

## RECENT ADVANCES IN THE MANAGEMENT OF STEROID SENSITIVE IDIOPATHIC NEPHROTIC SYNDROME

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**Abstract :** Nephrotic syndrome is one of the commonest renal problems encountered in day to day nephrology practice. About 90% children with idiopathic nephrotic syndrome have 'minimal lesion' (MCD) on renal histological examination and respond promptly to corticosteroid therapy with remission of proteinuria. Hence children without any atypical features are not subjected to biopsy and managed as presumed MCD. The ability to achieve a remission is the single most important step that helps in preventing the onset of chronic renal failure and progression to end stage renal disease (ESRD). A small proportion of patients who are steroid resistant are also at risk for various complications and renal insufficiency. Prednisone continues to be the sheet anchor of therapy. Based on the response to steroid treatment these patients can be classified on follow up into steroid response categories. Alternative agents are recommended for children who are frequent relapsers, steroid dependent and steroid resistant. These children should be managed in consultation with a pediatric nephrologist. These children need to be monitored for side-effects of the drugs as well as complications of the disease.

### INTRODUCTION

Nephrotic syndrome is one of the commonest renal problems encountered in day to day nephrology practice. In children it has a reported incidence of 2 per 100,000 per year and a cumulative prevalence of 16 per 100,000<sup>1</sup>. Its prevalence is strongly influenced by ethnic factors and it is more common in blacks and Asians as compared to Caucasians.

About 90% children with idiopathic nephrotic syndrome have 'minimal lesion' on renal histological examination and respond promptly to corticosteroid therapy with remission of proteinuria. Approximately three-fourths of these patients have one or more relapses that require repeated treatment with corticosteroids. Such patients are at high risk of corticosteroid toxicity, frequent serious infections and other complications. A small proportion of patients who are steroid resistant are also at risk for similar complications and renal insufficiency.

### DEFINITION

Nephrotic syndrome is characterized by heavy proteinuria, hypoalbuminemia, which is usually associated with hyperlipidemia and edema. A urine albumin > 40 mg/m<sup>2</sup> per hr (on a 6-12 hr sample) in children is considered as nephrotic range proteinuria. Alternatively a protein/creatinine (mg/mg) ratio > 2 is indicative of nephrotic range proteinuria<sup>2</sup>. Hypoproteinemia is defined as serum albumin < 2.5 g/dl and hyperlipidemia is considered to be present when serum cholesterol > 200 mg/dl. In most instances, the finding of 3+/4+ proteinuria (on dipstick or boiling test) is adequate for defining nephrotic range proteinuria. Precise quantitative assessment of proteinuria is not essential and a 24-hr urine protein measurement is not required for the diagnosis of nephrotic syndrome.

### HISTOPATHOLOGY

In children minimal change disease (MCD) is the commonest cause followed closely by focal glomerulosclerosis (FSGS). In our study

the distribution of histopathological types was significantly different in different age groups. MCD was the commonest histopathological type in children younger than 8 years while MPGN was the commonest type between 8 -12 years and between 12-16 years<sup>3</sup>. Although MCD remains the commonest cause of idiopathic nephrotic syndrome in children, there have been reports of increasing prevalence of FSGS in both children and adult patients with idiopathic nephrotic syndrome<sup>3</sup>.

### GENETICS

There is no gene that has been localised for the vast majority of children with steroid responsive nephrotic syndrome.. Mutations of NPHS1, NPHS2, ACTN4 and WTI genes are responsible for severe forms of SRNS in childhood, progressing to end-stage renal failure<sup>3</sup>. Positional cloning has revealed defects in these 4 different genes as monogenic causes of SRNS in familial cases (Table 2)<sup>4</sup>. However no gene has been localised for the vast majority of children with steroid sensitive nephrotic syndrome. We evaluated the associations of the HLA class II associations in Indian children with INS and studied the correlation with the severity of the clinical course in terms of the steroid response categories. We observed that the allele DR-b1\*150X was a marker of steroid resistance.

### INVESTIGATIONS

Screening investigations to be carried out at the initial episode are:

- Urinalysis, complete blood count, blood levels of total protein, albumin, cholesterol, triglycerides, urea and creatinine
- If persistent microscopic or gross hematuria: blood levels of antistreptolysin O, C<sub>3</sub>
- Evaluate for underlying illness, if clinically suspected (*e.g.*, antinuclear antibodies for systemic lupus erythematosus)
- Urine culture, if urinary tract infections are clinically suspected
- X-ray chest, Mantoux test

- g) Hepatitis B surface antigen
- f) Kidney biopsy : All children with idiopathic nephrotic syndrome are managed as presumed MCD. Kidney biopsy is recommended in children in the following situations: (i) age of onset of NS less than 1 year (ii) no response to 4 weeks of standard prednisolone therapy i.e who are steroid resistant (iii) children with 2 or more unusual clinical features (hypertension, gross hematuria) and /or laboratory abnormalities (abnormal renal functions)<sup>4</sup>.

## MANAGEMENT

It has been demonstrated that the adequacy of initial therapy effects the subsequent course of illness<sup>5</sup>. Moreover the ability to achieve a remission is the single most important step that helps in preventing the onset of chronic renal failure and progression to end stage renal disease (ESRD), especially in case of Focal Segmental Glomerulosclerosis (FSGS) and Membranoproliferative Glomerulonephritis (MPGN). Thus the economic benefits of timely and appropriate management of patients with NS are enormous. This is especially true for developing countries like ours where treatment for ESRD is neither easily available nor affordable for the vast majority. Appropriate therapy helps in minimizing side effects besides decreasing referrals to tertiary care centers.

### **Prednisone**

MCD is the commonest cause of nephrotic syndrome in children. Children without any atypical features are not subjected to biopsy and managed as presumed MCD.

It is believed that MCD, mesangial proliferative glomerulonephritis (MesPGN) and focal segmental glomerulosclerosis (FSGS) are different ends of the same spectrum of disease. All these entities are treated by a common protocol for steroids and cyclophosphamide<sup>2</sup>.

#### **(a) Treatment of Initial Episode**

Adequate treatment of the episode is extremely important. Current evidence suggests that treatment of the initial episode influences the subsequent course of the illness<sup>2</sup>. The intensity of initial treatment may decrease the rate of subsequent relapses. It is necessary to treat infections before starting treatment with prednisolone. The management consists of 6 weeks daily prednisolone therapy in doses of 60mg/m<sup>2</sup>/day followed by 6 weeks of 40mg/m<sup>2</sup>/alternate day for the next 6 weeks<sup>6</sup>. The prednisone is then tapered over the next 2-3 months (not exceeding a total duration of 7 months). We have shown that slow tapering of prednisone results in a lower relapse rate as compared to abrupt stoppage, after the initial 12 weeks in the management of first episode of nephrotic syndrome<sup>7</sup>.

#### **(b) Treatment of Relapse**

The patient should be examined for infections, which are treated before initiating corticosteroid therapy. Prednisolone is administered in a dose of 2 mg/kg/day (single or two divided doses) until urine protein is trace or nil for 3 consecutive days, or for two weeks. Subsequently, prednisolone is given in a dose of 1.5 mg/kg on alternate days for 4 weeks, and then discontinued<sup>8</sup>. The usual duration of treatment for a relapse is thus 5-6 weeks. Prolongation of therapy is not necessary for patients with infrequent relapses (see below). In case the patient is not in remission despite two weeks

treatment with daily prednisolone, such treatment might be extended for two more weeks.

Based on the response to steroid treatment these patients can be classified on follow up into steroid response categories (as per ISKDC guidelines); infrequent relapsers (IFR) children with less than 2 relapses over 6 months, frequent relapsers (FR) children with 2 or more relapses over 6 months, steroid dependent (SD) - children with 2 consecutive relapses within 2 weeks of stoppage or tapering of steroid, initial non responders (INR) - children with no response to steroid therapy for 4 weeks and subsequent non responders (SNR) - children who responded to steroid initially but secondarily become steroid resistant. Of the 116 children of idiopathic nephrotic syndrome with follow up of more than 6 months in our series who could be categorized into a definitive category, infrequent relapsers constituted the majority (37.9%) followed by FR (21.6%), SD (18.1%), INR (17.3%) and SNR (5.1%)<sup>9</sup>.

### **Alternative agents**

For patients who are FR and SD, a variety of therapeutic modalities have been tried<sup>5-10</sup>.

- (A) **Cyclophosphamide** Treatment with cyclophosphamide may be considered in patients showing, i) significant steroid toxicity, ii) severe relapses with hypovolemia or thrombosis and iii) poor compliance or follow up. Cyclophosphamide (2mg/kg/d) and chlorambucil (0.5mg/kg) have an established role in prolonging remission in FR (given for 8 weeks) and SD (given for 12 weeks). Intravenous pulse cyclophosphamide in monthly doses of 500mg/m<sup>2</sup> is an alternative modality. In our study the overall response rate of 49% was comparable to that reported previously. Furthermore the response was observed at 40% lesser cumulative dose<sup>11</sup>. An additional advantage of the IVCP regimen was a better tolerance and hence a better compliance. We have found this modality to be efficacious in steroid resistant MCD and FSGS.
- (B) **Levamisole**: Levamisole has a weak steroid sparing effect and is useful in milder cases. The other alternatives available include Levamisole (2.5mg/kg/alternate day for 3 months). A longer duration of therapy of 6-18 months concurrent with alternate day prednisolone has been found to be reducing the relapse rate of SDNS<sup>6</sup>.
- (C) **Long term low dose prednisolone** in a dose of 0.25mg/kg/day for 18 months have been found to be beneficial in FR group.
- (D) **Cyclosporine**: This given in a daily dose of 5mg/kg is another therapeutic alternative. Cyclosporine is recommended for patients that continue to relapse despite a course of cyclophosphamide. It has a response of 80%. However it has a number of side-effects including hirsutism, gingival hypertrophy, besides nephrotoxicity. However it is advisable to monitor serum levels of these agents periodically and perform kidney biopsies annually if therapy is prolonged beyond a year. In addition these patients have a potential of becoming cyclosporine dependent.
- (E) **Tacrolimus** Tacrolimus is a calcineurin inhibitor that is more potent in cytokine suppression than cyclosporine. The main mechanism of action of tacrolimus is through the inhibition

of IL-2 dependent T-cell activation, a process occurring during the early phase of T-cell activation Tacrolimus is newer calcineurin inhibitor that has far less cosmetic side-effects. It has been found to be an efficacious agent in steroid resistant nephrotic syndrome and can be used in children who are frequent relapsers or steroid dependent who continue to relapse despite other therapies. The advantages of using these drugs should be balanced against their potential nephrotoxicity. Hence it is advisable to monitor serum levels of these agents periodically and perform kidney biopsies annually if therapy is prolonged beyond a year. Most SD children can be maintained in remission with cyclosporine or tacrolimus, but relapses usually occur when the therapy is stopped.

- (F) **Mycophenolate Mofetil (MMF)** is another newer agent that has been used in children with FRNS and SDNS. It is a prodrug of mycophenolic acid (MPA) which is formed by hydrolysis. MPA is a potent, selective, uncompetitive, and reversible inhibitor of inosine monophosphate dehydrogenase. The latter is an enzyme required for de novo purine synthesis. MPA inhibits B and T-lymphocyte proliferation, as these cells are critically dependant upon de novo purine synthesis for their proliferation whereas other cell types can utilize salvage pathways for purine synthesis. It has response rate of 25% in children with FRNS whereas in SDNS these children relapse after stoppage of therapy. It is a useful agent in children who become cyclosporine dependent, as CsA which is potentially nephrotoxic, can be weaned off under cover of MMF. Pefloxacin, an antibiotic with immunomodulatory effect can also be used in dose of 25mg/kg/day both in relapsing and resistant cases<sup>12</sup>. A metanalysis revealed that cyclophosphamide was the only agent whose effect persisted beyond the stoppage of therapy.
- (G) **Rituxumab** is an anti CD 20 monoclonal antibody that has been found to be very effective in these children with steroid dependent nephrotic syndrome. The exact mechanism of action of rituxumab in idiopathic NS is not known. The following effects have been found that may possibly explain its efficacy viz. down regulation of  $\alpha$ -cell receptors, shedding of CD 23 cells and apoptosis of CD20<sup>+</sup> cells, general regulatory effects on the cell cycle, and increases in MHC II and adhesion molecules LFA-1 and LFA-3 (lymphocyte function – associated antigen). It has been found that 2 doses given at an interval of 2 weeks can lead to sustained remission in these children.

### Supportive care

This forms an important aspect of managing children with nephrotic syndrome.

**Diet** A balanced diet adequate in protein and calories is recommended. The child should receive 1.5-2 g/kg of proteins. Patients with persistent proteinuria are prone to malnutrition and should receive 2-2.5 g/kg of protein daily<sup>6</sup>. Not more than 30% calories should be derived from fat and saturated fats avoided. Carbohydrates are best given in complex forms (starch and maltodextrin). Salt restriction is not necessary in most patients with steroid responsive nephrotic syndrome. A modest reduction (1-2 g per day) is advised in the presence of marked edema. Salt should not be added to salads and fruits; snacks containing high salt are avoided during these periods.

Corticosteroids stimulate the appetite, and advice should be given about ensuring physical activity and preventing excessive weight gain.

**Edema control.** This is an integral part of supportive care. Treatment with corticosteroids usually leads to diuresis within 48-72 hours. Diuretics are thus avoided unless edema is significant and should not be used in children with diarrhea, vomiting or hypovolemia. In moderate or persistent edema, frusemide is administered in a dose of 1-3 mg/kg per day. Additional treatment with potassium sparing diuretics (e.g., spironolactone) is not required if frusemide is used in this dose for less than one week. Patients requiring higher doses and prolonged duration of treatment with frusemide should receive amiloride or spironolactone (dose 2-4 mg/kg daily). Blood pressure should be monitored frequently. A gradual reduction of edema, over one week, is preferred<sup>6</sup>. Edema not responding to the above therapy should be managed in a hospital under close supervision. For refractory edema, a combination of diuretics and albumin infusion may be used. Infusion of albumin is followed by administration of frusemide in a dose of 1-2 mg/kg intravenously. Though infusion of albumin results in increased urine output, the effect is not sustained, especially in patients with steroid resistant nephrotic syndrome. Albumin infusions are usually administered on alternate days to allow fluid shifts to occur and prevent fluid overload. Patients receiving albumin should be carefully observed for respiratory distress and congestive heart failure. Refractory ascites interfering with respiration or associated with breaks in the skin may be removed by repeated tapping.

## COMPLICATIONS

### Infections

These remain an important complication of children with nephrotic syndrome, especially in developing countries like ours. Besides being the commonest cause of mortality, infections result in significant morbidity. They may also be responsible for non-response to steroids or induce a relapse in a child who has already attained remission. A knowledge of the spectrum of infections is important not only from the therapeutic point of view, but also for planning preventive strategies like pneumococcal vaccination and prophylactic antibiotics. Evaluation of all patients both admitted as well as those being followed up on an outpatient basis reveals that urinary tract infections were the commonest (13.7%), followed by pulmonary tuberculosis (10.4%), peritonitis (9.1%), skin infections (5.2%), recurrent upper respiratory infections (5.2%), lower respiratory tract infections (3.9%) and pyomeningitis (0.6%)<sup>12</sup>.

### Thrombotic Complications

Children with nephrotic syndrome are at risk for venous and rarely, arterial thrombosis. Reduced intravascular volume and other abnormalities predispose to thrombus formation. Diuretics should be used judiciously. Puncture of deep vessels should not be done. Renal vein thrombosis is suspected in a patient with oligoanuria, hematuria or flank pain especially following an episode of dehydration. Ultrasound examination of the abdomen might show large kidneys and thrombi in renal veins. Femoral arterial thrombosis may occasionally occur. Deep vein thrombosis of calf veins is less common in children but may lead to pulmonary embolism. Saggital sinus and cortical venous thrombosis may follow episodes of diarrhea and present with convulsions, vomiting, altered sensorium and neurological deficits. Doppler studies and cranial CT scan are useful

in confirming the diagnosis. Patients with thrombotic complications require urgent treatment under the supervision of a specialist. The treatment is supportive and consists of early mobilization, treatment of sepsis, prompt treatment of dehydration and cautious use of anticoagulants.

#### **Hypertension**

This may be noted at the onset of nephrotic syndrome or occur due to steroid toxicity. Therapy may be initiated with ACE inhibitors, calcium channel or beta adrenergic blockers.

#### **Hypovolemia**

This complication can occur due to unsupervised use of diuretics especially if accompanied by septicemia, diarrhea or vomiting. The diagnosis is suggested by the presence of hypotension, tachycardia, cold extremities and poor capillary refill. Blood levels of urea and uric acid are elevated. Some children might complain of moderate to severe abdominal pain. A rapid infusion of normal saline or plasma in a dose of 15-20 ml/kg, or albumin 1g/kg is essential. The blood pressure should be monitored carefully. Albumin should be used with caution if the child is hypertensive because of the risk of pulmonary edema. Once adequate hydration is achieved, but the child remains oliguric, a single dose of frusemide (1-2 mg/kg intravenously) may be given. In case no urine is passed despite these measures, the diagnosis of acute renal failure is suspected.

#### **Metabolic bone disease**

There is recent evidence that children with idiopathic nephrotic syndrome (INS) are at risk for metabolic bone disease (MBD) due to biochemical derangements caused by the renal disease, as well as steroid therapy. The risk is greater in those who receive higher doses of steroids (FR, SD and INR). Prophylactic calcium and vitamin D supplements help in minimizing the risk of low bone density in these children.

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## LITERATURE REVIEW

### ***Laparoscopic Kidney retrieval in donor with an extended criterion: Assessing the safety and outcome***

Arvind R. Ganpule, Mahesh R. Desai and Shashikant Mishra. *Ann Natl Acad. Med Sci (India)*, 44 (3): 165-175, 2008.

There is an ever increasing need to accommodate deserving transplant recipients coupled with the relative paucity of active cadaver transplant programme. The terms extended donor criterion and marginal donors are confusing, they may simply mean usage of suboptimal quality cadaver renal grafts, non heart beating donors and living donors with some acceptable medical risks. We have identified old age, hypertension, diabetes mellitus, obesity, and anatomical anomalies such as multiple vessels and double ureters as extended indications for laparoscopic donor nephrectomy (LDN) as we feel these donors require consideration surgical/medical expertise and acumen to attain good results.

The term marginal kidney donor/extended donor criterion is not clearly defined. In the article we assess the safety and outcome of laparoscopic donor nephrectomy (LDN) in donors with an extended criterion. A retrospective analysis of our database was done to assess the outcome of extended donor. Analysis was done between normal donors (group 1) and donors with extended criterion (group 2). The parameters analyzed were pre and post operative serum creatinine in donors and recipients, serum creatinine at day 1, 7, 30 days and 1 year in recipients, operative time, warm ischemia time, analgesia requirement in donors and impact of extended criteria on recipient outcome. Group I and II recipients had comparable creatinine at 1 year. Donors with BMI more than 30 kg/m<sup>2</sup> required extended hospital stay. Recipient's creatinine, with single vs. multiple vessel donors was comparable at 1 year. Donors with urolithiasis had good recipient outcome. The donor creatinine was comparable in extended and non extended indication donors. In our study, LDN was found to be safe, feasible and efficacious in donors with extended indications such as old age, BMI more than 30, multiple vessels and anatomical anomalies. Recipient outcome for donors with normal vs. extended criteria was comparable at one year follow up. All donors with extended criterion had normal post operative creatinine levels at two years follow up; long term follow up would be of interest.