Nephrotic Syndrome in Infants and Children: An Updated Overview

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Abstract

Background: Idiopathic nephrotic syndrome (INS) is the most prevalent glomerular disease in children with an incidence ranging from 1 to 4/100,000 children/year. Nephrotic children are at high risk for severe pneumococcal infections as one of the life-threatening complications of nephrotic syndrome due to involvement of the immunosuppressive regimen and the acquired immune deficiency induced by nephrotic syndrome including decreased plasma IgG and low complement system components. Nephrotic syndrome (NS) is a common paediatric kidney disease. It is more common in children than adults. It is the clinical manifestation of glomerular diseases associated with characterized by leakage of protein from the blood into the urine through damaged glomeruli. It is classically defined by nephrotic-range proteinuria (≥40 mg/ m²/hour or urine protein/creatinine ratio ≥ 200 mg/mL or 3 + protein on urine dipstick), hypoaalbuminaemia (<25g/L) and oedema and hyperlipidemia (cholesterol>200mg/dl).

Nephrotic Syndrome

Epidemiology

The incidence of childhood NS is reported with substantial variability according to ethnic background and geographical location (3).

The incidence of idiopathic nephrotic syndrome (INS) varies among countries, Asia reporting a higher incidence in comparison to Western countries (3). The average incidence of nephrotic syndrome is 2-16.9 per 100,000 children worldwide (4).

The incidence of minimal change disease is higher in children with a reported incidence of 2 per 100,000 per year in Caucasian children and higher rates in Arabian and Asian children (5).

More than 95% of children with minimal change Nephrotic syndrome respond to corticosteroid therapy. The percentage of steroid responsiveness in mesangial proliferative disease is 50% and that with focal segmental glomerulosclerosis is 20% (6).
Thirty percent to 40% of steroid-resistant cases progress to end-stage renal disease within 5 years of disease process. Mesangial proliferative in 50%, membranoproliferative glomerulonephritis in 20–30%, focal segmental glomerulosclerosis in 21% of cases and membranous nephropathy in 7.3% progress to end-stage renal disease within 5 years of disease (6).

**Age:**
Childhood NS can occur at any age but is most common between the ages of 1½ and 5 years. Age at initial presentation has an important impact on the disease distribution frequency. 70% of MCNS patients are younger than 5 years; 20–30% of adolescent nephrotic patients have MCNS. FSGS develops in children at a median age of 6 years. During the first year of life, congenital (birth to age 3 months) and infantile (3–12 months) genetic disorders and congenital infections are much more common than MCNS and FSGS. (7).

**Sex:**
INS is a disease of pre-school aged children with peak age incidence of 2-3 years and affecting males more than females (8).

**Familial:**
Familial renal diseases may cause nephrotic syndrome, e.g. Alport's syndrome, nail-patella syndrome. Reflux nephropathy has a strong familial component and may cause renal failure (9).
INS is also a well-recognized phenomenon and the disorder has been reported in identical twins. In a report of 1877 children in Europe, 3.3% of children were found to have affected family members, most often siblings. The disorder tended to occur in the siblings at the same ages, and with similar biopsy findings and clinical outcomes (10).

**Aetiology**
The childhood nephrotic syndrome is principally idiopathic or primary, though a limited number of cases are secondary to glomerular and inclusive diseases and other infectious agents. Age reliant is also the etiology factor of nephrotic syndrome (11). Maximum cases presenting in the first 3 months of lifespan are mentioned as CNS (congenital nephrotic syndrome) and are caused by genetic diseases. While in the remaining of the first year of lifecycle (3–12 months) there has been no effective study of the etiology of nephrotic syndrome reported cases, there are a number of stats shows that up to 40% of reported cases meanwhile this time may also be due to genetic factors. At the time of first year and in the first decade of life, maximum presenting cases are due to primary or idiopathic nephrotic syndrome, at the time of first 10 years of lifecycle the number of secondary nephrotic syndrome cases increases (12).
Figure (I): Schematic drawing of the glomerular barrier. Podo = podocytes; GBM = glomerular basement membrane; Endo = fenestrated endothelial cells; ESL = endothelial cell surface layer (often referred to as the glycocalyx). Primary urine is formed through the filtration of plasma fluid across the glomerular barrier (arrows); in humans, the glomerular filtration rate (GFR) is 125 mL/min. The plasma flow rate (Qp) is close to 700 mL/min, with the filtration fraction being 20%. The concentration of albumin in serum is 40 g/L, while the estimated concentration of albumin in primary urine is 4 mg/L, or 0.1% of its concentration in plasma (13).

Genetic mutations in podocyte structure and function result in kidney dysfunction, presenting most often as either congenital or SRNS. Some of the earliest recognised genetic disorders involved genes encoding slit diaphragm proteins nephrin (NPHS1) and podocin (NPHS2) (14). Mutations in genes encoding the podocyte actin cytoskeleton, including CD2AP and INF2, are also associated with SRNS phenotypes. Finally, podocyte nuclear proteins (WT1), glomerular basement membrane proteins (LAMB2) and mitochondrial proteins (COQ2) are responsible for glomerular filtration dysfunction, leading to these more severe forms of progressive podocytopathies (14).

Immunedysregulation:
As immunosuppression with corticosteroids is the mainstay of treatment of nephrotic syndrome, it is logical to suspect immune dysregulation plays a pathogenic role in disease development. This hypothesis of immune dysregulation was initially postulated from clinical observations of NS occurring after exposure to allergens. Furthermore, there is evidence that Hodgkin’s and other T-cell lymphomas may trigger nephrotic syndrome, and chemotherapy can subsequently induce remission. Measles infection may also induce a temporary spontaneous remission in NS by depression of cell-mediated immunity and T-cell subsets. Although no particular cytokine triggers nephrotic syndrome, clinical patterns of disease occurrence certainly suggest that there is a role for T-cell dysregulation in the pathophysiology of disease (15).

CD80 (B7-1), a T-cell co-stimulatory molecule expressed in diseased podocytes, is a possible target for inhibitory therapy in the treatment of NS; however, the results of various trials are inconclusive (16).
Systemic circulating factors:
Circulating permeability factors may also play a role in the pathogenesis of nephrotic syndrome, as evidenced by the recurrence of proteinuria after renal transplantation in the setting of FSGS, and with induced remission of FSGS after plasma exchange, particularly in the early post-transplant period (17). Haemopexin is thought to alter the podocyte cytoskeleton, thereby increasing the albumin diffusion across the glomerular membrane. It has been identified in the urine of children with steroid-responsive NS and then shown to disappear during remission (17). It has also been postulated that the circulating factor might bind to galactose residues in the glycocalyx (17).
In FSGS, additional circulating factors include cardiotrophin-like cytokine 1 (CLC-1) which was isolated from the serum in patients with active FSGS and leads to increased glomerular permeability to albumin, as well as decrease nephrin expression in the glomeruli in ex vivo models (18). More recently, soluble urokinase-type plasminogen activator receptor (suPAR) has received much attention as a proposed circulating factor causing FSGS. Again, suPAR was a substance isolated from patient serum and was thought to act by deforming the podocyte cytoskeleton. In initial observational studies, suPAR was elevated in 70% of FSGS patients (significantly higher than in patients with MCD), and post-transplant levels were higher in those with recurrent FSGS than in those without (18).
Clinical features:
The characteristic presenting symptom in NS is oedema, with periorbital, labial/scrotal and lower extremity swelling (19). In more severe clinical scenarios, anasarca can develop, leading to ascites and pleural/pericardial effusions. This, in turn, can lead to abdominal pain from hypoperfusion and ileus, dyspnoea and cool extremities. Presence of abdominal pain should also trigger further investigation to rule out spontaneous bacterial peritonitis, a known and serious complication of nephrotic syndrome. In general, children with NS are at high risk of serious bacterial infections, such as peritonitis, sepsis and pneumonia owing to T-cell dysfunction and loss of immunoglobulins in the urine. Infection is the leading cause of morbidity, and, historically, mortality in children with NS (15).
Oliguria and intravascular volume depletion may also develop, sometimes leading to acute kidney injury (AKI), another important complication of nephrotic syndrome. Concomitant infections, use of nephrotoxic medications and SRNS add to the risk of developing AKI, especially in hospitalized patients with NS (20).
It is well recognized that NS is a hyper-coagulable state with a risk of developing deep vein thrombosis (DVT), cerebral sinus venous thrombosis, pulmonary embolism, renal vein thrombosis and, more rarely, arterial thromboses (21). The pathophysiology of the hypercoagulability is multifactorial and includes increased circulating prothrombotic factors (factor V and VIII and fibrinogen), dysfunction in platelet aggregation, urinary loss of anticoagulant factors (protein C and S, and antithrombin III) and intravascular volume depletion (21).
Oedema in nephrotic syndrome:
Two hypotheses have been proposed for the aetiology of oedema in nephrotic syndrome: the under fill and the overfill hypotheses (22).
Neither hypothesis fully explains the pathophysiology of oedema in NS as there is probably some overlap of children presenting intravascularly volume depleted and ‘under-filled’, euvolemic, or volume overloaded and ‘over-filled’.

**Complications:** Complications in nephrotic syndrome with massive proteinuria and hypoalbuminemia are:

1. **Infections:**
   - Bacterial: Peritonitis, cellulitis, sepsis, pneumonia, meningitis, urinary tract infections
   - Viral: Varicella, measles

2. **Hypovolemia and acute kidney injury** (acute renal failure)

3. **Thromboembolic complications** Venous:
   - Deep veins in extremities, cerebral venous sinuses, renal vein
   - Pulmonary, cerebral, extremities

4. **Loss of binding proteins**:
   - Vitamin D binding globulin, insulin like growth factor I and II, thyroid binding protein, Transferin, ceruloplasmin, cortisol binding protein

5. **Hyperlipidemia** and risk of cardiovascular disease.

6. **Complications due to use of medications**:
   - **Corticosteroids.** Cushingoid features (moon facies, hirsutism, shoulder hump, massive obesity, striae, reduction of muscle mass, thinning of skin), hypertension, behaviour disorders, osteoporosis, growth retardation, glucose intolerance, posterior subcapsular cataracts, myopathy, pseudotumor cerebri
   - **Cyclophosphamide.** Alopecia, hemorrhagic cystitis, bone marrow suppression, neutropenia, gonadal toxicity (azoospermia, ovarian fibrosis)
   - **Levamisole.** Neutropenia, vasculitis
   - **Mycophenolate.** Bone marrow suppression
   - **Cyclosporine.** Hirsutism, gingival hypertrophy, hypertension, nephrotoxicity
   - **Tacrolimus.** Diabetes, nephrotoxicity

**Treatment of nephrotic syndrome**

Treatment of NS includes 2 main items: general supportive management and definitive therapy (use of prednisolone or equivalent). (23).

**A- General Supportive Treatment:**

**1- Mobilization:**

- Bed rest may increase the risk of venous thrombosis. Children should be encouraged to mobilize as normal (23).

**2- Diet:**

- Reduce salt intake in the diet (avoid processed foods and adding salt to food). Give a diet with adequate calorific intake and sufficient protein content (1-2 g/kg daily). Dietary fat intake should be limited to <30% of calories. Fluid restriction is not usually necessary (if severe enough to need this then the patient may need admission) (23).

**3- Management of edema:**

- Children with severe symptomatic edema, including large pleural effusions, ascites, or severe genital edema, should be hospitalized. In addition to sodium restriction (<1500 mg daily), water/fluid restriction may be necessary if the child is hyponatremic. A swollen scrotum may be elevated with pillows to enhance fluid removal by gravity. Diuresis may be augmented by the administration of loop diuretics (furosemide), orally or intravenously, although extreme caution should be exercised. Aggressive diuresis
can lead to intravascular volume depletion and an increased risk for acute renal failure and intravascular thrombosis. When a patient has severe generalized edema with evidence of intravascular volume depletion (e.g., hemoconcentration, hypotension, tachycardia), IV administration of 25% albumin (0.5-1.0 g albumin/kg) as a slow infusion followed by furosemide (1-2 mg/kg/ dose IV) is sometimes necessary (24).

4- Management of dyslipidemia:
Dyslipidemia should be managed with a low-fat diet. Dietary fat intake should be limited to <30% of calories with saturated fat intake <10% calories. Dietary cholesterol intake should be <300 mg/day. There are insufficient data to recommend the use of 3-hydroxy-3-methylgluataryl coenzyme A (HMG-CoA) reductase inhibitors routinely in children with dyslipidemia (25).

5- Infection:
Streptococcus pneumoniae and Gram-negative organisms are the commonest pathogens causing possible peritonitis, septicemia and cellulitis. Prophylactic oral phenoxymethylpenicillin (12.5 mg/kg twice daily) administration is recommended while the child is edematous and any suspected infection should be promptly treated with broad-spectrum antibiotics while awaiting culture (23).

6- Immunization:
Live vaccines should not be given to immunosuppressed children. Children with steroid-sensitive nephrotic syndrome are considered immunosuppressed if they have received daily steroids for greater than 1 week in the previous 3 months. A live vaccine can however be given if the child is on a low dose alternate day regimen (23). Administration of polysaccharide pneumococcal vaccine (PPV23) has been recommended for all children with nephrotic syndrome aged ≥2 years (26).

Thromboembolism:
Children who present with the clinical signs of thromboembolism should be evaluated by appropriate imaging studies to confirm the presence of a clot. Anticoagulation therapy in children with thrombotic events appears to be effective as low-molecular-weight heparin, and warfarin. Mobilization should be encouraged to avoid thromboses whilst in a potentially hypovolemic state and indeed measures should be taken to avoid hypovolemia. Bed rest should also be avoided (27).

B- Definitive Therapy:
1. Corticosteroids
   1) First, prednisone 60 mg/m²/day or 2 mg/kg/day once daily for 4 weeks (maximum 60 mg).
   2) Next, prednisone 40 mg/m²/day or 1.5 mg/kg/day as a single dose every 48 h for 6 weeks (maximum 40 mg).

In recommendations by KDIGO (Kidney Disease: Improving Global Outcomes), in the chapter “Steroid-sensitive nephrotic syndrome” it is mentioned that daily treatment can be administered for 4-6 weeks. It is also suggested to indicate treatment on alternate days for a period of 2-5 months, gradually reducing the dose (28).

In this regard, various studies have shown that prolonging the initial treatment (i.e., the first time that the patient receives the steroid treatment) of INS in children for periods varying from 3 to 7 months significantly reduces the number of relapses per patient per year and the number of children with frequent relapses (2).

Approximately one third of children with INS will present a single episode of nephrotic problems and after responding to steroid treatment will not present relapses after 18-24 months of the initial response and will likely remain in permanent remission (29).
Approximately 10-20% of patients who respond to the initial steroid treatment will relapse several months after the first episode and will present permanent remission after an additional three to four relapses after responding to new steroid treatments. Finally, ~50% of children will continue to experience relapses and will be classified as frequently relapsing or steroid dependent (30).

In patients with steroid-dependent INS or with frequent relapses, a scheme of corticosteroids has been suggested that consists of administration of prednisone at doses of 40-60 mg/m²/day until the proteinuria is corrected for 4 to 5 days. Subsequently, prednisone is indicated on alternate days and the dose is reduced to 15-20 mg/m²/day according to the prednisone level at which the prior relapse occurred. This treatment is continued for 12 to 18 months, trying to maintain the dosage of prednisone as low as possible to minimize adverse effects. With this scheme it has been observed that the growth rate of the children is apparently not affected (31).

If the treatment on alternate days does not maintain remission of the NS, it has been suggested to administer the prednisone daily at the lowest possible dose to maintain the remission for at least 3 months (32).

Algorithm (III): Treatment algorithm for NS in newly nephrotic child according to KDIGO 2020 (33).

2- Alternative Therapies:
Steroid-dependent patients, frequent relapsers and steroid-resistant patients are candidates for alternative therapies, particularly if they have severe corticosteroid toxicity (cushingoid appearance, hypertension, cataracts, and/or growth failure). Steroid Resistance is defined as the failure to achieve complete
remission after 8 weeks of corticosteroid therapy. SRNS is usually caused by FSGS (80%), MCNS, or MPGN (34)).

A- Alkylating agents:
Cyclophosphamide and chlorambucil have been used with good effect in children with INS who have frequent relapses or are steroid dependent and who developed serious side effects with prolonged steroid treatment. Treatment is recommended at a dose of 2 mg/kg/day of cyclophosphamide as a single dose for 8 to 12 weeks, with maximum cumulative dose of 168 mg/kg (35).

Cyclophosphamide is begun after remission of proteinuria has been obtained with steroid treatment; the latter being progressively terminated during the following days. Chlorambucil is indicated at a dose of 0.1-0.2 mg/kg/day for 8 weeks with a maximum cumulative dose of 11.2 mg/kg (34).

Alternate-day prednisone therapy is often continued during the course of cyclophosphamide administration. During cyclophosphamide therapy, the white blood cell count must be monitored weekly and the drug should be withheld if the count falls below 5,000/mm³. The cumulative threshold dose above which oligospermia or azoospermia occurs in boys is >250 mg/kg. Two studies have shown that intravenous cyclophosphamide (500 mg/m²/dose for six monthly doses) was more effective than oral cyclophosphamide (2mg/kg/day for 12 weeks) in reducing the risk for relapse at 6 months but not at 2 years. Cyclophosphamide induced remission for at least 2 years in 70% of children with FRNS; however, it induced remission in fewer than 30% of children with SDNS. The potential side effects of cyclophosphamide (neutropenia, disseminated varicella, hemorrhagic cystitis, alopecia, sterility, increased risk of future malignancy). Because cyclophosphamide is rarely associated with hemorrhagic cystitis, it is suggested that cyclophosphamide should be administered when the child is in remission and can receive a high fluid intake (34).

B- Calcineurin inhibitors:
Cyclosporine is usually started at 4 to 5 mg/kg/day, adjusted dosing of cyclosporine according to blood levels is more effective in maintaining remission than fixed-dose administration. Tacrolimus is typically administered at 0.1 to 0.2 mg/kg/day (36). Cyclosporine is the most widely used calcineurin inhibitor in patients with SDNS or FRNS and it is proved to decrease the number of relapses. However, there is a high incidence of cyclosporine dependency and it is also associated with more relapses if it is restarted after a period of discontinuation. Cyclosporine is also used to treat SRNS and particularly FSGS. Gingival hypertrophy and hirsutism are common side effects. Nephrotoxicity is a significant side-effect and the trough levels should be regularly monitored. Tacrolimus has also been used in SSNS patients who have been resistant to cyclosporine. The mechanism of action of Tacrolimus is similar to cyclosporine and there are reports that both drugs have comparable efficacy. Tacrolimus has a more favorable side-effect profile. However nephrotoxicity remains an important adverse effect (37).

C- Mycophenolate mofetil (MMF):
MMF is inhibitor of the de novo purine pathway with inhibitory effects on T and B lymphocyte proliferation, in recent years MMF has been used in FRNS and SDNS. Treatment at a dose of 1200 mg/m²/day for at least 12 months is recommended, as most children will relapse when MMF is stopped. The side effects of MMF include gastrointestinal discomfort, malaise, diarrhea, acne and leukopenia (38).

D- Levamisole:
This anthelminthic agent has been shown to have immunomodulatory properties and can be used as a steroid sparing agent. Administered at 2.5 mg/kg on alternate days for at least 12 months for children with SDNS or FRNS. Unfortunately the effect is not sustained once the levamisole is discontinued. It is
associated with photosensitive rash, hepatotoxicity and bone marrow suppression. The latter is monitored with a full blood count every 3 months (39).

E- Rituximab:
Rituximab is anti CD20 monoclonal antibody, it is highly effective in inducing and maintaining remission in SDNS. The drug causes complete depletion of circulating B lymphocytes and may thereby modulate regulatory T lymphocyte activity. Rituximab is infused at a dose of 375 mg/m² over 6h (40). Remission rates tend to be higher with two to four once-weekly doses (40% to 60% at 11 to 29 months) as compared to single dosing (25% to 40% at 12 to 17 months). (41). Favorable reports have been published of cases of patients with steroid-dependent INS who have attained a prolonged remission of proteinuria (>9 months) with rituximab treatment in conjunction with corticosteroids and tacrolimus (40). Side effects include agranulocytosis (10%). However there are concerns about side effects that are rare but serious. Opportunistic infections, pulmonary fibrosis and progressive multifocal leukoencephalopathy have been seen in patients treated with rituximab for other reasons (37).

References


