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Review Articles

An Update of Management of Idiopathic Nephrotic Syndrome: A Review Article

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Abstract:

Nephrotic syndrome (NS) is a common childhood kidney disease characterized by protein leakage from the blood to the urine through the glomeruli, resulting of proteinuria, hypoalbuminemia, generalized edema and hypercholesterolemia. The prevalence of minimal change nephrotic syndrome is higher in Indian subcontinent. Such incidence in Bangladesh is yet unknown. This review article discusses historical background, epidemiology, pathogenesis, pathophysiology and classification of nephrotic syndrome. In this review article focuses have been made on management of children aged between 1 to 18 years with idiopathic nephrotic syndrome. This article also provides information of different guideline recommendations and a brief review of relevant treatment trials related to each recommendation.

***Keywords**: Nephrotic Syndrome, Steroid Resistant Nephrotic Syndrome, Steroid Dependent Nephrotic Syndrome, KDIGO Guidelines.*

Introduction:

The word "nephrosis" was introduced at the beginning of the 20th century, characterized by exudation and proliferation of inflammatory cells. Since then, the phrase "nephrotic syndrome" was used to refer group of related diseases. Nephrotic syndrome (NS) is a common childhood kidney disease characterized by protein leakage from the blood to the urine through the glomeruli, resulting in proteinuria (>40mg/m^2/hour), hypoalbuminemia (<2.5g/dl), generalized edema and hypercholesterolemia (>200mg/dl)[1].

This article describes the current view on pathogenesis of condition, and principles of management of childhood idiopathic nephrotic syndrome. Also summarize the importance of supportive care for these patients as well as the outcomes.

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Historical Background:

The history of nephrotic syndrome can go back to beginning of the era. In old Alexandria, urine was conceived to be produced in kidneys. "Bubbles floating on the surface on the urine denote affection of the kidneys, and the disease will be long" was the saying of Hypocrites[2]. In 1764, Cotungo, described a soldier with massive edema whose urine was heat coagulable. In 1836, Bright noted proteinuria in some edematous patient with certain renal disease. For a century, Glomerulonephritis was known as Bright's Disease. Muller used the term "Nephrosis" to differentiate a group of kidney disorders. Initially, tubules were suspected as source of the protein leak. Ultimately glomeruli became accepted as the source of protein leak in the 1940s. Munk[3] noted the association of lipoid droplets in the urinary sediment in patient with nephrosis and suggested the term lipoid nephrosis. Clovin and Goldberg used the term "Nephrotic Syndrome" to describe patient with edema, proteinuria and hyperlipidemia. Synthesized steroid hormones were used as a treatment of nephrotic syndrome since 1950[4,5].

Epidemiology:

Incidence: Nephrotic syndrome is a common clinical condition in Asian children[6]. The prevalence of minimal change nephrotic syndrome (MCNS) is also higher in Indian subcontinent[7]. Such incidence in Bangladesh

is yet unknown. There is a racial variation in susceptibility with a reported in incidence in Asian children of 9-16/100,000[7,8] in comparison to 2 to 7 children in USA[3], 2-4 new cases /100,000 children in UK[8,9]. Mortality was 50/1000 before antibiotic and steroid, which is now 5/1000[10].

Age and sex: The peak incidence of both MCNS and FSGS in pre-school age children, 80% of nephrotic children are less than 6 years old at presentation, with the median age at diagnosis being 2.5 years for MCNS and 6.0 years for FSGS[11,12]. The mean age at onset has been reported to be 3.4 years in Asians and 4.2 years in Europeans. In young children, boys are more commonly affected than girls (ratio 3:2) but in teenagers and adults, the sex ratio is approximately equal.[11]

Race: There is variation in the overall prevalence of NS in children and in the relative frequency of the different histological categories in different population. In the UK, there is higher prevalence of MCNS in children of families from the Indian subcontinent, than in the indigenous Caucasian population[3,12].

Genetic Aspects: Nephrotic syndrome is familial in 2-8% cases and in most cases siblings are involve[13]. Familial cases appear to be inherited in a polygenic fashion. The condition is much common in monozygotic twins than in dizygotic, which suggest that genetic factors play a more important role than environmental factors. It is reported that patients with steroid responsive nephrotic syndrome more frequently have the combined occurrence of HLA- DR3; HLA-DR7 and HLA -B8-DR3 where as patient with steroid resistant nephrotic syndrome more frequently have the combined occurrence of HLA-B8-DR8 and DR7.

Pathogenesis:

The pathogenesis of nephrotic syndrome still not identified. There is a strong evidence of immune dysregulation, mainly involving cell-mediated immunity (CMI). The tendency of nephrotic syndrome to manifest and relapse after viral infections or an atopic episode, the association with HLA antigens and the therapeutic response to steroids and cyclosporine A (CsA) support this view. Prolonged remissions following measles, which downregulates CMI also endorses this hypothesis. T-cell abnormalities has been variably reported in minimal change disease (MCD)[14,15,16,17]. Increased free radical generations and decreased anti oxidantdefenses may play crucial role in the pathogenesis of nephrotic syndrome.[16]

Immunological Dysfunction**:**

Immune response has been applied to know the pathogenesis of nephrotic syndrome. Antigen presentation to T-lymphocytes induces immune response, which may be Type 1 [dominated by α-interferon, interleukin (IL) 2] or Type-2 (IL4, IL10 or IL13). Type 1 cytokines predominate in cell-mediated immunity and Type 2 cytokines in some aspects of humoral immunity. Type 2 cytokines are particularly associated with atopy and class switching of B cells for production of IgG4 and IgE. Increased plasma levels of IgE, with normal IgG4 (with decreased IgG1 and IgG2), and association with atopy suggest type 2 cytokine bias in subjects with Minimal Change Disease (MCD). The mechanisms by which the cytokine bias might affect glomerular permeability is still not clear. Recent evidence suggests an activations of innate immunity in response to triggering of toll like receptors (TLRs) by microbial products, may directly affects podocytes.[13] *In vitro* studies suggest that podocytes express receptors for IL4 and IL13 may disrupt glomerular permeability and resulting in proteinuria. The benefits on treatment with levamisole, which augments type 1 and downregulates type 2 cytokines also support the above hypothesis[18].

Role of permeability factor**:**

In minimal change and focal segmental glomerulo sclerosis, systemic circulating factor, may increase glomerular permeability.Various vascular permeability factors including vascular endothelial growth factor, heparanase and hemopexin may be involved[19].

Genetics:

Genetic Mutations are present in 10-30% of sporadic onset steroid-resistant and in higher proportions of patients with familial nephrotic syndrome. Mutations in genes encoding several podocyte proteins have been identified in children with familial nephrotic syndrome (Table-I). This mutation involves the NPHS1 gene, encoding the protein nephrin. This transmembrane protein is present in the slit diaphragm in between the podocytes[20,21]. Mutations in nephrin are responsible for the congenital Finnish nephrotic syndrome[22]. Abnormalities of another gene, the NPHS2 gene encoding podocin, results in recessively inherited FSGS. Recent evidence suggests that the primary defect in idiopathic nephrotic syndrome might be at the level of podocyte (the glomerular visceral epithelial cell). Podocyte injury or structural inherited defects are implicated in the occurrence of glomerular proteinuria. Some viruses like HIV, parvovirus B19 may directly cause injury to the podocyte[20]. The role of immunosuppressive medications with these mutations

is limited and ultimately progress to end stage renal disease. Other implicated genes are WT1 (Wilms' tumour suppressor gene), FSGS2 and LMX1B (nail patella syndrome). Mutations in WT1 are associated with Denys-Drash syndrome and Frasier syndrome[23].

Table-I
Genetic Forms of Nephrotic Syndrome[23]

Gene/protein	Location	Pheno-type	Inheri-tance
NPHS/nephrin	Slit diaphragm	CNF	AR
NPHS2/podocin	Slit diaphragm	FSGS	AR
CS2AP//CD2AP	Near slit diaphragm	FSGS	
TRPC6/TRPC6	podocyte	FSGS	AD
WT1	podocyte	FSGS	AR
ACTINA4	Foot process	FSGS	AD
tRNA ^{Lcu}	podocyte	FSGS	
COQ2	podocyte	FSGS	

AD = autosomal dominant, AR = Autosomal recessive, CNF = congenital nephritic syndrome of the Finnish type, FSGS = focal segmental glomerulosclerosis

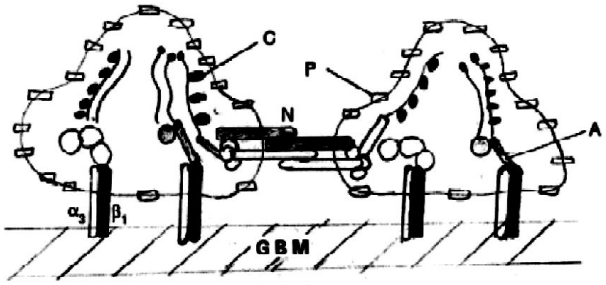

Fig.-1: *Ultra-structural cross section of podocyte processes anchored to the glomerular basement membrane (GBM), through integrins (á3, â1) form the glomerular slit diaphragm (glomerular filter). The chief cellular proteins include podocin (P), nephrin (N), á-actinin a @) and CD2 associated protein (C).[23]*

Pathophysiology:

Proteinuria and Hypoalbuminemia

Proteinuria is the result of alterations in the integrity of the glomerular filtration barrier. This barrier is composed of three layers: the fenestrated endothelium, the glomerular basement membrane, and the visceral glomerular epithelium, comprised of podocytes and their slit diaphragms. Podocytes may affect the structure and function of the glomerular basement membrane and regulate the integrity survival of glomerular endothelial cells. In the nephrotic syndrome, there is effacement of the foot process, but the rest of the cell usually is preserved. Endothelial cells have numerous openings that are 70 to 100 nm in diameter, called fenestrae, which form a physical barrier for passage of macromolecules from plasma into the renal tubule. Electron microscopic studies led to the identification of negatively charged particles (heparan sulfate proteoglycans) in the glomerular basement membrane, which preclude the passage albumin. Until recently, the podocytes were considered to play a passive role in the process of glomerular filtration. This concept changed dramatically with the discovery that mutation of proteins, located at the slit diaphragm, named nephrin, podocin and CD2AP complex[24].

Edema

Edema formation may results from a decrease in plasma oncotic pressure due to loss of serum albumin, causing water to extravasate into the interstitial space. This movement reduces the intravascular volume, leading to renal hypoperfusion and stimulate the renin-angiotensin-aldosterone (RAA) system. Aldosterone increases reabsorption of sodium, particularly at the level of the distal segments of the nephron. Vasopressin excess also contributes to the retention of water.[24]

Hyperlipidemia

Several mechanisms contribute to nephrotic syndrome dyslipidemia: overproduction due to low plasma albumin concentration and low oncotic pressure and impaired catabolism of apolipoprotein B and VLDL chylomicrons. Increased concentrations of very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and low-density lipoprotein (LDL) result in elevated serum cholesterol and triglycerides concentrations. The high-density lipoprotein (HDL) fraction is normal. Consequently the LDL/HDL cholesterol ratio is increased.[24]

Classification:

Nephrotic syndrome is primarily classified as[12]:

1. *Primary NS* that is not associated with systemic disease and accounts for 90% of childhood cases.
2. *Secondary NS:* that occurs as a part of systemic disease or is related to a drug or other toxin.

Based on response to steroid, nephrotic syndrome may be divided into two groups:

1. steroid-responsive: The steroid-responsive group consists largely of children with minimal change nephrotic syndrome (MCNS).
2. steroid-nonresponsive: This group is composed of children with other glomerular disease.

Etiological classification of nephrotic syndrome in childhood is as below.

A. Acquired
B. Congenital

Again, both of the cases of nephrotic syndrome may be primary and secondary.

A. Acquired causes
   a. Primary - 90%

      Idiopathic (90%)

      i) Minimum change nephrotic syndrome (MCNS) -85%
      ii) Mesangioproleferative nephrotic syndrome (MPNS) -5%
      iii) Focal sclerosis nephrotic syndrome (FSNS) -10%

   Some form of GN (10%)

      i) Membranous GN
      ii) Membranoproliferative GN

   b. Secondary - 10%

      i) Post infectious
         Virus - BV, Human immunodeficiency virus (HIV) others
         Bacteria - Syphilis, Spuntaneous bacterial endo-carditis (SBE)

      ii) Systemic Disease
         Collagen Vascular - Systemic lupus nephritis (SLE), Henoch schonlein purpura (HSP), Poly asteritis nodosa (PAN)
         Disease
         Diabetic Nephropathy
         Sickle cell disease
         Wegner's granulomatosis
         Good pasteur's syndrome
         Hereditary Nephritis - (Alport's syndrome)

      iii) Drugs
         Penicillamine
         Captopril
         Warfarin
         Lithium
         Gold
         Trimethodione
         Probenecid etc.

      iv) Malignancy- Leukemia, Lymphoma, Wilm's tumor
      v) Amyloidosis

B. Congenital nephrotic Syndrome- nephrotic syndrome that presents in the first 3 months of life.
   a. Primary
      1. Infantile microcystic disease
         • Finish Type - AR
         • Non finish type
      2. Diffuse Mesangial sclerosis
      3. Minimal -Lesion Nephrotic syndrome
      4. Focal segmental glomerulosclerosis
   b. Secondary
      1. Intrauterine infection - toxoplasmosis, CMV, Rubella, Syphilis
      2. Gonadal dysgenesis
      3. Nail patella syndrome
      4. Lowe's syndrome

Histological type of primary Nephrotic syndrome:

Table-II

Relative frequency of the various Histological types in a study of 521 patients by ISKDC[12]

Conditions	Frequency %
Minimal-lesion Nephrotic	76.6
Diffuse Mesangial Hypercellularity	2.3
Focal Glomerular sclerosis	8.6
Membranous glomerulonephritis	1.5
Membranoproliferative GN	7.5

Common Presenting Features:

The common age of presentation starts between 2-6 years of age. Such patient often has an antecedent history of infection that often precipitates relapses. Patient usually presents with periorbital edema, then involves ankles which is pitting in nature. With the time the edema can become generalized with ascites, pleural effusion, and urine output is diminished that associated with weight gain. Scrotal, penile/labial swelling may be present in severe case. Transient hypertension may occur in 10-15% cases. Hypovolaemia may cause circulatory failure and predisposes to thrombosis[25,26].

Steroid Sensitive Nephrotic Syndrome (SSNS):

The disease course is variable; while almost 40% have no relapses or a single relapse, more than 55% show multiple relapses that occur either infrequently or frequently. Usually within 7 to 10 days most of children will respond to steroid[27].

Evaluation at Onset: Treatment with corticosteroids starts with detailed evaluations. That includes history and physical examination (height, weight and blood pressure), with attention to detect infections and underlying systemic disorders.

Table-III

Common definitions to define the course of nephrotic syndrome[27]

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

Investigations at the first episode of nephrotic syndrome[28]

Essential

Urinalysis: proteinuria, red cells, castsUrine culture (suspected clinical features of urinary tract infection) 24-h quantitationComplete blood counts

Blood levels of urea, creatinine, albumin, cholesterol
Tuberculin test
Chest X-ray (positive tuberculin test, history of contact with tuberculosis) hepatitis B surface antigen, anti-HCV HIV

If required (indication)

C3 and antistreptolysin O (gross or persistent microscopic hematuria) Antinuclear antibodies (suspected systematic lupus erythematosus)

Indication for renal biopsy:[28]

A biopsy is usually not necessary in patients with frequent relapse or steroid dependence or before starting treatment with levamisole, cyclophosphamide, or MMF (*Mycophenolate Mofetil)*, but should be performed before therapy with calcineurin inhibitors. Biopsy is also necessary in cases including: (a) Age of onset<1 year (b) Gross hematuria, persistent microscopic hematuria or low serum C3, (c) Sustained hypertension (d) Renal failure not attributable to hypovolemia (e) Suspected secondary causes of nephrotic syndrome, (f)if Proteinuria persisting despite 8-weeks of daily corticosteroid therapy and (g) Before treatment with cyclosporine A or tacrolimus.

Management of the initial episodes:

Aim and Objective:

(a) to induce and maintain complete remission for long time, (b) to keep patient free from side effects of steroid therapy (c) to maintain normal renal function and (d) initial episodes of NS should be treated in adequate dose and duration. It is an important determinant of long term course of the disease[29].

Component of management of SSNS: The International Study of Kidney Disease in Children (ISKDC) and the Arbeitsgemeinschaft für Pädiatrische Nephrologie (APN) during 1960s, 1970s, and 1980s, and subsequent studies by individual research teams form the basis of the clinical management of SSNS and SRNS in children. It includes (a) Supportive Care, (b) specific management, and (c) treatment of complications.

Supportive care: Intensive supportive care is an important aspect of managing children with nephrotic syndrome.

Edema: Edema or anasarca is associated with an increased risk of infections.

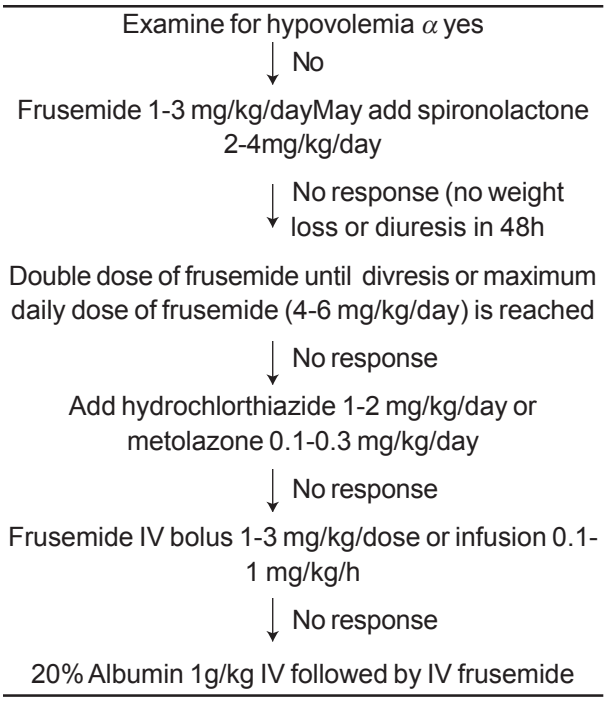

Fig.-2: *Management of edema on patients with nephrotic syndrome*

Monitoring of serum electrolytes is necessary in all patients receiving diuretics. Patients showing hypokalemia require potassium supplements or co-administration of spironolactone[30].

Hypovolemia: Hypovolemia may occur during a severe relapse or following administration of diuretics, particularly in children with poor oral intake, diarrhea and vomiting. Therapy with diuretics should be discontinued. When signs of hypovolemia are absent, an increase in oral fluid intake alone may sufficent. With features of hypovolemia, patients require admission and rapid infusion of normal saline (10-20 ml/kg) over 20-30 min is required. Patients, who do not response to two blouses of saline, should receive infusion of 20% salt poor human albumin (0.50-1.00 mg/kg)[30].

Infections: Common infections include peritonitis, cellulitis and pneumonia, which should be treated using appropriate antibiotics. The rate of peritonitis is 2–6%[31], and overwhelming infection still carries a mortality rate of 1·5%[32]. Susceptibility to bacterial infection is related to multiple predisposing factors. Impaired complement dependent opsonisation, delays clearance of encapsulated micro-organisms, especially *Streptococcus pneumonia*[33].So pneumococcal vaccination is recommended for patients who have nephrotic syndrome[34]. Prophylactic treatment with penicillin during relapses has been suggested but few data support this practice[35]. Patients are also predisposed to gram-negative bacterial infections.

Many children with idiopathic nephrotic syndrome are varicella non-immune. So, varicella exposure and infection require special consideration. Prophylactic treatment with varicella zoster immune globulin is recommended for susceptible non-immune patients (receiving immunosuppressive treatments) within 96hr of exposure to prevent the severity of the disease[36,37,38]. Once remission is achieved, immunisation with varicella vaccine seems safe and effective, although additional doses may be required to achieve full immunity. During active infections patients should receive intravenous acyclovir (1500mg/m^2/day in 3 doses) or oral acyclovir (80 mg/kg/day in 4 doses for 7 to 10 days) may also prevent serious varicella infection in patients receiving cortico-steroids[39]. Prednisolone should be avoided or tapered during infections.

Patients with nephrotic syndrome who are: (i) Mantoux positive, but no evidence of tuberculosis, should receive INH prophylaxis for 6 months, (ii) with active TB, should receive full course of anti tuberculous treatment.

Patients with nephrotic syndrome who are HBs +ve should be initially evaluate the disease activity by some investigations (HbeAg, SGPT). If HBeAg is +ve and SGPT>2 fold for normal then

(a) antiviral (lamivudin 2-3 mg/kg) for 6 months

(b) after 2 weeks of antiviral – start steroid in usual regimen

(c) follow up 3 monthly 2 times: HBeAg, SGPT, HBV DNA

(d) After 6 month: HBeAg+ve: antiviral therapy continued for another 6 months[36,37]

Hypertension:

The target blood pressure is between the 75-90th percentile for age, gender and height.An angiotensin converting enzyme inhibitor, enalapril (0.3-0.6 mg/kg/d in 2 divided doses) or ramipril is the medication of choice. Some patients require additional therapy with calcium channel blockers (e.g. amlodipine) or adrenergic blockers[40].

Thrombosis: Nephrotic patients are at significantly increased risk of thrombosis especially venous[26]. Although thrombosis risk is apparently lower in nephrotic children (1·8–5·0%), these events can be severe[41]. Multiple factors (including loss of antithrombin III, protein S and high levels of lipoprotein A, factor V, factor VIII and fibrinogen levels.) contribute to the dysregulated coagulation state of nephrotic syndrome. Fibrinogen concentration has been proposed as a surrogate marker. Other factors that increase thrombotic risk in nephrotic patients include aggressive diuretic use, corticosteroid treatment, and punctures of deep vessels, immobilisation, and the presence of in-dwelling catheters. Renal vein thrombosis is suspected in patients with oligoanuria, hematuria or flank pain, especially following an episode of dehydration. Sagital sinus and cortical venous thrombosis may occur following diarrhoea and present with convulsions, vomiting etc. Ultrasonography, Doppler studies and cranial MRI are useful to confirm the diagnosis. These patients require urgent and prompt treatment. Therapy includes corrections of dehydrations and other complications and the use of heparin or low-molecular-weight heparin (subcutaneously) initially, followed by oral anticoagulants for long period. Prophylactic treatment has no role.

Vaccination: The administration of live vaccines (oral polio, varicella.MMR) should be avoided until the child is off immunosuppressive medication for at least 4 weeks. The administration of pneumococcal vaccine is desirable. Children below 2 years of age should receive the pneumococcal conjugated vaccine, 0.5 ml intramuscularly, in the schedule advised by the Indian Academy of Pediatrics (Age<6mo:3 doses 4-8 week apart and booster at 15-18 mo, Age 6-12 mo:2 doses 4-8 week apart and booster at 15-18 month; age between 12-23 months: 2 doses 8 week apart). Above 2 years of age, one dose of the polysaccharide vaccine (PPPV23) is administered, following one dose of the conjugate vaccine; the gap between the injections should at least be 2 months. Children who continue to have relapses of nephrotic syndrome may receive one repeat dose of PPV23, 5 years after the primary vaccination[40]. Two doses of the varicella should be administered 4 week apart while the child is in remission and off immunosuppressive medications. Injectable polio vaccine should be administered to children with nephrotic syndrome and their siblings. If the child has received primary immunization with oral polio vaccine (at 6,10,14 weeks), 2 doses of the injectable vaccine are given at 2 months interval followed by a 3rd dose 6 months after the first dose, and a booster at 5 years[40].

Nutrition: A balanced diet, adequate in protein (1.5 to 2.0 gm/kg) and calories is recommended. During remission, children should eat a balanced, nutritious diet without restrictions. If disease is associated with edema, salt restrictions are advised (1to2gm/day).Undue restriction that make food unpalatable is not required. Patients with persistent and recurrent proteinuria should increase their daily intake of proteins to 2-2.5g/kg. Increase in physical activity can help achieve desirable body weight.

Stress dose of steroids: Patients who have received steroids at high doses for more than 2 week in the past year are at risk of suppression of the hypothalamo-pituitary-adrenal axis. These children require steroid supplements during surgery, anesthesia or serious infections. Steroids are given at a dose of.2-4 mg/kg/day (IV Hydrocortisone) followed by oral prednisolone at 0.3 to 0.6 mg/kg/d up to stress period and then tapered rapidly[40].

Specific Management

The initial (first) episode of nephrotic syndrome should be treated adequately as it is important determinant of long term course.

Drugs or medications: The standard medication for treatment is prednisolone or prednisone. This drug is applied after meals to reduce gastrointestinal side effects. Different treatment regimens have been used for initial episode of nephrotic syndrome.

The International Study of Kidney Diseases in Children (ISKDC) regimen: Prednisolone 60 mg/m^2/day in 3 divided doses (max 80 mg/day) followed by 40mg/m^2/day (max 60 mg/day) on alternate day for 4 weeks[42]. But this regimen is associated with a higher relapse rate. So, prolongation of initial steroid therapy (2mg/kg/day maximum 60 mg in single or divided dose for 6 weeks followed by 1.5mg/kg as a single morning dose on alternate day for 6 weeks) for 12 week or longer is associated with significantly reduced risk of subsequent relapses. This regimen is associated with higher frequency of adverse events.

The Cochrane group[43] reviewed published trials on the impact of the length of prednisone therapy in children with a first episode of NS. A meta-analysis of

six trials that compared 2 months of prednisone with 3 months or more (administered daily for 4 to 8 weeks at 60mg/m^2/day and then on alternate days) for the first episode showed that a longer duration significantly reduced the risk for relapse at 12 to 24 months (RR 0.70; 95% CI 0.58 to 0.84) without an increase in adverse events. There was an inverse linear relationship between duration of treatment and risk for relapse (relative risk 1.26 to 0.112 duration; R2 0.56; P 0.03). They concluded that children in their first episode of SSNS should be treated for at least 3 months, with an increase in benefit being demonstrated for up to 7 mo of treatment. Other trials have been demonstrated that steroid therapy for 6 months significantly reduced the risk for relapse compared with 3 months (4 trials; 382 children; RR 0.57; 95% CI 0.45-0.71) [44].

Indian Academy of Paediatrics (IAP): Based on current evidence, this group also recommends the six weeks regimens (Fig.-3).

The Arbeitsgemeinschaft für Pädiatrische Nephrologie (APN): The daily dose of 60 mg/m^2/day for 4 weeks and the starting dose of 40 mg/m^2 for alternate day therapy were also used empirically by the APN[45,46] and have not been examined in RCTs so while these doses are recommended, the quality of evidence supporting these data is very low. APN has demonstrated a reduction in RR for relapse in cyclosporine (150 mg/m^2/day for 8 weeks) and prednisolone compared with prednisolone alone for 6 months (104 children; RR 0.33; 95% CI 0.13-0.83), but not at 1 or 2 years[44,47]. The cumulative prednisolone dose after 2 years slightly but not significantly less in the cyclosporine treated group, and no significant elevations in blood pressure or falls in glomerular filtration rate (GFR) were documented. Eight weeks of add-on treatment with CsA at initial manifestation of SSNS seems to reduce the risk for younger children who experience relapses but does not abolish it.

Treatment of relapse: Before starting steroid, infections should be ruled out and treated accordingly. Treatment should be started according to flow chart.

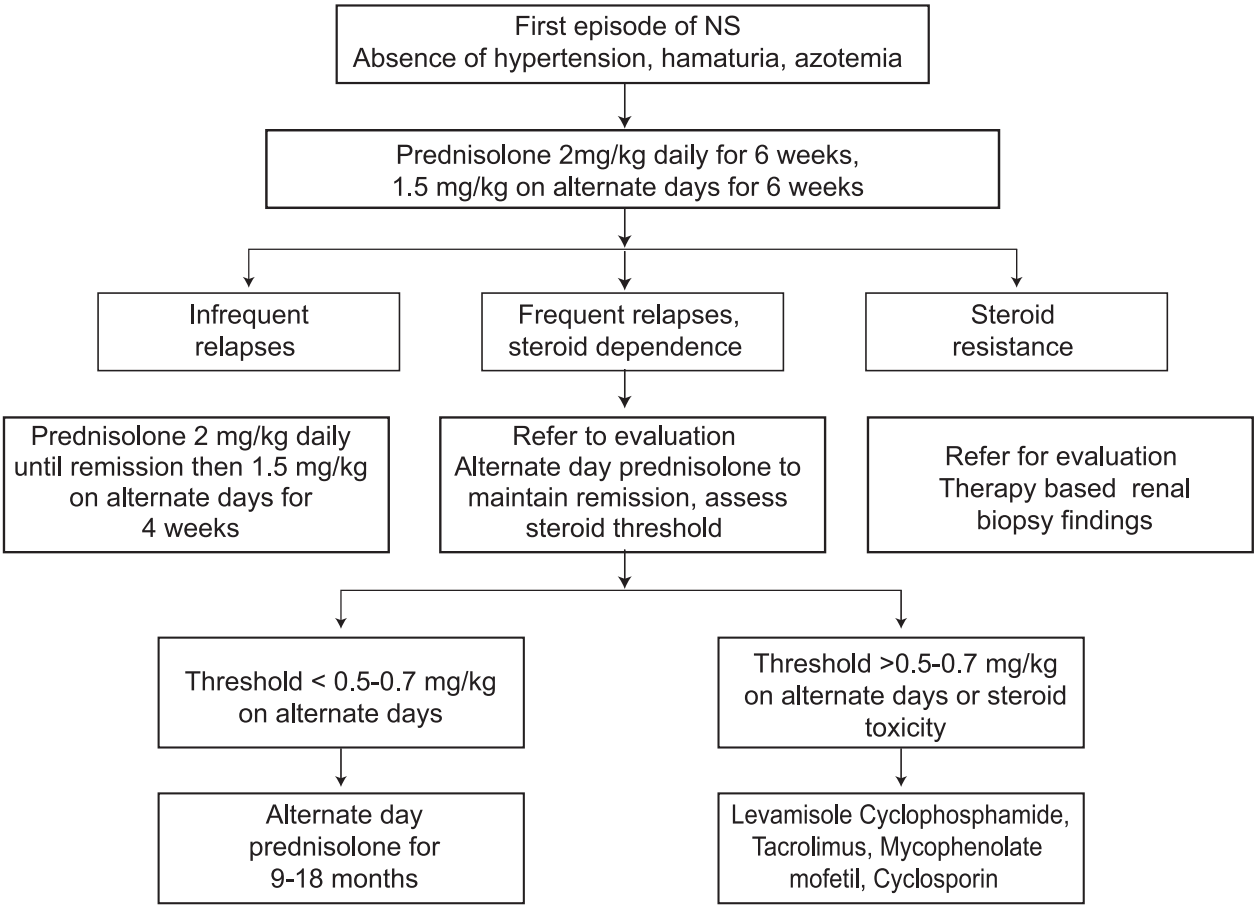

Fig.-3: *Management of patients with Relapse nephrotic syndrome(IAP Guidelines)*

***Few data on steroid regimens for frequently relapsing and steroid-dependent NS*:** The ISKDC proposed that relapsing SSNS should be treated with daily prednisone (60mg/m^2/day) till the child had been in remission for 3 consecutive days followed by 4 weeks of prednisone[40].

Additional steroid therapy during inter-current infections: Children commonly relapse when they have infections. Children with steroid dependent NS had significantly fewer relapses during 2 years follow up if they received daily rather than alternate-day prednisolone during upper respiratory tract infections (36 children, mean difference -3.30; 95%CI -4.03 to -2.57)[44,48].

Steroid sparing agents:
The additional use of an alternative agent should be considered in patients with: (i) prednisolone threshold (for maintaining remission) higher than 0.5-0 .7 mg/kg on alternate days or (ii) features of corticosteroid toxicity:

a. Levamisole: in addition to this, prednisolone dose is decreased in every 2 weeks to 0.25 to 0.50 mg/kg on alternate days.

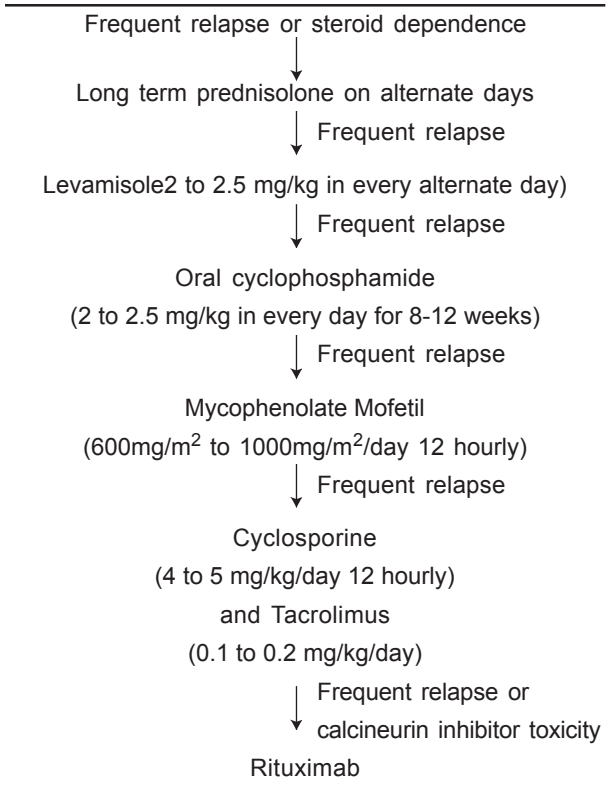

Fig.-4: *Alternative agents in used in steroid sensitive nephrotic syndrome*

b. Cyclophosphamide: the dose of prednisolone is 1-1.15 mg/kg on alternate days during cyclophosphamide therapy, gradually tapered and discontinued over 4-6 weeks.

c. Mycophenolate Mofetil: in addition to this, tapering doses of prednisolone are administered for 6-12 months.

d. Cyclosporine and Tacrolimus: both these agents have strong steroid sparing potential, with steroid discontinuation in patients following 6-9 months by tapering.

e. Rituximab:

When to refer to pediatric nephrologists[28]:
Indication of referral of patients are:

- Onset below 1-year of age
- Family history of nephrotic syndrome
- Nephrotic syndrome with hypertension
- Gross/persistent microscopic hematuria, impaired renal function or external features (e.g. arthritis, serositis, rash)
- Complications: refractory edema, thrombosis, severe infections, steroids toxicity
- Resistance to steroid therapy Frequently relapsing or steroid dependent nephrotic syndrome

KDIGO Guidelines: (Kidney Disease: Improving Global Outcomes)
The daily dose of 60 mg/m^2/day and the starting dose of 40mg/m^2 for alternate day therapy were used empirically by the ISKDC[49] and the APN[50] and have not been examined in RCTs. So, while these doses are recommended, the quality of evidence supporting these data is very low. Theoretical studies[51] have suggested that under-dosage with prednisolone can occur if a per-kilogram dose is used particularly in children weighing below 30 kg. Now KDIGO (Kidney Disease: Improving Global Outcomes) has published clinical practice guidelines on various glomerulo-nephritides including SSNS and SRNS in children using evidence-based principles[52].

Table-V

Definitions of nephrotic syndrome in children (KDIGO Guidelines)

Classification	Definition
Nephrotic syndrome	Edema, uPCR e”2,000 mg/g (e”200 mg/mmol), or e”300 mg/dl or 3+protein on urine dipstick, hypoalbuminemia d”2.5 mg/l (d”25 g/l)
Complete remission	uPCR <200 mg/g (<20 mg/mmol) or <1+ of protein on urine dipstick for 3 consecutive days
Partial remission	Proteinuria reduction of 50 % or greater from the presenting value andabsolute uPCR between 200 and 2,000 mg/g (20–200 mg/mmol)
No remission	Failure to reduce urine protein excretion by 50 % from baseline or persistent excretionuPCR >2,000 mg/g (>200 mg/mmol)
Initial responder	Attainment of complete remission within initial 4 weeks of corticosteroid therapy
Initial nonresponder/steroid resistance	Failure to achieve complete remission after 8 weeks of corticosteroid therapy
Relapse	uPCR e”2,000 mg/g (e”200 mg/mmol), or e”300 mg/dl or 3+ protein on urine dipstick
Infrequent relapse	One relapse within 6 months of initial response, or one to three relapses in any 12-month period
Frequent relapse	Two or more relapses within 6 months of initial response, or four or more relapses in any12-month period
Steroid dependence	Two consecutive relapses during corticosteroid therapy, or within 14 days of ceasing therapy
Late nonresponder	Persistent proteinuria during 4 or more weeks of corticosteroids following one or more remission

uPCR urine protein:creatinine ratio

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Practice Guideline for Glomerulonephritis[53]

Corticosteroids for the initial episode of steroid-sensitive nephrotic syndrome (KDIGO Glomerulonephritis Workgroup, 2012):

Corticosteroid therapy (prednisone or prednisolone) for at least 12 weeks as a single daily dose starting at 60 mg/m^2/day or 2 mg/kg/day to a maximum 60 mg/day for 4-6 weeks followed by alternate-day medication as a single daily dose starting at 40 mg/m^2 or 1.5 mg/kg (maximum 40 mg on alternate days) and continued for 2-5 months with tapering of the dose. The risk of relapse was reduced by 30% at 12-24 months by 72 weeks or more of prednisone compared with 8 weeks (six RCTs; 422 children; risk ratio (RR) of relapse 0.70; 95 % confidence intervals (CI) 0.58-0.84)[53, 54].

Comparison with previous guidelines for SSNS:

Table-VII

Comparison of KDIGO guidelines for steroid-sensitive nephrotic syndrome (SSNS) with some existing guidelines

	Children's Nephrotic Syndrome Consensus Conference USA, 2009[1]	Haute Authorité de Santé France, 2008[2]	Indian revised guidelines, India 2008[3]	KDIGO Guidelines International, 2012 [53]
Prednisone in initial episode	2 mg/kg/day×6 weeks	60 mg/m2/day×4 weeks	2 mg/kg/day×6 weeks	60 mg/m2/day (2 mg/kg/day)×4–6 weeks
	1.5 mg/kg alt day×6 weeks	60 mg/m2 alt day×8 weeks	1.5 mg/kg alt day×6 weeks	40 mg/m2 (1.5 mg/kg) alt day×2–5 months
	No taper	Taper by 15 mg/m2 every 2 weeks	No taper	with taper
	Duration 12 weeks	Duration 18 weeks	Duration 12 weeks	Minimum duration 12 weeks
Prednisone in IFa SSNS	2 mg/kg/day until urine protein–ve×3 days	60 mg/m2/day until 6 days after remission	2 mg/kg/day until urine protein –ve×3 days	60 mg/m2/day (2 mg/kg/day) until urine protein –ve×3days
	1.5 mg/kg alt day×4 weeks	60 mg/m2 alt day×4 weeks	1.5 mg/kg alt day×4 weeks	40 mg/m2 (1.5 mg/kg) alt day×4 weeks
		Taper by 15 mg/m2 alt day 4 wkly		
Prednisone in FRb and SDc SSNS	2 mg/kg/day until urine protein –ve for 3 days	60 mg/m2/day until 6 days afterremission	2 mg/kg/day until urine protein –ve for 3 days	60 mg/m2/day (2 mg/kg/day) until urine protein –ve for 3 days
	1.5 mg/kg alt day×4 weeks	60 mg/m2 alt day×4 weeks	1.5 mg/kg alt day×4 weeks	40 mg/m2 (1.5 mg/kg) alt day and taper for 3 months
	Taper by 0.5 mg/kg alt day over 2 months	Taper by 15 mg/m2 every 4 weeks to 15 mg/m2 and continue 12–18 months	Taper to 0.5–0.7 mg/kg alt day and continue 9–18 months	Lowest alt day or daily dose to maintain remission
				Daily during infection
Steroid-sparing agents	FR SSNS	FR & SD SSNS	FR & SD SSNS	FR & SD SSNS
	1. CPAd 2 mg/kg/day×12 weeks	Levh 2.5 mg/kg alt day	Lev 2–2.5 mg/kg alt day×1–2 years	CPA 2 mg/kg/day×8–12 weeks
	2. MMFe 25–36 mg/kg/day ×1–2 years	CPA 2 mg/kg/day×8–12 weeks	CPA 2–2.5 mg/kg/day×12 weeks	Chlorambucil 0.1–0.2 mg/kg/day×8 weeks
	3. CyAf 3–5 mg/kg/day or Tac 0.05–0.1 mg/kg/day×2–5 years	CyA 150 mg/m2/day	CyA 4–5 mg/kg/day or	Lev 2.5 mg/kg alt day× 1 year
	SD SSNS	MMF 1,200 mg/m2/day	Tac 0.1–0.2 mg/kg/day×1–2 years	CyA 4–5 mg/kg/day× 1 year
	1. CyA 3–5 mg/kg/day or Tacg 0.05–0.1 mg/kg/day		MMF 800–1,200 mg/m2/day ×1–2 years	Tac 0.1 mg/kg/day× 1 year if excess cosmetic effects with CyA
	2. MMF 24–36 mg/kg/day			MMF 1,200 mg/m2/day× 1 year
	3. CPA 2 mg/kg/day×12 weeks			

KDIGO kidney disease: improving global outcomes; SSNS steroid sensitive nephrotic syndrome; FR frequently relapsing; SO steroid dependent; MMF mycophenolate mofetil

a Infrequent relapse; b Frequent relapse; c Steroid-dependent; d Cyclophosphamide; e Mycophenolate mofetil; f Cyclosporine; g Tacrolimus; h Levamisole

Relapsing children:

For infrequently relapsing children, the US, Indian, and KDIGO guidelines use the same regimen originally used by the ISKDC and adapted by APN, while the French guidelines use a longer ones. For FR and SD SSNS, the US guidelines use a 3-month regimen of prednisone while the other guidelines suggest long courses of low-dose prednisone to maintain remission. The Indian and KDIGO guidelines suggest that second courses of alkylating agents not be used and the Indian guidelines recommend that chlorambucil not be used because of toxicity. Mizoribine is not considered in any guideline except KDIGO, which suggests that it should not be used[53].

Steroid Resistant Nephrotic syndrome:

Children aged 1-18 years, are unable to achieve complete remission with corticosteroid therapy within 8weeks are termed as SRNS. Approximately 20% will be classified as steroid resistant[58,59].

Resistant nephrotic syndrome (SRNS) may have minimal change disease (MCD), mesangial proliferative glomerulonephritis (MesPGN) or focal segmental glomerulosclerosis (FSGS), although other histopathologic diagnoses also occur. If partial or complete remission is not achieved, 50 % risk of progression to end-stage kidney disease within 5 years of diagnosis[60,61,62].

Evaluation

Children diagnosed with SRNS (initial or late) should undergo renal biopsy before starting specific treatment. About 10-20% patients with familial and sporadic SRNS and these patients are usually unresponsive to immunosuppressive medications, progresses rapidly to end stage renal disease. If facilities exist, mutational analysis should be offered to patients with: (i) congenital nephrotic syndrome (onset below 3 months of age) (ii) family history of SRNS, (iii) sporadic initial steroid resistance that does not respond to therapy with cyclophosphamide or calcineurin inhibitors, and (iv) pts with steroid resistant FSGS[53]. Baseline assessment of renal function, blood level of albumin and cholesterol, and quantification of starting urinary protein loss (spot urine protein to creatinine ratio in young children; 24-h protein excretion in older children) guides future evaluation of response to therapy. Patients should be evaluated for hepatitis B and C virus infection.

Management of SRNS:

The factor predicting renal outcome is the response of proteinuria to therapy rather than the renal histology. The aim of therapy in patients is thus to induce and maintain remission of proteinuria, while avoiding medication related adverse effects. Most regimen use a combination of immunosuppressive agents with prednisolone (given on alternate days) and an angiotensin converting enzyme inhibitor.

Drugs used in SRNS:

The benefits of immunosuppressive therapy must be assessed against the potential adverse effects at each relapse and remaining kidney function to determine whether it is in the child's interest to continue active therapy.

A. calcineurin inhibitor (CNI) as initial therapy for children with SRNS: CNI therapy be continued for a minimum of 6 months and then stopped if a partial or complete remission of proteinuria is not achieved. CNI is to be continued for a minimum of 12 months when at least a partial remission is achieved by 6 months. Low-dose corticosteroid therapy be combined with CNI therapy. Complete and partial remissions are less common in the presence of nephrotic syndrome associated with podocin mutations[63,64,65]. CNI therapy may induce at least a partial remission in these patients. Tacrolimus was compared with cyclosporine in one study[66]. and showed no significant difference in proteinuria control. The frequency of nephrotoxicity, hypertension, and diabetes mellitus were not different between cyclosporine and tacrolimus in this trial. Hypertrichosis and gingival hyperplasia were significantly more common with cyclosporine than with tacrolimus.

B. Mycophenolate mofetil: Observational studies involving 42 children with SRNS who were treated for a minimum of 6 months with MMF demonstrated a complete remission rate of 23- 62%, a partial remission rate of 25-37%, and, no remission in 8-40%[67,68,69,70].

C. High-dose corticosteroids: Children with SRNS received either methylprednisolone or dexamethasone i.v. for six doses combined with prednisolone orally, and the short-term outcome was assessed at the end of a 2-week regimen. In the 138-patient with FSGS, RCT[68], in the combination therapy MMF + dexamethasone, dexamethasone dose was high and had therapy duration of 6 months. In the MMF + dexamethasone arm, complete and partial remission rates were not greater than expected for MMF alone.

In a retrospective study of 52 children with SRNS and FSGS, the cumulative proportion of sustained remission was significantly higher in children treated with cyclosporine and methylprednisolone i.v. compared with cyclosporine with prednisone ora1ly[71].

D. Alkylating agents: Children with SRNS demonstrated no significant differences in the number achieving remission with cyclophosphamide and prednisone compared with prednisone alone, with an increase in adverse effects in the cyclophosphamide groups.

E. Rituximab: Observational studies[72,73] suggest that it is not as effective in SRNS as in SSNS.

Monitoring response to therapy:

Patients should be monitored every month until response to therapy is demonstrated, and then every 2-3 month. The aim of treatment is the achievement of complete remission, but occurrence of partial remission is also satisfactory.

Drug monitoring: Most agents used in the therapy of SRNS require monitoring for adverse effects. Monitoring of drug levels is recommended when using either cyclosporine or tacrolimus. A 12-h trough level should be estimated about 2-week after introduction of therapy, after any dose change, and if suspecting drug toxicity or poor compliance. Trough levels in the range of 80-120 ng/ml for cyclosporine and 4-7 ng/ml for tacrolimus are acceptable. Renal biopsy is advised in patients receiving prolonged therapy (2-3 year) with calcineurin inhibitors. Histological features of nephrotoxicity include nodular hyalinosis or striped interstitial fibrosis and tubular atrophy.

KDIGO Glomerulonephritis Workgroup, 2012: This guidelines has recommends

1. Minimum of 8 weeks treatment with corticosteroids to define steroid resistance.
2. The following are required to evaluate the child with SRNS

- a diagnostic kidney biopsy(FSGS lesions may be missed if the biopsy specimen has <20 glomeruli. The biopsy will also provide information on the degree of interstitial and glomerular fibrosis, which helps to assess prognosis.)
- evaluation of kidney function by glomerular filtration rate (GFR) or estimated GFR (eGFR) (Kidney function measured at the time of diagnosis is a predictor of the long-term risk for kidney failure)
- quantitation of urine protein excretion"(Proteinuria should be quantified at diagnosis and during treatment to allow treatment response to be defined as partial, complete, or no remission[61,74,75,76,77]. Urinary protein/creatinine ratio (uPCR) on the first morning specimen or measurements of 24-hurine protein may be used.)

Table -VIII

Regimens for treatment of steroid resistant nephrotic syndrome

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

*Prednisolone administered at 1 mg/kg on alternate days; dose reduced after 2-3 months**Six alternate day pulses, then 4 fortnightly pulses and 8 monthly pulses; oral cyclophosphamide for 12 wk; tapering prednisolone over 52 wk[72].

3. Children who fail to respond to CNIs (KDIGO Glomerulonephritis Workgroup, 2012):

   a. Renin-angiotensin system (RAS) blockade .

   Two RCTs demonstrated a significant reduction in proteinuria with angiotens inconverting- enzyme inhibitors (ACEi) therapy using enalapril[78] and fosinopril[67]. Monitoring eGFR and serum potassium levels is recommended during RAS therapy.

   b. Mycophenolate mofetil (MMF), high-dose corticosteroids, or a combination of these agents be considered in children who fail to achieve complete or partial remission with CNIs and corticosteroids. Cyclophosphamide not be given to children with SRNS.

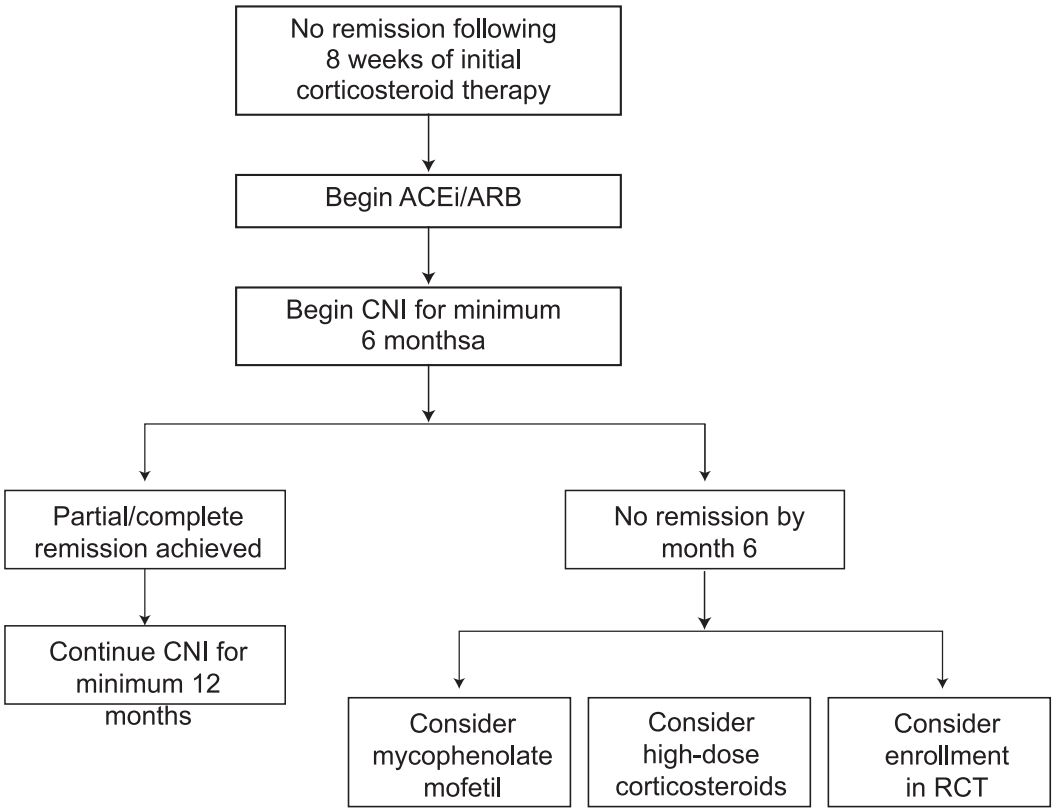

Fig.-5: *Management plan for children with SRNS*[77]

ACEI: Angiotensine Converting Enzyme inhibitor; CNI :Calcineurin inhibitor; RCT: Randomized Control Trial
ARB: Angiotensin receptor Blocker

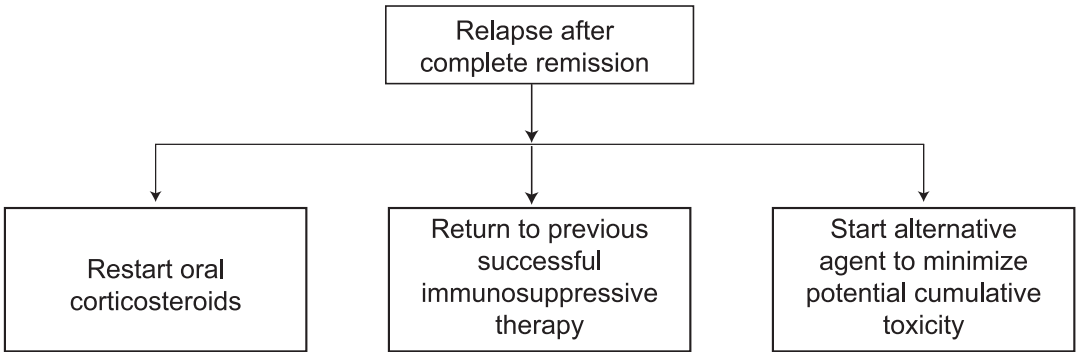

Fig.-6: *Management plan for children with SRNS with Relapse*[77]

Table-IX

Summary of published trials on steroid resistant nephrotic syndrome in children

Study (yr)	N	Intervention	Response
Controlled trials:			
ISKDC (1996)[79]	60	CP (PO) and prednisolone vs prednisolone for 12 months	25% remission in either group
Elhence *et al* (1994)[80]	13	CP (iv) and prednisolone vs CP (PO) and prednisolone	100% remission in iv group; 25% in PO (*P* = 0.02)
Ponticelli *et al* (1993)[81]	20	CsA vs supportive therapy for 6 months	40% remission in CsA; 0% in supportive (*P* <0.001)
Lieberman *et al* (1996)[82]	31	CsA vs placebo for 6 months	33.3% remission in CsA; nonein placebo (*P* <0.05)
Bagga *et al* (2004)[78]	25	Enalapril 0.6 mg/kg/day vs 0.2 mg/kg/dayfor 8 wk	Ua/Uc reduction. 62.9%t (high dose); 34.8% (low dose) (*P* <0.01)
Mantan *et al* (2004)[83]	49	CP (iv) and prednisolone vs dexamethasone (iv), CP (PO) and prednisolone (PO)	53.8% remission in CP; 47.8% in dexamethasone (*P*=0.6)
Uncontrolled trials:			
Tune *et al* (1995)[84]	32	MP (iv), CP (PO), prednisolone	60% remission
Adhikari *et al*(1997)[85]	12	MP (iv), CP (PO) and prednisolone vs CP (iv), MP (iv) and prednisolone	85.7% remission in MP (iv); 40% cent in CP (iv)
Hari *et al* (2004)[70]	81	Dexamethasone (iv) vs MP (iv) [CP (PO), prednisolone both groups]	Remission 35.1% in dexamethasone; 33.1% MP
Gulati & Kher (2000)[86]	20	CP (iv), prednisolone for 6 months	65% remission
Bajpai *et al* (2003)[87]	24	CP (iv), prednisolone for 6 months	29% remission

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

Natural history and prognosis

Steroid responsiveness is the most important prognostic indicator of nephrotic syndrome. Approx. 60-80% of steroid-responsive nephrotic children will relapse and about 60% of those will have five or more relapses. Age older than 4 years at presentation and remission within 7-9 days of the start of steroid treatment in the absence of micro haematuria are predictive of fewer relapses[88,89,90]. In a natural-history study of 398 children, the proportion that became non-relapsers rose from 44% at 1 year to 69% at 5 years, and 84% at l0 years.[91]

For the steroid-resistant FSGS patients, the clinical course is typically very challenging. With current treatments, a few children will ultimately achieve a sustained remission with one of the second-line or third-line drugs. For patients with refractory nephrotic syndrome, progression to end-stage renal disease is inevitable. Some of these children have such a difficult clinical course because of refractory oedema, severe infections, thromboembolic complications, or a combination of these. For this subgroup, the ultimate treatment goal is renal transplantation, despite the haunting reality that FSGS will recur in about 25% of renal allografts[92].

Immunosuppressive treatment is ineffective for patients with familial nephrotic syndrome; definitive treatment requires renal transplantation. Proper counseling is also vital. Parents are explained about the natural history of the disease and its outcome and adverse effect of repeated courses of high dose of medication. Parents' motivation and involvement is

essential in the long term management of nephrotic patient. They should be advised for urine examination in every morning during a relapse, during inter-current infections and if there is mild peri-orbital puffiness. Parents should maintain a diary showing the results of urine protein examination, drugs received and infections. Parents are to ensure normal activity and school attendance. Patients with both sensitive and resistant patterns, require frequent monitoring of chemical course and biochemical response, timely management of the disease with complication, in order to enable satisfactory long term outcome.

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