is indicated in steroid non-responsive cases before a decision is made to use cyclophosphamide (or cyclosporin) for minimal lesion or focal segmental glomerulosclerosis. Long term steroid therapy with dipyridamole and low dose aspirin may be useful in membranoproliferative glomerulonephritis, whilst membranous glomerulonephropathy should be left alone. At any stage of the long course of this disease, serious infections, hypovolemic shock or

thromboembolic episodes can occur even in MCNS, whilst many non-minimal change nephrotics progress ultimately to end stage renal failure.

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