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## *Personal Practice*

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### Management of Nephrotic Syndrome

#### B. Rath

Nephrotic syndrome (NS), the most common chronic renal disorder of children, is characterized by massive proteinuria (urinary protein  $\geq 40$  mg/m<sup>2</sup>/h in an overnight specimen or  $>1$  g/m<sup>2</sup>/day); hypoalbuminemia (serum albumin  $\leq 2.5$  g/dl), edema and often hyperlipidemia. Collection of 24 h urine being difficult in children, the urinary protein to creatinine ratio can be used as an alternative as it correlates well with the magnitude of proteinuria; a ratio of  $>2$  (mg/mg) being considered in the nephrotic range(1). The terminology used in subsequent discussion is summarized in *Table I*.

The important causes of NS in children are shown in *Fig. 1*. Minimal change nephrotic syndrome (MCNS), the most commonly encountered entity accounts for 75-80% of cases. Membrano-proliferative glomerulonephritis is rare under 6 years of age. Systemic lupus erythematosus presenting as NS is seen in adolescent girls while congenital NS is rare.

#### Investigations

The aim is to: (a) establish the diagnosis of NS, (b) exclude glomerulonephritis that

could present as NS, (c) exclude associated infections such as urinary tract infections, tuberculosis, peritonitis, *etc.*, and (d) assess body homeostasis and renal function. Urinalysis, urine culture, 24- h urinary protein or urinary protein creatinine ratio, total serum protein, albumin/globulin ratio, serum cholesterol, lipid profile, electrolytes, creatinine, urea, Mantoux test and X-ray chest are the usual investigations required. C3 level is indicated to rule out membranoproliferative/lupus/post-streptococcal glomerulo-nephritis.

**TABLE I**— *Summary of Terminology.*

Urinary remission	Urinary albumin nil or trace for 3 consecutive days
Steroid response	Disappearance of proteinuria and clinical and biochemical features of nephrotic syndrome with steroid therapy
Relapse	Urinary protein 2+ or more on 3 separate days within 7 days associated with edema
Infrequent relapse	Less than two relapses within 6 months of initial steroid therapy
Frequent relapse	Two or more relapses within 6 months of initial steroid therapy
Steroid dependence	Two consecutive relapses occurring during corticosteroid therapy or within 14 days of its cessation
Steroid resistance	Failure to achieve response despite 4 weeks of steroid therapy.

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### Treatment

The aim of treatment is to ensure a lifestyle as normal as possible. Diet, activity, control of edema and blood pressure are supportive whereas corticosteroids are specific therapy for NS.

#### Diet

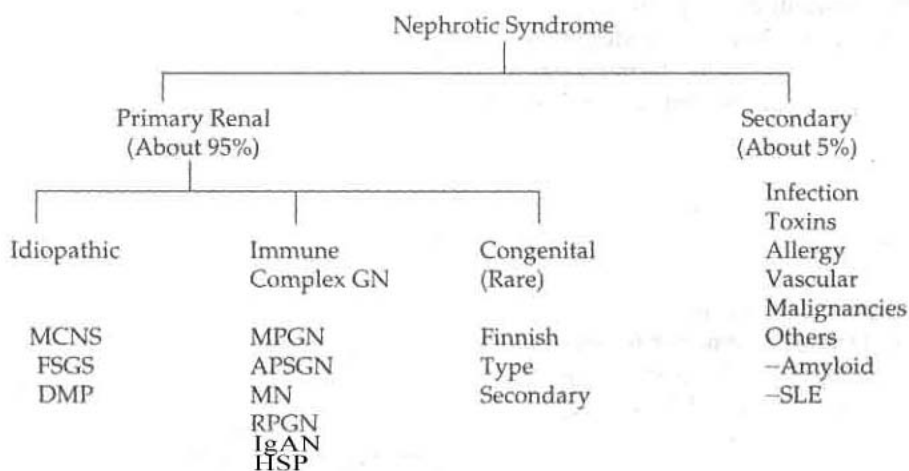
A diet having adequate calories and normal amount of protein for age is advised. Extra dietary protein neither increases serum albumin level nor body albumin pool; it gets excreted through urine. In adult nephrotics a diet containing 0.8 g of protein/kg was superior to another having 1.6 g of protein/kg(2).

Presence of edema warrants salt

restricted diet. Children who find such diet unpalatable and eat poorly may be allowed some amount of salt along with diuretics. Salt and fluid restriction are mandatory for severely edematous patients. Potassium supplementation is given if hypokalemia is likely.

The hyperlipidemia in nephrotics might predispose to atherosclerosis, glomerulosclerosis, increased platelet aggregation and hypercoagulability. In most steroid responders serum lipid profile comes back towards normal during remission(3). They need dietary fat restriction during the attack. However, hyperlipidemia might be a significant problem in steroid resistant cases and frequently relapsing children who should have frequent serum lipid

Fig. 1. Causes of Nephrotic Syndrome



- MCNS = Minimal change nephrotic syndrome
- FSGS = Focal segmental glomerulosclerosis
- DMP = Diffuse mesangial proliferation
- MPGN = Membrano proliferative glomerulonephritis
- APSGN = Acute post-streptococcal glomerulonephritis
- MN = Membranous nephropathy
- RPGN = Rapidly progressive glomerulonephritis
- IgAN = IgA nephropathy
- HSP = Henoch-Schonlein purpura
- SLE = Systemic lupus erythematosus

profile checkup. Persistent abnormality warrants dietary fat restriction, *i.e.*, dietary fat should provide <30% calories, should contain half of polyunsaturated fat and daily cholesterol intake should be <250 mg(4). Recent studies(5,6) have demonstrated effectiveness of lovastatin and simvastatin, respectively in reducing serum cholesterol in patients with nephrotic syndrome. Calcium, vitamin D and zinc supplementation should be given in patients with persistent nephrotic syndrome

#### *Activity*

Bed rest need not be enforced, activity should be encouraged(7).

#### *Measures to Control Edema*

Edema predisposes to intertriginous/skin infections and ascites to primary peritonitis. Tense ascites causes respiratory embarrassment and massive scrotal swelling. Mild edema may be tolerated. Moderate-severe edema warrants salt restricted diet and diuretics. Furosemide 1-2 mg/kg/day (upto 3-7 mg/kg/day in presence of severe edema and ascites) along with spironolactone 2-3 mg/kg/day in 3 divided doses are most commonly used diuretics. Metolazone, a powerful diuretic is not commonly available. Control of edema is difficult with usual doses of commonly used diuretics if serum albumin is less than 1.5 g/dl(8). Severe edema refractory to diuretics calls for salt poor albumin infusion 0.5-1 g/kg over 1-2 h followed by intravenous furosemide that may be repeated daily or twice daily if need arises(7). In absence of salt poor albumin, concentrated human albumin preparations can be used. Older children with severe edema and massive ascites who fail to respond to the above measures can be subjected to water immersion upto the neck (under supervision of course!) in a thermoneutral bath

upto 3 hours that causes natriuresis and diuresis(9).

The measures to control edema are not without hazards. Salt restriction may cause poor appetite; diuretics may cause hypovolemia, shock, hypokalemia, alkalosis and azotemia. Albumin is expensive, effect of intravenous administration is short lasting and occasionally may cause hypertension and congestive cardiac failure.

Clark and Barratt(7) advise routine use of prophylactic oral penicillin 125-250 mg twice daily till edema resolves.

#### *Hypertension*

Mild hypertension noticed in 25-30% cases of NS, may be secondary to hypervolemia or to vasoconstrictor response to hypovolemia (reactive hypertension in which case the core-periphery temperature difference exceeds 2° C) or prior corticosteroid administration. Reactive hypertension responds to volume expansion whereas hypertension due to other causes can be treated with atenolol (0.5-1.0 mg/kg once daily) and/or nifedipine (0.25-2.0 mg/kg/day in 3 divided doses).

#### *Infections*

Urinary tract infection, peritonitis, skin and respiratory tract infections, tuberculosis, septicemia and meningitis are associated with NS and may occasionally be asymptomatic(10). Infections may precipitate a relapse. Response to steroid therapy is unsatisfactory unless associated infections are controlled. Urine culture is mandatory each time before starting steroids. A peritoneal tap should be performed at the slightest suspicion of peritonitis. Obvious infections should be treated with appropriate antibiotics. Patients receiving rifampicin for tuberculosis may show reduced serum corticosteroid levels and apparent non-responsiveness to

standard therapy(11) or take longer time to enter into remission.

### Specific therapy

Treatment with corticosteroids (prednisone or prednisolone) is instituted once infection(s) is/are controlled. Only prednisolone is available in our country.

### Treatment of Initial Attack

Various treatment protocols for initial therapy are given in *Table 11(12-16)*. The standard therapy mentioned is a modified version(12) of the International Study for Kidney Disease in Children protocol. In the standard regimen, prednisolone is administered in doses of 60 mg/m<sup>2</sup>/24 h (2 mg/kg of expected weight/day in 3 divided doses) for 4 weeks followed by 40 mg/m<sup>2</sup>

(1.5 mg/kg) given on alternate morning for additional 4 weeks and then stopped abruptly. As is obvious from *Table II*, there is no agreement regarding the duration of the divided dose or alternate day therapy of prednisolone. Better long term outcome has been claimed with more intense initial regimen(13). Whichever regimen is chosen, nearly 80% patients enter into urinary remission in about two weeks. Antacids are given with steroids to prevent gastric irritation. Unfortunately in our country, steroids are often prescribed either in inadequate doses or for shorter periods(17). During therapy weight, urinary output, proteinuria and blood pressure should be monitored. Salt restriction should be terminated when edema resolves. Corticosteroid side effects such as cushingoid features, hyper-

TABLE II—Predniso(lo)ne Regimen for Initial Attack of Nephrotic Syndrome

Reference	Duration of therapy		Stopping	Remarks
	Initial(1)	Followed up(2)		
German Collaborative(APN)(12) Srivastava(4)	4 weeks	4 weeks	Abrupt	Standard regimen; practiced by most nephrologists
Ghai(13)	4 weeks	4 weeks	Over 12 weeks Decrease 0.5 mg/kg/ every 4 wks.	
Clark(7) Watson(14)	Till urine is protein free for 3 days	4 weeks	Abrupt	
Bernstein(15)	Till urine is protein free for 5 days	3-6 months	Abrupt	
German Collaborative Study (APN)(16)	6 weeks	6 weeks	Abrupt	Relapses significantly lower compared to standard regimen; superiority under scrutiny

Initial(1): Predniso(lo)ne 60 mg/m<sup>2</sup>/day or 2 mg/kg/day in 3 divided doses.

Followed up(2): Predniso(lo)ne 40 mg/m<sup>2</sup>/48 h single dose alternate morning.

tension, mood changes, *etc.* should be looked for.

Diarrhea, vomiting, sepsis, injudicious diuretic therapy *etc.*, cause hypovolemia which may lead to shock and thrombosis. Significant fluid loss should be replaced by intravenous fluids promptly. Thrombosis is an uncommon but important complication. It can be avoided by early recognition and treatment of hypovolemia, avoiding femoral venepuncture, hyperlipidemic state and ensuring mobility. If it occurs, it can be managed with a bolus dose of heparin 100 u/kg followed by 25 u/kg/h intravenously initially. Warfarin should be added to maintain prothrombin time 2-3 times the control for 2 months(18).

Zoster immunoglobulin should be given to any child of NS who is exposed to varicella while on high dose prednisolone or alkylating agent therapy. Treatment with oral acyclovir should be instituted immediately if a patient of NS develops varicella during or within 3 months of cessation of corticosteroid or other immunosuppressive therapy(7).

#### *Subsequent Course*

The subsequent course of NS is highly unpredictable. The patient could be a non-relapser (a small proportion), infrequent relapser (about 30%), frequent relapser (about 40%) or steroid dependent(4). However, there are no markers to predict the subsequent behavior of an individual case except the number of relapses in the first 6 months following initial therapy(19).

Relapses may follow respiratory, urinary tract or any other infection (symptomatic or asymptomatic) or may be spontaneous. As many as 25% of the cases may enter spontaneous remission(20). Hence, it is wise to wait for 5 to 10 days before starting steroids. Edema should be controlled in

this period. Treatment should be started immediately without waiting only if there is a past history of complicated severe NS(7).

Although pathophysiology of the initial attack and relapse is the same, multicentric studies have shown that-intensification of relapse treatment has little effect on the subsequent course(21). First two relapses as well as subsequent infrequent relapses can be treated as in initial attack(7,15).

#### **Frequent Relapsing Nephrotic Syndrome (FRNS)**

Such cases usually have associated hypocortisolism(22) and need steroids for longer periods to allow adrenals to recover. Prednisolone, 2 mg/kg/day, is given in 3 divided doses till urinary remission followed by 40 mg/m<sup>2</sup>/48 h for 3-6 months and then stopped abruptly(15) or continued in lower doses (0.5-0.75 mg/kg) for one year(4,13) or even longer. These patients are prone to steroid toxicity such as cushingoid features, hypertension, short stature, osteoporosis, posterior subcapsular cataract, aseptic necrosis of femoral head and steroid induced diabetes and need monitoring for the above complications. Unacceptable steroid toxicity and/or poor growth warrant use of alternative drugs(7).

Among the alternative drugs, levamisole being the least toxic should be tried first(23) in doses of 2.5 mg/kg twice weekly upto one year. It is effective in inducing permanent remission in at least half of FRNS. It might cause granulocytopenia and rash, hence blood counts should be done fortnightly.

The alkylating agents are more potent. They reduce the recurrence rate and prolong the duration of remission and sometimes may induce permanent remission. These drugs are most effective in steroid

responsive frequent relapsing cases, less effective in steroid dependent cases and least in steroid resistant cases specially if the underlying histopathology is other than minimal change(24). Previous response to steroids is a good predictor of efficacy of alkylating agents(24). Results are better if alkylating drugs are given alongwith prednisolone. Their side effects must be discussed with the parents and parental consent obtained before starting such drugs. Renal biopsy is not mandatory before starting alkylating agents for frequent relapsers. Occasionally patients with late steroid resistance may show steroid responsiveness following alkylating agent therapy (25).

Cyclophosphamide, 2.5-3.0 mg/kg/day, for 8-12 weeks (cumulative dose  $\leq 200$  mg/kg) is administered as a single dose in the morning. Good urine flow should be ensured to prevent hemorrhagic cystitis. Though cyclophosphamide and chlorambucil (0.1 to 0.2 mg/kg/day for 8-12 weeks; cumulative dose  $\leq 8$  mg/kg) are considered equipotent, the former is more commonly used as side effects are less serious. Both drugs can cause neutropenia and should be stopped once total leukocyte count is  $< 5000/\text{cu mm}$ , to be resumed once counts are back to normal(15). Irreversible gonadal toxicity is a worrying side effect. However, in prepubertal patients, the chances of permanent gonadal toxicity is comparatively lower(7).

### **Steroid Dependent NS (SDNS)**

Assessment of the minimum prednisolone, required to keep the child protein free, by slow tapering is important. The duration of prednisolone therapy is not well defined but usually extends upto several years. Prednisolone requirement exceeding 0.5 mg/kg/day in school age children or 1 mg/kg/day in toddlers is an

indication for considering alternative drugs(7) which induce complete or partial remission in some cases although the response is less satisfactory compared to FRNS(24).

### **Steroid Resistant NS**

Initially steroid resistant patients pose special problems. It is reassuring that majority of such cases under the age of 6 years have minimal change and are likely to respond ultimately(8) after variable period of time. The response in children above 6 years of age is poor as the underlying pathology is usually other than minimal change(8). Renal biopsy is mandatory in these patients before deciding the further course of action(7).

### **Other Modalities of Therapy**

#### *Pulse methylprednisolone/dexamethasone*

The most common drug advised in patients with steroid resistant NS is pulse methylprednisolone(4) infused intravenously in a dose of 20-30 mg/kg, on alternate days, 3-6 doses to be followed by tapering doses of prednisolone for 4-6 months starting with 1.5-2.0 mg/kg/48 h administered in a single dose. High dose steroids may cause hypertension in 10-20% of cases, often requiring antihypertensive therapy. Dyselectrolytemia that may cause cardiac dysarrhythmias is another complication. Some workers(26) have advocated the use of pulse dexamethasone therapy in equivalent doses as it is equipotent but much less expensive. Recently, methylprednisolone has been used in steroid resistant NS in doses of 30 mg/kg every alternate day for 2 weeks, weekly for next 8 weeks, alternate weekly between 11-18-weeks, once monthly between 19-52 weeks and finally once every other month between 53-78 weeks. Oral prednisolone in a dose of 2 mg/kg was administered on

alternate days after 10-18 weeks and slowly tapered over the next 60 weeks. The authors have claimed 66% complete remission and 9% partial remission using high dose methylprednisolone for prolonged period. However, others report less satisfactory results(27).

#### *Cyclosporin*

Cyclosporin is effective in frequent relapsing, steroid dependent and steroid resistant NS. Unfortunately, in steroid dependent cases proteinuria often recurs when the drug is discontinued, *i.e.*, it converts the patient from steroid to cyclosporin dependent. It is less potent in inducing remission compared to chlorambucil(28). Being very expensive, its use is limited in our country. However, the drug is preferred to alkylating agents when the patient is pubertal. Given in doses of 150-200 mg/m<sup>2</sup>/day alongwith low dose prednisolone (30 mg/m<sup>2</sup>/day) for 4 weeks followed by same dose alternate day for 5 months, it induced complete remission in 48% in minimal change and 30% in focal segmental glomerulosclerosis(29).

There are some reports claiming efficacy of nitrogen mustard (mechlorethamine 0.1 mg/kg/day for 4 consecutive days)(3) vincristine(31) and intravenous cyclophosphamide(32) in patients with steroid resistant NS. Angiotensin II converting enzyme inhibitors (*e.g.*, captopril, enalapril, lisinopril) reduce proteinuria and are thus helpful in non-responders(24). Few patients unresponsive to standard therapy might respond to hypoallergenic diet(33).

#### **Immunization in NS**

Any patient on high dose prednisolone for more than 1 week should not receive live vaccines till he is off the drug for more than 6-12 weeks. Oral polio vaccine should

not be administered even to siblings or close contacts when the patient is on high dose prednisolone or alkylating agent. Live vaccines can be given while the patient is on low dose alternate day prednisolone therapy. Killed vaccines/toxoids can be given at anytime(7). If the parents can afford, 14 or 23 valent pneumococcal vaccine should be given during remission when the patient is off prednisolone for more than 3 months(4). BCG being a live vaccine should be avoided as a diagnostic tool.

#### **Renal biopsy in NS**

Very few children with NS will require renal biopsy. Biopsy must be performed prior to starting steroids, if: (a) age of onset is <12 months, (b) patient has gross hematuria, significant azotemia or hypertension, or (c) plasma C3 level is low. Presently most nephrologists do not advise renal biopsy in cases of steroid sensitive FRNS needing alkylating agents. However, patients with corticosteroid resistant or SDNS should be biopsied for planning therapy and prognosticating the future course.

#### **Acute Stress**

After prolonged use of prednisolone the pituitary-adrenal axis is suppressed and may take as long as 6-9 months to recover. The recommendation (34) for managing an acute stress situation (accident, surgery, febrile illness *etc.*) during this period is administration of parenteral hydrocortisone 50 mg/m<sup>2</sup> alongwith cortisone 50-100 mg/m<sup>2</sup> to start with. The latter can be repeated daily till the patient is in acute stress(34). If cortisone is not available hydrocortisone can be held in similar dosage. Equivalent oral drugs can be used as soon as the patient can take orally and rapidly tapered to maintenance level of 5 mg prednisolone/m<sup>2</sup>. Subsequent tapering depends on the individual situation.

Some recommended Do's and Dont's for management of nephrotic syndrome are summarised in *Table III*.

### Parental Information and Education for NS

Parents must be informed about the nature of the disease. They should be warned that transient proteinuria can recur with fever and that relapses are not unusual and could be frequent. They should be taught how to test urine for protein and advised to maintain a record of albuminuria, drugs and intercurrent illnesses. They should be forewarned about the side effects of the

drugs used and advised clearly when to seek medical advice. When response to steroid is prompt, parents should be told that chances are above 90% that the disease will be benign, progress to CRF is unlikely and it is unusual for the disease to be active beyond puberty. Prognosis for non-responders is guarded. Follow up of the child at suitable intervals should be emphasized. NS being a chronic illness, causes lot of inconvenience, hardship and parental anxiety. Parents need emotional support and expect sympathetic attitude from attending physician.

**TABLE III**—*Summary of Do's and Dont's in management of nephrotic syndrome*

#### Do's

1. Establish diagnosis firmly
2. Rule out urinary tuberculosis, tract infection, peritonitis in each attack and a glomerulonephritis, in first attack or if there is late steroid resistance.
3. Give steroids in adequate doses for recommended period.
4. Check compliance and dosage.
5. Use diuretics judiciously.
6. Avoid hypovolemia. Institute intravenous fluids promptly if the patient develops diarrhea and vomiting.
7. Insist on the parents maintaining a diary, to record proteinuria, dose of corticosteroid used and intercurrent illness.
8. Explain about the disease to parents and answer their questions with patience.
9. Inform parents that for upto one year after completion of steroid therapy, the child will require steroid supplementation for severe illness or surgery.

#### Dont's

1. Do not intoxicate the child with steroids
2. Do not hesitate to refer difficult cases to a referral center.

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