

Steroid Sensitive Nephrotic Syndrome in Children

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Abstract

Nephrotic Syndrome (NS) is one of the most frequent glomerular diseases seen in children. Children who go into complete remission following treatment with corticosteroids are classified as having "steroid sensitive" NS. In developed countries over 80% of children with idiopathic NS have steroid sensitive disease although response to steroids is somewhat tempered in developing countries, especially in black children, the majority of whom have steroid resistant disease.

The exact pathogenesis of this condition remains elusive. Podocyte injury and proteinuria are the two main issues in the pathogenesis. Recent studies suggest alterations in both innate and adaptive immune responses. There is release of cytokines by T-cells as well as a strong contribution of B-cell immunity. Genetic studies have reported human leucocyte antigen (HLA) class II antigens DR and DQ associations linked to steroid sensitive NS and in small case studies, single gene mutations e.g. *PLCE1* although to date no homozygous mutations in *NPHS1* or *NPHS2* and *WT-1* genes have been reported.

Most children with steroid sensitive NS have multiple relapses and a significant percentage also develop steroid dependent NS. These children receive multiple courses of steroids and are at high risk of developing steroid toxicity. Patient with frequent relapses who develop steroid dependency thus require alternative treatment. Steroids sparing agents used include levamisole, cyclophosphamide, mycophenolate mofetil (MMF), calcineurin inhibitors (cyclosporine and tacrolimus), rituximab and vincristine. The steroid-sparing effects of these agents have greatly reduced the adverse effects seen with long-term use of steroids.

Despite the wide arsenal of agents available, therapy needs to be individualised to achieve optimal care of each child. More randomised controlled trials are required to evaluate the therapeutic and economic efficacy of this agent, define criteria for selection of patients for use of particular agents and to determine the safety profile of these drugs in children.

This article reviews the epidemiology, pathogenesis, clinical presentation, diagnosis, complications, management and long term outcome of children with steroid sensitive NS.

Keywords: Nephrotic syndrome; Steroid sensitive; Children; Review

Introduction

The Nephrotic Syndrome (NS) is characterised by a triad of massive proteinuria (>40 mg/m² per hour or 50 mg/kg per day), hypoalbuminaemia (≤ 2.5 mg/dL), and hyperlipidaemia (serum cholesterol >200 mg/dL or 6.5mmol/L) [1,2]. Other supporting characteristics include the presence of oedema and a raised β_2 globulin on serum electrophoresis, although these are not essential for the diagnosis. In physicians managing young children in whom 24 hour urine collections are difficult, the Children's Nephrotic Syndrome Study Group Consensus Conference recommended the use of the protein: creatinine ratio on a spot early morning sample of urine with a urine protein: creatinine (Up/Ucr) ratio ≥ 2.0 [2].

NS may be classified according to aetiology (primary or secondary), age of onset (congenital, infantile, acquired or late onset NS), or histopathology (e.g. minimal change disease, mesangial hypercellularity, focal segmental glomerulosclerosis (FSGS), membranous, membranoproliferative). However the most useful classification for management purposes is to define the disease according to its response to steroids (steroid sensitive or resistant with steroid sensitive disease being further classified into frequent relapses and steroid dependent NS) as patients who are steroid sensitive have an excellent prognosis with preservation of kidney function whilst those that are steroid resistant are more prone to complications with a high risk of having deterioration of kidney function and progression to end-stage kidney disease needing renal replacement therapy. More recently single gene mutations affecting podocyte differentiation and function have been described,

particularly in steroid resistant disease, predicting unresponsiveness to immunosuppressive therapy [3].

The characteristics of the NS presenting in childhood varies considerably in developing countries compared to developed countries, influenced by environmental factors, infections and ethnic origin, which determine the histological expression of the disease [4]. Whilst in developed countries steroid sensitive minimal change disease predominates, the NS amongst black children in Africa does not conform to the model established in other continents [5]. Black children have a paucity of minimal change disease and an increasing frequency of focal segmental glomerulosclerosis (FSGS), a high incidence of steroid resistant disease, a less satisfactory outcome and an identifiable causative agent in many [5].

Acquired NS is a disease characterised by recurrent relapses necessitating the use of immunosuppression with its attendant complications. Children with steroid resistant NS have an increased

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risk of developing end-stage kidney disease with a need for renal replacement therapy. Perhaps the greatest challenge is the risk of recurrence of the disease post-transplant, which is 30-50% for the first graft and higher for subsequent one [6]. The nature of the condition and the proportion of familial forms of NS have led to much work on the genetics of NS, with a resultant expansion in the knowledge of genes involved.

This article reviews the pathogenesis, clinical presentation, diagnosis, complications, management and long term outcome of children with steroid sensitive NS.

Epidemiology of Nephrotic Syndrome

The epidemiology of NS has been clearly delineated in developed countries from well-resourced registries and hospital records. Estimates on the annual incident of idiopathic NS range from 2-7 per 100 000 [4,7,8], and prevalence from 12-16 per 100 000 [8]. Idiopathic NS accounts for over 95 per cent of cases in developed countries; an underlying disorder such as systemic lupus erythematosus, Henoch-Schönlein purpura, infections such as parvovirus B19, human immunodeficiency virus (HIV-1) and hepatitis B or C being identified in less than 5% of cases. Over 80% of children with idiopathic NS will have minimal change disease characterized by normal renal histology on light microscopy and over 95% are likely to be steroid sensitive [8]. The majority of the remaining patients have focal segmental glomerulosclerosis and mesangioproliferative glomerulonephritis. Mesangiocapillary or membranoproliferative glomerulonephritis and idiopathic membranous nephropathy are uncommon in childhood and almost all are steroid resistant [5,9,10].

In developed countries the epidemiology of NS is strongly influenced by race, environmental factors and access to health care [5,11]. There is epidemiological evidence of a higher incidence of NS in children from South Asia [8,12]. In Africa, Black children have a pattern of disease that varies from that described in developing countries; there is a paucity of minimal change disease, steroid resistance in the majority, accelerated progression to end-stage kidney disease and an identifiable causative agent in many [5,13,14]. The lack of facilities for renal biopsy, absence of registries and access to proper documentation has made it difficult to determine the true incidence of NS in developing countries.

Pathogenesis of idiopathic nephrotic syndrome

Whilst the precise mechanism of podocyte injury and proteinuria which are the two main issues in the pathogenesis of idiopathic NS remain elusive, recent studies suggest alterations in both innate and adaptive immune responses, including evidence of impaired T-cell regulatory function [15].

i. Immunological dysfunction

Initial evidence for an immunological basis for NS pointed to a T-cell disorder. These cells release cytokines that act on the glomeruli to induce an increase in permeability to plasma proteins. Evidence for this hypothesis includes [16]:

- Absence of immune deposits in glomeruli in idiopathic NS.
- Occurrence of remission following measles infection that suppresses T-cell function.
- An association of NS with Hodgkin lymphoma.
- Response to immunosuppressive agents that inhibit T-cells e.g. corticosteroids and calcineurin inhibitors.

The dominant paradigm is an imbalance between T-helper 1 (Th1) and T-helper 2 (Th2) cytokines. Immune dysfunction results in production of a circulating factor that affects the slit diaphragm, resulting in selective proteinuria [17]. Although this circulating factor has not yet been clearly identified, it is presumably interleukin 13, although other molecules suggested include soluble urokinase plasminogen activator receptor, soluble CD80, vascular endothelial growth factor, and angiotensin-like-4 [17]. Recent evidence suggests an activation of innate immune responses to triggering of toll like receptors by microbial products, even directly on podocytes [18]. Signalling through nuclear factor Kappa β (NF- κ B) and toll like receptors mediated pathways may polarize adaptive immune responses towards Th-2 cells, or directly increase CD80 expression in podocytes, and/or helper responses [19]. Finally, the direct effect on podocytes of therapeutic agents like rituximab (an anti-B cell agent), provides evidence for interaction between B cells and T helper cells in the pathogenesis of NS.

ii. Mechanism of proteinuria

Proteinuria in NS is due to increased filtration of macromolecules (e.g. albumin) across the glomerular filtration barrier. The latter consists of the fenestrated capillary endothelial cells, glomerular basement membrane, and the podocytes which are highly specialised epithelial cells. The podocytes inter-digitating foot processes connect to form a slit diaphragm membrane which is a dynamic structure controlling the ultrafiltration of molecules by its signalling to the cytoskeleton of the podocyte [20].

The filtration of macromolecules across the glomerular filtration barrier is restricted by two mechanisms: charge-selectivity and size-selectivity. The endothelial cells and glomerular basement membrane have a net negative charge due to polyamines such as heparin sulphate proteoglycans that creates a charge barrier to the filtration of large anions such as albumin.

The glomerular capillary wall has size-selective pores located across the glomerular basement membrane at the slit diaphragm between the adjacent epithelial cell foot processes with an approximate radius of 40 to 45Å (albumin has a radius of approximately 36Å). In certain forms of NS (other than minimal change disease), structural injury seen by light microscopy results in an increase in the number of large pores in the glomerular basement membrane. This structural damage allows movement of normally restricted proteins of varying sizes (including large neural proteins, such as IgG) across the filtration barrier [21].

iii. Genetics

Genetics screening paradigms for congenital and infantile NS are well established. Genetic mutations are present in 10-20% of patients with SRNS, and in a higher proportion of patients with familial NS (13% for autosomal recessive and 30% in autosomal dominant NS) [22,23]. The age of disease onset is an important predictor of the odds findings an abnormality in a particular gene linked to steroid resistant NS. The first evidence for genetic mutation in steroid sensitive NS was reported in 14 children from seven families with variable forms of idiopathic NS and mutations in the *PLCE1* gene leading to an autosomal recessive phenotype [24]. To date no homozygous mutations in *NPHS1* or *NPHS2* and *WT-1* have been identified in patients with steroid sensitive NS [25]. Several studies have reported associations of human leukocyte antigen (HLA) class II antigens DR and DQ associations linked to steroid sensitive NS [26]. Patients with steroid resistant NS on the other hand show mutations in genes coding key podocyte proteins that constitute the slit diaphragm or the podocyte cytoskeleton. These genes

include *inter alia* *NPHS1*, *NPHS2*, *CD2AP*, *TRCP6* and *ACTN4*. Genes expressed in the glomerular basement membrane include *LAMB2* whilst others are expressed in mitochondria (*COQ2*), or encode transcription factors necessary for normal development (*WT1* *LMX1B*) [15] (Table 1).

NS in children has been shown to be associated with HLA class II alleles based on serologic and DNA typing. Studies have demonstrated strong associations with HLA DR and HLA DQ with relatively weak associations with HLA A and B alleles. In developed countries, HLA antigens, which have all been performed on Caucasian children with MCNS or steroid-responsive NS (SRNS), have detected associations with HLA B and DR locus genes. In a report from South Africa, HLA Bw44, which is part of HLA B12, was found to be significantly more frequent in Indian children with minimal change NS or steroid sensitive NS than in controls (45 and 12%, respectively, p less than 0.04; relative risk 5.8). In contrast, black children with membranous nephropathy (the majority of whom were Hepatitis B carriers) had a significantly increased frequency of HLA Bw21 (15% in patients and 1% in controls, p less than 0.04; relative risk 22.1) [27]. In another study, atopic systems were demonstrated to be more common in children with steroid sensitive NS than in matched controls, and HLA-B12 was more common in children with steroid sensitive NS than in adult controls. Atopic symptoms (particularly hay fever), positive prick tests with grass pollen antigens, and a higher mean serum concentration of IgE antibody to timothy grass pollen were more common in nephrotic children with HLA-B12 than in those without HLA-B12. There was also an increased frequency of the haplotype HLA-A1 and HLA-B8, mainly among the non-atopic patients [28].

Pathology

Minimal change disease with minor glomerular abnormalities on light microscopy is present in over 80% of patients with idiopathic NS [29]. Immuno fluorescence is negative in the majority of cases for glomerular deposits of immunoglobulin or complement and the only significant findings are on electron microscopy that shows effacement of podocyte foot processes with disruption and disorganisation of actin filaments and fusion of epithelial foot processes. Mesangial proliferation characterised by the presence of >3 cells per mesangial lobe, is found in a small proportion of cases.

In most cases of steroid resistant NS and in 5-10% of cases of steroid sensitive NS histopathological findings show FSGS [30]. Various subtypes of FSGS have been described based on the location of sclerosis. These include: (i) tip lesions, (ii) cellular variant, (iii) perihilar lesions, (iv) unclassified, and (v) collapsing variant. The collapsing variant is most often associated with human immunodeficiency virus, parvovirus infection or lupus and has rapid progression to end-stage kidney disease (within 2 -3 years) if left unchecked. There has been a rising incident of FSGS in recent years, the reason(s) for which remain elusive [31]. Approximately 15% of patients with steroid resistant NS show membranous proliferative glomerulonephritis, membranous nephropathy, IgA nephropathy or amyloidosis. Several syndromic forms are associated with diffuse mesangial sclerosis [15].

Steroid sensitive nephrotic syndrome

The commonest form of Steroid Sensitive (SS) NS in children is idiopathic NS [4]. This is in contrast to adults where it accounts for only about 25% of cases [32]. Histopathological findings in these children include predominantly minimal change disease with the remainder having diffuse mesangial proliferation or FSGS on light microscopy.

The children have a disease course that is variable: about a third have one attack and following a course of corticosteroids, maintain remission; 10-20% experience relapses several months after stopping treatment and after three or four episodes of relapses, maintain remission following a standard course of corticosteroid therapy, the remaining 40-50% of patients experience frequent relapses either shortly after treatment is stopped (frequent relapses) or when the dose of steroids is decreased (steroid dependent). Although patients with steroid dependent NS have a prolonged course, provided they remain steroid sensitive, this group of children as well as those with frequent relapses who are all steroid sensitive, have an excellent prognosis with minimal risk for progression to end-stage kidney disease. The definitions of the various forms of NS based on response to steroids are shown in Table 2.

Clinical presentation

The disease may present in the first year of life but usually manifests between the ages of two and seven years. The major presenting symptom is sudden onset of oedema often preceded by an upper respiratory tract infection or allergic reaction like an insect bite Oedema becomes

Gene	Locus Protein	Location	Inheritance	Gene	Phenotype; specific histology, if any
<i>NPHS1</i>	19q13.1	Nephrin	Slit diaphragm	AR	Congenital nephrotic syndrome; characteristics changes
<i>NPHS2</i>	1q25-31	Podocin	Slit diaphragm	AR	Congenital nephrotic syndrome or early onset SRNS; focal segmental glomerulosclerosis (FSGS)
<i>PLCE1/NPHS3</i>	10q23	Phospholipase C epsilon 1	Intracellular	AR	Early onset SRNS; diffuse mesangial sclerosis (DMS); FSGS
<i>WT1</i>	11p13	Wilms' tumor 1	Intracellular	AD	Early onset SRNS, Denys-Drash or Frasier syndrome; DMS (Denys-Drash syndrome) FSGS (Frasier syndrome)
<i>LAMB2</i>	3p21	Laminin-β2	Glomerular basement membrane	AR	Pierson syndrome, early onset SRNS; DMS (syndromic); FSGS (isolated)
<i>CD2AP</i>	6p12.3	CD2 associated protein	Slit diaphragm	AD	Adult onset SRNS (heterozygous), early onset FSGS (homozygous), FSGS
<i>ACTN4</i>	19q13	α-actinin-4	Intracellular	AD	Adult onset SRNS (incomplete penetrance; slow progression); FSGS
<i>TRCP6</i>	11q21-22	Transient receptor Potential ion channel 6	Cell surface	AD	Adult onset SRNS; FSGS
<i>INF2</i>	14q32	Inverted formin 2	Intracellular	AD	Adult onset SRNS; FSGS
<i>LMX1B</i>	9q34.1	LIM-homeodomain transcription factor 1β	Intracellular	AD	Nail-patella syndrome, SRNS
<i>APOL1</i>	22p	Apolipoprotein L1	Intracellular	Complex	Adult onset SRNS (incomplete penetrance); FSGS

Table 1: Genetics of Nephrotic Syndrome.

Remission:	Urine protein <4 mg/m ² /h or nil/trace on Albustix for 3 consecutive early morning specimens.
Relapse:	Urine protein >40 mg/m ² /h or Albustix 3+ or 4+ for 3 consecutive early morning specimens, having been in remission previously.
Frequent relapses:	Two or more relapses within 6 months of initial response or four or more relapses in any 12 months.
Steroid dependence:	Two consecutive relapses during corticosteroid therapy or within 14 d of its discontinuation.
Steroid resistance:	Absence of remission despite therapy with daily prednisolone at a dose of 2 mg/kg per day for 4 wk (in some institutions 3 methylprednisolone pulses are given in addition before steroid resistance is diagnosed).
Early non responder:	steroid resistance during the first episode.
Late non responder:	steroid resistance in a patient who had previously responded to corticosteroid therapy

Adapted with permission from: Sinha A, Bagga A. Nephrotic syndrome. *Indian Journal of Pediatrics* 2012; 79(8): 1045-55

Table 2: Definitions.

clinically detectable when fluid retention exceeds 3 to 5 percent of body weight. The initial manifestation is usually periorbital oedema that is often misdiagnosed as a manifestation of allergy. As oedema is gravity dependent, once the child is in an upright position, periorbital oedema decreases while oedema of the lower extremities increases. In the reclining position, oedema is localized to the back and sacral area. Other dependent areas that become oedematous include the scrotum, penis, or labia. The oedema is soft, pitting and the shin over the area becomes stretched and shiny.

Some patients may develop anasarca with marked periobital oedema resulting in swollen shut eyelids, marked peripheral oedema, abdominal distension due to ascites, marked scrotal or vulval oedema and pleural and pericardial effusion. Rapid formation of ascites is often associated with abdominal pain and malaise. Abdominal pain may also be due to hypovolemia, peritonitis, vascular thrombosis or rarely pancreatitis. In severe cases cardiovascular shock secondary to the sudden fall in the serum albumin level may develop leading to abdominal pain and symptoms of peripheral circulatory failure with cold extremities and hypotension [33,34].

Other clinical findings include the following: umbilical or inguinal hernias; dyspnoea from respiratory compromise due to pleural effusions or severe ascites; nonspecific complaints such as malaise, fatigue, irritability and headaches and sometimes gross haematuria. Gross haematuria is rare but seen in children with glomerulonephritis that develop NS. Microscopic haematuria may be present in up to 20% of cases of idiopathic NS. Sometimes respiratory symptoms may be due to lung infection or pulmonary embolus due to the hypercoagulable state associated with NS.

The blood pressure is usually normal in most children. Hypertension is common in children with glomerulosclerosis who have advanced chronic kidney disease (stage III-V) or glomerulonephritis [35].

Diagnosis of nephrotic syndrome

In the initial evaluation of a child with NS, history and physical examination is directed towards exclusion of a possible secondary aetiology, noting prior treatment and evidence of infections [36]. Although oedema is usually the initial presenting sign, the diagnosis of NS is confirmed by the presence of nephrotic range proteinuria and hypoalbuminaemia.

Urine tests

Urine protein excretion: A quantitative measurement of protein excretion is based upon a timed 24-hour urine collection. Nephrotic range proteinuria is defined as >50 mg/kg/day or 40 mg/m²/hour, however the mean value during the first few days may be higher as urinary concentration of proteins also depends on plasma albumin concentration. Also if the plasma albumin is extremely low this may result in falsely low urinary albumin excretion and replenishing with albumin infusions to determine true urinary protein excretion is needed.

Urine dipstick analysis: Urinary dipstick analysis measures protein concentration rather than the rate of protein excretion and therefore cannot be used to accurately define nephrotic range proteinuria. 'Nephrotic range' proteinuria on urinary dipsticks analysis is defined as 3+ or more (300- 2000mg/dl) urine protein in the first morning urine for three consecutive days [15]. This is often used as a screening test while awaiting information from quantitative protein excretion studies.

Accurately timed urine collections are different in young children. Hence an alternate method using the total protein: creatinine ratio on a spot urine sample is used. A urine protein: creatinine ratio >300mg protein/mmol creatinine or >2 (protein in mg/dl/creatinine in mg/dl) equates to nephrotic range proteinuria [15].

Urine microscopy: Patients with NS usually have inactive urine sediment. Microscopy usually reveals oval fat bodies and hyaline casts with no or few red cells and other cellular elements. Haematuria may be seen in 20% of children with minimal change disease but is more common in FSGS and glomerulonephritis [35].

Blood tests

Serum proteins: Hypoalbuminuria is a defining criteria for NS with the severe albumin usually <25g/L. In severe cases of NS, serum albumin drops to levels <10g/L [1]. Serum globulins are relatively preserved with normal or slightly decreased levels of serum alpha-1 globulin and increased alpha-2 and beta globulin. Gamma globulins vary according to the aetiology of NS but typically are reduced in idiopathic NS (particularly minimal change disease).

Lipids: Total serum lipids (including cholesterol and triglycerides) are elevated with the increase in serum cholesterol inversely correlated to the serum albumin concentration.

Blood urea and severe creatinine: In about 30 to 40 percent of children with idiopathic NS the blood urea and serum creatinine levels may be elevated (blood urea being disproportionately higher than severe creatinine), due at least in part to hypovolemia [15,37]. Nephrotics have hyperfiltration with the estimated glomerular filtration rate (eGFR) typically elevated above normal corrected for age and sex.

Other blood studies: Full blood count may show increased haemoglobin and haematocrit due to volume contraction, particularly in minimal change disease. Thrombocytosis with platelet counts between 500 000 to 1 million counts per microlitre is a common finding. Haemo concentration and thrombocytosis may contribute to hypercoagulability and thrombotic complications [38].

Serum complement is typically normal in children with idiopathic NS. Low C3 is typically seen in membranoproliferative glomerulonephritis, whilst both low C3 and C4 are found in lupus nephritis.

Electrolytes disturbances

Hyponatremia resulting from hypovolemia stimulating of the release of antidiuretic hormone (ADH) with decreased free water excretion may be present in some cases. Hypocalcaemia and hypomagnesaemia are common in patients given diuretics and sometimes are symptomatic necessitating replacement therapy.

Screening for secondary causes of nephrotic syndrome

In developing countries secondary forms of NS are common and hence it is important to exclude these based in clinical and laboratory findings. Although the clinical presentation of NS is stereotyped, some findings on clinical examination such as lymphadenopathy, skin rash, arthritis, hepatosplenomegaly, signs of chronic lung disease and nutritional status with severe wasting may suggest a secondary aetiology.

Routine screening for common aetiological agents is therefore undertaken in most units based in the epidemiology of disease in the particular region. Viral studies include the following: hepatitis, human immunodeficiency virus cytomegalovirus, Epstein Barr virus, parvovirus, herpes type 1 and 2 or other viruses endemic to the region. Screening for common bacterial infections include: β -haemolytic streptococcal infections (throat swab anti-streptolysin O antigen or anti-DNAase) and tuberculosis (tuberculin skin testing, chest X ray, Quantiferon gold, and the geneExpert tests). In various regions parasitic infestations e.g. schistosomiasis are common and should be excluded. Screening for anti-immune disease (e.g. systemic lupus erythematosus) should include tests for anti-nuclear antibodies.

Differential diagnosis

Need to exclude other causes of oedema in childhood. NS is distinguished from other causes of oedema by the presence of hypoalbuminaemia and nephrotic range (massive proteinuria (>50 mg/kg per day or ≥ 40 mg/m²/hour). The differential diagnosis for oedema includes:

- Heart failure
- Protein energy malnutrition
- Chronic liver disease
- Protein losing enteropathy
- Increased capillary permeability due to allergic reaction or hereditary angioedema. The oedema in this setting is typically found to be focal

Complications of Nephrotic Syndrome

Complications of idiopathic nephrotic syndrome NS may arise as a result of the disease itself or secondary to treatment. In children with secondary forms of NS, these may include complications of the primary disease causing the NS.

There are five major complications directly related to the nephrotic state in children with idiopathic NS include: severe infections, thromboembolism, renal impairment, anasarca, hypovolemia and growth retardation.

(i) Infection

Factors predisposing to an increased risk of infection in children with NS include: reduced serum concentration of immunoglobulin [39], impaired ability to make specific antibodies [40], decreased levels

of alternative complement pathway viz. factor B and D [41-43] and immunosuppressive treatment.

The most frequently encountered infections include: upper respiratory tract infections, urinary tract infections, peritonitis, pneumonia, acute gastroenteritis and empyema.

Children with NS are at increased risk of developing bacterial infections, especially with encapsulated bacteria, due in part to loss of opsonizing factors [41,43]. Ascites and pleural effusions provide a natural culture medium for bacterial growth thus predisposing to pneumonia, empyema, and peritonitis [44]. Other serious infections include septicaemia, meningitis and cellulitis [45,46].

Common gram positive organisms include *Streptococcus pneumoniae*, *Streptococcus haemolyticus* and *alpha-haemolytic Streptococcus* [47,48]. In developing countries gram negative organism such as *Escherichia coli* and *Klebsiella pneumoniae* are also common [44].

The mortality rate in children with infections primarily due to NS has significantly decreased following the use of antibodies and glucocorticoids [49,50]. To prevent serious complications and death from pneumococcal infections, all children with NS should receive pneumococcal vaccine if not previously immunised.

Viral infections, particularly varicella, can cause significant morbidity and mortality in patients with NS [51-53]. Vaccination is effective in preventing varicella infections and for children already infectious, treatment with high dose acyclovir is indicated.

(ii) Thromboembolism

Factors that increase the risk of thromboembolism in children with NS include: hemoconcentration; immobility (common in patients with anasarca); severe infections; and a hypercoagulable state (due to thrombocytosis; decrease levels of antithrombin III, free proteins, and plasminogen from increased urinary loss); increased platelet activation, hyperfibrinogenemia; high molecular weight fibrinogen moieties in the circulation [54,55].

The incidence of thrombotic complications is between 2 and 3 percent [54]. Both arterial and venous thrombosis has been reported with common sites being the pulmonary artery, renal vein, deep leg veins, inferior vena cava, and femoral iliac artery [54,56,57]. Other sites include the cerebral and meningeal arteries, mesenteric and hepatic veins [54,56,58,59].

Thromboembolic complications may be associated with significant mobility including pulmonary embolism and renal vein thrombosis [60-62]. Pulmonary embolic episodes are silent [63]. Many pulmonary embolisms in children with NS should be suspected if they present with pulmonary or cardiovascular symptoms and can be confirmed by angiography or radioisotope scanning [64].

Prophylaxis anticoagulation is not recommended unless the patient has a high risk for thrombosis or a previous thromboembolic event. Factors that increase the risk for thrombosis include: serum albumin concentration less than 2 g/dL (20 g/L); fibrinogen greater than 6g/L and/or antithrombin III level less than 70 percent normal.

(iii) Acute kidney injury

Children with NS can have reduced glomerular filtration rate because of one or more of the following mechanisms viz. hypervolaemia and glomerular injury due to the underlying glomerular pathology.

Progression to chronic kidney disease (stage I-IV) leading to end-

stage kidney disease (stage V) occurs in some patients, especially in children with steroid resistant NS but rarely in children with steroid sensitive disease.

(iv) Anasarca

This is associated with the following complications viz. scrotal or vulvar oedema resulting in inability to walk and large pleural effusions and/or ascites leading to impaired diaphragmatic movement resulting in respiratory distress.

(v) Hypovolemia

This is most common in children with minimal change disease resulting in a decrease glomerular filtration rate. Clinical signs included tachycardia, signs of peripheral vasoconstriction (cold, clammy peripheries with reduced volume pulses), and oliguria. Laboratory findings include raised plasma renin, aldosterone, and norepinephrine levels [45]. Typically hypovolemia occurs during the first presentation or a severe relapse. Overzealous use of diuretic, sepsis and gastroenteritis can lead to hypotension and, if severe, shock.

(vi) Growth

Children with NS can develop growth retardation due to malnutrition or as a complication of long-term steroid treatment.

Management of the Initial Episode of Nephrotic Syndrome

Once secondary forms of NS have been excluded, a presumptive diagnosis of minimal change disease can be made based upon various clinical and laboratory findings. In over 90 percent of cases children with minimal change disease will respond to steroids within eight weeks [29]. Based on this observation, empiric steroid treatment can be initiated with a high probability of steroid responsiveness in idiopathic NS without the need for a kidney biopsy if the following criteria are satisfied.

- Age older than 1 year and less than 10 years.
- Absence of hypertension and gross haematuria.
- Normal serum complement.
- Normal kidney function.

The above groups of patients with steroid responsive disease have a favourable outcome and thus kidney biopsy, an invasive procedure not without attendant complications, can be avoided in over 80% of children in this group.

It is of paramount importance that the initial episode be treated appropriately, both with respect to steroid dose and duration, as initial therapy is an important determinant of long-term outcome [65]. Only prednisone and prednisolone are of proven benefit in the treatment of proteinuria in NS and other steroid preparations such as hydrocortisone, triamcinolone, methylprednisolone, betamethasone, and deflazacort should not be used as initial treatment [1]. Prednisone or prednisolone should be given after meals to reduce gastrointestinal side effects. Prophylactic use of antacids is not necessary and should be introduced if gastrointestinal symptoms develop. The dose is 2 mg/kg per day (maximum 60 mg) given as a single or divided dose for 6 weeks, followed by 1.5 mg/kg (maximum 40 mg), usually as a single morning dose on alternate days for the next 6 weeks and tapered over the next 8-12 weeks. The benefits of prolonged steroid treatment should

be balanced against its side effects and if the latter are pronounced, steroids can be stopped abruptly after the alternate day course.

Factors Predicting Steroid Sensitivity and Relapses

One of the most difficult challenges facing physicians is to predict steroid responsiveness or resistance in children presenting with idiopathic NS for the first time before treatment has commenced. Response to steroids is associated with a good long-term prognosis for resolution of disease with minimal complications [66]. Although some of the clinical and laboratory findings given above are helpful, they are not strongly predictive. Therefore the search is on for newer ways to predict initial steroid sensitivity in idiopathic NS and also to predict whether a child with steroid sensitive NS will relapse frequently.

A study using urine protein profiles on capillary electrophoresis mass spectrometry (urinary proteomics) suggested that these biomarkers could predict steroid sensitivity or resistance before embarking on steroid therapy [67]. These data however require confirmation in large prospective studies.

Suboptimal cortisol secretion in children with steroid sensitive NS on long-term alternate day prednisolone was associated with significantly more relapses than with children having normal levels of secretion [68]. This suggests that adrenocortical suppression increases the risk of relapse.

Over expression of P-glycoprotein, encoded by the multidrug resistant gene MDR1, is associated with reduced intracellular concentrations of many drugs including corticosteroids. MDR-1 polymorphisms were found more frequently in children with frequently relapsing steroid sensitive NS than controls [69]. Increased expression of P-glycoprotein on CD3 lymphocytes were demonstrated in steroid sensitive NS during relapse, 3-4 weeks after steroid treatment and 2 months after completing treatment compared to controls [70]. In another study, P-glycoprotein expression was significantly higher in frequently relapsing and steroid-dependent patients compared to those with infrequent relapses [69].

Treatment for Relapses

Most relapses are precipitated by infections, usually minor infections such as upper respiratory tract infections, resulting in low grade proteinuria (1+ to 2+ on urinary dipsticks analysis). Symptomatic treatment of these infections usually leads to disease remission. More pronounced proteinuria (3+ to 4+ on dipsticks analysis) necessitates the need to institute steroid treatment.

Prednisone or prednisolone is given in a dose of 2mg/kg per day (maximum 60mg) until urine protein is negative or trace for three consecutive days (remission). In developing countries where many patients cannot afford urine dipsticks or have low levels of literacy, such treatment is given for 2 weeks and the patients then reviewed. If remission is achieved, the dose of steroids is dropped to 1.5 mg/kg per day given on alternate days for four weeks and rapidly tapered or abruptly stopped. There is no evidence to show that prolonged treatment of relapses impacts long term outcome. In children not in remission despite two weeks of treatment with daily steroids, the treatment is extended for two more weeks. Patients who fail to achieve remission after 4 weeks are classified as having late steroid resistance.

Infrequent relapses, defined as less than four relapses per year, require treatment as per standard protocol given above [29].

Treatment for Frequent Relapses and Steroid Dependent Nephrotic Syndrome

Patients with frequent relapses or steroid resistant NS require more prolonged treatment. One treatment method is to keep the patient in long term alternate day steroids, usually a dose of 0.3-0.7 mg/kg body weight for 9-18 months. Changing from alternate day to daily steroid administration prevents relapses from minor infections [71].

An alternate treatment strategy is to use steroid sparing agents which should be considered in patients with:

- (i) Steroid dose > 0.7mg/kg necessary to maintain remission.
- (ii) Children who develops signs of steroids toxicity.

Examples of steroids sparing agents used include levamisole, cyclophosphamide, mycophenolate mofetil (MMF), calcineurin inhibitors (cyclosporine and tacrolimus), rituximab and vincristine (Table 3)

i. Levamisole

This medication may not be easily available in several countries but can effectively reduce the frequency of relapses and steroid dependency. It is given in a dose of 2-2.5 mg/kg body weight on alternate days for 12-24 months. Steroid dose whilst in this treatment is reduced every 2-4 weeks to 0.25-0.5 mg/kg on alternate days and in some patients can eventually be stopped. The drug is usually well tolerated and adverse effects include flu-like symptoms, neutropenia, hepatotoxicity, convulsions and skin rash. Leukocyte counts should be monitored every 2-3 months whilst on treatment.

ii. Cyclophosphamide

This is one of the most frequently used steroids sparing agents. The dose is 2-2.5 mg/kg/day for 8-12 weeks; the cumulative dose should not exceed 168 mg/kg. In view of potential toxicity, repeat courses are not advisable. Steroid treatment using a dose of 1-1.5 mg/kg on alternate days is continued during treatment and discontinued over 4-6 weeks. Leucocyte counts should be monitored every two weeks and the medication discontinued if below 3000-4000/mm³. Children must be encouraged to increase fluid intake and void frequently whilst on treatment. Side effects include leukopenia, alopecia, nausea, vomiting and haemorrhagic cystitis. Long-term toxicity include the increased risk of gonadal and bladder malignancy. Another alkylating agent that is now no longer used because of its low margin of safety and significant toxicity is chlorambucil.

iii. Mycophenolate Mofetil (MMF)

This is now being increasingly used as an alternate to cyclophosphamide, particular when there are concerns about long-term gonadal toxicity. The major limitation to its use in the developing world is its high cost. The dose is 600-1000 mg/m²/day or 20-25 mg/kg/day in two divided doses for 12-36 months. Prednisone is maintained at a dose of 1-1.5 mg/kg given on alternate days during treatment and then tapered over 4-6 weeks. Leukopenia is a common side effect and leucocyte counts should be monitored every 1-2 months and treatment stopped if it drops below 4000/mm³. Other common side effects include abdominal pain and diarrhoea which usually resolve after 1-2 weeks.

iv. Cyclosporine and tacrolimus

This treatment is usually reserved for children who fail treatment with the agents above. Cyclosporine A is given in a dose of 4-5 mg/kg/day for 12-24 months and dosage adjusted to maintain a 12-hour trough level between 80-120 mg/ml. Tacrolimus dose is 0.1-0.2 mg/kg/day adjusted to a trough level between 7-15mg/ml. Prednisone is continued using a dose of 1mg/kg on alternate days and tapered over 6-9 months once remission is achieved. Both agents have the potential for acute and chronic nephrotoxicity and renal function should be monitored closely until stable and then every 3 months. Cyclosporine has the potential for more cosmetic side-effects (hirsutism, gum hypertrophy), hypertension and hypercholesterolemia. Tacrolimus is associated with an increased risk of hyperglycaemia (particularly with concomitant use of steroids), elevated liver enzymes, diarrhoea, tremors, headache and seizures. In view of long-term nephrotoxicity a kidney biopsy is recommended every 3 years whilst on treatment.

v. Rituximab

In view of its cost, the drug is not frequently used and may not be readily available in some developing countries. Its use is reserved for patients with marked steroid dependency who fails to respond to other drugs or in patients with toxicity secondary to other drugs. It should only be used at a specialised centre. A significant proportion of patients relapse after rituximab treatment. Most relapses occur simultaneously with the recovery of B-cell lymphocyte counts [72]. Maintenance therapy using mycophenolate mofetil is effective in preventing relapses after treatment with rituximab in many cases [73]. Side effects include infusion related reactions (hypotension, fever and rigors), serious infections, and progressive multifocal leukoencephalopathy [74].

There are no controlled data or large series on other biologicals that are effective in the management of NS. There is only one report of successful anti-tumour necrosis factor (TNF) treatment in steroid sensitive NS (ref 50 Ped Nephrol (2011) 26: 881-892).

Drug	Advantage	Problem	Comment
Levamisole cases	Low toxicity	Less effective in severe cases of steroid dependency. Availability	First option for less severe
Cyclophosphamide (chlormabucil)	Short course may induce long-term remission	Long-term toxicity, especially infertility	Seems to be more effective in older and female patients, no repeated courses
Mycophenolic acid inhibitors (MPA)	No nephrotoxicity	MPA dependency, less effective than calcineurin inhibitors Proportion of patients that reach long-term remission is unclear	Alternative to calcineurin Therapeutic drug monitoring may have no impact on steroid resistance
Cyclosporine	Effective in severe steroid-dependency	Cyclosporine dependency side effects	Tapering to low doses possible
Tacrolimus	Effective in severe steroid-dependency	Tacrolimus dependency Long-term side effects unclear	Tapering to low doses possible
Rituximab	Effective in severe steroid-dependency	Long-term side effects are unknown	Proportion of patients with drug free

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Table 3: Treatment options for steroid sensitive nephrotic syndrome.

vi. Vincristine

There has been one report in 2005 of patients treated with vincristine for steroid dependent NS who were relapsing despite cytotoxic or calcineurin treatment [75]. Vincristine was used in a dose of 1-1.5 mg/m² that was given weekly for 4 weeks intravenously, followed by monthly courses for 6 months. Patients showed a decrease in the frequency of relapses decreasing from 4 in a 12-month period prior to treatment to 1.5 for a 12-month period following treatment. Adverse effects were minimal. The median sustained remission was 5 months, but only frequently relapsing patients remained in remission 4 years after vincristine treatment. This was followed by another study in 2006 that also showed positive results with the use of vincristine [76]. These two reports suggest that vincristine may have a role as a steroid- and cyclosporine-sparing agent, contributing to long-term remission in some patients. It may be particularly of value in patient with poor compliance with oral medication. Future controlled studies are needed to carefully evaluate the role of this drug in NS.

Vitamin D and Calcium Prophylaxis

There has been considerable debate on whether children with steroid sensitive NS, given standard doses of treatment, be commenced on vitamin D and calcium prophylaxis. Corticosteroids are known to increase the risk for fractures however; no studies have demonstrated that corticosteroid treatment of steroid sensitive NS increases fracture risk [77]. In a randomised controlled trial comparing vitamin D and calcium prophylaxis with no prophylaxis, bone mineral density was significantly lower in treated than non-treated patients [78]. Hypercalciuria occurred in both groups. The authors concluded that prophylaxis with vitamin D and calcium during high-dose corticosteroid therapy for relapse reduced bone loss and could be administered safely.

Rational Choice of Agents for Frequent Relapses and Steroid Dependent Nephrotic Syndrome

The two major criteria that dictate the disease if steroid sparing agents that are used in steroid dependent and frequently relapsing nephrotic syndrome are:

- (i) Absence of significant side effects and
- (ii) Long-term efficiency

In developing countries, with resource limitations, cost as well as availability of the agents, are important considerations. The present armamentarium of agents available unfortunately do not satisfy all these criteria and lack of large randomised controlled studies also fail to provide evidence-based choices for any particular agent.

Given the more favourable toxicity profile of mycophenolate mofetil compared to other agents; many centres are using this agent as first choice for a steroid-sparing agent. In countries where levamisole is available, this is also being increasingly used. Some experts however have suggested the use of cyclophosphamide in patients with frequently relapsing, but not steroid dependent NS, the long-term remission rate is much lower and doses used do not warrant the significant potential toxicity [1].

Cyclosporine, although effective in maintaining remission requires prolonged treatment which increases the risks of nephrotoxicity. Hence its use is mainly restricted to patients that fail to maintain remission after a course of mycophenolate mofetil or cyclophosphamide without a significant steroid dose.

Long-term Outcome of Steroid Sensitive Nephrotic Syndrome

Limited data is available in adult long-term outcome of patients who were children with steroid sensitive NS. Almost all patients maintain normal renal function in adulthood. The number of relapses as a child is the only predictive factor of relapses occurring later in life. In a report from a single centre, only one patient of a total of 102 patients developed end-stage kidney disease [79]. Long-term sequelae in these patients are generally related to side effects of medication.

Conclusion

Although steroid sensitive nephrotic syndrome is largely viewed as a relatively benign chronic disease in childhood, many children nearly two thirds of children have frequent relapses or become steroid-dependent. The precise aetiology and pathogenesis of this disease remains elusive although some progress is being made, particularly regarding its genetic origins, in elucidating its cause. Despite the wide arsenal of highly potent drugs available to treat children with frequent relapses and steroid dependency, the induction of a cure, i.e. treatment-free remission, should be the ultimate goal in the management of this disease. Steroids remain the mainstay of treatment and with the introduction of newer therapeutic agents, the prognosis of this disease has greatly improved. The steroid-sparing effects of these agents have greatly reduced the adverse effects seen with long-term use of steroids.

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Conflict of Interest

None

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