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Ranjit Roy

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Gulshan Niger Chowdhury, Shusmita Biswas, Sazzad Hossain
Nazmun Nahar Shampa, Jannatul Ferdous Sonia,
Abdullah Al Mamun, Tahmina Jesmin
Syed Saimul Huque, Afroza Begum

Planning:
Shireen Afroz

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Ranjit Roy[1], Mostafa Kamal[1], Amina Akhter[1], Aditi Chowdhury[1], Rummana Tazia Tonny[1], Nadira Sultana[1], Gulshan Niger Chowdhury[2], Shusmita Biswas[3], Sazzad Hossain[1], Nazmun Nahar Shampa[2], Jannatul Ferdous Sonia[2], Abdullah Al Mamun[1], Tahmina Jesmin[1], Syed Saimul Huque[1], Afroza Begum[1]

[1]Bangabandhu Sheikh Mujib Medical University, Department of Pediatric Nephrology, Dhaka, Bangladesh, [2]Bangladesh Shishu Hospital And Institute, Dhaka, Bangladesh, [3]Sylhet MAG Osmani Medical College and Hospital, Sylhet, Bangladesh

Planning: Shireen Afroz

ABSTRACT:

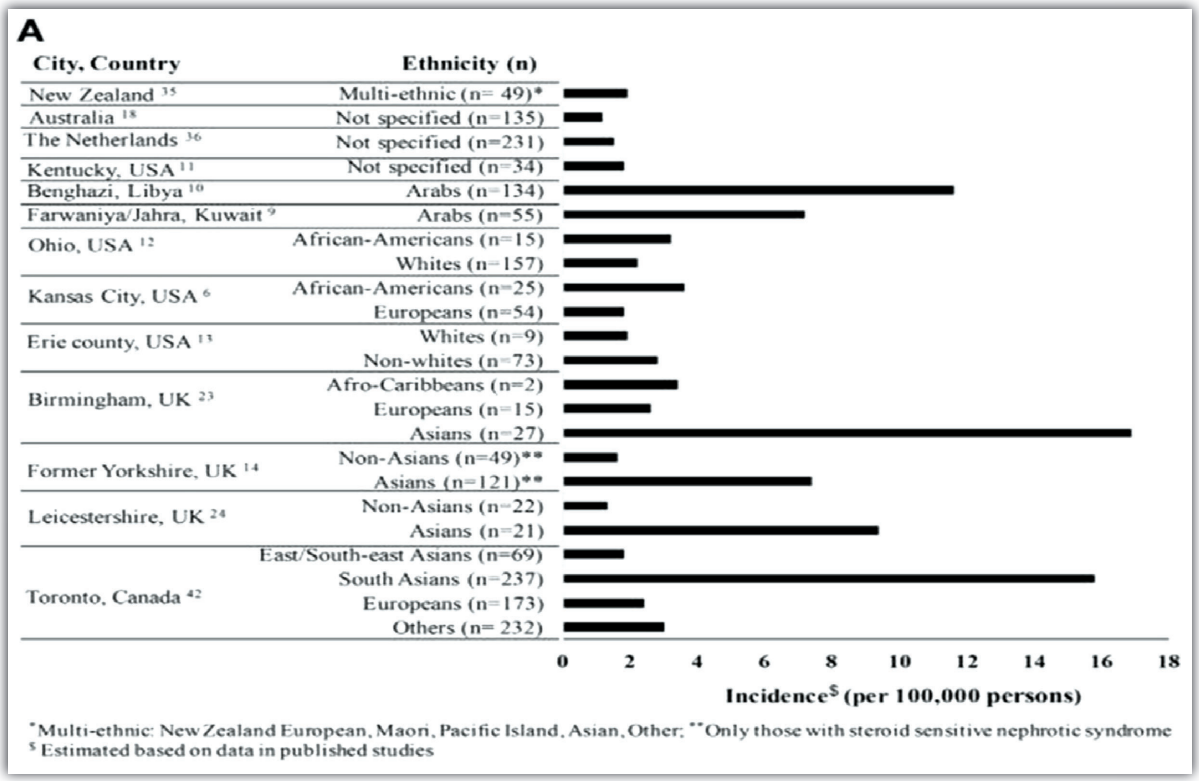
Nephrotic syndrome is characterized by massive proteinuria, consequent hypoalbuminemia, and edema. Frequently it is triggered by infection and asthma. The annual incidence of nephrotic syndrome is 1.2 to 16.9 per 100,000 children, occurring most frequently in South Asian populations. The disease is responsive to steroid in 85-90% of instances and steroid resistance in rest 10-15% of patients and very small group of severe genetic diseases present as congenital (0-3 months) and infantile (4-12 months) nephrotic syndrome. Steroid responsive group has a frequent relapse and dependent course a in large majority. Different steroid-sparing agents in sensitive cases and other immunosuppressives are used in resistant patients with ultimate good outcomes in the majority of instances. There are variations in practice patterns in immunosuppressive use, asthma, infection, and edema control. Hence a team of pediatric nephrologists worked together to develop a practice recommendations on the management of steroid-sensitive, steroid-resistant and congenital nephrotic syndrome. Therefore, global data were reviewed to develop an updated written standard of care recommendations. Team members performed systemic review of literature on relevant PICO (Patient or population covered, Intervention, Comparator, Outcome) questions, and recommendations were formulated and graded at several in-person meetings. New ideas were taken and therapeutic options were defined.

Keywords: Steroid-sensitive nephrotic syndrome (SSNS), steroid-resistant nephrotic syndrome (SRNS), congenital nephrotic syndrome (CNS), immunosuppressive treatment.

INTRODUCTION

In 1929, Henry Christian used the term nephrotic syndrome (NS). At that time penicillin was also discovered, and subsequent use of other antibiotic that have improved infection control of nephrotic syndrome and enhanced outcomes. The use of steroid began in nephrotic syndrome in 1950 and the outcome improved further. Before steroid therapy was introduced, the annual mortality rates for children with NS were 20% attributed chiefly to severe bacterial infection.

Nephrotic syndrome is characterized by massive proteinuria, hypoalbuminemia, and edema. The average incidence of nephrotic syndrome is 4.7 (range 1.2–16.9) per 100,000 persons in studies reported from 1946 to 2014, and the proportion with steroid resistance is 12.4% (range 2.1–27.3%) from 1986 to 2014. Hence, there is a considerable variation in disease burden by country of origin and steroid responsiveness, suggesting the potential role of ethnicity in susceptibility to disease (1–14). The proportion of steroid resistance also varies by ethnicity from 20% among Europeans, 16–27% among Africans, 27–54% among Asians, and 20–39% among South Asians (15–18).



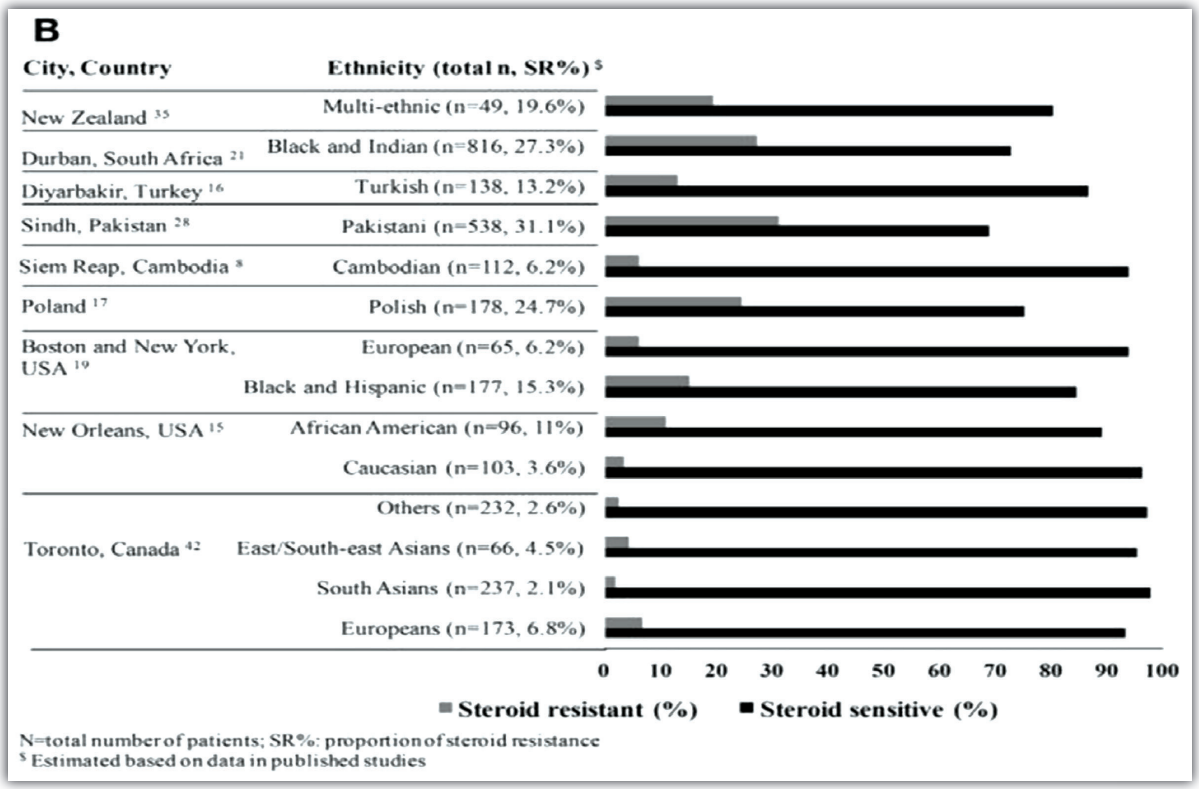


Figure 1: Adapted from (19). (A) Incidence of childhood nephrotic syndrome per 100.000 persons by ethnicity reported from 1946 to 2014, (B) Variability of steroid responsiveness by ethnicity among children with nephrotic syndrome in reported studies from 1986 to 2014.

The incidence of SRNS ranges from 2.1 to 27.3% and varies with country of origin with the highest rates seen in African and African-American children and the higher rates seen in children of South Asian ancestry in Canada and the UK (19). SSNS is more common in boys than girls with a male: female ratio of around 2:1 and a peak incidence between 1–4 years (20).

METHODS:

Overview of the project

We followed the RIGHT (Reporting Items for Practice Guidelines in Healthcare) Statement for Practice recommendations (21). An expert group decided to establish a complete management update on nephrotic syndrome through multiple meetings. This group consists of 14 members of pediatric nephrologists. They decided to make it from multiple guidelines, and international, high quality nationally acceptable published data and views of renowned pediatric nephrologists. The whole group held multiple face-to-face meetings to aggregate all potential global current data about nephrotic syndrome in pediatric populations.

Group members were asked by a questionnaire to provide a level of agreement on a 5-point scale (strongly disagree, disagree, neither agree/disagree, agree, strongly agree) (Delphi method). For topics that failed to achieve a 70% level of consensus, the recommendations were re-evaluated and modified by our expert group and then reviewed again until a consensus level of >70% was achieved. We also consulted all guidelines of the world and tried to learn their views, views that were corollary with ours were taken in this recommendations, some may be modified according to our views.

Developing the PICO questions

We developed PICO (Patient or Population covered, Intervention, Comparator, Outcome) questions as follows (22): Population: Children (since birth to < 18 years) with nephrotic syndrome (NS); Intervention and Comparators: Treatment compared with no treatment, other treatment, or placebo; Outcomes Addressed: Recommendations for the treatment, and follow-up of children with NS (including efficacy to induce remission and side effects of medications). Definitions of nephrotic syndrome were reviewed and modified by our expert panel.

Literature search

As many as available published articles about nephrotic syndrome by pediatric nephrologists and renowned portals were searched and views of all contemporary authors around the globe were taken from those published literature by March 2024; all systematic reviews and other published data on the treatment of nephrotic syndrome(NS) in children, prospective uncontrolled trials, observational studies, and registry studies on diagnosis and treatment of children with NS, restricted to human studies published in English language were retrieved.

Grading system

We followed the grading system of the American Academy of Pediatrics (23) (Fig. 1). The quality of evidence was graded as High (A), Moderate (B), Low (C), Very low (D), or Not applicable (X). The latter refers to exceptional situations where validating studies cannot be performed because benefit or harm predominates. The letter X was used to grade contraindications of therapeutic measures and safety parameters. The strength of a recommendation was graded as strong, moderate, weak, or discretionary (when no recommendation can be made).

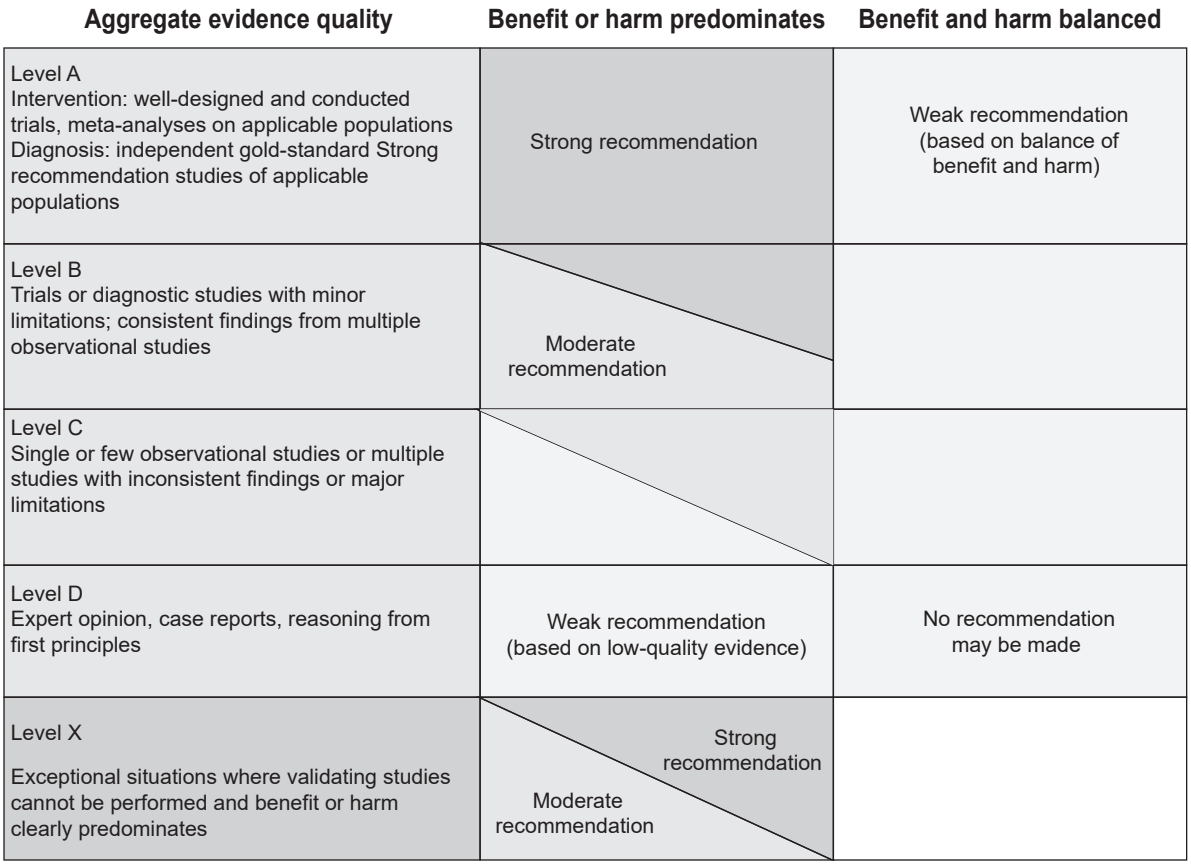


Figure-2: Grading of evidence and assigning strength of recommendations as currently used by the American Academy of Pediatrics (24).

ETIOPATHOGENESIS:

Role of T-cell and B-cell

A series of clinical observations led Shaloub in 1974 to propose that steroid sensitive nephrotic syndrome (SSNS) was due to an abnormality of function in T cells (25). The disease was noted to remit in children who had measles, which led some people to propose using measles as a therapeutic strategy (26–28). A major effect of measles is to inhibit cell-mediated immunity thereby shutting down T-cell function. Further, the response of nephrotic syndrome to T cell suppressive agents such as steroids or calcineurin inhibitors (CNI) also supported their role in nephrotic syndrome. These features all suggest that lymphocytes are key cells in SSNS. Recent success in treating recurrent focal segmental glomerulosclerosis (FSGS) and steroid sensitive nephrotic syndrome (SSNS) with the CD20 B cell-depleting antibody rituximab raises the possibility of either B cells influencing T cells or B cells themselves being primary players in nephrotic syndrome. It is unclear if this is a function of the role of B cells as antigen-presenting cells or because of antibody production.

Circulating factor

Minimal change disease (MCD) appears to exist in a spectrum with FSGS. A proportion of children with MCD on clinical and histological grounds evolve into FSGS (25). In both, there appears to be a circulating factor with the children with FSGS being less responsive to therapeutic agents. Within this group is a subset

of children where the disease resides in structural changes in the glomeruli with genetic mutations in key glomerular slit process proteins including nephrin, podocin, actinin4, and WT-1. These are associated with no response to steroids and progression to end-stage kidney disease (ESKD) and do not show evidence of a circulating factor as demonstrated by rapid recurrence of disease in a transplanted kidney.

The higher rates of recurrence in children with FSGS receiving living-related kidneys suggests that there may be a degree of HLA restriction of response and this is also supported by HLA linkage studies showing that increased incidence of disease is tied to certain alleles such as HLA B8, B13, DWQ2, DQB10301 and DR7 (29–32). Various growth factors and cytokines have been proposed as pathogenic in SSNS over the years. The initial identification of the factor, vascular permeability factor (VPF) now called vascular endothelial growth factor (VEGF), was thought to have identified the key protein leading to nephrotic syndrome (33–35).Thirty to sixty percent of nephrotic syndrome is found to be associated with bronchial asthma, allergic rhinitis, allergic conjunctivitis, atopic dermatitis. Thymus derived regulatory T suppressor cells express regulatory cytokines like TGF-B and IL-10 and regulatory molecules like CTLA-4

A key marker of these cells is the expression of the transcription factor foxp3 (36–38). There is now another T cell subset that is an alternative to regulatory T cells called the Th17 cell because it expresses the cytokine IL-17. Th17 cells are induced by IL-23 but can be generated by IL-6 and TGF-ß thus acting as an alternate pathway of development to regulatory T cells (39). There are now data linking Th17 cells to nephrotic syndrome and the biological effect of these cells on podocytes (40,41). Urinary reports are confounded by concurrent proteinuria but there has been a recent report of an IL-17 increase in the urine of patients with SSNS (42). Other non-T cell inflammatory proteins associated with SSNS include neopterin which is produced by activated macrophages and is increased in SSNS (43).

Mechanisms of Proteinuria:

The glomerular capillary wall comprises the fenestrated endothelial cells, glomerular basement membrane (GBM), and the dynamic structure between interdigitated podocyte foot processes, called the glomerular slit diaphragm (SD). The endothelial cells contain an anionic glycocalyx on the cell surface and form a fenestrated layer on the luminal side of the GBM. Despite the large pore size of the fenestrae (375–400 Angstrom (Å), the endothelial cells can form an electrostatic barrier for negatively charged proteins, including albumin having a radius of 36 Å. (44,45). Recent studies in animal models have confirmed the importance of endothelial cells and the glycocalyx in the selectivity of the filtration barrier (46,47). Another line of evidence for the role of endothelial cells in the filtration barrier function comes from animal studies showing that inhibition of vascular endothelial growth factor (VEGF) leads to endothelial cell dysfunction and proteinuria (33,48).

The GBM is an acellular network formed by a scaffold of cross-linked collagen IV, laminins, and proteoglycans. GBM plays a central role in the size- and charge-selectivity with a variable contribution of each component. Type IV collagen provides mainly structural support to the glomerular capillary wall and contributes relatively less to the selectivity of the filtration barrier. This conclusion was derived from the usually mild proteinuria observed in patients with Alport syndrome (49). Proteoglycans contain negatively charged glycosaminoglycan side chains. Heparan sulfate proteoglycans (HSPG) are responsible for the anionic charge of the GBM, and their role in the filtration barrier is widely accepted (50). However, recent studies in murine models have questioned the role of HSPG (51–53). By contrast, laminins were shown to play an essential role in the GBM organization and the filtration selectivity. Laminins are heterotrimeric proteins that self-assemble into a network. Animal studies show that laminin-521 is crucial for a filtration barrier (54–56). Mutations in LAMB2 cause Pierson syndrome, characterized by congenital nephrotic syndrome and ocular abnormalities (57).

Mechanisms of Glomerular Injury:

The etiology of SSNS is unknown. It is suggested that SSNS may result from activation of the immune system in response to an infection (58). The clinical observation that manifestations of SSNS frequently follow an upper respiratory infection seems to support such a conclusion.

Genetic basis:

Three percent of children with SSNS have a first-degree relative with the same disease (59). Ethnic background affects the incidence and severity of INS, with Black and South Asian children having a higher incidence than White children (60,61). Black children are also more likely to show corticosteroid resistance and FSGS compared to White children (15,60). All of the genetic variants proposed to cause Mendelian SSNS can be classified as variants of uncertain significance, and many of them are shown to occur at high frequency in the general population (62,63). Most of the variants reported in the literature are from small, single-family studies and have not been validated in independent larger cohorts. By contrast, the familial clustering of SSNS is well recognized (64).

The vast majority of relevant genetic variants identified in complex diseases lie outside coding regions (65,66). Many of those are found to be in areas relevant to gene regulation, such as promoters and enhancers. Genome-wide association studies (GWAS) using candidate gene approaches found the strongest association within the HLA genetic region, HLA-DR/DQ, specifically in and around HLA-DQA1 and HLADQB1 (67,68). The exome-wide association study, which was not limited to a selection of genes, identified four variants (rs1129740, rs9273349, rs1071630, and rs1140343) in the HLA-DQA1/HLA-DQB1 locus in association with SSNS in a South Asian cohort (1). Thus, GWAS has confirmed the longstanding observation that the immune system plays a critical role in SSNS (67,69–72). An increased number of risk alleles in the HLA-DR/DQ region (rs1063348) and (rs28366266) was associated with an increased SSNS risk as well as decreased age at onset of disease. Additionally, the lead variant (rs1063348) around HLA-DQB1 was associated with significantly decreased expression of HLA-DRB1, HLADRB5, and HLA-DQB1 in glomeruli of children with SSNS (69). Additional support for the involvement of the HLA-DR/DQ region in SSNS came from a GWAS investigating a large European cohort (70). GWAS in Japanese SSNS patients confirmed the association with HLA-DR/DQ in a different ethnicity (67,71). The above findings underline the central role of the immune system in SSNS but also demonstrate a complex mechanism of SSNS.

Membranous Nephropathy enabled identification of a non-HLA locus at PLA2R1 which has been incredibly informative in understanding disease pathology. In SSNS non-HLA loci have been identified (BTNL2, CALHM6/DSE, PARM1, TNFSF15, and NPHS1) but the signals are not as strong and to date are not reproducible across all ethnic groups but cohort size has been relatively small (69–71).

A recent example includes a large familial study focused on the partially responsive nephrotic syndrome, where six genes were found to be associated with the disease (MAGI2, TNS2, DLC1, CDK20, ITSN1, and ITSN2) (73)

Role of the Thymus

The association of nephrotic syndrome with T cell lymphomas and thymomas, the timing of thymic involution occurring around puberty at the same time as the resolution of relapses for the majority of children with uncomplicated SSNS, and the exquisite sensitivity of thymocytes to steroids all suggest a Role for early T cells or other thymically derived cells in SSNS. Further evidence of early thymic emigrants in single-cell analysis of CD2 positive cells from children with FSGS also supports a role for T cells, which are early emigrants from the thymus.

Role of Infection:

While there has been no clear infectious agent identified as inducing nephrotic syndrome, there is an identifiable viral prodrome in around 50% of cases of relapse. Some groups have postulated that inflammation through TLRs may upregulate CD80 on podocytes leading to activation through CD80 and nephrosis (74).

Podocyte-Specific Pathway:

Response to corticosteroids is thought to result from its immunosuppressive effects, although studies suggest that glucocorticoids might also have a direct nonimmune function mediated by Kruppel-like factor 15 (KLF15), targeting podocytes (75,76). Another protein implicated in the pathogenesis of MCD, hemopexin, is a plasma protein that binds sialoglycoproteins in podocytes, leading to proteinuria, foot process effacement, and cytoskeletal rearrangement (77,78). Another mediator upregulated in MCD and FSGS, C-maf inducing protein (c-mip), leads to proteinuria without inflammatory lesions or cell infiltration in transgenic animals (79).

Table 1 **Definitions of diseases course**

Term	Definition
Nephrotic-range proteinuria	Urinary protein creatinine ratio (UPCR) ≥ 200 mg/mmol (2 mg/mg) in a spot urine, or proteinuria ≥ 1000 mg/m2 per day in a 24-h urine sample corresponding to 3 + (300–1000 mg/ dL) or 4 + (≥ 1000 mg/dL) by urine dipstick
Nephrotic syndrome	Nephrotic-range proteinuria and either hypoalbuminemia (serum albumin < 30 g/L) or edema when serum albumin is not available
Complete remission	UPCR (based on first morning void or 24 h urine sample) ≤ 20 mg/mmol (0.2 mg/mg) or < 100 mg/m2 per day, respectively, or negative or trace dipstick on three or more consecutive days
Partial remission	UPCR (based on first morning void or 24 h urine sample) > 20 but < 200 mg/mmol (> 0.2 mg/mg but < 2 mg/mg) and serum albumin ≥ 30 g/L
Steroid-sensitive nephrotic syndrome (SSNS)	Complete remission within 4 weeks of PDN at standard dose (60 mg/m2/day or 2 mg/kg/day, maximum 60 mg/day)
Steroid-resistant nephrotic syndrome (SRNS)	Lack of complete remission within 4 weeks of treatment with PDN at standard dose,
Confirmation period	Time period between 4 and 6 weeks from PDN initiation during which responses to further oral PDN and/or pulses of IV MPDN and RAASi are ascertained in patients achieving only partial remission at 4 weeks. A patient not achieving complete remission by 6 weeks, although partial remission was achieved at 4 weeks, is defined as SRNS
SSNS late responder	A patient achieving complete remission during the confirmation period (i.e. between 4 and 6 weeks of PDN therapy) for new onset NS
Relapse	Urine dipstick ≥ 3 + (≥ 300 mg/dl) or UPCR ≥ 200 mg/mmol (≥ 2 mg/mg) on a spot urine sample on 3 consecutive days, with or without reappearance of edema in a child who had previously achieved complete remission

(table continued)

Term	Definition
Infrequently relapsing nephrotic syndrome	< 2 relapses in the 6 months following remission of the initial episode or fewer than 3 relapses in any subsequent 12-month period
Frequently relapsing nephrotic syndrome (FRNS)	≥ 2 relapses in the first 6-months following remission of the initial episode or ≥ 3 relapses in any 12 months
Steroid-dependent nephrotic syndrome (SDNS)	A patient with SSNS who experiences 2 consecutive relapses during recommended PDN therapy for first presentation or relapse or within 14 days of its discontinuation
Significant Steroid toxicity	New or worsening obesity/overweight (BMI > 27 kg/m2) (80)(13), sustained hypertension, hyperglycemia (fasting glucose >100 mg/dL, postprandial >140 mg/dL, HbA1c >5.7%) (81); Behavioral/psychiatric disorders, sleep disruption; Impaired statural growth (height velocity < 25th percentile and/or height < 3rd percentile) (82) or (short stature (height < -2 SDS) (80) with height velocity (<-3 SDS for age)) in a child with normal growth before start of steroid treatment; Cushingoid features, striae rubrae/distensae, glaucoma, ocular cataract, bone pain, avascular osteonecrosis, myopathy;
Sustained remission	No relapses over 12 months with or without therapy
SSNS controlled on therapy	Infrequently relapsing NS or sustained remission while on immunosuppression in theabsence of significant drug-related toxicity
SSNS not controlled on therapy	Either frequently relapsing NS despite immunosuppression or significant drug-related toxicity while on immunosuppression
Complicated relapse	A relapse requiring hospitalization due to one or more of the following: severe edema, symptomatic hypovolemia or AKI requiring IV albumin infusions, thrombosis, or severe infections (e.g., sepsis, peritonitis, pneumonia, cellulitis)
Recurrent nephrotic syndrome post-renal transplantation:	A child with SRNS presenting post-renal transplantation with a relapse of nephrotic-range proteinuria in the absence of other apparent causes and/or podocyte foot process effacement on kidney biopsy. This diagnosis should also be considered in case of persistent proteinuria (UPCR ≥ 100 mg/mmol (1 mg/mg) in a previously anuric patient, or an increase of UPCR ≥ 100 mg/mmol (1 mg/mg) in a patient with prevalent proteinuria at the time of transplant in the absence of other apparent causes.

[a]In adults, nephrotic range proteinuria is defined by proteinuria > 3.5 g/24 h (or > 3000 mg/g or > 3 g/10 mmol creatinine) (83). These cut-offs should also apply to adolescents (> 16 years)

[a]False positive if urine pH >7.0; false negative if specific gravity :1010

reproduced from IPNA SSNS guideline (84)

Clinical features

Nephrotic syndrome may begin during infancy, but usually occurs between the ages of 2 and 7 years (68,85). No age is immune. The onset of illness is often preceded by an upper respiratory tract infection in 30–50% cases (86), followed by edema, which becomes clinically detectable when fluid retention exceeds 3–5% of body weight (87)

Periorbital edema is the leading clinical sign of NS in children with a typical presentation. It may be asymmetrical initially and is frequently misdiagnosed as allergy or as conjunctivitis. Edema is gravity-dependent periorbital puffiness decreases during the day, while it localizes at the lower extremities in the upright position, and to the eyelids and the dorsal part of the body in a reclining position. The edema is painless, soft and pitting, keeping the marks of clothes or finger pressure. Anasarca may develop with ascites, and pleural and pericardial effusions. Efforts are underway to standardize the assessment of edema.

Common sites of bacterial infections in children with SSNS include pneumonia, peritonitis, UTI, sepsis, cellulitis, and meningitis (88,89). Infection is responsible for 19-44% causes of hospitalization.(90). History should be taken for fever episodes, pain, abdominal discomfort, fatigue. Search for risk factors for secondary causes (e.g., sickle cell disease, HIV, systemic lupus erythematosus, hepatitis B, malaria, parvovirus B19, medications), screen for tuberculosis, HIV in endemic region.

Atopy is more common in children with SSNS compared with children without SSNS (91) and more common in SSNS than SRNS (92) but an acute allergic reaction rarely precipitates a relapse (93). Asthma is prevalent in 30-60%, other common are allergic rhinitis, atopic dermatitis, allergic conjunctivitis (90). Hypertension is present in 5–20% at presentation in children but generally hypertension does not persist (86,88). Hypertension is due to drug (steroid, CNI), retained fluid (overfill states), disease process. transient hypertension due to peripheral vasoconstriction.

Complications of NS may be the presenting symptoms or signs of the disease (e.g., abdominal pain related to severe hypovolemia, ascites, peritonitis, or pneumonia, dyspnea as a consequence of pleural effusion, ascites, pneumonia, or pulmonary embolism). Complication of nephrotic syndrome is described latter in this manuscript.

Kidney function is generally normal though serum creatinine may be elevated at presentation in association with intravascular volume depletion and rarely acute kidney failure.

We recommend following can categorize as atypical/bad prognostic features of nephrotic syndrome, age < 2 years, > 15 years, hypertension, azotemia, hematuria (25% of minimal can have microscopic hematuria), low complement level, extra renal features suggest vasculitis, secondary and syndromic causes, positive family history (found in 3-5% with underlying gene, this has higher probability of SDNS, SRNS), anemia (due to acute sickness concomitant malnutrition and chronic underlying renal histology)

Physical examination

Physical examination includes blood pressure, assess volume status and extent of edema (ascites, pericardial and pleural effusions), lymphadenopathy, signs of infection (respiratory tract, skin, peritonitis, urinary tract), anthropometry. Vaccination status should be check/completed according to national standards esp., for encapsulated bacteria: pneumococcal, meningococcal, haemophilus influenzae, Hep B, SARS-CoV2, influenza vaccine, and varicella.

A physical examination for extrarenal features suggestive of genetic conditions is recommended. Dysmorphic features or genitourinary malformation, ambiguous genitalia or eye abnormalities (microcoria, aniridia), rash, arthritis, sensorineural hearing deficit, neurological or skeletal manifestations may present. Patients with extrarenal features suggestive of monogenic SRNS should primarily undergo genetic testing. Diagnostic work-up in patients with congenital NS (age < 3 months) should be done according to recent clinical practice recommendations (94,95) and as it is done in this manuscript.

Parental consanguinity, family members with nephrotic syndrome, proteinuria, hematuria, kidney failure (include the age of onset, response to medication, kidney function, kidney biopsy and genetic tests), family members with relevant non-kidney manifestations, e.g., early onset diabetes, sensorineural hearing defect, neurological disorder, and epilepsy should be searched.

After the neonatal period, if family history is positive for SSNS, PDN therapy should be started as per this SSNS recommendations. If family history is positive for a monogenic cause of SRNS, we recommend primary genetic testing.

Impact of typical presentation and age:

In children, NS with onset at age above 1 year and typical presentation is most often SSNS associated with MCD. The likelihood of MCD is highest between ages 2 and 7 and decreases thereafter (68,85). Kidney biopsy allows the exclusion of the differential diagnoses (e.g., membranous nephropathy) and the confirmation of a primary podocytopathy (MCD, FSGS, or diffuse mesangial sclerosis (DMS)). Findings of DMS or membranous nephropathy have therapeutic implications as these entities are treated with specific protocols (membranous nephropathy) or may require genetic testing (DMS). Moreover, it allows the detection and grading of tubular atrophy, interstitial fibrosis, and glomerulosclerosis as prognostic markers (68). However, there is not enough evidence to identify a clear age limit above which the probability is high enough for non-MCD pathology (e.g., membranous nephropathy), and thus the need for a kidney biopsy in children with NS. Therefore, we suggest that the decision of performing a kidney biopsy in older children (> 15 years) be made on a case-by-case basis (96). Atypical features suggesting the need for a kidney biopsy include macroscopic hematuria, low C3 levels, sustained hypertension, low estimated glomerular filtration rate (eGFR) not related to hypovolemia, arthritis and/or rash, or other extrarenal findings suggesting glomerulonephritis. (84)

We also suggest a kidney biopsy be performed in patients with nephrotic syndrome and persistent microscopic hematuria in populations with a high incidence of glomerular diseases such as IgA nephropathy in East Asia. To reduce unnecessary kidney biopsies, the finding of more than 30 RBCs/HPF of fresh voided urine may be used as a criterion for performing a kidney biopsy in clinical practice (97).

Infantile onset NS

About 50% of children with infantile onset NS (age 3–12 months) have a genetic cause of NS which usually does not respond to PDN treatment (98,99). The finding of DMS on kidney biopsy is highly suggestive for an underlying genetic defect, i.e., pathogenic variants in WT1, PLCE1, or PDSS2 genes (100–103). Therefore, we suggest following one of three strategies for infantile NS without extrarenal manifestations (i) primary genetic testing, if the results are rapidly available, with standard PDN treatment given if genetic testing is negative; (ii) primary kidney biopsy, followed by standard PDN treatment in the case of MCD and FSGS, genetic testing in the case of DMS, and specific treatment in the case of other underlying kidney histopathology's; and (iii) starting standard PDN treatment and then initiating genetic testing and kidney biopsy in case of SRNS. (84)

Urinalysis

Nephrotic range proteinuria is defined as urine protein excretion >50 mg/kg/day or 40 mg/h/m^2. The morning "spot" urine protein/creatinine ratio above 2 mg/mg (200 mg/mmol) is the most commonly reported cut off value for nephrotic range proteinuria and corresponds to a dipstick value +3 or above.

In most cases, proteinuria is highly selective, consisting of albumin and low molecular weight proteins. Selectivity of proteinuria, estimated by the Cameron index, is the ratio of clearance of IgG (molecular weight 150 kDa) to transferrin (80 kDa). The index in selective proteinuria is below 0.10. Nonselective proteinuria (value >0.20) is often associated with SRNS and FSGS.

Urine microscopy shows casts in patients with nephrotic range proteinuria while granular casts in UTI, GN. RBC cast is found due to underlying glomerulonephritis, UTI, hypovolemic acute tubular necrosis, CNI induced interstitial nephritis.

Urinalysis shows ≥3–4+ protein on urinalysis with a urine protein-creatinine ratio (uPCR) ≥ 200 mg/mmol (≥ 2000 mg/g).

Microscopic hematuria is present at diagnosis in 20–30% of children but rarely persists and macroscopic hematuria is rare occurring in less than 1% of children with SSNS (86,88). Hematuria may be due to hypovolemia with acute tubular necrosis (ATN), UTI, underlying glomerulonephritis and rarely due to renal venous thrombosis. Microscopic hematuria has limited histopathologic or prognostic significance.

The use of a spot urine may be preferred to avoid sampling error and because of its excellent correlation with 24-h urine protein excretion (104). Although urinary dipstick analysis is useful for screening and home monitoring, we recommend confirming nephrotic range proteinuria at least once by quantification of proteinuria either by spot urine sampling (if possible, first-morning void) or on a 24-h sample before initiating treatment for the first episode. First morning urine samples help rule out orthostatic proteinuria during follow-up to diagnose relapses (104,105).

Urine sodium excretion is low and associated with sodium retention and edema. For volume assessment. Point of care ultrasonography is becoming popular with ultrasonography of inferior vena cava showing contracted state with volume depletion.

Table 2 Investigation

Essential at onset

- Protein/creatinine ratio (in first morning void) Recommended at least once before starting treatment of the first episode
- Urinalysis: including hematuria and glomerulonephritis (GN) features
- Blood levels of urea, creatinine, electrolytes, total protein, albumin; lipid profile
- Complete blood counts: Suspected systemic infection or hypovolemia

For infection screening: as described elsewhere in this manuscript.

- Hb%, total count, differential count, ESR, peripheral blood count (PBF): ESR has prognostic value, very high ESR has diagnostic value it differentiates from acute GN
- C- reactive protein (CRP)
- Procalcitonin, ferritin are acute phase reactants of infection
- Urine for dipstick, routine microscopic examination (R/M/E) and C/S: Urinary tract infection (UTI)
- Chest X-Ray: To see pleural effusion, consolidation, TB, asthma and cardiomegaly compatible
- Blood and body fluid / specimen C/S
- HBsAg, anti HCV (Elisa), anti-HIV

For tuberculosis

- Mantoux test (MT): the risk of latent infection in childhood is high. Tuberculin test is suggested prior to the first course of steroid treatment. In case of immunosuppressive condition >5mm is significant.
- Failure to identify and strong suspicious clinical and radiologically tuberculosis should undergo sputum for AFB for 3 days, Gene expert, gene expert ultra in stool, IGRA (includes t spot in serum, TB QuantiFERON)
- Interferon gamma release assay (IGRA) in patients aged 2 years. TB T-spot test is preferred in immunocompromised patients

Complement C3, C4, antinuclear antibody, anti-streptolysin O: Gross, persistent microscopic hematuria; sustained hypertension; suspected secondary cause (systemic lupus, IgA vasculitis, C3 glomerulopathy) Periodic monitoring, if relapsing illness

Blood creatinine; albumin, electrolytes

Biochemistry

The total serum protein level is markedly reduced. Characteristically, albumin concentration usually falls below 2 g/dL and is often less than 1 g/dL.

Serum electrophoresis shows low levels of albumin and γ-globulins, and increased α-2 and β-globulins. Blood levels of IgG are markedly decreased, IgA is slightly reduced, IgM is increased, and IgE is normal or increased. (106,107).

Hyperlipidemia in nephrotic syndrome results from: (i) increased hepatic synthesis of cholesterol, triglycerides, and lipoproteins in response to decreased intravascular oncotic pressure; (ii) decreased catabolism of lipoproteins due to reduced activity of lipoprotein lipase that transforms VLDL to LDL via IDL; and (iii) reduced activity of LDL receptor and increased urinary loss of HDL (88,108)

Serum electrolytes are usually within the normal range. A low sodium level may reflect renal retention of water due to hypovolemia and the syndrome of inappropriate antidiuresis. Mild reduction of plasma sodium concentration might be due to reduced fraction of plasma water, as seen in patients with severe hyperlipidemia (pseudohyponatremia).

Although serum total calcium is low as a result of hypoalbuminemia, levels of ionized calcium are normal. Serum creatinine is usually within the normal range but may be high due to intravascular volume depletion or acute kidney injury or CKD (109). Hemoglobin levels and hematocrit are increased in patients with plasma volume contraction. Thrombocytosis is common and may reach $5*10^8$ or 10^9/l.

Genetic test discussed later in this manuscript.

Ultrasonography: For volume assessment USG of IVCCI, IVC/Ao ratio, right atrial diameter can be done.

Table 3 **Volume assessment by ultrasonography**

	+ IVC/Ao caliber index	IVC collapsibility index (IVCCI)
Hypervolemia	>1.2	>60%
Normovolemia	0.8-1.2	20-60%
Hypovolemia	<0.8	<20%

Ref – Adopted from (90).

Renal biopsy

Clinicopathological studies show that kidney biopsy is not routinely required in children with idiopathic nephrotic syndrome prior to therapy with corticosteroids (20,110,111). Remission of proteinuria following steroid therapy is the most important predictor of long-term outcome (112,113). The chief indication of kidney biopsy is in patients who fail to show complete remission of proteinuria despite 6-weeks daily therapy with prednisolone (steroid resistant illness) (114,115).

A biopsy is indicated in patients with gross hematuria or persistent microscopic hematuria at the onset (> 5 red cells per high power field on 3 or more occasions, in urine centrifuged at 400 g for 4-5 minutes); or extrarenal features of a systemic disease (20,110,111,113,116,117). An age of onset of more than 15-years is often cited as an indication for performing a kidney biopsy. Review of literature in adolescent onset nephrotic syndrome suggests that a combination of features, including persistent microscopic hematuria, low C3 and steroid resistance, detects all patients with membranous nephropathy or proliferative GN (20,110,111,118,119) This might obviate the need for a kidney biopsy in adolescents presenting with typical nephrotic syndrome that is steroid sensitive. Sporadic published data showed adolescent nephrotic syndrome are steroid sensitive with have less relapses. Since infants (<12-months-old), including those with congenital nephrotic syndrome, are likely to show histological features other than minimal change

disease or an underlying genetic change, we advise next-generation sequencing in these patients (115). Patients with onset of idiopathic nephrotic syndrome beyond infancy should receive therapy with prednisolone, and are advised to undergo kidney biopsy if they show steroid resistance.

The large majority of patients with SSNS show minimal change disease, and less commonly, FSGS or mesangioproliferative GN (20,110,111,120). More than 90% of children with minimal change disease, 50% with mesangioproliferative GN, and 30% with FSGS have steroid-sensitive disease. Patients with frequent relapses do not require a biopsy before initiating therapy with steroid-sparing agents like levamisole, cyclophosphamide, mycophenolate mofetil (MMF), or rituximab (121). The exception is following the use of CNI. When analyzed based on renal histology, the median age at presentation was 3 years for MCNS, 6 years for FSGS, and 10 years for MPGN (30). While there is limited guidance to support kidney biopsy in patients with SSNS before the therapy with CNI (122,123) information on the extent of tubular atrophy and interstitial fibrosis is useful when planning therapy.

Therapy with CNI might result in acute nephrotoxicity, manifested as acute tubular injury and isometric tubular epithelial vacuolization (124,125). Chronic nephrotoxicity, characterized by striped tubulointerstitial fibrosis has been reported in 25-43% biopsies following therapy (for 2.5-3.5 years) with cyclosporin or tacrolimus (126–128) While a recent report found low risk of nephrotoxicity despite prolonged use of tacrolimus (129), most reports suggest similar risk with both medications(127,130).

We therefore suggest considering kidney biopsy before initiating therapy with CNI, particularly in patients with prolonged disease and unclear course, and to inform the clinician regarding baseline histological changes and of nephrotoxicity, kidney biopsy should be performed following prolonged therapy with CNI, or if the therapy is associated with decline in eGFR that persists despite reduction in CNI dose (122,131).

Apart from renal histology, the biopsy provides information on extent and morphology of glomerulosclerosis and associated tubulointerstitial changes. The diagnosis of IgA nephropathy, C3 glomerulopathy and early membranous nephropathy is suggested by immunofluorescence studies.

While kidney biopsies from all patients with nephrotic syndrome should be examined by electron microscopy, the facility is often not available.

Ultrastructural examination helps to confirm the diagnosis of minimal change disease (effacement of podocyte foot processes; no electron dense deposits), differentiate primary from secondary FSGS (diffuse versus focal foot process effacement), categorize membranous nephropathy, C3 glomerulopathy, Alport syndrome and identify disorders of glomerular basement membrane (132).

Adequate tissue

In diffuse disease, such as membranous glomerulopathy, one glomerulus may be adequate for diagnosis. However, in other diseases, such as FSGS, crescentic glomerulonephritis, or lupus nephritis, diagnostic lesions may be focal. The greater the number of glomeruli sampled, the lower the probability of missing a focally distributed lesion (133).

A biopsy sample of 20–25 glomeruli for light microscopic assessment is sufficient to distinguish between mild disease (less than 20% of glomeruli involved), moderate disease (20–50% of glomeruli involved), and severe disease (more than 50% of glomeruli involved). The sample site must also be considered in evaluating the adequacy of tissue.

The biopsy needle ideally advances through the cortex with little medulla. Inclusion of the corticomedullary junction in pediatric biopsies is useful because the segmental lesions of focal segmental glomerulosclerosis (FSGS) start in this location in the earliest stages of disease. An adequate biopsy specimen should preferably include the corticomedullary junction and approximately 20 glomeruli to exclude the diagnosis of FSGS (133).

The internal diameter of the 18 g needle (300 μm) is slightly larger than the diameter of a normal glomerulus (200–250 μm, in patients 2 years and older) (134,135). As a result, an 18 g needle results in about 50% lost, fragmented, or floating glomeruli (136). It is therefore highly recommended that a 16 g needle is always used in children beginning at age two and the 18 g needle reserved for infants and young toddlers.

Allotment of Tissue

Renal tissue should be studied by light microscopic techniques with special stains (hematoxylin and eosin, modified silver stain [periodic acid/methenamine, also called Jones' stain], periodic acid-Schiff [PAS], and/or Masson trichrome), IF and EM (137–140). For light microscopic examination, Satisfactory results may be obtained with Zenker's, Bouin's, or Carnoy's fixatives, formalin, or paraformaldehyde. Material for IF studies may be snap frozen immediately at 20 C in solutions of isopentane, dry ice, acetone, or Freon and embedded in Tissue-tech, OCT, or other compounds for frozen sections. Tissue for EM may be fixed in glutaraldehyde, formaldehyde, or other appropriate nonmercury fixatives.

HISTOPATHOLOGY

Minimal Change Disease (MCD)

On light microscopy, the glomeruli show normal capillary walls and normal cellularity. Swelling and vacuolation of epithelial cells (podocytes) and slight increase in mesangial matrix are often observed. Mild mesangial hypercellularity and scattered foci of tubulointerstitial lesions (141). Vascular changes are absent. Ultrastructural changes are always present, involving podocytes and the mesangial stalks. Podocyte foot process fusion is generalized and constant. There is no direct correlation between the degree of ultrastructural injury and the severity of proteinuria (142). Other epithelial changes consist of microvillus formation and the presence of numerous protein reabsorption droplets. The glomerular basement membranes are normal with no deposits; endothelial cells are often swollen. Mesangial alterations include mild mesangial cell hypercellularity, increased matrix, and finely granular osmiophilic deposits along the internal aspect of the basement membrane. Immunofluorescence examination is negative in most cases.

Diffuse Mesangial Proliferation

The biopsy shows a marked increase in mesangial matrix associated with hypercellularity, although these features are often observed in those with SRNS (111,141,143). Peripheral capillary walls are normal. Electron microscopy shows foot process fusion, similar to the changes observed in MCD. The presence of mesangial hypercellularity has been found to have prognostic significance with a higher rate of progressive kidney disease in some studies (143) .

Mesangial Proliferative Glomerulopathy (MesPGN)

Light microscopic examination of MesPGN shows generalized, diffuse mesangial cell hyperplasia, involving over 80% of the glomeruli. Increased numbers of mesangial cell nuclei are clearly present within mesangial matrix which is either normal or only mildly increased in amount. There is generally no obvious lobulation of the glomerulus, and segmental sclerosis is absent. As in MCD, glomerular basement membranes remain thin and capillary loops clearly patent. By definition, spikes are not seen in silver-stained sections. There is no significant interstitial change (either tubular atrophy or fibrosis) to suggest glomerular loss. Glomerular immaturity, characterized by hypercellularity and a layer of cuboidal epithelium along the surface of the glomerular tuft, may be seen in some cases, particularly in younger children. Recent studies have suggested that these cases may have a less favorable clinical course (144).

Many cases of MesPGN show positive granular mesangial IgM ± C3 and very occasionally small amounts of C1q or IgG, although a proportion of cases have negative immunofluorescence. Some have considered these immune-positive cases as MesPGN, while others separate the positive cases into further distinct categories, most commonly IgM nephropathy.

As noted earlier, these three “entities” (MCD, MesPGN, IgM Nephropathy) probably represent a spectrum rather than separate diseases.

On electron microscopy there is mesangial cell hyperplasia with effacement of epithelial cell foot processes and microvillus transformation of epithelial cells. Dense deposits are not typically found, and the glomerular capillary basement membrane is normal.

Focal Segmental Glomerulosclerosis (FSGS)

Although FSGS is frequently observed in patients with SRNS, it may be observed in up to 10% of children with SSNS. FSGS in steroid resistant disease, a proportion of cases will respond, at least initially, to steroid therapy (145,146) , and thus brief mention of the pathological features is made here.

FSGS affects a variable proportion of glomeruli (141,147). These lesions initially affect glomeruli in the juxtamedullary cortex. The focal changes are limited to a part of the tuft; other capillary loops show no modification. The lesions predominate in the deeper cortex at the corticomedullary junction (148) . Segmental lesions affect a few capillary loops, which stick together either at the hilum or at the periphery of the tuft or at both (149,150).

In FSGS, segmental (involving only a portion of the tuft) and focal (involving some but not all glomeruli) sclerosis of glomeruli is present. The light microscopic changes are not specific for primary idiopathic FSGS and other causes of segmental sclerosing lesions need to be excluded (151). The sclerosed segments show collapse of the glomerular capillary with increase in matrix material though with variable patterns of glomerular involvement (152). Hyaline material is often present within the sclerotic lesions. A clear “halo” is observed at the periphery of the sclerotic segments. The segmental lesion has a different aspect depending on whether it affects a group of capillary loops free in Bowman space or is adherent to Bowman capsule. The “free” sclerotic segments are always surrounded by a “crown” of flat or hypertrophied podocytes. The podocytes form a continuous layer overlying the damaged areas of the tuft and in close apposition to the clear “halo.” When the sclerotic lesion is adherent to Bowman capsule, there is a direct synechiae between the collapsed capillary loops and Bowman basement membrane. The rest of the tuft and the non-sclerotic glomeruli show “minimal changes” with foot process fusion. Glomerular hypertrophy is common in FSGS, and when such hypertrophy is found in MCD, it might be predictive of progression to FSGS (134). Tubular atrophy and interstitial fibrosis are often present and proportional to the glomerular damage (111,153). Focal glomerular lesions should therefore be suspected when focal tubular and interstitial changes are found associated with minimal glomerular changes.

Typically idiopathic primary FSGS shows negative immunofluorescence though non-specific uptake of IgM may be seen, commonly within sclerosed segments. Deposits similar to that of IgM nephropathy may also be present.

On electron microscopy, the FSGS lesion is characterized by the presence of paramesangial and subendothelial, finely granular, osmiophilic deposits (153) with either disappearance or swelling of endothelial cells and an increase in mesangial matrix material. Fatty vacuoles may be seen, either in the middle of the abnormal deposit or in the cytoplasm of endothelial and mesangial cells. The peripheral synechiae, between podocytes and basement membrane, is formed by the apposition of acellular material in which thin and irregular layers of newly formed basement membranes are visible. Non-sclerosed glomeruli show epithelial cell foot process fusion though this may not be complete or as widespread as in typical untreated MCD. However, this is often not helpful in making this distinction as steroid therapy may partially restore foot processes in MCD.

Of interest, in the NIH multicenter trial of steroid-resistant FSGS patients, 138 patients age 2–38 years were randomized to cyclosporine or mycophenolate mofetil with dexamethasone (152). Classical (nos) FSGS was the most frequent lesion (68%) followed by collapsing (12%), tip (10%), perihilar (7%), and the cellular type (3%). Proteinuria in (nos) FSGS was more likely to be subnephrotic. A pathologic classification of FSGS, designated the Columbia classification, is proposed with five histological variants.

The rate of progression to end-stage kidney disease was highest in collapsing (47%), intermediate in NOS (20%), and lowest in the tip variant (7%). This is notable, as these tip patients were nonresponsive to steroids, and thus not representative of typical tip lesion patients who respond to immunosuppression

This classification has clinical implications in terms of response to therapy and risk of progression to renal failure. The clinical course is reported to be benign when the location of these sclerotic lesions is peripheral (tip lesions), although such findings have not been confirmed by others (148,155) .The former lesion was predictive of favorable response to therapy in a pediatric series (117) . Patients with collapsing glomerulopathy have severe nephrotic syndrome, unsatisfactory response to corticosteroids, and rapidly progress to renal failure.

Table 4 **Columbia classification and clinical correlates.**

Variant	Morphology	Clinical correlates
Collapsing or collapsing glomerulopathy	Segmental or global wrinkling and collapse of the glomerular capillary walls with prominent hypertrophy and hyperplasia of the overlying parietal podocytes. Presents with abrupt onset of severe nephrotic syndrome with	Poor response to steroids and CNIs; poor prognosis; seen with HIV nephropathy, parvovirus, cocaine abuse
Tip	Segmental sclerosis at the proximal tubular pole	Usually primary and frequently responds to steroids and CNI. Good outcomes close to MCD (154).
Cellular	Hyperplasia of parietal podocyte sometimes endocapillary proliferation, foam cells, and leukocyte infiltration with severe foot process effacement	Least common variant and seen in mostly with primary FSGS and sometimes in other causes of FSGS
Perihilar	Segmental sclerosis at the vascular pole	Usually seen with adaptive FSGS (single kidney, obesity); may not have the classical features of nephrotic syndrome and may only present with subnephrotic or nephrotic range of proteinuria
Not otherwise	Specified (NOS) Segmental sclerosis, not meeting the features of other variants	Most common variant and could be found in any form of FSGS

Source – D'Agati, Pathologic classification of focal segmental glomerulosclerosis: a working proposal (152)

IgM-Associated Nephropathy

IgM Nephropathy shows light microscopic features that may mimic those of either MCD or MesPGN. The sampled glomeruli may appear completely normal on routine stains, or may show diffuse mesangial hypercellularity. Some cases will show a combination of features, with some but not all glomeruli appearing hypercellular. As with MCD and MesPGN, segmental sclerosing lesions are not seen in an adequately sampled specimen, glomerular capillary loops remain thin walled and patent, and there is no basement membrane thickening or evidence of spike formation. Interstitial changes are absent. Patients with MCD show mesangial deposits of IgM, IgG, C3, and rarely IgA on immunofluorescence microscopy. Most commonly granular deposits of IgM are confined to the mesangium and are generally seen in all glomeruli regardless of their histological appearance. Lesser amounts of C3 are common, and some cases may also show small amounts of C1q or IgG. In these cases, the IgM should remain as the dominant reactant. On electron microscopy there may be a mild increase in mesangial matrix. Immune deposits are often absent though some cases will show occasional small dense deposits that are located in paramesangial regions. Effacement of epithelial cell foot processes is usually seen to a varying degree, usually with microvillus transformation. Habib et al. reported on 54 children with INS and glomerular IgM deposits in the glomeruli. There was no correlation between IgM deposits and the initial response to corticosteroids or the final outcome (156). The impact of mesangial IgM deposits on the clinical course is unclear. Some experts suggest that IgM nephropathy is a distinct entity associated with hypertension, CKD, and steroid dependence or resistance (157) . Others show that mesangial IgM deposits do not correlate with outcomes in patients with nephrotic syndrome (158) .

IgA Nephropathy with Nephrotic Syndrome

IgA nephropathy may present with clinical nephrotic syndrome indistinguishable from MCD in approximately 8–10% of cases. Nephrotic IgA nephropathy may show light microscopic features of MCD, MesPGN, or a focal GN (proliferative or sclerosing), however it is defined by the presence of dominant mesangial IgA deposition (frequently with some associated C3, and in approximately 50% of cases with lesser amounts of IgG and/or IgM), usually with electron microscopic evidence of immune deposits.

C1q Nephropathy

C1q nephropathy is an uncommon disorder that may also present with clinical nephrotic syndrome. This entity, first described by Jennette and Hipp in 1985, presents with mesangial deposition of immunoglobulins and complement components, predominantly C1q, and mesangial electrondense deposits (159,160). Histology of these cases most commonly with MesPGN (20%) and FSGS (7–13%) seen in some cases. C1q deposits may be found in association with MCD or FSGS (161) . The disappearance of C1q deposits or development of FSGS has been reported on follow-up biopsies (162–164). Distinction is made with immunofluorescence finding of predominant C1q deposition in the mesangium and electron dense deposits on electron microscopic examination. Clinical features vary from asymptomatic proteinuria or hematuria to nephrotic or nephritic syndrome, and no clinical or serologic evidence of systemic lupus erythematosus. Although C1q deposits in patients with MCD may be associated with frequent relapses and shorter relapse-free periods, corticosteroid dependence, steroid resistant, and need for second line therapy, chronic immunosuppression and combined therapy but without impact on progression or long-term outcomes (165,166). Overall prognosis is good in particular for those with minimal changes on light microscopy.

Indications for referral to a pediatric nephrologist

We recommend referral to a pediatric nephrologist in case of (84,96):

– SRNS
– Atypical features not consistent with idiopathic NS
– Positive family history for NS

– Congenital or infantile onset NS
– Age at onset of NS above 15 years
– Secondary NS
– SSNS late responder
– FRNS or SDNS
– SSNS patient with drug toxicities or complicated relapses (grade X, moderate recommendation)

Evidence and rationale SSNS follow a chronic course in most children and ideally, all children with SSNS should be cared for by or in conjunction with a pediatric nephrologist at the outset. In some countries, the scarcity of pediatric nephrologists or the distance from tertiary referral centers, require general pediatricians to take primary responsibility (167).

MANAGEMENT OF SSNS

Children are classified according to their response to immunosuppressive therapy. Between 10 and 20% of patients have steroid-resistant nephrotic syndrome. Fortunately, the majority of children have steroid-sensitive nephrotic syndrome (SSNS).

These patients respond for the most part within 4 weeks to an oral course of prednisone (PDN). Overall, most studies show a relapse rate of 70–90% at 12 months after onset of SSNS (168–172). Among these patients, 50–70% will have frequently relapsing nephrotic syndrome (FRNS) if they experience ≥ 2 relapses within 6 months or ≥ 4 relapses within 12 months of presentation, or steroid-dependent nephrotic syndrome (SDNS) if they relapse while receiving PDN or within 14 days after PDN discontinuation. The remaining 30–50% are classified as having infrequent relapsing nephrotic syndrome (68,112,173). Eventually, most patients will achieve permanent remission, but approximately one third patients still have active disease when reaching adulthood (174). Non compliance is found 74% of NS because of increased healthcare cost, health facility, poverty, educational background, ignorance, and idiopathic. We recommend to look into this aspect before leveling SRNS, SDNS, FRNS and embarking into unnecessary investigation and toxic immunosuppression (2). Since 1950, oral corticosteroids have been the mainstay of the treatment of children presenting with SSNS (175,176). Since few prospective studies have compared the relative efficacy and safety of steroid-sparing agents, most guidelines did not specify the precise order or specific choice of alternative therapy (83,88)

Dose, duration, and dosing strategy of PDN in the initial episode of NS

- *After completing the initial diagnostic workup of a child presenting with nephrotic syndrome as outlined above, and a decision is made to start PDN, we recommend that infants > 3 months and children or adolescents (1–18 years) with their first episode of idiopathic NS should receive daily PDN for either:*
  - *4 weeks at 60 mg/m2 or 2 mg/kg (maximum dose 60 mg/day), followed by alternate day PDN at 40 mg/m2 or 1.5 mg/kg (maximum dose of 40 mg on alternate days) for 4 weeks, or*
  - *6 weeks at 60 mg/m2 or 2 mg/kg (maximum dose 60 mg/day), followed by alternate day PDN at 40 mg/m2 or 1.5 mg/kg (maximum dose of 40 mg on alternate days) for 6 weeks (grade A, strong recommendation).*
- *We recommend administering oral PDN as a single morning dose for the treatment of the initial episode and subsequent relapses (grade B, moderate recommendation).*
- *We do not recommend a tapering schedule during alternate day dosing (grade A, strong recommendation).*
- *We suggest that PDN dose should be calculated by either weight or body surface area based on the estimated dry weight (grade B, weak recommendation).*

Evidence and rationale Glucocorticoids are widely used in the treatment of NS, and their efficacy is well-established in children > 1 year of age with a typical presentation. In children between 3 and 12 months of age at onset, there is no evidence-based clear-cut approach to management. The management approach should consider the availability of time-sensitive genetic testing. In the absence of extrarenal features, priority may be given either to genetic testing, kidney biopsy or starting PDN, and assessing at 4 weeks (84). The first established corticosteroid protocol for the treatment of the first episode of SSNS was developed in the 1970s by the International Study of Kidney Disease in Children (ISKDC) (1). The scheme included a 4-week course of daily PDN at a dose of 60 mg/m2 for 4 weeks, followed by PDN at a dose of 40 mg/m2 on alternate days for an additional 4 weeks. Later, a randomized controlled trial (RCT) by the Arbeitsgemeinschaft für Padiatrische Nephrologie showed that therapy with prednisolone for 6-weeks daily and 6-weeks alternate day was better in terms of reduced incidence of relapses over the next 12-24 months (177).

In 2007, a systematic review of the Cochrane Database suggested the superiority of protocols extending corticosteroid therapy to three to six months after the initial episode of SSNS, with an estimated reduction in the risk of relapse of 30% (178). However, most studies included in this analysis had methodological flaws, resulting in a high risk of bias. In the wake of this review, the 2012 KDIGO guidelines also recommend a prolonged steroid regimen with a maintenance dose of 40 mg/m2 on alternate days for 2 to 5 months after the daily induction therapy (121). several scientific bodies have proposed alternative protocols, using longer treatment schedules in the attempt to reduce early relapses (179,180). However, three recent randomized controlled trials (RCTs) have challenged this view (168–170,181). The trial by Sinha et al. failed to show differences in the proportion of patients with sustained remission at 12 and 24 months when compared to a 3- vs. an extended 6-month course of prednisolone (169). Likewise, Yoshikawa et al. observed no differences at the same time points, when comparing 2- vs 6-month courses of prednisolone (170). Finally, Webb et al. have compared the standard ISKDC 8-week treatment with an extended 16-week course of PDN and observed no differences in the relapse rate at 12 months (168).

A meta-analysis that included three of these studies, showed that the risk of frequent relapses at 1-2 years' follow-up was lower for 3-months or longer versus 2-months therapy (RR 0.68; 95% CI 0.47-1.0), but not for 5-months or longer versus 3-months therapy (RR 0.78; 95% CI 0.50-1.22) (181). This review concludes on the futility of performing further studies to evaluate the optimal duration of prednisone for the initial episode of SSNS (181). Since there are no adequately powered well-designed RCTs comparing 2 months with 3 months of PDN therapy, we recommend either an 8-week or a 12-week course of treatment of the initial episode of SSNS in line with KDIGO (83,122). The recent PREDNOS 2019 identified no differences in behavioral effects between different treatment durations (168).

While post-hoc analyses in two studies suggest a trend for benefit with prolonged therapy in young children, this finding requires confirmation (182,183). We also believe that prolonged therapy has no benefit (grade A recommendation) in terms of relapse rate and steroid toxicity. Different studies have highlighted wide variability in the modality and dosage of steroids for SSNS (171,184,185). A retrospective analysis of patients treated for the first episodes suggest that the lowest induction PDN dosing to minimize the risk of relapse is between 2000 and 2500 mg/m2 (171). A PDN dose of 60 mg/m2 is often considered equivalent to a dose of 2 mg/kg (121). Of notice, no study to date has provided conclusive indications of the best way of expressing PDN doses in growing children (186).

Two small RCTs (187,188) and one observational study (182) have demonstrated no differences in efficacy with a lower toxicity profile when PDN is administered as a single morning dose rather than divided doses. However daily prednisolone is administered in single or divided-doses, with similar time to remission (187).

The potential benefits of the single-daily dose regimen include better adherence to therapy, lesser risk of hypothalamic–pituitary–adrenal (HPA) axis suppression and sleep disturbances. Dividing the dose has some practical considerations for medication use in children by minimizing the number of pills or volume of the liquid with each dose.

We do not recommend a tapering schedule during alternate day dosing. None of the four RCTs (168–170,181) cited above used a tapering schedule of PDN in the experimental arm.

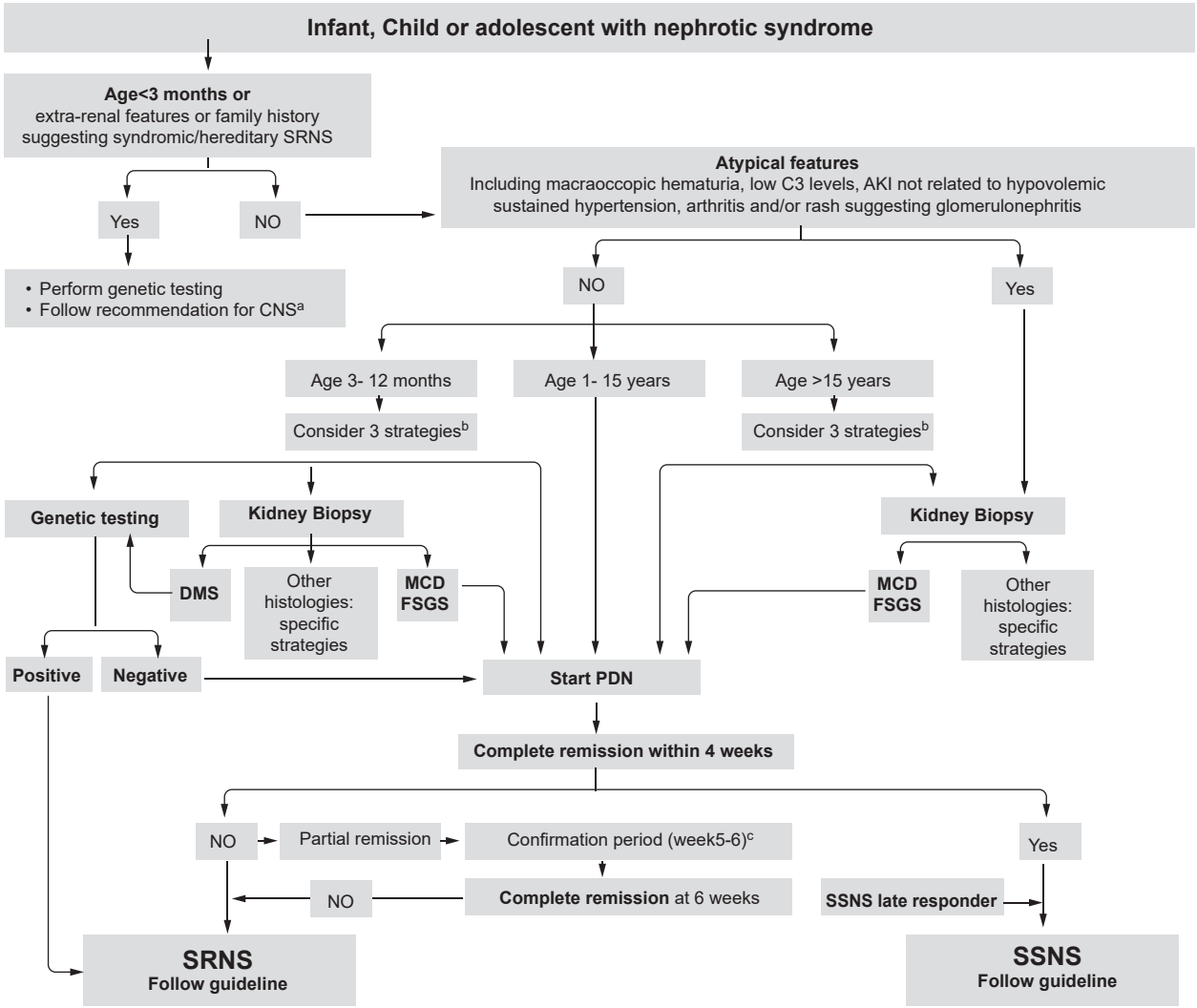


Figure 3: Treatment algorithm for the initial management of a child with nephrotic syndrome. Patients are managed according to age, clinical presentation, and response to a 4-week treatment with oral prednisolone/ prednisone (PDN). aIn children with congenital NS, we recommend following the published guideline for CNS (94). bIn children between 3 and 12 months of age at onset (infantile NS), there is no evidence based clear-cut approach to management. We suggest following one of the following three options in children without extrarenal manifestations: (i) primary genetic testing, if the results are rapidly available, with standard PDN treatment given if genetic testing is negative; (ii) primary kidney biopsy, followed by standard PDN treatment in the case of MCD and FSGS, genetic testing in the case of DMS, and specific treatment in the case of other underlying kidney histopathologies; (iii) starting standard PDN treatment, assessing at 4 weeks and then initiating genetic testing and kidney biopsy in case of SRNS. Patients > 1 year of age

at onset are characterized according to response to a 4-week-treatment with oral prednisolone (PDN). We suggest that the decision of performing a kidney biopsy in older children (> 12 years) be made on a case-by-case basis. cPatients showing incomplete remission at 4 weeks enter the confirmation period in which responses to further oral prednisolone (PDN) with or without methylprednisolone (MPDN) pulses in conjunction with either angiotensin- converting enzyme inhibitors (ACEi) or angiotensin-receptor blockers (ARBs) are ascertained, and genetic and histopathological evaluation is initiated (114). dIn children with SRNS, we recommend following the published recommendations for SRNS (114). Further details are given in Table 2 and in the text. NS nephrotic syndrome, AKI acute kidney injury, CNS congenital NS, SSNS steroid-sensitive NS, SRNS steroid-resistant NS, MCD minimal change disease, FSGS focal segmental glomerulosclerosis, DMS diffuse mesangial sclerosis

Maximum dose of PDN

The traditional dose of PDN for induction of remission during the first episode of NS is 60 mg/m2 per day or 2 mg/kg per day. Most country-based or international guidelines (83,113,183,189) recommend a maximum dose of 60 mg/day though the German guidelines recommend a maximum dose of 80 mg/day (183,184). No studies have formally evaluated the efficacy of doses higher than 60 or 80 mg/day in SSNS. Our opinion coincide with 60 mg/m2/day, maximum of 60 mg/day (grade A recommendation).

Although lower doses of PDN are associated with reduced risk of side effects, these doses may not be as effective. A single small RCT (n = 60) showed that a lower dose of PDN (40 mg/m2/day) during the initial episode of NS was associated with a longer time to remission compared to the standard dose (60 mg/m2 per day; 11.4 ± 4.0 vs. 9.6 ± 2.6 days) (190). At 24 months, the sustained remission rate was lower in boys receiving 40 mg/m2 per day but there was no difference in girls (191). A retrospective cohort of children with SSNS demonstrated that a lower cumulative dose of PDN (< 2500 mg/m2) used during the induction therapy for the first episode of NS is associated with shorter time to first relapse, higher rate of relapses and higher use of steroid-sparing agents, compared to higher doses (> 3000 mg/m2) (171). Therefore, we recommend treating the first episode of NS with a dose of 60 mg/m2 per day (or 2 mg/kg per day). While nearly all protocols recommend treatment on alternate days after the induction phase, some recommend progressive tapering of the PDN dose, while others recommend stopping treatment without tapering (192). We also strongly recommend non-tapering dose of prednisolone.

Dosing by body surface area or weight

Younger children in particular will receive higher mg of PDN (up to 15% (193)) using a body surface area (BSA) compared to weight per kilogram dosing strategy. Limited knowledge exists regarding whether PDN dose should be calculated by weight or BSA. To avoid PDN overdosing in fluid-overloaded children, we suggest calculating the PDN dose based on the estimated dry weight. However, estimation of body surface area involves complex formulae with variable results (194).

Two small RCTs with 146 participants compared weight based dosing with BSA-based dosing in young children (weight < 30 kg, BSA < 1 m2) with their initial episode of SSNS and with relapse of SSNS. There were no statistically significant differences for efficacy or steroid toxicity when comparing weight-based versus BSA-based dosing of PDN but follow-up duration was short in both studies. One patient in the BSA group developed hypertensive encephalopathy (195). Mean cumulative PDN dose was lower with weight-based dosing in both studies (195,196). However small dosing, using weight-based calculations, was associated with increased risk of frequent relapses in some (197,198). Based on pharmacokinetics and variations by age, Experts therefore prefer to administer prednisolone based on body surface area for young children (199). We also hold similar view (grade A recommendation).

When height is not available, PDN doses which approximate to 60 mg/m2 and 40 mg/m2 can be estimated from the formulae: 2 × weight + 8 and weight + 11, respectively (199). Recently, simplified formulas have been proposed to correct for this distortion; specifically, a dose of 2 mg/kg + 10 was shown to produce a very accurate approximation of the PDN dose calculated in mg/m2 for doses not exceeding 60 mg (199).

Type of steroid agent to induce remission/ maintaining remission in children with SSNS

We recommend that prednisone and prednisolone be used interchangeably, and at the same dose, in both the initial presentation and relapse (grade B, moderate recommendation).

Evidence and rationale For the management of childhood NS, both prednisone and prednisolone have been used interchangeably, and at an equivalent dose. Prednisone is a prodrug of prednisolone (200). The conversion of prednisone to the biologically active prednisolone occurs mainly in the liver. This interconversion is not a limiting factor, even in patients with severely impaired liver function (201,202). NS does not influence the conversion of prednisone to prednisolone (203,204). Acute NS and the hypoalbuminemic state do not reduce absorption of PDN or the conversion of prednisone to prednisolone (204,205). In clinical practice, prednisolone and prednisone are usually given orally. Prednisolone is palatable and is the preferred choice for young children and also available (206,207).

Deflazacort vs. prednisone/prednisolone

Deflazacort is a synthetic glucocorticoid oxazoline derivative of prednisolone. Six milligrams of deflazacort have approximately the same anti-inflammatory potency as 5 mg of prednisolone or prednisone. There was no difference between deflazacort and PDN in the number achieving remission in the first episode of SSNS in two small RCTs (208). However, fewer children relapsed following deflazacort treatment compared with PDN (208,209). There is a report of toxic epidermal necrolysis in two children with NS who received deflazacort (210). At this time, there are insufficient data to recommend the use of deflazacort rather than PDN in the treatment of NS.

Intravenous methylprednisolone at equivalent doses of oral prednisone (equivalent dose is 5 mg for every 4 mg of IV methylprednisolone) may be used in situations where a patient is unable to tolerate oral medications or if adherence may be a problem. Intravenous therapy should be limited to a short duration with the intent to switch back to oral medication at the earliest opportunity. (84)

Use of deflazacort, betamethasone, dexamethasone or methylprednisolone is not advised. Prednisolone is best given following food; therapy with antacids, ranitidine or proton pump inhibitors is not routinely required, may be given in good amount of occasion. We also share same view with the other international study findings. Adverse effect of steroids discussed in later.

Combined treatment with steroids and a non-steroidal agent for the initial episode of SSNS

We do not recommend adding other immunomodulatory or immunosuppressive drugs to PDN for the treatment of the initial episode of NS (grade C, weak recommendation).

Evidence and rationale Studies aiming to reduce the number of relapses by adding a non-glucocorticoid immunosuppressive (steroid-sparing) agent to PDN therapy for the initial episode of NS are scarce. An RCT demonstrated that adding 8 weeks of cyclosporine (CsA) to PDN within the first 4 weeks of treatment of the first episode of NS (after establishing remission over 3 days) reduced the risk of first relapse within the first 6 months (RR 0.33, 95% CI 0.13–0.83), but no difference was observed at 12 months (RR 0.72, 95% CI 0.46–1.13) (211). There are RCTs in progress in children studying the benefits of adding mycophenolate mofetil (MMF) (212) or levamisole (LEV) (213) to PDN during the initial episode of NS, as soon as children have entered remission, but there are no published results to inform the guideline.

Moreover, a significant percentage of children with SSNS are infrequent relapsers and will never require a steroid-sparing agent. Therefore, due to the potential unnecessary side effects and to added cost, initial therapy combining steroids and a steroid-sparing agent cannot be currently recommended.

Monitoring during the acute phase and follow-up

- *We recommend educating families to monitor urine protein at home to enable early identification of response to PDN and of relapses (grade X, moderate recommendation).*
- *We suggest using the heat coagulation or sulfosalicylic acid test as alternative methods for home monitoring if dipstick testing for proteinuria is not available (grade C, weak recommendation).*
- *We recommend regular monitoring for patients with NS during the acute phase and during follow up).*
- *We recommend considering a kidney biopsy in patients with SSNS during follow-up if the findings may influence therapy or clarify prognosis. This includes patients on prolonged CNI exposure (> 2 years) especially with high doses, and/ or with signs of CNI toxicity such as unexplained decrease in eGFR (grade B moderate recommendation).*

TREATMENT OF RELAPSES

The disease course varies in patients with SSNS; 35–40% have a single episode or infrequent relapses, and 50–55% show frequent relapses (FRNS) or steroid dependence (SDNS) (112,214).

Unfortunately, no biological marker has been identified to predict the rapidity of relapse, allowing individualized therapy. A single study has identified the presence of IgM on the surface of T lymphocytes as a marker of difficult forms of SSNS, but this needs to be confirmed in larger multi-center studies (215). In general, younger children at onset (3-year) tend to have more severe courses of NS (216,217).

Other risk factors for frequent relapses and steroid dependence include delayed time to remission, and inadequate initial steroid therapy, patients with a fast relapse (duration of initial remission less than 6 months) are also at risk for subsequent frequent relapses (112,214,216,218).

The time needed to respond to PDN has been found in several studies to correlate with the rapidity of relapse and severity of disease (170,172,217). A post hoc analysis of a prospective study comparing two different PDN regimens, suggested that children younger than four years of age may benefit from longer initial courses of PDN (219), but this analysis was underpowered.

First line therapy of relapsing SSNS

- *We recommend that SSNS relapse be treated with single daily dose of PDN (2 mg/kg per day or 60 mg/m2 per day, maximum 60 mg) until complete remission (UPCr ≤ 20 mg/mmol (0.2 mg/mg) or negative or trace dipstick on 3 or more consecutive days) and then decreased to alternate day PDN (1.5 mg/kg per dose or 40 mg/m2 per dose, maximum 40 mg) for 4 weeks (grade B, moderate recommendation).*
- *We do not recommend a tapering schedule during alternate day dosing (grade A, strong recommendation).*

Rationale Almost one-half of the relapses are precipitated by minor infections, usually of the upper respiratory tract. Treatment of infection may rarely induce remission, avoiding the need for corticosteroid therapy. A relapse has conventionally, albeit empirically, been treated as outlined above, but guidelines vary in the duration of therapy. Remission is achieved by 7-10 days, and daily therapy is seldom necessary beyond 2 weeks. In case of persistent proteinuria, daily therapy with prednisolone may be extended, to

maximum of 6-weeks. Lack of remission despite treatment with 6-weeks' daily prednisolone indicates late steroid resistance that requires specific evaluation and management. Different PDN schedules have been proposed by scientific societies, mostly based on consensus among specialists (87).

A single RCT assessed whether reducing the duration of alternate day PDN relapse therapy to 2 weeks after remission is non-inferior to the standard 4-week duration (220). The time to first relapse, development of FRNS or SDNS, and adverse effects were similar in both groups. Cumulative dose of PDN was lower in the short duration group. Non-inferiority was not proven with this trial.

A further RCT The PROPINE study evaluated extension of the alternate-day treatment period from 36 to 72 days in children with FRNS/SDNS, with a comparable cumulative PDN dose in both groups (221). The proportion of children relapsing within 6 months was not different between the study arms (58% long duration vs. 42% short duration, p = 0.26). A further study comparing a 2-week and 6-week period of alternate-day PDN with different cumulative PDN doses is ongoing (222)

Paediatric nephrologists have generally treated relapses with daily prednisone (60 mg/m2/day) till the child achieved remission and then continued alternate day therapy (40 mg/m2) for 4 weeks or more (223). Two observational studies and a small RCT have demonstrated that most children with relapsing SSNS achieve and maintain remission with prednisone given at a dose of 30 mg/m2/day (190,224,225). These data need confirmation in an adequately powered RCT.

In children with FRNS, observational studies have demonstrated that low-dose alternate-day prednisone (mean dose 0.48 mg/kg on alternate days) or low-dose daily prednisone (0.25 mg/kg/day) reduced the risk of relapse compared with historical controls with maintenance of growth rates (226,227). Guidelines recommend low-dose alternate-day prednisone in children with FRNS and SDNS (228). However a recent RCT (229) in 61 children with FRNS or SDNS found that children receiving daily prednisone (0.2–0.3 mg/kg/day) had significantly fewer relapses than children receiving alternate day prednisone (0.5–0.7 mg/kg/day) with no increase in adverse effects. In study, which included 87 relapse episodes in 50 patients, 70% of patients achieved remission within 1 week using a PDN dose of 1 mg/kg/day (225).

Similarly, PDN was prescribed at doses of 1.0, 1.5, and 2.0 mg/kg/day in a prospective trial including ten patients per group; although the number of patients was very limited, the response rate appeared similar in the three groups (216).

Optimal approach to children with FRNS and SDNS

- *We recommend the use of maintenance treatment in all patients with FRNS or SDNS (grade B, moderate recommendation).*
- *In patients with FRNS, we recommend either the introduction of a steroid-sparing agent as detailed below or low-dose maintenance PDN given as an alternate-day or a daily dose (grade A, strong recommendation).*
- *We recommend introduction of a steroid-sparing agent in children:*
  - *who are not controlled on therapy, or*
  - *who suffer a complicated relapse, or*
  - *with SDNS (grade B, strong recommendation)*
- *We recommend that the selection of the steroid-sparing agent be made in conjunction with patients or guardians in order to choose the most appropriate medication for each individual according to their values and preferences. This requires not only information on the efficacy of these medications, but also disclosure of possible side effects as listed in Table 5 (grade X, strong recommendation).*

- *We recommend the introduction of one of the following steroid-sparing agents (alphabetical order): calcineurin inhibitors (CNIs), cyclophosphamide (CYC), levamisole (LEV), and mycophenolate mofetil (MMF)/mycophenolic sodium (MPS) (grade A, strong recommendation).*
- *We recommend using RTX as a steroid-sparing agent in children with FRNS or SDNS who are not controlled on therapy after a course of treatment with at least one other steroid-sparing agent at adequate dose, especially in case of non-adherence (grade B, moderate recommendation).*
- *We recommend switching to a different steroid-sparing agent when a patient is not controlled on therapy with the initial agent (grade X, strong recommendation).*
- *We recommend considering tapering and discontinuation of maintenance treatment with PDN, LEV, MMF/MPS, or a CNI in all children in sustained remission for at least 12 months (grade X, moderate recommendation).*
- *We recommend that the choice of immunosuppressive strategy for patients with frequent relapses be based on considerations of its efficacy and adverse effects, patient age, steroid threshold, severity of relapses and features of steroid toxicity (Figure-4).*

Evidence and rationale SSNS is a relapsing–remitting condition. Children with frequent relapses, who require frequent courses of oral PDN, particularly in the presence of comorbidities, may develop steroid toxicity (Table 5). In children with FRNS or SDNS, it is necessary to balance risks and benefits of the intervention on an individual basis.

The occurrence of two or more relapses in the first 6- months is usually associated with high frequency of relapses in the subsequent 12-24 months [3]. Patients experiencing 4 relapses annually receive ~165-200 mg/kg (4.6-5.6 g/m2) prednisolone, corresponding to 0.45-0.55 mg/kg (12.5-15.5 mg/m2) daily. As 12-weeks' prednisolone therapy for the initial episode (~115 mg/kg; ~3.4 g/m2) might be associated with adverse effects (202,230), the risk of steroid toxicity in patients with 3 relapses in any 6-months or 4 relapses annually is considerable (231). The objective is to keep each patient controlled on therapy with minimal adverse effects. In some centers, the initial approach in children with FRNS is low-dose maintenance oral PDN, while in other centers a steroid-sparing agent is immediately started.

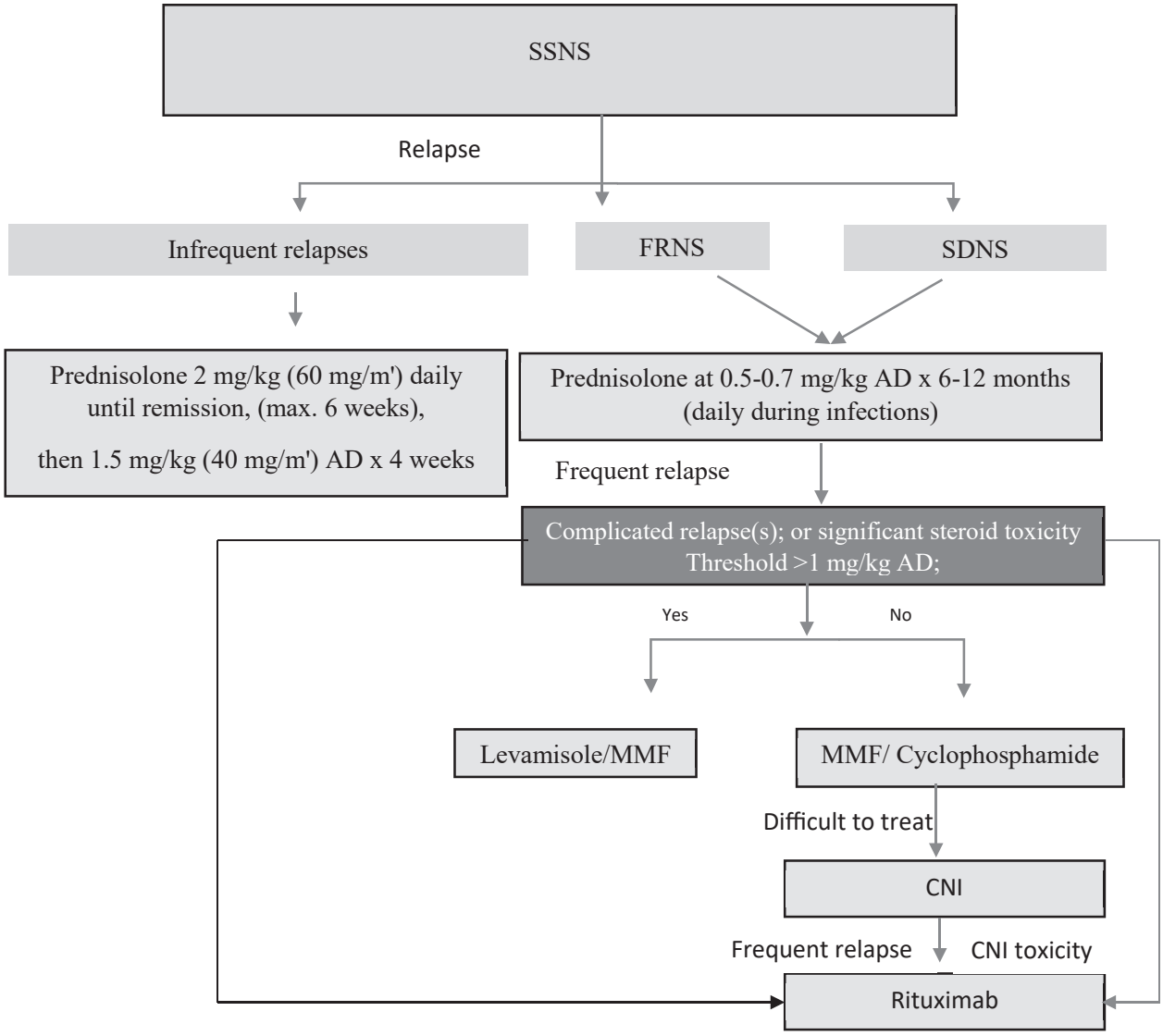


Figure-4: Adapted and modified from ISPN guideline (88). Management of frequently relapsing or steroid dependent nephrotic syndrome. The initial strategy is to administer prednisone at a dose of 0.5–0.7 mg/kg on alternate days for 6–12 months. Daily therapy at the same dose for 5–7 days, during minor infections, prevents infection associated relapses. Patients who relapse at prednisone threshold >0.7 mg/kg or show steroid toxicity require therapy with steroid-sparing medications (Table 3).

Levamisole or mycophenolate mofetil (MMF) are preferred agents for mild disease. Patients with high steroid threshold (>1 mg/kg on alternate days) or with significant steroid toxicity (Table 2) may be treated with MMF at higher doses (1000–1200 mg/m2/day) or cyclophosphamide. The use of cyclophosphamide is avoided in children <5–7 year-old and in peripubertal boys due to reduced efficacy and risk of gonadal toxicity, respectively. Patients who relapse despite therapy with two or more steroid sparing agents are considered for therapy with calcineurin inhibitors (CNI; cyclosporine or tacrolimus) and rituximab. (Modified from Indian Pediatrics 2021)

Daily or alternate

• In patients with frequent relapses, we suggest tapering prednisolone to a dose of 0.5-0.7 mg/kg on alternate days, for 6-12 months. (2B).

The use of low-dose PDN in children with FRNS to maintain remission is primarily based on two historic small single-arm, uncontrolled studies with alternate day (227) or daily dosing (226). Alternate- day dosing has been more widely adopted, although this is not evidence-based. Therapy with alternate-day prednisolone is the initial strategy for managing patients with frequent relapses (228,232). Alternate-day prednisolone, often used as the control limb in RCTs, showed satisfactory response in 43-82.5% patients.

Data from a case series (226) and an open-label RCT (229) suggests that low dose (0.2–0.3 mg/kg) daily prednisone is associated with fewer relapses than twice the dose (0.5–0.7 mg/kg) on alternate days with no differences in adverse effects. The strategy led to lower steroid requirement and was not associated with toxicity (229). These findings require confirmation in studies with longer follow up that are powered to examine adverse effects, including suppression of the hypothalamo-pituitary-adrenal axis.

There was some clinical evidence of reduced glucocorticoid toxicity with the daily dosing schedule. The preferred use of daily or alternate day low dose PDN for relapse prevention in FRNS requires additional study. Transition to steroid-sparing agents is recommended in patients not controlled on therapy as defined in Table 1.

The duration of therapy is at physician discretion, based on its efficacy and assessment of toxicity through monitoring of weight, height, blood pressure, ocular toxicity and hyperglycemia (table 5). In patients with frequent relapses, guidelines recommend that corticosteroid therapy for the relapse be prolonged and tapered over 3 months or longer (122,123,228). The dose at which relapses occur (steroid threshold) is a marker of disease severity. Prolonged therapy with alternate-day prednisolone might maintain remission in patients with low threshold relapses (<0.7 mg/kg on alternate days).

Daily PDN treatment at onset of infection to prevent relapse

- *We do not recommend the routine use of a short course of low-dose daily PDN at the onset of an upper respiratory tract infection (URTI) for prevention of relapses (grade B, moderate recommendation).*
- *We suggest considering a short course of low dose daily PDN at the onset of an URTI in children who are already taking low dose alternate day PDN and have a history of repeated infection-associated relapses (grade D, weak recommendation).*

Evidence & rationale: One cross-over trial also supports the use of low-dose daily prednisolone in preventing infection-associated relapses in patients off corticosteroids (233).

Since relapses are precipitated by minor infections, four RCTs have examined the role of increasing the frequency to short term (5–7 days) daily administration of steroids in reducing infection-related relapses (233–236). Although all studies showed reduced relapse rates with the intervention, one had a small sample size (236), and another did not examine long-term benefits (234). One prospective large RCT showed that daily administration of small dose of prednisone during infections independently reduced annual relapse rates by 59% (rate ratio, 0.41; 95% CI 0.3, 0.6) without the risk of steroid toxicity. Six patients needed to be treated to prevent the occurrence of frequent relapses in one (235). Based on the above findings, expert guidelines suggest that the frequency of administration of prednisone be increased from alternate day to daily during episodes of fever or upper respiratory tract infection (88,122).

However results from a large RCT with 271 children evaluated found that giving 6 days of daily low-dose prednisolone at the time of an URTI did not reduce the risk of relapse of nephrotic syndrome in children in the United Kingdom (237). Asthma triggered relapse of nephrotic syndrome is benefitted by rescue dose of prednisolone 1-2 mg/kg/day for 2-4days. We recommend its use.

Steroid-sparing agents

- *We recommend use of a steroid-sparing agent in patients failing therapy with alternate-day prednisolone, steroid toxicity or complicated relapses (Fig. 1). (1B) ISPN*
- *In patients failing alternate-day prednisolone, we recommend therapy with either levamisole or MMF for 12-24 months. (1B)*
- *We recommend MMF or cyclophosphamide in patients with significant steroid toxicity, high steroid threshold, complicated relapses, of failure of therapy with levamisole.*

Steroid-sparing agents used in children with SSNS include CNIs (cyclosporin A (CsA), tacrolimus (TAC)), cyclophosphamide (CYC), immune modulators (levamisole (LEV), anti-proliferative agents (mycophenolate mofetil (MMF)/mycophenolic sodium (MPS)), and anti-CD20 monoclonal antibodies, primarily rituximab (RTX).

Steroid-sparing interventions are necessary in patients who continue to relapse frequently or show evidence of steroid toxicity while on alternate-day prednisolone (Figure 4). There is insufficient evidence to establish the best initial option and the optimal sequence of agents from least to most effective or least to most toxic.

The choice of agent should be based on family and physician preferences and the risk profile for drug-associated complications. Factors to consider include disease type/ severity, age—including onset of puberty, potential adherence, side-effect profile, comorbidities, cost and availability. Potent medications are preferred in patients with high threshold (>1 mg/kg on alternate day) relapses, relapses associated with life threatening complications, or with significant steroid toxicity (Definition table 1 and drug Table 5). The presence of stable remission (up to one relapse in 6 months) during such therapy is acceptable, and except in severe steroid dependence, prednisolone is tapered and discontinued over few months. Therapy may be modified in patients with frequent relapses or significant adverse effects. A proportion of patients with SSNS show disease characterized by multiple relapses despite therapy with steroid-sparing agents, and/or medication-associated toxicity.

We propose defining difficult-to-treat nephrotic syndrome as patients with: (i) frequent relapses or infrequent relapses with significant steroid toxicity; and (ii) failure of 2 or more steroid sparing agents: levamisole, cyclophosphamide or MMF. These patients might merit therapy with agents such as CNI and rituximab.

While the approach to management indicated in Figure 4 treatment flowchart suffices in most instances, individual situations may require different preference. Patients diagnosed either with steroid dependence soon after initial therapy, or with significant steroid toxicity at diagnosis of frequent relapses may be considered directly for steroid sparing therapies. Therapy with oral cyclophosphamide is avoided in young patients and in pubertal or post-pubertal boys. Therapy with CNI may be preferred to MMF in very young patients with significant steroid toxicity, even though the definition of difficult-to-treat SSNS is not met.

CALCINEURIN INHIBITORS

- *When using CNIs, we recommend therapeutic drug monitoring to ensure optimal dosing (see below) (grade B, moderate recommendation).*
- *When using cyclosporin A (CsA), we recommend a starting dose of 3–5 mg/kg/day (maximum dose 250 mg) divided into 2 doses (every 12 h) to achieve trough blood levels of 60–100 ng/mL or 2 h post-dose levels of 300– 550 ng/mL (grade B, moderate recommendation).*
- *When using tacrolimus (TAC), we recommend a starting dose of 0.1–0.2 mg/kg/day (maximum dose 10 mg) in 2 doses (every 12 h) to achieve trough blood levels of 3–7 ng/mL (grade C, moderate recommendation).*

- *We recommend that the lowest effective CNI dose should be given to maintain patients controlled on therapy (grade X, strong recommendation).*
- *We recommend avoiding prolonged use of CNIs for more than a total of 2–3 years (grade B, moderate recommendation).*
- *If CNIs have to be continued, we recommend that a kidney biopsy be considered after 2–3 years to exclude toxicity (grade B, moderate recommendation).*

Evidence for efficacy of CNIs in SSNS

CNIs have been used to treat relapsing SSNS for nearly 30 years (238–242). Cyclosporin has been used to treat children with frequently relapsing or steroid dependent SSNS since 1985 (243). Because of the lack of cosmetic side effects, TAC may be preferred to CsA. A Cochrane systematic review did not identify any RCTs comparing CsA with TAC in children with SSNS (244).

CNIs are effective in maintaining remission in children with FRNS and SDNS. A single RCT performed in Japan and including 108 children with FRNS/SDNS demonstrated that CsA compared with placebo reduced the risk of relapse (relapse rate ratio 0.55 (95% CI 0.37–0.82)) (245). Observational studies have also demonstrated reduced relapse rates with CsA compared with PDN (131,131,239,246–249).

However, Cyclosporine is effective for FRNS or SDNS, although most patients experience relapses after discontinuing the drug (cyclosporine dependence) (131,239,246–251).

Two small trials enrolling 95 children demonstrated no significant difference in the risk of relapse during treatment between alkylating agents given for 6 or 8 weeks and cyclosporin given for 6 or 9 months (240,252,253). However most children treated with cyclosporin relapsed when therapy was ceased so the risk of relapse with alkylating agents was lower than with cyclosporin after cyclosporin had been ceased for 12–15 months. In a prospective 2 year follow up of 44 children, in whom cyclosporin was discontinued after completion of an RCT, 37 (84%) experienced a relapse (251).

Ishikura et al. reported that 84.7% of patients had a relapse within 2 years after completion of the 2-year CsA therapy and 59.2% of patients had regression to FRNS (251). There are small RCTs comparing alkylating agents or MMF with CsA. Compared with alkylating agents, the number of patients relapsing by the end of therapy (6–9 months) on CsA may not differ (2 studies, 95 children: RR 0.91, 95% CI 0.55 to 1.48). However, following cessation of these medications and because the effect of alkylating agents but not CsA is prolonged after cessation, fewer children relapse after receiving alkylating agents compared with CsA alone (risk of relapse at 12–24 months; 2 studies, 95 children: RR 0.51, 95% CI 0.35 to 0.74) (244).

Two small RCTs suggested that the number of patients relapsing by 12 months may not differ between MMF and CsA (2 studies, 82 children: RR 1.90, 95% CI 0.66 to 5.46) but there is considerable imprecision in these findings. The addition of a third study to the meta-analysis indicated that the relapse rate/year may be higher with MMF than with CsA (mean difference 0.83 (95% CI 0.33 to 1.33) (244).

In RCTs, MMF is less likely to cause hypertrichosis and gum hypertrophy compared with CsA (244,254–256) but no differences in other adverse effects (hypertension, impaired kidney function and infections) were identified. Three large observational studies (257–259) found higher efficacy in maintaining remission with CNIs compared with MMF. However, adverse effects were more common with CNIs.

The use of TAC in SSNS is based on the effectiveness of CsA in SSNS (239), on the results of observational studies (241,257,259) and the efficacy of TAC in pediatric kidney transplantation. Although there are no RCTs, several case series suggest that tacrolimus is effective in patients with FRNS or SDNS (242,260,261). In a nonrandomized prospective study on 72 patients, tacrolimus and MMF were found to be similarly effective in maintaining remission (257). A retrospective study also suggested that tacrolimus was more effective than MMF in prevention of relapses, but resulted in adverse events such as infections and pancreatitis (259). Tacrolimus may therefore be considered for treating FRNS or SDNS when

cyclosporine cannot be used because of cosmetic side effects (hypertrichosis, gingival hypertrophy). In a retrospective cohort study of 340 children with FRNS or SDNS examining the relative efficacy and safety of tacrolimus, MMF and levamisole as the first non-corticosteroid agent, the 30-month relapse free survival was 62% with tacrolimus, 39% with MMF and 24% with levamisole (259). Fewer adverse effects were seen with levamisole (three reports) compared with tacrolimus (33 reports). Serious adverse effects mainly related to infection were only seen with tacrolimus.

Tacrolimus toxicity profile Particular caution is required when TAC is used in patients with a family history of diabetes mellitus or if risk factors for impaired glucose tolerance (e.g., obesity) are present (262). Renal interstitial fibrosis has also been reported, as with CsA. One report described a significant association between higher TAC trough levels and renal interstitial fibrosis (260). Potential onset of diabetes mellitus and chronic nephrotoxicity are important side effects of tacrolimus; the latter often correlates with high trough levels of the agent (260). Tacrolimus is now the preferred CNI agent for SSNS where available largely because of the cosmetic effects of cyclosporin though it is also nephrotoxic and may be associated with diabetes mellitus. No RCTs have compared tacrolimus with cyclosporin in children with SSNS. In a prospective uncontrolled study of 74 children (50 on tacrolimus; 24 on cyclosporin), relapse frequency during 2 years follow-up did not differ significantly between treatments (241). Nephrotoxicity defined as an increase in serum creatinine >25% above baseline was less common in tacrolimus treated children and diabetes mellitus was not reported. There are also some observational data in children with SDNS suggesting that tacrolimus may be associated with less CNI nephrotoxicity than cyclosporin (129).

Cyclosporin A toxicity profile Nephrotoxicity is the most problematic side effect of CsA, and its risk is increased after use for > 2 years (126,128). CsA-induced chronic nephrotoxicity cannot be diagnosed based only on urinalysis or blood tests. It is advisable to avoid prolonged use of CsA and to consider its discontinuation or to perform a kidney biopsy after 2–3 years to avoid/detect toxicity. However, there is no definitive evidence supporting the necessity of kidney biopsy in SSNS treated with CNIs. Recent clinical studies of micro emulsified CsA (131,263) have demonstrated a lower incidence of nephrotoxicity.

Chronic nephrotoxicity is the most problematic side effect of cyclosporine; its risk is increased after prolonged use (2 years or more) (126,128). Since it is not possible to diagnose cyclosporine-induced chronic nephrotoxicity by urinalysis and blood tests, a kidney biopsy might need to be performed in case of long-term administration; prolonged therapy is avoided (264). CNI toxicity is well documented in children receiving this therapy outside the transplant setting (265) though few studies have correlated clinical toxicity with morphologic features (266,267). The toxic effects are essentially the same in transplant and non-transplant settings. CNI toxicity may be characterized by reduction in glomerular filtration rate with no discernible histological abnormality or by acute and chronic tubular and/or vascular changes in the kidney. Acute changes of toxic tubulopathy are classically described as “isometric” vacuolation of proximal tubular epithelial cells. However this is often a focal phenomenon and may only be seen in a small number of tubules in a biopsy sample. The vacuoles are of similar size (hence “isometric”) and occur on the basis of dilatation of the smooth endoplasmic reticulum of the cells.

Non-specific changes of acute tubular necrosis may be seen in some cases, with intraluminal desquamation of epithelial cells, dilatation of the tubules and regenerative nuclear changes. Acute vascular changes may result in microvascular thrombosis, endothelial and myocyte necrosis. Chronic vascular changes include nodular hyaline arteriopathy, which arises on the basis of individual myocyte necrosis of arteriolar smooth muscle, and “striped” interstitial fibrosis and tubular atrophy that reflect focal ischaemic damage. Ultimately, chronic CNI nephrotoxicity can result in glomerular changes of chronic ischaemia and/or focal and segmental glomerulosclerosis. The morphological nephrotoxic effects of tacrolimus are essentially the same as those seen with cyclosporin and include acute tubular necrosis, acute and chronic vascular changes, and interstitial fibrosis. Cyclosporin-induced tubulointerstitial lesions on kidney biopsy are reported in 30–40% of children who have received cyclosporin for 12 months or more (126,268,269).

Cyclosporin associated arteriopathy is uncommon. Risk factors for fibrosis are total duration of cyclosporin therapy, having heavy proteinuria for more than 30 days during therapy (126) and higher trough cyclosporin levels (270), higher 2 h peak cyclosporin levels and concurrent use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (269). Arteriopathy but not interstitial fibrosis improves after cyclosporin has been ceased for 12 months or more (271). Treatment with cyclosporine may result in cosmetic side effects (hypertrichosis, gingival hypertrophy), infections, hypertension, and the posterior reversible encephalopathy syndrome (131,239,246–251,272). Cosmetic side effects, such as hypertrichosis and gum hyperplasia, are common with CsA (131,246–250,272). Infections, hypertension, and posterior reversible encephalopathy syndrome (PRES) are also known complications of CsA therapy. A potentially serious adverse effect of CNI is posterior reversible encephalopathy syndrome (PRES) (273). Nephrotic syndrome per se and hypertension also are predisposing factors for PRES.

Cyclosporin drug monitoring The dose of CsA should be adjusted with drug monitoring based on assays validated against tandem mass spectrometry. Blood concentration of cyclosporine should be monitored, usually by 12-h trough or C2 (2-h post-dose) levels. According to a multicenter, prospective RCT of Sandimmun® conducted in Japan on 44 children with FRNS, sustained remission was significantly higher in the dose-adjusted group (initially the dose was adjusted to maintain blood trough levels within 80–100 ng/mL for the first 6 months, and then within 60–80 ng/mL for the next 18 months) compared with the 2.5 mg/kg fixed-dose group (initially the dose was adjusted to maintain blood trough levels within 80–100 ng/mL for the first 6 months, but then fixed at 2.5 mg/kg for the next 18 months) (50 vs. 15%; $p < 0.01$). A multicenter observational study assessed Neoral® (250), a microemulsified preparation of CsA, in 62 children with FRNS, with adjustment of the dose using the same target trough levels as stated above. This study reported that microemulsified CsA was effective and safe (relapse-free survival rate at month 24, 58%; incidence of nephrotoxicity, 8.6%), similar to conventional CsA (131). The AUC 0–4 (area under the time-concentration curve) of CsA is best predicted by C2 (CsA blood concentration at 2 h post-dose) in kidney transplant patients (274). Similar findings were reported in children with NS (275).

A multicenter, prospective, RCT in Japan on 93 children with FRNS compared two different target C2 levels: a higher C2 Group (target C2 600–700 ng/mL for the first 6 months, followed by 450–550 ng/mL for the next 18 months) and a lower C2 group (target C2 450–550 ng/mL for the first 6 months, followed by 300–400 ng/mL for the next 18 months). At 24 months, the relapse rate was significantly lower in the higher C2 group than the lower C2 group (0.41 vs. 0.95 times/person-year; hazard ratio, 0.43; 95% confidence interval, 0.19 to 0.84; $p < 0.05$). The rate and severity of adverse events were similar in both treatment groups (238).

Cyclosporin (microemulsified) is usually commenced at 4–5 mg/kg/day in two divided doses with subsequent dosing altered to achieve 12 h trough whole blood levels (C0) of 80–150 ng/mL (67–125 nmol/L) initially. In an RCT the sustained remission rate at 2 years was significantly higher in children with C0 levels maintained between 80–100 ng/mL (50–67 nmol/L) [mean dose 4.8 mg/kg/day] compared with children treated with a fixed dose of 2.5 mg/kg/day (sustained remission rates 50% versus 15%) (239). Hypertension and mild arteriolar hyalinosis were less common in the fixed dose group. The cyclosporin dose, required to maintain trough levels, may be reduced by one third by administering ketoconazole as a cyclosporin sparing agent with reduction in drug costs (276). Studies in children with SSNS have demonstrated better correlations between area under the curve concentrations of cyclosporin and 2 h post dose levels (C2) than with trough levels (275). A Japanese RCT compared the effect of two different C2 levels on the relapse rate in children with FRNS or SDNS (238). Children were randomized to receive cyclosporin to achieve whole blood C2 levels of 600–700 ng/mL (499–582 nmol/L) for 6 months followed by 450–550 ng/mL (374–457 nmol/L) for 18 months or to achieve C2 levels of 450–550 ng/mL (374–457 nmol/L) for 6 months and then 300–400 ng/mL (250–333 nmol/L). The sustained remission rate was slightly but not significantly higher in the high C2 level group compared with the lower C2 level group but the relapse rate was significantly lower in the high level group; adverse effects did not differ between groups.

Absorption of oral CsA after pre-meal administration (15–30 min prior to a meal) is greater than post-meal administration so it may be preferable to administer CsA before meals. The main priority is to give it in a consistent manner. (84). Concomitant use with other drugs requires adequate attention since macrolide antimicrobials and many other drugs can affect metabolism. Grapefruit juice should be avoided as it inhibits metabolism of CsA and causes increased blood concentrations of the drug. (84)

Drug monitoring of tacrolimus The starting dose of tacrolimus was 0.5–1.5 mg/kg/day in two divided doses; subsequently the dose was adjusted to 12 h trough levels of 5–12 ng/mL (6–14 nmol/L). There are also some observational data in children with SDNS suggesting that tacrolimus may be associated with less CNI nephrotoxicity than cyclosporin (129).

General considerations of benefit/risk of using CNIs CsA is very effective in the treatment of FRNS/SDNS and allows steroid tapering and discontinuation in the majority of patients (131,239,246–250). The shortcoming of CsA therapy is that many patients experience relapse after termination of CsA therapy (CsA dependence) (246–248,250,251). Moreover, CNIs have a variety of side effects, including nephrotoxicity. In comparison to CsA, TAC has fewer cosmetic side effects.

Tapering and discontinuing of CNIs If a child remains in sustained remission for at least 12–24 months and off steroids, CNI discontinuation should be considered to avoid nephrotoxicity (128,251). Tapering CNI dose to zero over about 3 months rather than discontinuing abruptly may be preferable because in case of a reappearance of proteinuria during tapering, reestablishing the initial CNI dose may be sufficient to avoid a relapse and a course of oral PDN while establishing that the patient still needs maintenance therapy.

The duration of administration of CNIs is controversial with some authors suggesting that duration should not exceed 2 years (126). However other authors have suggested that longer periods of CNIs may be well tolerated (277). There are few data on kidney histology in children with SSNS who have received tacrolimus but increases in interstitial fibrosis correlated with trough tacrolimus levels (260). These few data suggest that as with cyclosporin, the lowest possible dose of tacrolimus should be used to maintain remission.

CYCLOPHOSPHAMIDE

- *We recommend starting when the patient is in steroid induced remission and using either a single course of 2 mg/kg per day (maximum dose 150 mg) given orally for 12 weeks (grade B, moderate recommendation). or a single course of 3 mg/kg per day (maximum dose 150 mg) for 8 weeks given orally (grade B, moderate recommendation).*
- *We recommend that the maximal cumulative dose of CYC not exceed 168 mg/kg (grade C, moderate recommendation).*
- *We recommend that, if adherence is uncertain, a single course of monthly intravenous CYC (500 mg/m2 per dose (max single dose 1 g) × 6 months) can be given (grade B, moderate recommendation).*
- *We suggest administering CYC in combination with alternate-day oral PDN starting with a dose of 40 mg/m2 (1.5 mg/kg) and reducing to 10 mg/m2 (0.3 mg/kg) over the course of treatment (grade D, weak recommendation).*
- *We recommend monitoring for neutropenia (absolute neutrophil count < 1500/μL) with complete blood counts every 2 weeks (grade D, weak recommendation) and ceasing CYC if the child develops leukopenia (< 4000/ μL) or neutropenia (< 1500/μL) or significant thrombocytopenia (< 50,000/μL) (grade X, strong recommendation) and restarting after recovery of blood cell counts using a lower dose (grade X, strong recommendation).*
- *We recommend maintaining a high fluid intake to ensure a high urine output during treatment (grade C, moderate recommendation).*

Evidence and rationale

Efficacy of CYC

A meta-analysis of 4 RCTs with 161 participants (244) comparing CYC with PDN or placebo showed a reduction in the number of relapses by 6 to 12 months (4 studies, 161 children; RR 0.47 [95% CI 0.34, 0.66]). A single course of monthly intravenous doses of CYC at a dose of 500 mg/m2 per dose (max single dose 1 g) × 6 months can be given when adherence is an issue (278,279).

A review of 38 RCTs and observational studies assessing alkylating agents (CYC and chlorambucil) (280) including 1504 patients and 1573 courses and published between 1960 and 2000, indicated sustained remission rates of 72% after 2 years and 36% after 5 years for FRNS; the rates were 40% and 24%, for SDNS respectively. The maintenance of sustained remission declines with time, i.e., 44–57% at 1 year, 28–42% at 2 years, 13–31% at 5 years (281–285). The effect may be lower in children below 3–5.5 years of age (282,284,286).

Cyclophosphamide, the most commonly used steroid-sparing agent, has been documented in RCTs to effectively treat FRNS (287,288). The Cochrane review reported that cyclophosphamide significantly reduced relapse risk at 6– 12 months compared to prednisone alone (4 studies, 161 children; risk ratio (RR) 0.47, 95% CI 0.34–0.66) (244). Several reports demonstrate that cyclophosphamide is not sufficiently effective for SDNS (282,283,289,290). A systematic review reported that remission rates in children with FRNS were 72% after 2 years and 36% after 5 years; rates in patients with SDNS were 40% and 24%, respectively (280).

In many countries, cyclophosphamide has been largely replaced by other non-corticosteroid medications because of its adverse effects. The main advantage of cyclophosphamide over levamisole, MMF and CNIs is that it often results in a prolonged period of remission after the medication is ceased. Rituximab also leads to a prolonged period of remission off treatment. Two recent observational studies (291,292), which compared outcomes of children treated with cyclophosphamide with those treated with rituximab, found that 1 and 2 year relapse-free survivals were similar between treatments but adverse effects were more common with cyclophosphamide. Importantly more children treated with rituximab were able to cease steroids completely (292). However rituximab is expensive and may not be available in resource limited countries.

Cyclophosphamide treatment should be initiated after the patient has achieved remission and has been treated with the recommended dose of PDN for relapse. Published literature examining the use of CYC does not directly address whether co-intervention with PDN is necessary to reduce relapses or risk of adverse effects. Descriptions of continuation of PDN or concomitant administration of PDN while on CYC vary widely in the literature. Protocols ranged from PDN 10–40 mg/m2 either daily or alternate days, to 60 mg/m2 every other day. Tapering at the end of treatment was also highly variable (240,252,280,281).

Due to substantial variation in practice, administering CYC in combination with alternate-day oral PDN starting with a dose of 40 mg/m2 (1.5 mg/kg) and reducing to 10 mg/m2 (0.3 mg/kg) over the duration of treatment was considered as reasonable practice by the guideline committee. Alternate-day oral PDN may help to reduce the risk of neutropenia when starting CYC initially. Usually, significantly lower doses of cyclophosphamide are prescribed typically 2–2.5 mg/kg for 8– 12 weeks (total dose 180–200 mg/kg), with a maximum daily dose of 100 mg and only as a single course (88,121,122). In six RCTs combined in meta-analysis, oral cyclophosphamide 2–3 mg/kg/day for 8–12 weeks or chlorambucil 0.2 mg/kg/day administered for 8 weeks reduced the risk of relapse by 60% in frequently relapsing SSNS at 6–12 months after treatment compared with prednisone alone (244).

Two studies have shown that intravenous cyclophosphamide (500 mg/m2/dose for 6 monthly doses) was more effective than oral cyclophosphamide (2 mg/kg/day for 12 weeks) in reducing the risk for relapse at 6 months (RR 0.56; 95% CI 0.33–0.92) but not at 2 years (244,278,279); in both studies the cumulative dose of cyclophosphamide was lower in the intravenously treated groups.

Toxicity profile Leukopenia occurred in 32.4% of patients on CYC and was more common with CYC alone than with CYC plus PDN protocols (22/38 vs. 8/52) (280). The Latta meta-analysis reported reversible alopecia in 17.8%, infections in 1.5%, hemorrhagic cystitis in 2.2%, and malignancy in 0.2%. The incidence of gonadal dysfunction (amenorrhea and premature menopause in females and infertility for males and females) is dependent upon the patient's age, sex, and cumulative dose of CYC, regardless of how the medication is administered (293–295). Major side effects of this agent include gonadal dysfunction (azoospermia), leukopenia, infection, alopecia, hemorrhagic cystitis, and hepatic dysfunction. The risk of azoospermia is higher in boys of pubertal age (Tanner stage 2 or greater) or postpubertal age, when cumulative dose of cyclophosphamide exceeds 100–300 mg/kg, although higher doses may be safe in prepubertal boys (280,294).

The threshold cumulative dose for safe use of cyclophosphamide remains uncertain because of individual reports of oligospermia in boys receiving less than 200 mg/kg. These data suggest that single courses of cyclophosphamide at a dose of 2 mg/kg/day should not exceed 12 weeks (cumulative dose 168 mg/kg). There are few data on gonadal toxicity with chlorambucil in SSNS. In male patients treated for lymphoma, total doses of 10–17 mg/kg led to azoospermia (296); similar total doses are used in SSNS. Gonadal toxicity is less severe in women with most reports observing little or no toxicity with alkylating agents in SSNS (280). The 2012 KDIGO guidelines advise that second courses of alkylating agents should not be given because of their potential long term toxicity (121).

Females CYC may induce depletion of ovarian follicles and shrinkage and fibrosis of the ovaries. Women treated before the age of 25 are at a lower risk of infertility than those treated after the age of 30 (297). CYC is associated with congenital (or fetal) malformations and should be avoided during the first 10 weeks of gestation. Girls and younger women are less likely to experience ovarian failure with CYC exposure as they have a greater ovarian reserve. Thus, it appears that women < 20 years are unlikely to experience ovarian failure with an initial course of CYC (0 to 4%), whereas the risk is significant in women > 30 (23 to 54%) and > 40 (75%) (293,298).

Males CYC causes a decrease in sperm count and with higher doses and treatment duration can lead to irreversible azoospermia. The severity and risk of gonadal toxicity due to CYC depend on the gonadal activity at the time of treatment (prepubertal vs. sexually mature males) and the total cumulative dose. Testicular injury is reported to occur in boys and men after 7 to 9 g of CYC; recovery is documented in some patients (294). Lentz et al. reported no increased risk of gonadal injury at total doses below 168 mg/kg (299).

The risk of female infertility is considered to be lower and a cumulative dose ~200 mg/kg is reported safe, as infertility occurred at a dose of 300 mg/kg or higher (280,294).

Approximately 32% of patients with nephrotic syndrome develop leukopenia, during cyclophosphamide therapy. The dose of cyclophosphamide is reduced if the leukocyte count drops below 4500/mm3; therapy is suspended when the count falls below 3000/ mm3 (280).

LEVAMISOLE

- *We recommend levamisole at a dose of 2–2.5 mg/kg given on alternate days (with maximum dose of 150 mg) after remission was achieved by PDN at recommended dose (grade B, moderate recommendation).*
- *We recommend ANCA measurement at baseline, if available and every 6–12 months during therapy (grade X, moderate recommendation).*
- *We recommend monitoring clinically for rash and measuring complete blood count and hepatic transaminases every 3–4 months (grade X, moderate recommendation).*

It is thought to promote Th1 over Th2 responses and to activate more CD4+ than CD8+ cells (300,301). Although levamisole is more active on T cells than on B cells, it also enhances humoral immune response,

promotes neutrophil survival, chemotaxis, and phagocytosis, and may act as an adjuvant to boost response to vaccines. Finally, levamisole may also exert its action directly on podocytes through activation of the glucocorticoid receptor (301).

Levamisole is a synthetic antihelminthic agent with immunomodulatory properties (302). Its use in childhood nephrotic syndrome was first described by Tanphaichitr and co-workers in 1980 (303) and since then many studies have described its benefits (302).

Several retrospective reports have suggested efficacy of levamisole in reducing the frequency of relapses of SSNS (300). In a systematic Cochrane review, the risk of relapse of NS was calculated to be halved with levamisole treatment for four to 12 months (244). In nearly all studies, levamisole has been prescribed on alternate days or in two weekly doses on consecutive days (301). The usual dose is 2.0–2.5 mg/kg (301).

Specifically, European patients relapsed more frequently but had SDNS more often (89%), compared to Indian patients (42%) (304). Although underpowered, this analysis suggests that levamisole should be prescribed primarily to children with FRNS, as also suggested in other reports (305).

Evidence & Rationale

A recent international multicentre RCT has enhanced the quality of evidence for the effectiveness and safety of LEV. Gruppen (2018) (304) compared LEV therapy to placebo in 99 children with FRNS or SDNS and found a significant reduction in the number of relapses at 12 months (RR of relapses on LEV 0.77, 95% CI 0.61 to 0.97) (244). Thus, 26% of children in the LEV group compared with 6% in the placebo group remained in remission at 12 months. Eight RCTs (474 participants) combined in a meta-analysis (244) indicated a benefit of LEV over PDN, placebo or no treatment (RR 0.52, 95% CI 0.33 to 0.82). Small comparative RCTs comparing LEV with CYC (306) showed no difference in efficacy but were not powered to show a difference (244).

An RCT found no difference in efficacy between MMF and LEV but MMF levels were not measured (307). The Gruppen 2018 (304) and Sinha 2019 (307) studies suggest that LEV may be more effective in FRNS than SDNS. These recent RCTs (304,307) used a dose of LEV of 2.5 mg/kg/alternate day, maximum 150 mg, for 12 months. Most other recent studies used doses of 2–3 mg/kg on alternate days for 6–24 months. Some observational studies have used doses of 2–2.5 mg/kg daily for 4–24 months (308–314) with three studies (312–314) suggesting reductions in relapse rates in patients who had not responded to alternate-day LEV. These data require further larger RCTs, powered to detect a difference, if any, for confirmation

Levamisole is usually administered in a dose of 2.5 mg/kg on alternate days. Levamisole given for 4 months to 1 year reduced the risk of relapse by 50% in comparison with prednisone alone in 6 trials (474 patients; RR 0.41, 95% CI 0.27–0.61) (244,315–318) but was ineffective in a seventh trial, in which a lower total dose of levamisole was given (244). However several of these RCTs were at high risk of bias because of methodological problems, which may lead to an overestimation of treatment effects (319).

Toxicity profile Adverse effects of levamisole are uncommon. Common adverse effects include rashes, leukopenia, gastrointestinal effects and abnormal liver function tests (301). These are generally transient and reversible on discontinuation of therapy. Rarely ANCA positive arthritis (2% in Gruppen 2018 (301, 304, 323), rash and other vasculitis symptoms have been reported which is female predominance and cutaneous involvement, frequently involving the ear cartilage (323), which resolve upon LEV discontinuation (320,321). Rare cases of agranulocytosis have been reported, in particular in adulterate use with cocaine (322).

Balance of risks and benefits While most adverse effects are transient and reversible on discontinuation, the main emerging threat is ANCA-positive vasculitis particularly with prolonged use. Regular monitoring as indicated in Tables 4 and 5 is advised with cessation of therapy if ANCA titers are positive.

Tapering/discontinuation Available studies do not comment on this. Discontinuation without tapering should be considered once the patient is in sustained remission and off steroids for at least 12 months. (84)

General considerations on the use of levamisole LEV is an immunomodulant which has been used for over 3 decades in NS. Its low cost makes it a useful option, particularly in low resource settings. However, it is unavailable in some countries. Lack of nephrotoxicity and ease of monitoring are other major advantages. When introducing this agent, some physicians prefer to maintain low-dose alternate-day PDN on non-LEV days for a few months, then oral PDN is tapered and stopped, and the patient remains on LEV alone.

MYCOPHENOLATE MOFETIL/MYCOPHENOLIC SODIUM

- W*hen using mycophenolate mofetil MMF, we recommend a starting dose of 1200 mg/m2 BSA (maximum dose 3000 mg) divided into two oral doses every 12 h (grade B, moderate recommendation).*
- *Alternatively, we recommend using the corresponding mycophenolic sodium (MPS) dose, i.e., 360 mg of MPS corresponds to 500 mg MMF (grade B, moderate recommendation).*
- *We suggest starting MMF/MPS therapy while the child is still receiving alternate-day steroid therapy since the immunosuppressive effect of MMF/MPS is delayed (grade C, weak recommendation). In most children, alternate-day steroids can then be tapered and discontinued within 6–12 weeks.*
- *We recommend using therapeutic drug monitoring, aiming for a 12-h mycophenolic acid (MPA) area under the curve above 50 mg h/L in patients not controlled on MMF therapy despite using recommended dosing (grade B, moderate recommendation).*
- *We recommend that sexually active adolescent females only receive MMF/MPS if they are using adequate c*ontraception (grade X, strong recommendation).

Evidence and rationale–Dosing and therapeutic drug monitoring The standard dose for MMF in RCTs is 1200 mg/m2/day divided into two doses every 12 h orally with a maximum daily dose of 3000 mg. (Therapy with MMF is given in two divided doses, 600 to 1200 mg/m2 (20-30 mg/kg) daily (324))

Five hundred mg of MMF corresponds to 360 mg of MPS. Patients may be started on half dose and dosage may be increased after 1 week in case of no side effects, e.g., leukopenia or GI discomfort.

Monitoring of MMF/MPS Patients should be monitored for side effects as indicated in Tables 5. Therapeutic drug monitoring indications are given below.

Data from one RCT suggests that patients with higher blood levels of MMF (determined by area under the curve, AUC) show efficacy similar to cyclosporine (255). Others emphasize the need to achieve mycophenolic acid AUC levels exceeding 45-60 µg*h/ mL (325–327) or trough levels >2-3 µg/mL (328–331). While pharmacokinetics of MMF is variable, adequate levels are achieved with high doses (329–331). In the absence of facilities for therapeutic drug monitoring, we propose initiating therapy at the lower end of dose range and escalating as tolerated, to 1000-1200 mg/m2, if the patient continues to relapse.

Therapeutic drug monitoring Assessment of mycophenolic acid (MPA) trough levels is not recommended as there is a poor correlation with efficacy and safety using single pre-dose measurements (329,330). A limited sampling strategy for assessing pharmacokinetic profiles was established in children with NS on MMF monotherapy being in remission (331), whereas such a profile is not available for those on MPS. It requires three measurements of plasma MPA at times 0 min (before administration, C0), 60 min (C1), and 120 min (C2) after administration, and allows a good estimation of MPA-AUC 0-12 using the formula eMPA − AUC 0−12 = 8.70 + 4.63 * C0 + 1.90 * C1 + 1.52 * C2 (331). In children with FRNS with MPA AUC 0-12 > 50 mg × h/L estimated using the formula eMPA—AUC = 7.75 + (6.49 * C0) + (0.7 6 * C0.5) + (2.43 * C2)

(255,332), the efficacy of MMF was similar to that of CsA (255). The latter formula was originally established in adult heart transplant patients treated with concomitant CsA. We recommend using therapeutic drug monitoring in patients not controlled on MMF therapy despite adequate dosing aiming for eMPA-AUC 0-12 > 50 mg × h/L. For this purpose, either one of the above mentioned formulas can be used (255,331,332). It should be noted that immunoassays for the determination of MPA plasma levels measure 10–20% higher MPA plasma levels than high-performance liquid chromatography (HPLC) or mass spectrometry (MS)

Higher MPA exposure is required in children with nephrotic syndrome compared with levels in kidney transplant recipients (333). Studies of therapeutic drug monitoring show that the target MPA area under the curve (AUC) needs to be above 45–50 µg h/mL to maintain remission though there is large between-patient variability (255,326,334). Post hoc analysis of the Gellermann study revealed that the relapse rate in children with higher MPA exposure (mean MPA-AUC 74.0 mg h/mL) did not differ from that seen in cyclosporin treated children (255). None of the RCTs reported to date have used therapeutic drug monitoring to determine the correct dose of MMF for individual patients so it remains possible that results of these RCTs would differ if drug monitoring had been included. Currently therapeutic drug monitoring of MMF in children with nephrotic syndrome is not widely available. No consistent single time point for measurement has been identified that correlates with AUC data and can be used to monitor children with FRNS or SDNS receiving MMF.

A retrospective analysis has confirmed this finding, suggesting that when treating SSNS, MMF should be prescribed at higher doses than those commonly used in kidney transplantation, and that treatment should be preferably guided by targeting AUC levels > 45 µg·h/ml (326). Since measuring the AUC of MMF is not available in all centers, treatment could be started using a standard dose of 1200 mg/m2/day, and the dose could be prudently increased to a maximum of 1800 mg/m2/day in relapsing children who do not experience side effects.

Efficacy of MMF/MPS MPS is used in adults with nephrotic syndrome and minimal change disease (347) but has rarely been used in children though its efficacy can be expected to be similar to MMF (339). Numerous observational studies have demonstrated a reduction in relapse rate during MMF treatment compared with prednisone treatment (333, 335–339) though no RCT has compared MMF with prednisone alone.

Mycophenolate mofetil (MMF) and mycophenolate sodium (MPS) are converted to mycophenolic acid (MPA), which is an inhibitor of the de novo purine pathway with inhibitory effects on T and B lymphocyte proliferation (340). MMF has become an important corticosteroid sparing agent in children with FRNS or SDNS and is often used as the initial non-corticosteroid immunosuppressive agent (341).

MMF is a well-accepted steroid-sparing therapy for patients with FRNS and SDNS (324). It is still unclear if MMF can induce remission without PDN; until more data are available, PDN should be prescribed for treating relapses. The efficacy of MMF was suggested by a number of uncontrolled studies using the drug in monotherapy or in combination with low doses of PDN in the early 2000s (330,335,340,342–344). In 2008, a small trial suggested superiority of CsA, compared to MMF (254).

RCTs suggest that MMF was well tolerated and beneficial in patients with FRNS or SDNS, but less effective than cyclosporine or tacrolimus (254,255,345). A review of 7 prospective and 6 retrospective series (508 patients) showed that therapy with MMF for 6-19 months lowered relapse rates, and reduced requirement of prednisolone and/or CNI (324).

While placebo-controlled, blinded RCTs are lacking, MMF was found to be comparable to levamisole but inferior to cyclosporine in maintaining satisfactory remission or reducing the frequency of relapses in 3 open-label RCTs (244). MMF had efficacy similar or inferior to tacrolimus in a non-randomized comparison, perhaps more efficacious in young children (346), and more effective than levamisole in patients with steroid dependence (307).

Four RCTs compared MMF with other steroid-sparing agents in FRNS and SDNS. Three RCTs compared MMF (800–1200 mg/m2/day in two divided doses) with CsA (4–5 mg/kg/day) in 142 children. Two RCTs (254,255) combined in meta-analysis found no difference in the number of children with relapse between MMF and CsA (82 children: RR 1.90, 95% CI 0.66 to 5.46) (244). However, the relapse rate/year was higher in children treated with MMF compared with CsA (3 studies, 142 children: mean difference 0.83, 95% CI 0.33 to 1.33) when a third study was included, but adverse effects of hypertension, hypertrichosis and gum hypertrophy were lower and GFR higher in MMF treated children (244).

Three observational studies involving 312 children with FRNS or SDNS compared MMF with TAC (257,259) or CsA (258). MPA levels were not monitored in these studies. Two of these studies (258,259) found better efficacy for maintaining remission with CNIs compared with MMF though adverse effects were more common with CNIs. MMF is recommended as steroid-sparing therapy in the Children's Nephrotic Syndrome Consensus Conference (113), KDIGO (122), and the Indian Society of Pediatric Nephrology (88) guidelines, for patients with FRNS or SDNS.

Toxicity profile The safety of MMF in children with SSNS is satisfactory, with the main side effects being gastrointestinal, abdominal pain, loss of appetite, diarrhea, and weight loss which have been reported in 3–11% of patients (324) and only 4% of 130 children in a large observational study (259). This is less likely to occur with enteric-coated MPS. However, some individuals tolerate MMF better than MPS. Other adverse effects are leukopenia, anemia, thrombocytopenia, an increased risk of infections, and elevated hepatic transaminases. These adverse effects are uncommon and usually mild. MMF/MPS is teratogenic in the early months of pregnancy so effective contraception should be used by all sexually active female adolescents during MMF/MPS therapy. In utero exposure to MMF has been associated with prenatal defects so women should be counselled that they will need to cease MMF before becoming pregnant (333). In males, recent evidence in patients receiving MMF/MPS after kidney transplantation and a large meta-analysis of different drugs (348) indicates that the risk of congenital malformations is comparable to that of the general population (349). Since the absorption of MMF is widely variable, it is desirable that its trough and AUC levels be monitored (254,328). Monitoring for side effects should be done as indicated in Table 5.

General considerations of benefit/risk of using MMF/MPS There is now extensive documentation of the successful and safe use of MMF in children with FRNS and SDNS but studies did not differentiate between these groups. In clinical practice, MMF appears more effective in children with FRNS. Its advantages consist in lack of nephrotoxicity and of cosmetic side effects compared to CNIs.

Tapering and discontinuing of MMF/MPS There are no studies on the duration of MMF/MPS use or on when to discontinue MMF/MPS. If the child achieves control on therapy for at least 12 months, then consideration may be given to tapering MMF over 3–6 months and then discontinuing it. As with CNIs, the advantage of tapering over abrupt discontinuation is that in case of proteinuria, re-establishment of MMF at initial dose may be sufficient to avoid a relapse while establishing that the child still requires maintenance treatment. The use of more extended periods may be considered, especially in peri-pubertal age or in the presence of previous severe steroid toxicity.

Therapy with MMF is an important step in the management of patients with FRNS or SDNS. Patients who respond to therapy with reduction in frequency of relapses may receive treatment for 1–3 years (88,122).

RITUXIMAB

- *We recommend using RTX as a steroid-sparing agent in children with FRNS or SDNS who are not controlled on therapy after a course of treatment with at least one other steroid-sparing agent at adequate dose, especially in case of non-adherence (grade B, moderate recommendation). This is especially preferable, both in terms of safety and of effectiveness, above the age of 7–9 years (grade C, weak recommendation).*

- *When using RTX, we recommend a dosage of 375 mg/m2 for each infusion, ranging from 1 to 4 infusions (maximum single dose 1000 mg) preferably when the patient is in remission (grade C, moderate recommendation).*
- *We recommend monitoring CD19(+) total B cell counts at baseline and following RTX treatment at 7 days postinfusion to ensure adequate B cell depletion indicated by an absolute CD19 cell count < 5 cells/mm3 or < 1% of total lymphocytes (grade B, strong recommendation).*
- *We recommend monitoring IgG levels at baseline and periodically following RTX treatment to detect hypogammaglobulinemia (IgG below age-related normal range) (grade B, strong recommendation).*
- *We recommend premedication with paracetamol/acetaminophen, antihistamines and/or steroids (grade B, moderate recommendation).*
- *Following RTX infusion/s, we recommend tapering off oral PDN and other steroid-sparing agents within 2–3 months (grade B, strong recommendation).*

Rituximab (RTX), originally licensed for the treatment of B cell non-Hodgkin's lymphoma in 1997, is a chimeric monoclonal antibody that targets CD20-positive B-cells, leading to CD-20 positive B cell depletion by apoptosis, antibody dependent cytotoxicity, and possibly disruption of B cell/T-cell interaction and upregulation of regulatory T cells (350). several case series and retrospective cohort studies have provided initial evidence that RTX may be a useful alternative for SSNS (reviewed in reference (350)). In the past ten years, randomized controlled trials and single arm studies have been published, demonstrating the efficacy of this therapy (351–358). A recent review published in this journal has covered in depth data on rituximab for the treatment of nephrotic syndrome (359). Overall, data from these trials and from cohort studies are difficult to compare because patients differ in the severity of their nephrotic syndrome, in the number of RTX infusions, in the dose of RTX, and in the strategy for tapering other immunosuppressive agents after RTX infusion (291,351–356,360–366).

Evidence and rationale In terms of dosing regimen, the original course of RTX used for lymphoma patients requiredn375 mg/m2 given as an IV infusion weekly for 4 doses. The RTX protocols used in the available RCTs and observational studies in children with FRNS/SDNS included single, 2, 4, and 7 infusions. In addition to variability in the number of RTX infusions, there has been variation in RTX dosing, ranging from 375 to 1500 mg/m2 per treatment, although most studies used 375 mg/m2. The dose of 750 mg/m2 has not been associated with a better response rate than 375 mg/m2; however, a lower dose of RTX (100 mg/m2) has been associated with the risk of earlier relapse (reviewed in (367) and in (359)). In terms of infusion number per course of RTX treatment, the use of a single infusion at standard dose followed by monitoring of CD19 (+) cells at 7 days is derived from studies performed in adults with ANCAassociated renal vasculitis and membranous nephropathy. If at 7 days post-infusion, the percentage of total B cells is < 1% of total lymphocytes this indicates adequate B cell depletion (368). Reconstitution of B cells is defined when total B cell counts are > 5/mm3 in absolute number (369).

Efficacy of RTX

During the last decade, a number of RCTs have shown that RTX is reasonably safe in the short term and relatively effective when compared to other immunosuppressants as a steroid-sparing treatment. However, studies differ in terms of populations, number of doses of RTX, additional medications and comparators. Unlike other immunosuppressants, the lack of long-term follow-up in RTX treated patients must be considered at the time of clinical decision.

Eight RCTs have evaluated the efficacy of RTX in children with FRNS or SDNS. Four RCTs evaluated 1 to 4 doses of RTX in children with SDNS and CNI dependence compared with placebo (358,369) or CNIs (351,357). Four studies compared 1 to 2 doses of RTX in children with SDNS or FRNS on low-dose PDN compared with TAC (356), low dose PDN (352,370), or low dose MMF (371). A meta-analysis showed that

the number of patients with relapse fell by 80% by 6 months and 50% by 12 months after treatment (244). Longer duration of remission was seen in children whose relapses were previously managed with PDN alone (352,370). Moreover, a large retrospective study assessing RTX use in more than 500 children with FRNS/SDNS showed that patients were 19% more likely to relapse for each additional steroid-sparing agent received prior to RTX, and that younger age at first infusion was associated with earlier relapse (359,372,373).

Approximately, 20% of patients with SSNS continue to show difficult-to-treat FRNS or SDNS during or after immunosuppressive therapies. RCTs and multiple case series suggest that treatment with rituximab, a chimeric anti-CD20 monoclonal antibody, was well tolerated and reduced relapse rates and enabled discontinuation of steroids and other medications, such as MMF and calcineurin inhibitors (364,365,374–376). An open-label RCT in Italy showed that a single dose of rituximab and lower doses of prednisone and calcineurin inhibitors was non-inferior to standard therapy with calcineurin inhibitors and steroids in maintaining short-term remission (351).

A multicenter double-blind placebo-controlled trial in Japan examined the efficacy and safety of rituximab versus placebo in 48 children with complicated FRNS or SDNS (354). The rituximab group received 375 mg/m2 body surface area of the IV medication once weekly for 4 weeks. The control group received placebo at the same frequency. Prednisone and immunosuppressive drugs were gradually tapered, and patients were followed for 1 year. The 50% relapse-free period (267 vs. 101 days; HR 0.27; 95% CI 0.14–0.53, P < 0.0001) and the daily steroid dose was lower in those treated with rituximab than placebo (9.15.9 vs. 20.99.3 mg/m2/day, P < 0.0001) up to 1 year. Most adverse events were mild; rate of serious adverse events and infusion reactions was similar. Based on these results, the Ministry of Health of Japan approved the use of rituximab for patients with complicated FRNS or SDNS in 2014. An open label RCT in Korea showed similar results (357).

Follow-up of the above RCT (377) and cohorts show that most patients have recurrent relapses after recovery of peripheral B cell counts, notably switched memory B cells (366). Further modifications, including repeated courses of rituximab or additional therapies, may be necessary for maintaining long-term remission. Studies suggest that repeat rituximab infusions after B cell recovery or four-times infusions at 3-month intervals induced long-term remission without serious adverse events in children with SDNS (375,378). However, the effect of persistent B-cell depletion on the developing immune system in children is unknown. Additionally, poor efficacy of vaccination under persistent B-cell depletion is a problem.

Rituximab has been used as a first-line treatment for uncomplicated SDNS in many centers in European countries. Although some RCTs indicated potential for rituximab as first-line drug for early uncomplicated FRNS or SDNS (352,356,370), further studies are required to clarify the efficacy and safety of this drug for uncomplicated FRNS or SDNS.

Rituximab is a mouse-human chimeric monoclonal antibody which binds to the CD20 antigen expressed on B cells. Treatment leads to a suppression of CD19 cells to below 1% and relapse generally occurs when levels of CD19 cells recover. Rituximab has now been evaluated in seven RCTs using one (351,352,370), two (356–358) or four doses (354) of rituximab (375 mg/m2 per dose). In five studies including 296 children with difficult to treat SDNS, the risk for relapse was reduced by 63% at 6 months (4 studies, 239 children; RR 0.27; 95% CI 0.15–0.47) and 36% at 12 months (2 studies, 168 children; RR 0.74; 95% CI 0.58–0.94) (244). In two studies (60 participants), which assessed RTX in children with SSNS treated with high (≥0.7 mg/kg/day) or low doses (≤0.4 mg/kg/day) of prednisone without other immunosuppressive agents, the risk of relapse was reduced by 94% and 74% at 6 and 12 months compared with prednisone alone (352,370).

To gain further information about the optimum dosing regimen of rituximab, a study evaluated retrospectively the different dose regimens used in 11 tertiary centres in Asia, Europe and North America (379). Among 511 children with complicated relapsing SSNS (defined as relapsing despite ongoing

treatment with prednisone and at least one additional agent), 191 received low dose rituximab (375 mg/m2), 208 received medium dose rituximab (750 mg/m2) and 112 received high dose rituximab (1125–1500 mg/m2). Fifty five percent (379) of children received concurrent immunosuppressive treatment (CNI, MMF, prednisone). Children who received low dose rituximab had shorter relapse-free periods (8.5 months) compared with those receiving medium dose (12.7 months) or high dose (14.3 months) rituximab. However when rituximab was combined with immunosuppressive therapy, relapse-free survival did not differ between different dosage groups. Two RCTs is underway to determine whether MMF compared with placebo maintains remission in children with SSNS after successful treatment with rituximab (380,381).

Toxicity profile Adverse events were generally limited to mild infusion reactions. Adverse effects are generally mild with infusion reactions (13%) and infections (4%) being most common (379). The main adverse effects reported with rituximab have been acute episodes of bronchospasm, hypotension, fever and arthralgias occurring during or immediately after intravenous infusion. Premedication with anti-histamine and anti-pyretic agents is recommended.

RTX-related neutropenia (RRN) has been well documented in the literature, although the exact mechanism is not well known. In children, RRN is usually not associated with serious bacterial or viral infections and most of the reported infections are self-limiting. Supplementation with granulocyte colony stimulating factor (G-CSF) may not be needed, especially in late onset neutropenia, i.e., neutropenia occurring 4 weeks after last RTX infusion (382–384).

Mild to moderately serious infections are reported to be less commonly seen with rituximab compared with tacrolimus (356). However rare but serious adverse effects reported in children with nephrotic syndrome treated with rituximab including including fatal hepatitis from reactivation of hepatitis B virus (386), progressive multifocal leukoencephalopathy (387), pulmonary fibrosis (388), fulminant myocarditis (389), Pneumocystis pneumonia (390,394), bacterial pneumonia including Pseudomonas aeroginosa pneumonia (395), ulcerative colitis (391), agranulocytosis (392), and hypogammaglobulinemia (393).

Though not yet reported in children with SSNS, a survey of patients with SLE treated with rituximab identified 57 patients with multifocal leucoencephalopathy caused by JC polyomavirus (396).

However, prolonged and significant reduction of total memory and switched memory B cells together with hypogammaglobulinemia has been demonstrated in patients following RTX, particularly in young patients with SSNS (385).

Fifty six children (14%) of 400 children in whom IgG levels were measured had persistent hypogammaglobulinemia at 1 year following rituximab infusion (379). Among 27 children who had received rituximab more than 2 years previously, most had a sustained reduction in total and switched memory B cells while 11 children had hypogammaglobulinaemia (385). Younger patients appear to be at increased risk of hypogammaglobulinaemia (397). More information is required to determine the longer term impact of these immunological abnormalities.

No deaths or serious adverse reactions were recorded in RCTs on the use of RTX in children with SSNS.

Because of the uncertainty about long term adverse effects and its cost, rituximab use was previously restricted to children with steroid and CNI dependent SSNS. However a study from the USA has demonstrated that the 1 year overall treatment costs of using rituximab compared with CNIs may not differ significantly (398). Increasingly rituximab is being used in children with FRNS or SDNS because it can achieve long periods of remission off treatment (370) though the long term effects of prolonged B cell depression and hypogammaglobulinaema remain to be elucidated.

Exclusion of certain infections and monitoring for side effects should be done as indicated in Tables 5.

General considerations of risk and benefit RTX treatment has proven reasonably safe and effective for both FRNS and SDNS. Given its uncertain long-term safety profile, it is advisable to use RTX as a second-line steroid-sparing agent in children who are not controlled on therapy with a first-line steroid-sparing agent. Since long-term side effects such as hypogammaglobulinemia appear to be more likely and efficacy appears to be less convincing in younger children, the use of RTX may be reserved for older children.

Repeat infusion treatment with RTX Following the first course of RTX, diverse approaches to repeated courses have been proposed, based either on disease relapse, on B cell reconstitution or on time elapsed from the initial treatment. Evidence for the most correct approach is lacking (358). Based on a recent retrospective survey, 30 of 346 included children tolerated up to 7 courses of RTX infusions (mainly dosed with 375 mg/m2/course) with an acceptable side effect profile (most common hypogammaglobulinema, followed by infections and neutropenia) and good efficacy (399).

The efficacy, safety, and cost-effectiveness of various dosing regimens should be compared to determine an appropriate rituximab treatment regimen for complicated FRNS or SDNS. In a retrospective cohort, the time to first relapse was significantly shorter in patients who received 1–2 doses of initial rituximab infusion compared with those who received 3–4 doses. However, the proportion of patients with long-term remission was not related to the number of initial doses (400). An international large retrospective cohort study suggested that children with complicated FRNS or SDNS on low-dose rituximab without maintenance immunosuppression had the shortest relapse-free survival (379). Further studies are required to determine the optimal dose and long term safety of rituximab, and the role of maintenance therapy.

Tapering and discontinuing of other immunosuppressive agents post-RTX It is unknown to what degree other immunosuppressive agents should be tapered or discontinued following RTX administration. In most studies, PDN at alternate-day doses was tapered off within 2 months before CNIs were reduced and stopped. If patients were taking MMF and mizoribine, these drugs were discontinued after the first dose of RTX.

A recent study (379) demonstrated that treatment response depends on both RTX dose and on the use of maintenance immunosuppression. The study documented that in complicated FRNS and SDNS patients, giving “low dose”, i.e., 375 mg/m2 RTX and maintaining immunosuppression (IS), most frequently with MMF but in some cases with either CNI or oral PDN, was equivalent in terms of median relapse-free period to giving higher doses without maintaining IS after RTX (379).

In SDNS, a small prospective cohort study found that relapse-free survival 12 months after RTX therapy was higher in children receiving MMF than in children not receiving MMF (401). An RCT evaluating MMF post-RTX treatment in “complicated” FRNS and SDNS showed that this approach was helpful in preventing relapse in 80% of patients (369). An RCT comparing maintenance MMF to repeated RTX infusions in children with SDNS is ongoing (RITURNS II Study, NCT03899103).

The use of CNIs following RTX infusions may be equally helpful, but this has not been formally assessed. These data suggest that in children with SDNS not controlled on RTX alone, following subsequent RTX infusions, the strategy of maintaining an oral steroid-sparing agent (MMF or a CNI) for at least 6 months may promote sustained remission.

RTX discontinuation As with all steroid-sparing agents and even more with RTX given its long-lasting effect, once the child is controlled on therapy, RTX infusions should be discontinued.

Other anti-CD20 monoclonal antibodies In addition to RTX, other monoclonal antibodies targeting B cells or modulating their function or depleting plasma cells have been employed in the treatment of SSNS.

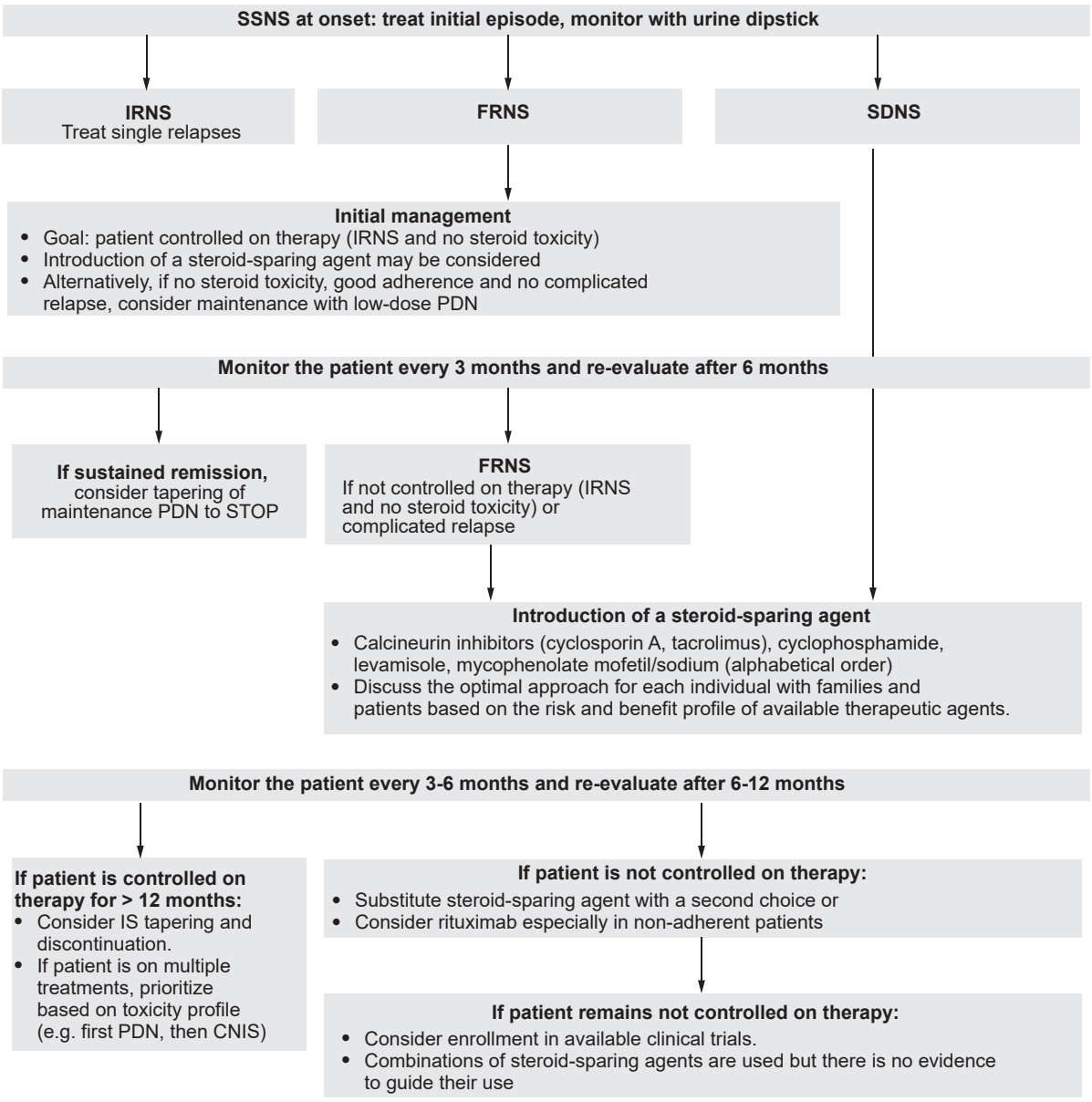


Figure-5: Algorithm for management of children with SSNS. Details on the risk and benefit profile of the various steroid-sparing agents are given in Table 5. IRNS infrequently relapsing nephrotic syndrome, FRNS frequently relapsing nephrotic syndrome, SDNS steroid-dependent nephrotic syndrome, PDN prednisone/prednisolone, CNI calcineurin inhibitors.

[a]As recommended in the text

Late Steroid Resistance

Overall, 4–10% of children with SSNS may develop late (secondary) steroid resistance (8,402,403). Patients with late steroid resistance often achieve complete remission with immunosuppressive therapy, such as calcineurin inhibitors (402). Even in calcineurin inhibitor-resistant patients, significantly more patients with late resistance are reported to achieve remission with rituximab than those with initial steroid resistance (403,404). In contrast, patients with late steroid resistance experience significantly more recurrence (recurrent FSGS) in renal allografts than patients with initial steroid resistance (405).

Choice of First Corticosteroid Sparing Agent for Children with FRNS or SDNS

RCTs to date have not provided sufficient data on the comparative efficacy and adverse effects of corticosteroid sparing agents to allow definitive recommendations on which medication should be the first agent used in FRNS or SDNS. Most international (121) and national guidelines (88,113) have not provided recommendations on which medication should be preferred as the first corticosteroid sparing agent. New guidelines from KDIGO and the International Pediatric Nephrology Association are awaited. Table 13.4 lists the advantages and disadvantages of each corticosteroid sparing medication. The choice of first agent will depend on clinician and family preferences based on an assessment of the benefits and harms as well as the cost and availability of medications.

Combination of more than one steroid-sparing agent

We recommend enrolling children with severe FRNS or SDNS who have failed to achieve stable remission or who present significant treatment toxicity despite at least one steroid-sparing agent at adequate dose, in a clinical trial, if available (grade X, strong recommendation).

Evidence and rationale

The combination of different steroid-sparing agents is not supported by adequate evidence. There are no RCTs that compare the combination of CNI plus MMF vs. CNI or MMF alone. There is a single observational study involving 130 Pakistani children with SSNS. Of these 20 had suboptimal response to MMF and CsA was added. Nineteen out of 20 benefited but only 4 had CR and 9 were CNI-dependent. In a retrospective publication on the use of RTX (379), the prolonged use of MMF or other steroid-sparing agents following a single cycle of RTX was found to induce stable remission in those receiving low-dose RTX (375 mg/m2 per course) but there was no increase in benefit in those receiving higher doses of RTX (750 mg/m2 or higher). We suggest that if children with FRNS or SDNS are controlled on therapy with more than one immunosuppressant (i.e., steroid-sparing agent plus maintenance PDN or CNI plus MMF), discontinuation of the most toxic agent be implemented.

Other steroid-sparing agents

We recommend that mizoribine, azithromycin, azathioprine or adrenocorticotropic hormone (ACTH) not be used to treat children with SSNS (grade B, moderate recommendation).

Evidence and rationale

A single RCT found no definitive benefit of azithromycin compared with PDN in the initial episode of SSNS (406). Single RCTs found no benefit of azathioprine, ACTH or mizoribine in children with FRNS/SDNS(407–409).

Table 5 **Immunosuppressive drugs**

Medication	Dose	Duration	Adverse effects	Recommended monitoring
Prednisone	0.5–0.7 mg/kg on alternate daysa,b Reduce dose if sustained remission Low Dose Alternate-Day PDN ≤ 0.5 mg/kg/alt day, max 20 mg alt day Low Dose Daily PDN ≤ 0.25 mg/kg/day, max 10 mg/day	6–12 months	Cushingoid features; striae rubrae/distensae, glaucoma, cataract, bone pain, avascular necrosis short stature; raised intraocular pressure; glucose intolerance; cataract; elevated Transaminases Obesity/weight gain, hypertension, behavioral/psychiatric disorders, sleep disruption,	Screen for side effects, hypertension Anthropometry q 3–6 months; eye evaluation q 6–12 months; glucose and transaminases q 3–6 months Quarterly: blood pressure, height, weight Yearly: ophthalmological examination
Levamisole Prolonged remissions in some children with FRNS, Not approved for SSNS in some countries	2–2.5 mg/kg/alternate day (maximum dose 150 mg) In some cases, LEV is initially alternated with oral PDN on non-LEV days 2–2.5 mg/kg on alternate days Continued treatment	2–3 years required to maintain remission	Leukopenia, ANCA positive vasculitic rash, high transaminases, seizures, arthritis, neutropenia, abnormal LFTs	Blood counts q 2–3 months; transaminases q 4–6 months Quarterly: CBC, LFTs Twice-yearly: ANCA titers (also at baseline)
Cyclophosphamide Less effective in SDNS Only one course should be given	2 mg/kg per day (maximum dose 150 mg) over 12 weeks (oral) or 3 mg/kg per day (maximum dose 150 mg) over 8 weeks Single morning dose preferable No more than a single course (max TCD 168 mg/kg) Give in conjunction with alternate day oral PDN starting with a dose of 40 mg/m2 (1.5 mg/kg) and reducing to 10 mg/m2 (0.3 mg/kg) over the duration of treatment	8–12 weeks	Leukopenia, alopecia, infections; discolored (blue) nails; hemorrhagic cystitis; risk of gonadal toxicity and malignancies, seizure, GI upset (abdominal pain, diarrhea), jaundice Fertile individuals must be warned of the need to avoid unplanned pregnancy (CYC can cause fetal malformation)	Blood counts q 2 weeks Maintain hydration; discontinue drug during serious infection or if total leukocyte count <4,000/mm3, Co-administer with prednisone 1 mg/kg AD; taper and discontinue prednisone after 4–8 weeks

(table continued)

Table 5 Immunosuppressive drugs (Cont'd)

Medication	Dose	Duration	Adverse effects	Recommended monitoring
Chlorambucil	Prolonged remission off therapy Inexpensive		Less effective in SDNS Potential serious short- and long-term adverse effects, Only one course should be given	Monitoring of blood count during therapy
Mycophenolate mofetil	600–1200 mg/m2/ day in divided doses[c]; (maximum dose 3000 mg) MPS: 360 mg corresponds to 500 mg of MMF Therapeutic drug monitoring using a limited sampling strategy: The most effective MPA AUC0–12 is above 50 mg × h/ L[d]	2–3 years	Abdominal pain, diarrhea, nausea, weight loss; (may be improved by the use of MPS). viral warts; leukopenia; anemia elevated transaminases, Risk of birth defects & pregnancy loss in first trimester of pregnancy Verrucae Fertile females must be warned of the need to avoid unplanned pregnancy (MMF/MPS can cause fetal malformations)	Screen for adverse effects Blood counts and transaminases q 3–6 months Quarterly: CBC LFTs
Cyclosporine	Start: 3–5 mg/kg per day (maximum dose 250 mg) in 2 divided doses, Target: C0 60–100 ng/mL or C2 300–550 ng/mL (aiming for the lowest possible dose to maintain remission)	2–3 years	Both: Acute and chronic nephrotoxicity, hyperkalemia, hepatotoxicity, hypertension; dyslipidemia (TAC), tremors, seizures, headache; Hypomagnesemia tremor, posterior reversible encephalopathy syndrome (PRES) Hirsutism (CsA), gum hyperplasia (CsA), diabetes mellitus (TAC) TAC drug levels can increase in case of intense diarrhea Consider risk of toxicity due to drug interactions (e.g., macrolide antibiotics, certain anti-epileptic agents, and grapefruit juice increase drug levels)	Screen for cosmetic side effects, tremors, diarrhea, hypertension Creatinine, potassium at 2–4 weeks, q 3–6 months Liver function tests, glucose, uric acid, magnesium and lipids q 3–6 months Quarterly: Blood pressure CBC, creatinine, eGFR, K+ LFTs, lipids Uric acid (CsA) Mg+ (TAC) Fasting glucose (TAC) Drug levels Consider discontinuation or a kidney biopsy after 2–3 years to avoid/detect toxicity
Tacrolimus	Start: 0.1–0.2 mg/kg per day (maximum dose 10 mg) in 2 divided doses Target: C0 level between 3 and 7 ng/mL (aiming for the low- est possible dose to maintain remission)	2–3 years		

(table continued)

Table 5 **Immunosuppressive drugs (Cont'd)**

Medication	Dose	Duration	Adverse effects	Recommended monitoring
Rituximab	375 mg/m2 for 1–4 doses per course (maximum single dose 1000 mg) at weekly intervals Aim for CD19 depletion (< 5 cells/mm3 or < 1% total lymphocytes) Premedication is often used with antihistamine, paracetamol and steroids Repeated courses can be given Administer in remission after appropriate pre-medication under close supervision and monitoring Exclude hepatitis B and C, HIV, EBV, tuberculosis / any active infection	Two doses one week apart[e]	Infusion reactions - Chills, fever; serum sickness; bronchospasm; acute lung injury Neutropenia; infection, activation of latent viruses, tuberculosis P. jirovecii pneumonia; reactivation of hepatitis B or JC virus; transient or persistent IgG deficiency Risk of prolonged B cell depression and hypogammaglobulinemia Serious adverse effects: myocardial dysfunction, risk of progressive multifocal leukoencephalopathy (PML) If infection is suspected, undertake diagnostic work-up including chest x-ray etc	**Pre-dose:** Blood counts, transaminases; hepatitis B and HIV serology; immunoglobulin G (IgG) level **Post-therapy:** Monitor CD19 and blood counts; IgG level; consider cotrimoxazole Prophylaxis Quarterly: CBC LFTs CD19 counts and % IgG (at baseline, quarterly in the 1st year, then yearly)

CBC complete blood count, C0 trough level, C2 2 h post dosing, eGFR estimated glomerular filtration rate, CBC complete blood cells, LFTs liver function test, LEV levamisole; cyclosporin A, CsA; TAC, tacrolimus; GI gastrointestinal, AUC area under the curve

Evidence and grading are given in the text

[a]May reduce dose further if remission is sustained

[b]During infections, administer alternate day prednisolone at 0.5 mg/kg every day for 5–7 days to prevent relapse

[c]Patients may be started on half dose. Dosage may be increased after 1 week in case of no side effects, e.g., leucopenia or GI discomfort

[d]A limited sampling strategy for assessing pharmacokinetic profiles was validated in children with NS being in remission on MMF monotherapy. It requires three measurements of plasma MPA at times 0 min (before administration, C0), 60 min (C1), 120 min (C2) after administration), and allows a good estimation of MPA-AUC0-12 using the formula eMPA − AUC0−12 = 8.70 + 4.63 * C0 + 1.90 * C1 + 1.52 * C2 (331) . Alternatively, the formula: eMPA—AUC0−12 = 7.75 + (6.49 * C0) + (0.76 * C0.5) + (2.43 * C2) which was originally established in adult heart transplant patients treated with concomitant CsA can be used (255,331,332)

[e]One to two additional doses are given at weekly intervals if CD19+ cells are>5/μL (or>1% of CD45+ cells) despite two doses of rituximab (Modified from Indian Pediatrics 2021)

STEROID RESISTANT NEPHROTIC SYNDROME

INTRODUCTION:

The annual incidence of nephrotic syndrome in most countries studied to date is ~1.2–17.0new cases per 100,000 children (410) . The incidence of SRNS ranges from 2.1 to 27.3% and varies with country of origin with the highest rates seen in African and African-American children and the lowest rates seen in children of South Asian ancestry (19). Steroid resistant nephrotic syndrome (SRNS) is seen in about 15–20% of all cases of childhood nephrotic syndrome (3). In other reports, monogenic SRNS is non responsive, responsible for 10–30% of all SRNS. Bangladesh data revealed Complete remission was achieved in 66% of cases, and 14% developed CKD.

Following 4 wks of therapy with standard dose of prednisolone (PDN)(60mg/m2/day maximum 60-80mg/day), is defined as steroid resistant nephritic syndrome. We believe upper limit of prednisolone dose should be 60mg (Level 1, Grade A recommendation). Time period between 4 and 6 weeks from PDN initiation during which responses to further oral PDN and/or 3 pulses of IV methyl PDN at 20-30mg/kg are ascertained in patients achieving only partial remission at 4 weeks after control of infection and asthma.

We agree either of the two choices of 3 pulses of methylprednisolone or 2 weeks of oral prednisolone at 60mg/m2/day is equally good.(Grade B recommendation).

It is also certain 3 pulses of IV methylprednisolone gives earlier qualification of definition of SRNS and hence measures 1 week earlier.A patient not achieving complete remission by 6 weeks, although partial remission was achieved at 4 weeks, is also defined as SRNS(84).

Steroid resistant nephrotic syndrome (SRNS) remains a challenge for pediatric nephrologists. While 20% of children in Western countries have steroid resistant nephrotic syndrome, studies from Africa reported steroid resistance in 50–90% of children with nephrotic syndrome, with higher proportions of children with steroid responsive disease in more affluent and diverse urban centers.

The underlying histopathology usually affects the course of the disease and the response to treatment. Renal histology shows focal segmental glomerulosclerosis (FSGS), minimal change disease (MCD), and mesangioproliferative glomerulonephritis (MPGN). Other patterns, including C3 glomerulopathy (C3GP), membranous nephropathy (MN) and IgA nephropathy, and secondary causes of nephrotic syndrome are uncommon. MesPGN was the commonest underlying histopathology in children who presented with SRNS in one study (411).

Idiopathic nephrotic syndrome in the United Kingdom was found to be more common among Asian children living in the UK and Canada com¬pared to European children (412). These data in conjunction with the data from African countries suggests that the interaction of environmental and genetic factors play an important role in the pathogenesis of nephrotic syndrome.(14) The steroid resistance can be grouped into primary resistance in which there is failure of complete remission after treatment during the first time of nephrotic syndrome presentation, while in the secondary resistance the child initially responds well to steroid regimen for a period of time, after which he shows recurrence of symptoms and failure of complete response to steroid treatment (61).

The children with SRNS tend to progress to end-stage renal disease (ESRD) due to the progressive damage of the glomerular filtration barrier (GFB) (413). Different aggressive and potentially toxic treatment regimens have been tried to forestall disease progression, with varied outcome (414). Partial remission of massive proteinuria is considered as better outcome than no remission (415). Outcome of treatment is quite variable, in good number of patients outcome is guarded. Upto fifty percent of steroid resistant nephrotic syndrome may progress to end stage renal disease (ESRD) within 5 years of diagnosis (416).

Table 6	Definitions relating to SRNS
SRNS	Lack of complete remission within 4 weeks of treatment with daily oral PDN at standard dose; if partial remission: 2 weeks additional therapy (confirmation period).
Primary resistant	Failure of complete remission after treatment during the first time of nephrotic syndrome presentation
Secondary resistant	Patients who initially responds well to steroid regimen for a period of time, after which he shows recurrence of symptoms and failure of complete response to steroid treatment.
Nonresponse	Urine protein 3 +/4 + (dipstick), Up/Uc >2, or 24 h urine protein >1000 mg/m^2/day; albumin <3.0 g/dL or edema
Monogenic disease	Pathogenic or likely pathogenic variation, defined by American College of Medical Genetics and Genomics, in a gene associated with nephrotic syndrome.
CNI responsive SRNS	Partial remission afetr 6 months of treatment and/or complete remission after 12 months of treatment with a CNI at adequate doses and/or levels .
CNI-resistant disease	Nonresponse to cyclosporine or tacrolimus, given in adequate doses and titrated to blood trough levels, for 6 months.
	We recommend this definition is feasible for only partial remission SRNS cases. In case of massive proteinuria with huge anasarca,decision about further immuno-suppressive drugs needed to be taken along with odema and infection control .(Grade B recommendation)
Multi drug resistant SRNS	Absence of complete remission after 12 months of treatment with 2 mechanistically distinct steroid sparing agents (including CNIs) at standard doses.

Adapted from IPNA guideline (114), CNI: Calcineurin inhibitor, PDN: Prednisolone
SRNS : Steroid resistant nephrotic syndrome, Up/UC : Urinary protein creatinine ratio.

Etiology and pathogenesis of SRNS

Genetic SRNS

Genetic SRNS is defined as SRNS caused by a pathogenic variant (or pathogenic variants) in a gene that affects the establishment and maintenance of the glomerular filtration barrier (99).In recent decades, the medical world has gained a great deal of knowledge regarding the genetic origins of SRNS. The condition is known to be caused by mutations in more than 70 genes that encode important podocyte proteins. The fraction of families in whom a single-gene cause was identified inversely correlated with age of onset. Within clinically relevant age groups, the fraction of families with detection of the single-gene cause was as follows: onset in the first 3 months of life (69.4%), between 4 and 12 months old (49.7%), between 1 and 6 years old (25.3%), between 7 and 12 years old (17.8%), and between 13 and 18 years old (10.8%).(114).

Infection associated glomerulinephritis is common in Sub-Saharan Africa (418–420). interaction of environmental and genretic factors play an important role in the pathogenesis of nephritic syndrome.

The genes linked to SRNS are broadly categorised as follows: cytoskeleton (ACTN4, MHY9, MYO1E, INF2, and actin regulatory genes); mitochondrial proteins (COQ2, COQ6, and ADCK4); nuclear proteins (WT1, LMX1B, NUP93, NUP107, NUP205, and SMARCAL1); structural elements of the slit diaphragm (NPHS1, NPHS2, CD2AP, and PLCE1); actin regulatory genes; glomerular basement membrane and matrix proteins (LAMB2, ITGA3, and COL4A3–5); mitochondrial proteins (COQ2, COQ6, and ADCK4); nuclear proteins (WT1, LMX1B, NUP93, NUP107, NUP205, and SMARCAL1); and other intracellular proteins (TRPC6, SCARB2, APOL1, DGKE, CUBN, and GAPVD1) with a broad spectrum of illness(421) .

Beyond the podocyte, pathogenic variants in genes encoding for key molecular components of the glomerular basement membrane are increasingly being recognized as monogenic causes of SRNS. These include COL4A3 and COL4A4, which encode for type 4 collagen of the GBM, and LAMA5 and LAMB2, forming laminin LM-521; α5β2γ1 that is a key component of the glomerular basement membrane. While COL4A3 and COL4A4 mutations typically present with the more classic phenotype of Alport syndrome, they may also phenocopy FSGS and present with SRNS (412)

According to reviews by Bierzynska and colleagues and Preston and colleagues, nephrotic syndrome may also be linked to syndromic features with mutations in specific genes, such as Denys-Drash syndrome and Frasier syndrome (WT1), Pierson syndrome (LAMB2), nail-patella syndrome (LMX1B), Epstein syndrome, Sebastian syndrome, and related illnesses (MYH9), MELAS syndrome and Leigh syndrome (mitochondrial genes), Galloway-Mowat syndrome (WDR73), and Schimke dysplasia (SMARCAL1) (422)

Table 7 Genetic causes of FSGS and SRNS

Gene	Protein	Mode of Inheritance
Slit diaphragm genes		
NPHS1	Nephrin	AR
NPHS2	Podocin	AR
PLCE1	Phospholipase C epsilon 1	AR
CD2AP	CD2-associated protein	AD, AR
TRPC6	Transient receptor potential channel C6	AD
CRB2	Crumbs family member 2	AR
FAT1	FAT atypical cadherin	AR
KIRREL1	kirre like nephrin family adhesion molecule 1	AR
Transcription factors and nuclear genes		
WT1	Wilm's tumor protein 1	AD
LMX1B	LIM homeobox transcription factor 1-beta	AD
SMARCL1	SMARCA-like protein	AR
NUP93	Nuclear pore complex protein 93	AR
NUP107	Nuclear pore complex protein 107	AR
NUP205	Nuclear pore complex protein 205	AR
NUP160	Nuclear pore complex protein 160	AR
NUP85	Nuclear pore complex protein 85	AR
NUP133	Nuclear pore complex protein 133	AR
XPO5	Exportin 5	AR
E2F3	E2F transcription factor	AD
NXF5	Nuclear RNA export Factor 5	X-linked recessive
PAX2	Paired box protein 2	AD
LMNA	Lamin A and C	AD
WDR73	WD repeat domain 73	AR
Cytoskeletal and membrane genes		
ACTN4	Alpha-actinin 4	AD
INF2	Inverted formin 2	AD
MYO1E	Myosin 1E	AR
MAGI2	Membrane Associated Guanylate kinase, inverted 2	AR

Table 7	Genetic causes of FSGS and SRNS (Cont'd)	
Gene	Protein	Mode of Inheritance
ANLN	Anillin actin binding protein	AD
PTPRO	Protein-tyrosine phosphatase-R O	AR
EMP2	Epithelial membrane protein 2	AR
CUBN	Cubilin	AR
PODXL	Podocalyxin	AR, AD
ARHGAP24	Rho GTPase-activating protein 24	AD
ARHGDIA	Rho GDP dissociation inhibitor alpha	AR
DAAM2	Dishevelled associated activator of morphogenesis 2	AR
SYNPO	Synaptopodin	AD
SYNPO2 (Also localized to mesangial cells)	Synaptopodin 2	AR
DLC1	Deleted in liver cancer 1	AR
KANK 1/2/4	Kidney ankyrin repeat-containing protein	AR
ITSN1/2	Intersectin protein	AR
CDK20	Cyclin-dependent kinase 20	AR
NOS1AP	Nitric oxide synthase 1 adaptor protein	AR
Mitochondrial, lysosomal, metabolic, and cytosolic genes		
COQ2	Coenzyme Q2 4-hyroxybenzoate polyprenyl transferase	AR
COQ6	Coenzyme Q6 monooxygenase	AR
PDSS2	Prenyl-diphosphate synthase subunit 2	AR
ADCK4	AarF domain containing kinase 4	AR
SCARB2	Scavenger receptor class B, member 2	AR
PMM2	Phosphomannomutase 2	AR
ALG1	Asparagine-linked glycosylation 1	AR
TTC21B	Tetratricopeptide repeat protein 21B	AR
CDK20	Cyclin-dependent kinase 20	AR
CFH	Complement factor H	AR
DGKE	Diacylglycerol kinase epsilon	AR
Glomerular basement membrane genes		
LAMB2	Laminin subunit beta-2	AR
ITGB4	Integrin beta 4	AR
ITGA3	Integrin alpha 3	AR
COL4A 3/4/5	Type IV collagen alpha 3,4,5	AR, AD, X-linked
Endosomal regulator genes		
GAPVD1	GTPase Activating Protein And VPS9 Domains 1	AR
ANKFY1	Ankyrin Repeat And FYVE Domain Containing 1	AR

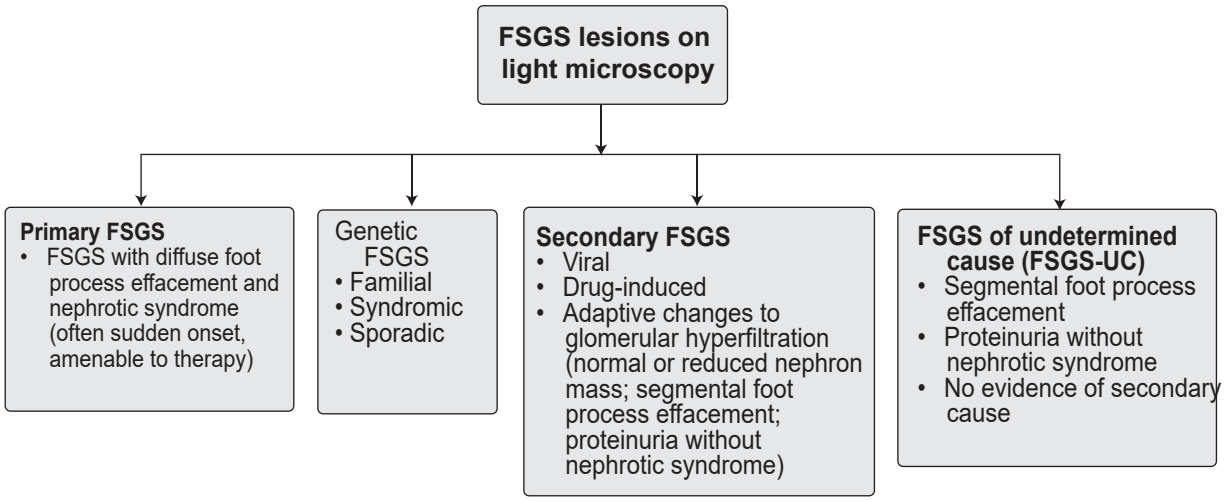


Figure-6: Etiopathgenesis of FSGS

Etiopathgenesis of FSGS:

Idiopathic FSGS:

The term idiopathic FSGS describes a phenotype of SRNS in which FSGS lesions on the kidney biopsy are believed to be caused by a presumptive permeability factor =,, after other secondary factors have been excluded.

Table 8 Etiology of FSGS

Primary / idiopathic FSGS (80% of all cases)	
Familial FSGS	*Hyperfiltration*
Infections	Obesity
HIV infection	Bilateral or unilateral renal dysplasia
Hepatitis B and C	Reflux nephropathy
Cytomegalovirus	Other causes of glomerulonephritis associated with nephron loss
Epstein-Barr virus	*Aging*
Parvovirus B19	*Ischemia*
SARS-CoV-2 (COVID-19)	Renal artery stenosis
Drugs/toxic agents	Hypertensive kidney disease
Gold	Calcineurin inhibitor nephrotoxicity
Interferon-α	Acute and chronic renal allograft rejection
Lithium	Cholesterol crystal embolism
Pamidronate	Cyanotic congenital heart disease
Mercury	
Heroin	

Maladaptive Injury Response:

Several processes associated with intraglomerular hypertension (increased single-nephron GFR) are described to cause glomerular hypertrophy and podocyte activation, hypertrophy, stress, and denudation, leading to extracellular matrix deposition and glomerular sclerosis (423).

Obesity related glomerulopathy:

Association between obesity and nephrotic syndrome was first described in 1974. Various factors are presents in the pathophysiology of obesity induced glomerulopathy (424). Increased renal plasma flow and hyperinsulinemia-induced efferent arteriolar constriction leads to intraglomerular hypertension, hyperinsulinemia enhances the synthesis of growth factors like insulin like growth factor 1 which promote glomerular hypertrophy.

Low Nephron Mass:

The impact of fetal programming on the development of adult disease has been of interest ever since Barker hypothesized that intrauterine growth restriction (IUGR), indicated by low birthweight, predisposes individuals to type 2 diabetes, hypertension, dyslipidemia, and cardiovascular disease in adult life. The strong epidemiologic relationship between intrauterine growth retardation and adulthood hypertension led Brenner to posit an inverse relationship between nephron mass and hypertension (425). Birth weight is a strong determinant of nephron number and glomerular size (426,427)

Infection-associated FSGS

Several viruses and parasites are known to be associated with FSGS such as HBV that causes from MCD, FSGS and membranous nephropathy to inflammatory conditions such as membranoproliferative GN and IgA nephropathy (428). Parvovirus B19 causes various kidney lesion like collapsing and idiopathic forms of FSGS, membranous nephropathy and MCD (429,430). Nephropathy is caused by HIV associated nephropathy (HIVAN) (431). Rarely EBV and CMV infection are associated with FSGS (432). Recently infection with COVID 19 have been associated with development of FSGS (433).

Drug induced podocytopathy:

Several medications have been associated with the development of FSGS. A collapsing variant of FSGS was first described following therapy with bisphosphonates in 2001(434) , with characteristic abundance of cells in Bowman space, which appeared to derive from parietal epithelial cells (435) Monoclonal antibodies that inhibit the function of vascular endothelial growth factor (VEGF, e.g., bevacizumab, axitinib) induce proteinuria in a dose-dependent manner. VEGF is considered critical for glomerular endothelial cell and podocyte cross-talk, which is necessary to maintain normal podocyte structure. Hence, VEGF leads to swelling and detachment of glomerular endothelial cells, vacuolization of endothelial cells, disruption of slit diaphragms, and downregulation of nephrin . Anthracyclines, like adriamycin and doxorubicin, are reported to lead to collapsing FSGS (436) and their injection in mice provides a reliable in vitro model for proteinuric disease. Therapy with interferon α, β, and γ is associated with minimal change, FSGS, or collapsing FSGS (436)

The long-term use of anabolic steroids was associated with FSGS in nine of ten bodybuilders, along with glomerulomegaly in four cases. Podocyte injury was considered secondary to post-adaptive glomerular changes driven by increased lean body mass and/or direct nephrotoxicity of anabolic steroids (437)

Non-genetic SRNS

Circulating factors are considered the most likely cause of non-genetic SRNS in most of its patients. This notion is very likely based on circumstantial data, but identifying the circulating substances causing SRNS has proven difficult .After receiving a kidney transplant, a significant percentage of children with non-genetic SRNS have rapid relapse; these individuals frequently react to immunological adsorption or plasma exchange. A vascular permeability factor was first identified in 1975. Haemopexin, interleukin-13, cardiotrophin-like cytokine-1, and soluble urokinase-type plasminogen activator receptor are additional significant hypothesised circulating components. Thus yet, independent research groups have not confirmed any of these proposed factor, following are the list of the circulating factors.

Patients with severe acute respiratory syndrome due to coronavirus 2 (SARS-CoV-2) can develop nephrotic syndrome with renal histology findings of FSGS due to direct podocyte infection and or cytokine production (438).

Table 9	Circulating factors identified in SRNS

CIrculotlng factors	Molecular weight (kDa)	Major targets
VPF	60-160	Anionic charges of endothelium
FSGS factor	30-50	Podocyte
Hemopexin	54-70	Anionic charges of podocyte endothelium
CD80 (87-1)	55-60	Podocyte
suPAR	20-50	Podocyte integrin
CLCF-1	22	Podocyte
Angptl-4	45-65	Anionic charges
IL-13	10-17	Podocyte adaptors
IL-8	11	Anionic charges
CD40 autoantibody	150	Podocyte integrin
Heparanase	57-60	Anionic charges

(angptl-4: angiopoietin like-4; CD: cluster of differentiation; CLCF-1 : cardiotrophin-like cytokine factor-1; FSGS: focal segmental glomerular sclerosis; IL-13: interleukin-13; IL-8: interleukin-8; MCD: minimal change disease; suPAR: soluble urokinase plasminogen activator receptor; VPF: vascular permeability factor)

Diagnostic evaluation of patients with SRNS

Urine

Spot urine protein to creatinine ratio (first morning void) or 24-h urine protein creatinine ratio.

Urine microscopy and culture

Blood

Complete blood counts, serum creatinine, albumin, electrolytes, calcium, inorganic phosphate, fasting lipid profile, Fasting glucose, HbA1c,TSH, FT4 alkaline phosphatase, S Mg, Vitamin D level, Complement C3, C4; Antinuclear antibody, AntiDs-DNA, ASO, ANCA.

Screening for viral infection

AntiHBs titre, Ani HCV, HIV, CMV, EBV, Parvovirus B19, Syphilis (if clinically suggestive)

Eye screening (patients on prednisolone for >6 months): Because posterior subcapsular cataract (33.3%) is the commonest finding found in patients with nephrotic syndrome on steroid therapy. Others are glaucoma (20%), ptosis, mydriasis, and eyelid skin atrophy, keratitis, thinning of cornea and sclera, repeated bacterial and viral infection.

Ultrasonography of kidneys: Renal echogenicity and size of kidney

Kidney biopsy (light, immunofluorescence, electron microscopy): Biopsy may be avoided in patients with familial steroid- resistance or with extrarenal features, where genetic diagnosis is preferred; a biopsy is also not required in patients with congenital nephrotic syndrome

Genetic tests: (i) onset during infancy (ii) family history of steroid-resistance (iii) extrarenal features (iv) non-response to calcineurin inhibitors (v) prior to transplantation

When considered later in the course of the disease, genetic screening is not indicated in patients who have responded to intensified immunosuppressive (IIS) therapy and in patients with secondary SRNS. Reliable PodoNet data shows on 2.97 % of monogenic SRNS respond to intensified immunosuppression (IIS) (439)

Kidney biopsy / histology

Renal histology has traditionally been used as a major diagnostic and prognostic factor for children with SRNS. However, new research indicates that there is considerable histological heterogeneity amongst monogenic causes of SRNS, suggesting that the results of a biopsy may not always match the results of a genetic test. Renal histology can help clinicians identify the most likely "culprit" gene in the event that rapid genetic testing is not available. For instance, if DMS is found in a child who presents with SRNS, it would be wise to perform mutational analysis on some genes (LAMB2, WT1, NPHS1, PLCE1) more than others. A histological diagnosis is also helpful from a clinical research standpoint since it helps to determine phenotypic patterns more thoroughly.The most common histological diagnosis in children with SRNS are mesangioproliferative glomerulonephritis (5–8%), minimal change disease (25–40%), and FSGS (40–50%).When analyzed based on renal histology, the median age at presentation was 3 years for MCNS, 6 years for FSGS, and 10 years for MPGN (440). A histological finding suggestive of FSGS is thought to be a risk factor for the development of CKD. Membranous nephropathy, IgA nephropathy, or proliferative glomerulonephritis are present in about 10–15% of individuals, necessitating further testing. Patients with well-characterized monogenic forms of SRNS, those with family diseases, such as congenital nephrotic syndrome, or those with a known genetic aetiology already established do not need to have a kidney biopsy.

Prior to starting a particular treatment, a kidney biopsy should be performed on every patient with SRNS. Light, immunofluorescence, and electron microscopy are used to evaluate biopsies. To detect focal pathology such as FSGS, a suitable biopsy should have approximately 20 glomeruli and from the corticomedullary junction. A biopsy can be used to: (i) determine the pathology, the degree of glomerulosclerosis and interstitial fibrosis for diagnosis and prognosis; and (ii) rule out secondary causes of nephrotic syndrome and differential diagnoses such as lupus nephritis,C3GP,IgA nephropathy. To evaluate the toxicity of calcineurin inhibitors (CNIs), the course of the disease, or any changed pathology, a repeat biopsy is necessary.Biopsy may also reveal Ig M nephropathy,C1q nephropathy which may have SRNS or SDNS and even CKD.(433) .

Because most patients with nongenetic SRNS have MCD or FSGS, focus will be on these two entities. In MCD, light microscopy will reveal normal-appearing glomeruli with normal cellularity and capillary walls. Mild focal mesangial predominance may be seen; if more than 3 mesangial cells/per mesangial area away from the vascular pole region are present in at least 80% of glomeruli, this is termed diffuse mesangial hypercellularity variant of MCD.

The involvement of the complement system in FSGS is also supported by a recent study demonstrating Cd4 positive staining in 73% of FSGS patients compared to 21% of MCN and 10% of controls (441)

Table 10 **Pathologic findings in SRNS.**

	South- Asia[a] n = 326	South- Africa n = 183	Poland n = 34	USA[b] n = 253
Histology				
MCD	38.4	36.1	5.9	45.4
FSGS	41.5	36.1	32.4	26.5
MESGN	14.1	8.1	55.8	10.3
MEMB	4.0	–	–	1.2
MPGN	1.0	–	5.9	7.5
Others	1.0	19.7	–	9.1

[a] Two studies one each from Pakistan and India

[b]Summary of two studies, some of the patients were diagnosed with frequent relapsing and steroid dependent NS

Genetic studies

In clinical practice, genetic testing is becoming a vital diagnostic and predictive tool for managing children with SRNS. Approximately 90 genes have causal variations linked to monogenic SRNS. The majority of genes do not exhibit a strong phenotype-genotype association. The identification of mutations in SRNS patients may enable to avoid unnecessary useless toxic immunosuppression (421).

A practical approach to the administration of various immunosuppressive medications and the avoidance of adverse effects. Fewer people with genetic etiology may sporadically exhibit partial remission with CNI. Immunosuppressive drug use is not advised for patients with monogenic illness according to the most recent IPNA guidelines.We agree avoidance of immunosuppression where reliability of genetic testing is good and we are also aware about around 3% response rate in genetic SRNS of PodoNet registry.(Grade B recommendation).

Choosing specific treatments that could cause a remission and/or halt the development of ESKD, For instance, certain mutations respond to specific targeted therapy, e.g., coenzyme Q10 for defects in CoQ pathway (442). Forecasting the clinical trajectory and recurrence of post-transplant illness is also important. Patients with monogenic aetiology have a much lower chance of allograft recurrence as compared to those without a known genetic cause (443). Finding a monogenic aetiology makes it easier to screen for potential linked living kidney donors and to provide guidance for future pregnancies (444).

The diagnosis of monogenic illnesses and sporadic phenocopies (e.g., Alport syndrome, Dent disease, cystinosis) are made possible by the identification of the causal variant. A precise diagnosis enables monitoring for extrarenal problems, such as in patients with WT1, and counselling regarding the course of kidney disease (445). Continued research into new SRNS genes will expand our knowledge of the pathophysiology of SRNS, help define disease phenotype more precisely, and enable personalized treatment approach. Pathogenic mutations in genes encoding proteins of podocyte structure and function are present in about 20–30% of patients with SRNS. 50–60% of monogenic diseases in children are caused by mutations in NPHS1, NPHS2, WT1, COQ2, PLCE1, and LAMB2.

Using a dipstick, siblings of patients with a monogenic aetiology may be checked for proteinuria. Genetic screening is not necessary for healthy children who have a family history of the condition. Genetic testing in children with late-stage steroid resistance is likewise not recommended, as harmful mutations are not found in these patients.

Method of Genetic Testing

Compared to Sanger sequencing, next-generation sequencing (NGS) panels offer a greater diagnostic yield and are more practical and affordable. NGS panels incorporate many genes important to the phenotype. Genes linked to several renal disorders that might exhibit characteristics resembling those of SRNS are included in these panels. Targeted gene analysis is made easier with clinical exome sequencing (Mendeliome gene panel), which contains all of the exons of genes identified in the Online Mendelian Inheritance of Man (OMIM) database. If a causative mutation is not found in the gene-panel, the remaining genes in the clinical exome may be searched for variants. For novel disease-causing genes, whole exome sequencing may be taken into consideration. When extrarenal symptoms or a positive family history with a particular disease-causing mutation are present, Sanger sequencing is recommended if the mutation is extremely likely to cause the disease (446).

The American College of Medical Genetics and Genomics has established criteria for determining the pathogenicity of variations found by genetic testing, which must be carried out by accredited and skilled laboratories. SRNS patients require a diligent effort to rule out secondary disease processes. Tests for sys¬temic autoimmune disorders, including antinu¬clear antibody (ANA), anti–double stranded DNA (anti-dsDNA) antibodies, ANCA, and com¬plement C3 levels should be performed and test¬ing for hepatitis

B and C, HIV, malaria,C3 glomerulopathy, Ig A nephropathy,Alport Syndrome, parvovirus B19 and depending on geographic area and eth¬nicity, sickle cell disease, tuberculosis, and even syphilis may be indicated.

Treatment

Treatment for steroid-resistant nephrotic syndrome (SRNS) is challenging and children who suffer from SRNS require aggressive treatment to achieve remission. With any immunosuppressive strategy, the intent is to induce complete remission of proteinuria (protein/creatinine ration <0.2 mg/mg), which is associated with favorable long-term outcomes (447). However, also achievement of a partial remission has been shown to improve prognosis (448). This is often defined as proteinuria of >0.2–2 mg/mg creatinine or cessation of edema and increase of serum albumin >25 g/l. A suggested definition of nonresponse is persistence of proteinuria >2.0 or presence of edema with serum albumin <25 g/l (449). We suggest cutoff value of serum albumin <30 g/l

First line therapy in children with SRNS: CNI

- When a child's diagnosis of SRNS is confirmed, the first-line immunosuppressive medication, CNI (either tacrolimus, cyclosporine or voclosporin) should be initiated (84). Following CNI beginning, PDN should be used to level SRNS for 4-6 weeks when CNI is to be started. PDN is tapered off at 40 mg/m2 every alternate day for 4 weeks, 30 mg/m2 every alternate day for 4 weeks, 20 mg/m2 every alternate day for 4 weeks, and 10 mg/m2 every alternate day for 8 weeks before stopping. Withholding or postponing CNI treatment for individuals with AKI or an eGFR < 30 ml/min/1.73 m2.
- Treatment with calcineurin inhibitors (ciclosporin and tacrolimus) is the standard of care for patients with non-genetic SRNS, and approximately 70% of patients achieve a complete or partial remission and show satisfactory long-term outcome .(161) Additional treatment with drugs that inhibit the renin–angiotensin axis is recommended for hypertension and for reducing remaining proteinuria.
- While CNis are generally not recommended in patients with reduced eGFR due to their nephrotoxic effects, their use may be justified in SRNS patients with CKD and no other option for disease control (114)
- Calcineurin inhibitors suppresses IL2-mediated T-cell activation and have been used in the treatment of nephrotic syndrome since the mid-1980s. In addition to immunosuppressive action, cyclosporine has been found to have a direct hemodynamic effect and is able to stabilize the actin-cytoskeleton of podocytes; these two effects may be the explanation for its effect in non-immunologic, genetic SRNS (450).
- Information from 9 RCTs examining the efficacy of cyclosporine or tacrolimus for SRNS indicates that these agents induce remission in up to 70% cases (250 patients; 95% CI 64.1–75.3%), which is more than reported for other therapies. Meta-analysis indicates that use of either CNI is associated with higher likelihood of remission at 6–12 months versus no treatment (2 RCT; RR 3.5; 95% CI 1.0–9.6) or therapy with IV cyclophosphamide (3 RCT; RR 1.98; 95% CI 1.25–3.13). Cyclosporine and tacrolimus have similar efficacy (2 RCT; RR 1.1; 95% CI 0.9–1.3) and comparable risk of nephrotoxicity or hypertension (451). Data collated in disease registries report lower rates of remission (41–76% patients), possibly due to selection bias, attrition, and confounding (452). Both the IPNA and KDIGO guidelines recommend first-line use of CNI for patients with SRNS. Cyclosporine and tacrolimus are available options and seem to be equally effective (453). Selection of either treatment partly depends on local preference and experience as well as consideration of side effects typically aiming at trough levels of 80–150 ng/mL for cyclosporine and 4–8 ng/mL for tacrolimus. The median time to remission is 2–4 months (451)

- Though therapy with tacrolimus and cyclosporine show similar efficacy (20), tacrolimus is favoured over cyclosporine because it has fewer side effects(414). Patients with seizures, those at risk for diabetes, and young children who have not reached puberty and are unaware of their looks are better served by cyclosporine.
- Patients with nonresponse despite therapy with CNI in adequate doses for 6 months can be considered for other immunosuppressive strategies including discontinuation of CNI (114) unless they have achieved partial remission. Therapy should be withheld during episodes of acute kidney injury (AKI) or in patients with persistently low eGFR. Treatment with cyclosporine has significant nephrotoxicity (449). This is a common effect of all calcineurin inhibitors; hence cyclosporine therapy needs regular monitoring. Long-term CNI therapy beyond carries a risk of irreversible chronic nephrotoxicity, characterized by striped pattern of tubule-interstitial fibrosis and peripheral arteriolar nodular hyalinosis (455). Risk factors for histological nephrotoxicity, observed in 10–25% cases treated for 2 years or longer, include high CNI dose, persistent heavy proteinuria, and hypertension (127). Voclosporine is less nephrotoxic and more effective (454). Patients who attain remission with CNI but continue to experience disease relapses despite adequate trough levels are considered for switch to alternative therapies. Certain individuals who experience relapses in their condition may be moved to alternate therapy, such as MMF or rituximab (367).
- Up to 70% of patients responding to CNI therapy experienced relapses after stopping at six or twelve months (451). An early relapse could be avoided by gradually reducing CNI/MMF rather than terminating abruptly (456). Recently, however, combination of a calcineurin inhibitor with pulse methylprednisolone was able to achieve sustained remission in 84% of children in a single center study so that this approach might be an alternative for individual refractory patients (457). However, a recent randomized controlled trial found continued therapy with tacrolimus twice as effective in maintaining remission compared to switch to MMF after 6 months (90% vs. 45%) (345).

Relapse on CNI treatment

Children with primary SRNS in the PodoNet registry treated with CsA or tacrolimus in the year following diagnosis, 30% achieved complete and 19% partial remission (453). CsA and tacrolimus show similar efficacy in inducing remission (460), but tacrolimus has less cosmetic side effects e.g hirsutism,gum hyperplasia.It is recommended that serum trough levels should be used to track adherence to CNIs. Oral PDN 60 mg/m^2 should be given daily until remission occurs, or for a maximum of 4 weeks,and then the dosage should be tapered off.

Cyclophosphamide

Children with MCD in North America who have SRNS can experience a long-term remission when treated with IV cyclophosphamide (458). Intravenous cyclophosphamide can be started for patients with MCD who cannot get CNI because of its side effects. Complete or partial remission is seen in 10–50% of patients in studies that used IV cyclophosphamide (every month for six months) (447). Oral cyclophosphamide is not recommended for individuals with SRNS (461)

Mycophenolate mofetil

If immunosuppression is considered in a child with SRNS and an eGFR < 30 ml/min/1.73 m2, MMF rather than CNIs be used due to the risk for nephrotoxicity with CNI (84). In patients with SRNS who have attained full remission on CNI therapy for at least 12 months, conversion to MMF as an alternative immuno-suppressive agent rather than continuing CNIs. If MMF alone cannot maintained remission consider using combined MMF and CNI (458).

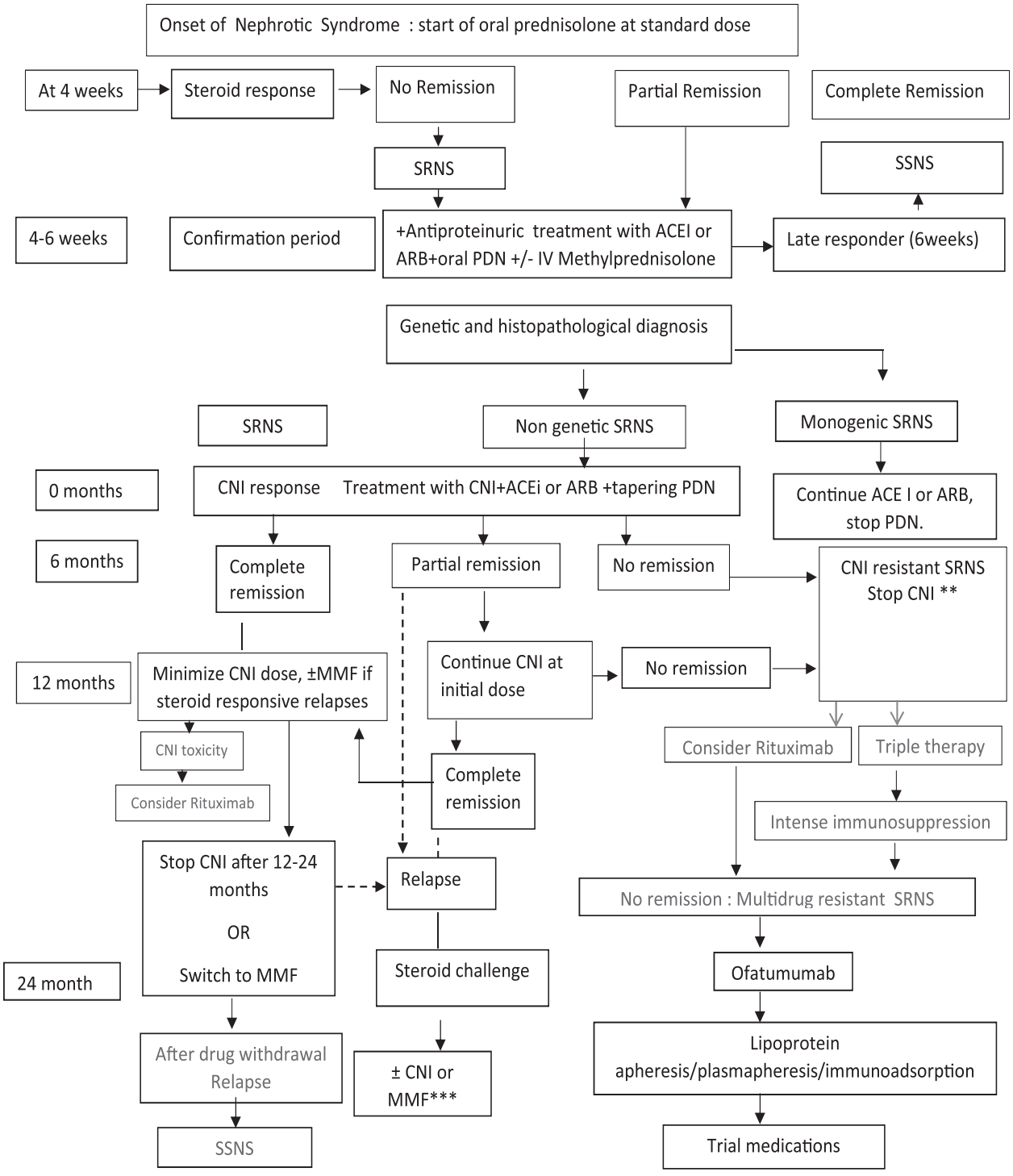


Figure-7 Algorithm for the management of children with nephrotic syndrome. Patients are characterized according to response to a 4-week treatment with oral prednisolone (PDN). Patients showing no complete remission enter the confirmation period in which responses to further oral prednisolone (PDN) with or without methylprednisolone (MPDN) pulses in conjunction with either angiotensin-converting enzyme inhibitors (ACEi) or angiotensin-receptor blockers (ARBs) are ascertained and genetic and histopathological evaluation is initiated. Patients with nongenetic SRNS should be candidates for further immunosuppression, whereas those with monogenetic forms are not (further details are given in the text). In the setting of low resource countries where genetic and/or histopathology assessment is not available, immediate immunosuppressive treatment with CNI may be started. If CNI are not available intravenous or oral cyclophosphamide may be started. CNI non response or significant nephrotoxicity Rituximab is a good option, triple

therapy may an alternate option. Failure of rituximab or triple we should have intense immunosuppressive (IIS), non response of which may need to Ofatumab (if available). Failure at stage SRNS need to undergo plasmapheresis, and finally trial therapies like stem cell transfusion, new biological agents.

* =We suggest tapering PDN after CNI initiation as follows: 40 mg/m2 QOD for 4 weeks, 30 mg/m2 QOD for 4 weeks, 20 mg/m2 QOD for 4 weeks, 10 mg/m2 QOD for 8 weeks, and discontinuing thereafter; ** = CNI may be continued in case of partial remission; *** = in cases of no complete response within 4 weeks, frequent relapses or side effects of medications, we recommend following the refractory SRNS protocol; SRNS, steroid-resistant nephrotic syndrome; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin-receptor blocker; PDN, prednisolone; IV, intravenous; CNI, calcineurin inhibitor; MMF, mycophenolate mofetil

Rituximab(RTX)

Rituximab should be considered for SRNS patients who do not have a hereditary or syndromic condition and who do not achieve at least partial remission with CNIs and with CNI toxicity (462). We recommend RTX in CNI toxicity (level A strong recommendation). One to two weekly doses of 375 mg/m2 IV rituximab to achieve a CD19 count of less than 5/µl or less than 1% of total lymphocyte count. A maximum of four doses (one to two additional doses) may be administered at 1-2weekly intervals if the CD19 goal is not met. Rituximab repeat doses may be administered to individuals who achieve complete or partial remission after B-cell reconstitution, which usually takes place after 6–9 months. Rituximab maintains remission for 18 months in nephrotic syndrome. The pharmacokinetics of rituximab are altered in proteinuric patients; enhanced drug clearance leads to reduced area under the curve and shorter half-life, justifying considerations for higher doses and frequent redosing (463).Rituximab's long-term safety in children with NS is unknown, and it may be linked to more severe side effects (464) . Pneumocystis jiroveci pneumonia, viral myocarditis, fatal hepatitis B infection and severe and/or persistent hypogammaglobulinemia are among the serious illnesses that are increased by rituximab (461). For children with refractory SRNS, MMF may therefore be a safe and useful maintenance therapy to take into consideration as an additional immunosuppressant after rituximab induction to sustain remission (465). It is advised to finish the age-appropriate vaccination regimen and to take cotrimoxazole prophylaxis at 5mg/kg/dose in every alternate dayfor 3-6months.RTX is eliminated in urine upto 50% of total dose,but still can be as an agent to induce and maintain remission in SRNS, SDNS with FRNS. After receiving rituximab, serum IgG levels should be checked because they were found to be low in about 30% of patients (367). In a multicenter open label single-arm trial, 9 (39.1%) of 23 patients with CNI-refractory SRNS achieved remission within 6 months of treatment with rituximab (362). A review of therapy with rituximab in 234 pediatric patients with refractory SRNS (13 case reports, 10 case series) showed remission in 50.4% (range 18.8–80%) patients, including complete remission in 29.8% and partial remission in 22.9% cases (404). A systematic review, including 226 patients with CNI-refractory SRNS (7 case series and 1 RCT), reported remission in 46.4% cases (466).

Combination of Immunosuppressive drugs:

- *We also recommend triple therapy in CNI toxicity, nonresponsive, or SRNS with renal impairment. (level B, moderate recommendation.*
- *We also recommend intense immunosuppression with ≥4 drugs with which includes either of prednisolone, MMF/azathioprine, levamisole, CNI (tacrolimus, cyclosporin), cyclophosphamide using only non-toxic agents (level B, moderate recommendation)*

Treatment-resistant FSGS carries a high risk of progression into ESRD, attempts to achieve remission with other biological drugs and interventions are important. Every single patient achieving complete remission should be viewed a success. If no response with a single-drug approach cannot be achieved, combination of different drugs may be an option. For instance, information on 49 patients (4 case series) with CNI-refractory or CNI dependent SRNS, summarized in a recent review, indicate that therapy with the combination of CNI and MMF might enable remission in 33 (67.3%) patients with CNI-refractory disease,

without major adverse events (324).

Triple Therapy can be effective when CNI fails or has toxicity. Triple therapy is comprised of CNI plus prednisolone and third agent (MMF/ mizoribine) are 75% responsive, CNI+ MMF+ IV CPM for 3 months are 71% complete response, Prednisolone+TAC+MMF are 75% response (458).

Multi-therapy with rituximab, IV methylprednisolone pulses, and cyclosporine or MMF was associated with complete remission in six patients with CNI-refractory SRNS; however, redosing was associated with hypogammaglobulinemia (459). Controlled studies with vigilance for infections should evaluate the safety and efficacy of strategies involving intense immunosuppression.

Adjunctive treatment

ACEi/ARB

Proteinuria persists in SRNS children who respond partially or not at all to calcineurin inhibitors. Angiotensin-converting enzyme (ACE) inhibitor therapy is advised as studies on both adults and children shown that it reduces the degree of proteinuria by 30–40% in a dose- and time-dependent way (467). Patients who exhibit side symptoms, primarily cough, from ACE inhibitors are recommended to start taking angiotensin receptor blockers, such as valsartan and irbesartan. Proteinuria is further reduced by about 15% when an ACE inhibitor and an angiotensin receptor blocker are used in combination. It is not advised to combine dual treatment since patients who receive it run the risk of hypotension, hyperkalemia, and decreased renal function. Combined treatment with ACEi and ARBs is not recommended as it increases the risk for adverse events. ACE inhibitor therapy may lead to a phenomenon known as 'aldosterone escape' with a long-term increase in plasma aldosterone levels. The addition of aldosterone blockade with ACE inhibition reduces urine protein excretion by 30–58% in patients with both diabetic and non-diabetic proteinuria (468). Therapy with RAAS blockers (ACEI or ARB) is recommended for all patients with SRNS since it is associated with dose-dependent reduction in proteinuria, known to retard CKD progression via the TGF-ß pathway. It has been used in combination with indomethacin (chemical nephrectomy, especially in genetic forms of SRNS) (450).

Biologics in SRNS

Ofatumumab

A fully human anti-CD20 monoclonal antibody is called ofatumumab.(469). In neprhrological context, ofatumumab was firstly administered in five children with SRNS not responding to rituximab at the dose of 300 mg/1.73m2 followed by five weekly infusions (2 g/1.73m2 per infusion). At 12 months of follow up, complete and partial remission were achieved in three and two subjects respectively (470). In a more recent randomized controlled trial in children with multi-drug NS (MRNS), Ofatumumab (single infusion at 1.5 g/1.73m2) was compared with placebo and failed to induce remission (471). Overall, ofatumumab induced NS remission in around 40% of treated children for SRNS(472) .One study shows it did not respond to the treatment (473). Meanwhile, Ofatumumab has been withdrawn from the market.

In recent clinical study, the humanized anti-CD20 antibody obinutuzumab (single dose 1 g/1.73m2) was combined with the anti-CD38 monoclonal antibody daratumumab (single dose 16mg/ kg) in 14 subjects with SDNS/frequent-relapsing NS that relapsed after previous treatments with rituximab. As main results, authors reported that the association of obinutuzumab and daratumumab .(474)

Trial medication:

Abatacept

Antigen-presenting cells expressed on the surface a costimulatory ligand named B7-1 (CD80), fundamental for the binding with the T- cell receptors CD28 and Abatacept(39) is an inhibitor of the B7-1 (475). More recently, one study proposed the administration of abatacept, based on the B7-1 podocytes expression at

kidney biopsy, in 12 subjects with NS recurrence after KT and resistant to conventional treatments with plasmapheresis and rituximab (476). There is necessity of randomised clinical trials to evaluate the effects of abatacept in proteinuric renal illness and confirmatory research on podocyte B7-1 expression.

Adalimumab

An anti-TNFa human monoclonal antibody is called adalimumab. It is authorised for use in treating rheumatoid arthritis and gastrointestinal disorders, including juvenile idiopathic arthritis, psoriasis, Crohn's disease, and arthritis in children (477). There have been reports of increased TNFa in the urine of FSGS patients. Additionally, in vivo research revealed that TNFa may cause glomerular permeability to rise and endothelial cell damage . Adalimumab was therefore thought to be a promising treatment for proteinuric illness based on these earlier findings. However, additional clinical trials are lacking, and available results continue to be against the use of adalimumab in FSGS.(478)

Anakinra:

In animal models of FSGS, regulation of C3 convertase in podocyte by decay-accelerating factor (CD55) is fundamental to enhance proteinuria and glomerular sclerosis(479). Recent studies showed that C3a/C3aR ligations on podocytes induce the podocytes to release active IL-1β that through the ligand with type 1 interleukin receptor (IL-1R1), with an autocrine loop, lead to the actin cytoskeleton rearrangement and podocyte loss.(480) The loss of podocytes may be avoided preventing the binding IL-1β/IL-1R1, suggesting therefore a causal link(481). The administration of Anakinra remarkably reduced the amount of proteinuria (482)

Lipoprotein apheresis

Patients with FSGS who have a plasma circulation permeability factor (CPF) frequently react favourably to therapeutic plasma exchange (TPE) and immunoadsorbtion. More significantly, it has been demonstrated that TPE or preemptive lowers the likelihood of recurrent FSGS following transplant (458). Apheresis was performed using Liposorber LA-15 or LA-40 filters (Kaneka Pharma America LLC), based on dextran sulfate cellulose adsorption, for median 12 (range 4–24) sessions over 9 (2–52) weeks, with or without concomitant use of steroids, cyclosporine, and/or statins. Complete and partial remission were reported in 19 (40.4%) and 14 (29.8%) patients, respectively. However, a prospective multicenter study on 17 patients (15 children) with drug resistant primary or recurrent FSGS reported remission in only 2 of 4 patients at 3 months and 2 of 3 patients at 6 months after therapy (483). The effectiveness of oral galactose, adrenocorticotropic hormone, anakinra, and novel treatments like combining rituximab and daratumumab is not well-studied.

Galactose

Galactose might reduce proteinuria by binding to putative circulating factors and inhibiting their activity (484). Case reports in children and adults suggest that patients with FSGS/SRNS may benefit from orally given galactose(485). a more recent phase II clinical trial showed that three out of seven FSGS patients treated with oral galactose showed at least a 50% reduction in proteinuria at 6 months after initiation and a sustained effect for 3–12 months after discontinuation of galactose (486), which raised the possibility of galactose as an adjuvant agent in treating SRNS.

Sparsentan

Endothelin type A (ETA) receptor antagonists have emerged as promising therapies that may enhance RAS inhibitory action (487). Sparsentan is a dual endothelin type A (ETA) and angiotensin II type 1 receptor antagonist. Adverse events of sparsentan were comparable to irbesartan, showing that sparsentan was generally safe and well tolerated.(488) Although it requires further clinical experience, this novel agent seems to be a promising non-immune modulating option for SRNS. Data focusing on paediatric patients are needed in the future.

Mesenchymal stem cells (MSCs)

Mesenchymal stem cells (MSCs), known for their immunomodulatory and anti-inflammatory effects, have been considered as a potential therapeutic agent for treating immune-related diseases, including nephrotic syndrome (489).

Retinoids

Retinoids are analogues of vitamin A that regulate cellular differentiation. It has been suggested that retinoids are capable of restoring podocyte structure in that they reduce proteinuria in animal models of kidney diseases (490).

APOL1 inhibitors:

Novel APOL1 inhibitorsare currently in clinical development. A Phase II trial investigating the APOL1 inhibitor VX-147 has started recruitment(491) . Antisense oligonucleotides are short, synthetic, modified chains of nucleotides that bind to the target mRNA, inducing its degradation and preventing the mRNA from being translated into a detrimental protein product. Preclinical studies with antisense oligonucleotides are showing promise as a novel therapeutic approach for APOL1 associated nephropathy (492). APOL1 contributes to innate immunity and protection against Trypanosoma, the cause of African sleeping sickness. The APOL1 protein forms a channel that contributes to Trypansomal lysis.(447)

Treatment of monogenic SRNS:

Monogenic SRNS can be of autosomal recessive (AR), autosomal dominant (AD), X-linked, or mitochondrial inheritance (493)Most genetic forms of SRNS do not respond to current immune-suppressive therapies; however, a small subset of patients with monogenic SRNS will achieve partial or complete remission with specific immunomodulatory agents, presumably due to non-immunosuppressive effects of these agents. (494). Generally, >95% of patients with monogenic SRNS will not respond to treatment with immu¬nomodulatory agents (495) and hence it is recommended to withdraw immunosuppressive therapy. RAS inhibitors should be administered at maximally effective and tolerated doses. There are anecdotal reports of individuals with muta-tions in WT1, PLCE1, and MYO1E who achieved partial or complete remission when exposed to immunosuppressive treatments, in particular cal¬cineurin inhibitors (496). Specific gene disorders can sometimes benefit from new therapeutic strategies. Mutations in the genes related to biosynthesis of coenzyme Q 10 (CoQ10, ubiquinone) cause primary CoQ10 deficiency resulting in various clinical phenotypes. A portion of these patients present with SRNS, often with extrarenal manifestations such as sensorineural hearing loss or neurologic deficit (497). In monogenic SRNS related to primary CoQ10 deficiency, early initiation of CoQ10 supplementation has been reported to reduce proteinuria and delay disease progression (498). Vitamin B12 mutations in the cubilin (CUBN) gene have been reported in children with intermittent proteinuria (11). Cubilin is a coreceptor for the intestinal vitamin B12-intrinsic factor complex, and it is also essential for tubular reabsorption of protein in the proximal tubule(499) . It is therefore conceivable that treatment with vitamin B12 may ameliorate proteinuria associated with CUBN mutation.

In edematous patients, long-term sodium restriction is appropriate with a maximum goal of approxi¬mately 2500 mg/day. In patients with persistent hyperlipidemia due to inability to control nephro¬sis, a low saturated fat diet should be instituted with their HMG CoA-reductase inhibitor. Protein intake should only be supplemented at the Recommended Daily Allowance (RDA) (500).

Long term outcome of SRNS:

It is clear that the worst outcomes occur in SRNS, with 34–64% progressing to ESRD within 10 years of diagnosis (501). Emerging data in the literature has drawn attention to secondary SRNS patients of which 80% patients will progress to ESKD. In particular, African-American and Hispanic children with FSGS have poorer outcomes, with one study demonstrating 50% progress to ESRD within 3 years (502). Risk factors

Table 11 **Supportive care of children with steroid-resistant nephrotic syndrome**

Complication	Pathophysiology	Management
Thrombo-embolism	Urine loss of coagulation regulators→ hepatic production of hemostatic proteins → lack of Ambulation →dehydration; thrombocytosis → platelet aggregation	Prevention: Ensure ambulation, optimal hydration; remove central venous catheters, avoid arterial punctures; use compression stockings Treatment: Heparin, low molecular weight heparin, warfarin and as described in this manuscript. Preventive anticoagulation: If previous thrombosis, risk factors
Hypertension	Glomerular disease; high renin, aldosterone, epinephrine, norepinephrine; reduced atrial natriuretic peptide	Target blood pressure 50-75th percentile for age. Lifestyle measures; restrict salt intake ACE-I, angiotensin receptor blockers
Acute kidney injury	Hypovolemia; medications (ACEi, calcineurin inhibitors)	Supportive care: Attention to fluid and electrolytes; management of complications of acute kidney injury
Linear growth retardation	Exposure to glucocorticoids; malnutrition; adrenocortical suppression	Regular monitoring of height, height velocity; steroid minimization Limited evidence for growth hormone therapy
Obesity	Exposure to steroids; reduced physical activity	Monitor weight, BMI; minimize steroids; modify lifestyle,exercise.
Dyslipidemia	Increased LDLs Reduced clearance of chylomicron, very LDL	Modify lifestyle (dietary change, physical activity, weight control) >8 year-old with LDL cholesterol >160 mg/dL, or >130 mg/dL with risk factors*: Atorvastatin 10-20 mg daily
HPA suppression	Corticosteroid therapy	Stress dose if receiving oral steroids >2 weeks within past 1 year
Bone health	Urinary loss of Vitamin D; osteoblast suppression, osteoclast induction	Vitamin D (400-800 IU); calcium (250-750 mg) supplements
Hypothyroidism	Urinary loss of thyroid binding globulin, transthyretin and albumin	No treatment if remission is expected; follow-up borderline levels Low free T4, TSH >10 mU/L: Treat with T4

Adopted from IPNA SRNS guideline

for disease progression included lacking responsiveness to intensified immunosuppression (IIS) protocols, genetic disease, and FSGS on biopsy. Ten –year ESKD free survival rates were 94%, 72%, and 43% in patients with complete remission, partial remission and IIS resistance respective. A multi-center study of 75 children with FSGS reported that within 5 years from the diagnosis of FSGS, 21% of children had developed ESKD, 23% had developed CKD, and 37% had developed persistent proteinuria, while only 11% remained in remission (503). There are well over 40 genetic mutations associated with FSGS, and new

mutations continue to be identified. Patients with genetic mutations are less likely to respond to immunosuppressant therapy and more likely to develop ESRD (504). The risk post-transplant recurrence appears to be mainly determined by the underly¬ing disease etiology, i.e. immune-mediated vs. genetic. Whereas patients with secondary steroid resistance have about 80% risk of recurrence, the risk appears to be close to zero in patients with genetic forms of SRNS (505). ESKD-free survival rates were 27% and 17% in patients with a genetic diagnosis, contrasting with a favorable prognosis in children with sporadic non-genetic SRNS responsive to intensified immunosuppression, who exhibited a 15-year renal survival rate of 96%. Information on disease activity in SRNS on the long term is limited. Outcomes on medium-term range from sustained remission after CNI are discontinued, to a relapsing illness that requires switch to less toxic regimens (506). SRNS may turn to SSNS in the course of time, and treated as SSNS.

Multicenter observational cohorts demonstrate that etiology of disease and response to immunosuppression are the chief determinants of long-term outcome. Based on information from four studies, the odds ratio for nonresponse in patients with genetic versus nongenetic disease is estimated at 4.0 [95% CI 2.5, 6.5; P <0.0001] and that of kidney failure at 2.9 [2.2, 3.7; <0.0001] (447,452). Among patients with undifferentiated or nongenetic SRNS, response to immunosuppression predicts kidney survival, with significantly higher risk of kidney failure in patients with persistent nonresponse (507).

Pooled data from five large multicenter collaborative studies including 1107 patients with SRNS indicates complete remission in 26.7% [95% CI 24.2–29.4%] cases, partial remission in 18.4% [16.2–20.8%] cases, and nonresponse in 54.8% [51.9–57.7%] patients (447,452). The lower rates of remission as compared to randomized.

Bangladesh data showed 76 SRNS cases 66% of achieved complete remission, 10% achieved partial remission, 3% remained unremitting, 14% developed CKD (508).

CONGENITAL NEPHROTIC SYNDROME

INTRODUCTION:

Gautier and Miville first described congenital nephrotic syndrome (CNS) in 1942 and defined as the triad of nephrotic range proteinuria (>200mg/mmol creatinine), hypoalbuminaemia and clinically detectable edema, occurring in the first three months of life. It is a separate entity from idiopathic childhood nephrotic syndrome. Congenital nephrotic syndrome is most frequently genetic in aetiology, with a minority being secondary to congenital infections such as syphilis or toxoplasmosis. Inheritance of genetic congenital nephrotic syndrome is autosomal recessive, with an incidence of 1–3 per 100,000 live births (509)

Nephrotic syndrome (NS) appearing later during the first year (4–12 months) is defined infantile, and manifesting thereafter is called childhood NS . These definitions have been used for decades in order to help the clinical diagnosis, although recent findings indicate that NS caused by a particular gene defect can manifest at various ages, questioning the rationale of the classification (510) In rare cases, CNS can be caused by congenital infections or maternal allo-immune disease, but most cases are caused by genetic defects in podocytes (511). Infantile Nephrotic syndrome has 50% genetic, and rest are non genetic. ,Thereby they have less severe disease and better response pattern. Several genes have been implicated in the aetiology of isolated CNS (most commonly NPHS1, which encodes nephrin; NPHS2, which encodes podocin; WT1, which encodes Wilms tumour suppressor protein 1; and PLCE1, which encodes 1-phosphatidyl inositol 4,5-bisphosphate phospho-diesterase ε1) or in less common syndromic forms of the disease (most commonly WT1 or LAMB2, which encodes laminin subunit β-2 . As pathogenic variants in these genes alter the physiology of podocytes, genetic forms of nephrotic syndrome are now referred to as podocytopathies. In 2018, a joint initiative of the European Reference Network for Rare Kidney Diseases (ERKNet) and the European Society for Paediatric Nephrology (ESPN) established a Work Group to develop guidelines for the clinical diagnosis, management and treatment of CNS. As evidence regarding the optimal management of CNS is frequently missing or inadequate, here we provide a consensus report based on expert opinion rather than a clinical practice guideline. (94)

Table 12	The etiology of congenital nephrotic syndrome (CNS)

Primary CNS
Nephrin gene mutations [NPHS1, Finnish type of CNS (CNF)]
Podocin gene mutations (NPHS2)
WT1 gene mutations (WAGR, Denys-Drash syndrome, Frasier syndrome, isolated CNS)
LAMB2 gene mutations (Pierson syndrome, isolated CNS)
PLCE1 gene mutations
LMX1B mutations (nail-patella syndrome)
LAMB3 gene mutations (Herlitz junctional epidermolysis bullosa)
Mitochondrial myopathies
CNS with or without brain and other malformations (no gene defect identified as yet
Other genes are SGPL1, ARHGDIA, MAGI 2, CRB2, OCRL (LOWE SYNDROME) PODXL, PMM2, CD2AP
Secondary CNS
Congenital syphilis
Toxoplasmosis
Malaria, Measles,Pertusis,Herpes simplex,Herpes Zoster
Cytomegalovirus,
Rubella,
Hepatitis B,
HIV
Maternal systemic lupus erythematosus
Neonatal autoantibodies against neutral endopeptidase (NEP)
Maternal steroid–chlorpheniramine treatment

Genetic CNS

Genetic abnormality is identified >85% of patients with CNS. Nephrin, podocin, PLCE1, WT1 and LAMB2 comprises > 80% of pathogenic genes. NPHS1 mutations are the most common. AHGDIA, MAG12, CRB2, Lowe Syndrome (OCRL) also regarded as genetic causes of CNS (512,513)

Finnish variety CNS (CNF, NPHS1)

Mutations in NPHS1 are the commonest cause and are particularly prevalent in Finland (“Finnish-type” CNS) where the incidence of CNS rises to 1 in 8,200 to 10,000 (1). It is the severe form of CNS which is inherited in an autosomal recessive manner. The Incidence is higher in Finland (1 :8200 live birth), so named as the Finnish type of CNS (CNF) . A recent survey found 80 cases among non-Finnish population and more than 200 NPHS1 mutations have been identified (514).

NPHS1 encodes production of nephrin. It is the structural component of slit diaphragm being key to maintain its integrity. Mutation in the NPHS1 leads to loss of nephrin expression in slit diaphragm loss of intracellular components of nephrin and podocin and other intra-podocyte processes leads to a reduction of actin polymerization and GBM functionality. Fin major and fin minor mutation are the causes of 98% of the NPHS1 mutation seen in the Finnish population (515,516).

Typically, infants with NPHS1 mutation will be born in late prematurity (35–38 weeks’ gestation).Through their antenatal course, ultrasound scans may highlight a relatively large placenta and there may be a suggestion of crowding, restricting movement in utero. This can lead to flexion deformities of the elbows, hips and knees, and may also have an impact on respiratory development. Infants can also present with a small nose and low set ears, and there is evidence of delayed ossification with gaping anterior and posterior fontanelles (517–519).

Compared with many other genetic disorders, NPHS1 shows relatively little phenotypic variation. Most of these children are born prematurely, with a birth weight ranging between 1,500 and 3,500 g. The placental weight is over 25% of the newborn weight in practically all cases. Amniotic fluid may be meconium stained,

but the infants do not usually have major respiratory problems. Importantly, NPHS1 infants do not have extrarenal malformations. On the other hand, minor functional disorders, such as muscular hypotona, cardiac hypertrophy (25%) and dystonic cerebral palsy (8%) are found during the nephrotic stage. Proteinuria begins in utero and is detectable in the first urine sample after birth. Microscopic hematuria and normal creatinine values during the first months are typical. Heavy protein loss (up to 100 g/L) results in oliguria and severe edema if not treated. Hyperlipidemia is also present, as in other forms of NS. The NPHS1 kidneys are large having increased cortical echogenicity and indistinct corticomedullary border on US scan . In renal histology, no single histological finding is pathognomonic for NPHS1. Expansion of glomerular mesangium and dilations in the proximal and distal tubules are the most characteristic findings. Interstitial fibrosis and inflammatory infiltrates, especially around the glomeruli, increase with time. Effacement of podocyte foot processes and disappearance of the filamentous image of slit diaphragm (SD) are seen in electron microscopy disappearance of the filamentous image of slit diaphragm (SD) are seen in electron microscopy. NPHS2 is the 2nd most common gene found in 17-39% of CNS with milder proteinuria, hypertension and slow renal impairment by mean 6.6 yeard. Histologically they are FSGS and MCD (510,515). NPHS2 is the second most common gene found in 17-39% of CNS with mild proteinuria, hypertension and showed renal impairment by mean 6.6 years. Histological they are FSGS and MCD.

WT1 mutation: Wilms' tumor suppressor gene (WT1) encodes for a transcription factor WT1, which plays a crucial role in the embryonic development of the kidney and genitalia. Mutations in WT1 may cause several types of developmental syndromes (Denys-Drash syndrome, Frasier syndrome and WAGR syndromes) manifesting in childhood (520–522). WT1 mutations can also cause an isolated kidney disease with nephrotic syndrome (NS) appearing in the first 3 months of life. They account for a few percent of CNS cases. Patients may have moderate proteinuria, and renal biopsy most often reveals diffuse mesangial sclerosis (DMS) of glomeruli. (98)

WAGR syndrome: The syndrome is comprised of Wilms tumor, aniridia, genitourinary anomalies and mental retardation (523,524).

Denys-Drash syndrome (DDS): WT1 mutation may present with early onset NS in the context of Denys Drash syndrome (DDS) with underlying diffuse mesangial sclerosis . DDS associated with genotypical males (46XY) present with Wilm's tumour, pseudohermaphroditism (i.e. phenotypically female) and progressive glomerulopathy. Those of the female genotype (46XX) present with Wilm's tumour and glomerulopathy without the pseudo-hermaphroditism (525).

Frasier syndrome (FS): This condition is characterized by male pseudo hermaphroditism, gonado-blastoma and progressive glomerulopathy (526). Proteinuria appears at 2-6 years of age and renal histology is FSGS. Patient develops ESRD by 4 year and resistant to medication. Transplantation is the only option. In FS bilateral gonadectomy is highly recommended to avoid gonadoblastoma followed by transplantation (527).

Pierson syndrome: Pierson syndrome is caused by autosomal recessive mutations in the LAMB2 gene that codes for laminin β2, a protein widely expressed in the glomerular basement membrane, retina, lens capsule and neuromuscular synapses . The syndrome, characterized by microcoria (small pupillary size) with abnormal lens shape and cataract, is associated with NS that develops 'in utero' or within the first 3 months of life. The renal histopathologic lesion is diffuse mesangial sclerosis and the outcome is usually a rapid progression to renal failure. In addition, patients surviving infancy develop blindness and severe neurological deficits (54)

Mutation of phospholipase C epsilon (PLCE 1) (NPHS3): Mutations of phospholipase C epsilon cause autosomal recessive form of early onset NS .DMS is the chief histology and FSGS may found. Some may respond to cyclosporine and prednisone.(101). They have microcephaly,eye abnormalities,developmental delay and muscular dystrophy.

Nail patella syndrome (NPS): Nail-patella syndrome (NPS) is an autosomal dominant disorder caused by mutations in the LMX1B gene and is characterized by nail dysplasia, skeletal abnormalities (Absent/ hypoplastic patella, iliac horns, deformity of elbow) and nephropathy. The renal pathological findings of NPS nephropathy vary from minor glomerular abnormalities to FSGS under light microscopy and irregular increases in the thickness of the GBM are observed with the progression of the disease. Renal involvement is the major determinant of the prognosis for NPS. May progress to CKD in 10-20% patients. Renal involvement in NPS is caused by a LMX1B gene mutation, which dysregulates the production of collagen, and corticosteroids have no effect on this gene mutation. So treatment: is supportive with ACEI/ARB which reduce proteinuria (528).

Mitochondrial disorder: The mitochondrial respiratory chain produces cellular energy mainly through oxidative phosphorylation. Abnormal electron transfer in the respiratory chain not only diminishes energy production but also leads to an increased production of reactive oxygen species (ROS); kidney glomerulus appears particularly vulnerable to ROS and lipoperoxide damage (529).

Coenzyme Q10 (CoQ10) has a number of vital functions in all cells, both mitochondrial and extra-mitochondrial. In mitochondrial oxidative phosphorylation, CoQ10 serves as a lipid soluble antioxidant and plays an important role in fatty acid beta-oxidation and pyrimidine and lysosomal metabolism, as well as directly mediating the expression of a number of genes, including those involved in inflammation (530).Mitochondrial disorders(CoQ10 disease) are due to mutations of nuclear genes namely CoQ2, CoQ6, PDSS2,ADCK 4 and mitochondrial maternal DNA cause collapsing and crescentic FSGS.CoQ10 disease may occur as isolated glomerulopathy or may have multisystemic involvement.

Deficiency in CoQ10 has been implicated in the pathogenesis of a wide range of disorders may have fatal multisystem disease, isolated SRNS, or isolated CNS disease. Features of mitochondrial disease include nystagmus, retinitis pigmentosa, visual impairment , sensorineural deafness, hypotonia, seizure, encephalopathy, cardiomyopathy, muscle weakness with increased creatinine phosphokinase (CPK), feeding difficulty, liver failure, diabetes mellitus, lactic acidemia, anemia and/or pancytopenia. Diagnosis is confirmed by next generation gene sequencing (NGS) , Renal and skin biopsy may help to measure CoQ10 . Patients may respond well to oral CoQ10 supplementation. And dose is ubiquinone 15-50 mg/kg/day. However, the condition must be recognized sufficiently early; once damage to kidney is established, only minimal recovery is possible (531).

Galloway and Mowat syndrome: It is a rare autosomal recessive disorder due to WDR 73 gene mutation, described by Galloway in 1968. It is combination of CNS, hiatus hernia, congenital microcephaly. Dysmorphic features like hypertelorism, dysplastic ear, micrognathia and childhood death is common. OGSEP,LAGE 3,TPS3,TP53RK and TPRKB encoding 4 subunits of KEOPS complex found to have rule in brain and renal development (532,533).

SGPL1: The condition is autosomal dominant and characterized by primary adrenal insufficiency , immunodeficiency and sensorineural hearing loss (534–536).

LAMB3 (Hertitz junctional epidermolysis bullosa) : Herlitz junctional epidermolysis bullosa (H-JEB) is a hereditary bullous disease caused by absent expression of laminin-5, a component of anchoring filaments within the dermal-epidermal basement membrane zone. one study found a patient with H-JEB who presented with congenital nephrotic syndrome, that may contribute to early death in this disease The patient had massive albuminuria, attributable to failure of the glomerular filtration barrier, and high urinary N-acetylglucosaminidase levels, indicating renal tubular involvement. Immunohistopathologic analysis of the patient's renal tissue revealed compositional changes in laminin isoforms of the glomerular basement membrane and no detectable laminin-5 in the renal tubular basement membrane, which suggests that laminin-5 may play an important role in renal function. Combination therapy with meticulous skin care and treatment strategies established for congenital nephrotic syndromes may rescue patients with this disease (537).

Congenital membranous nephropathy due to anti-NEP antibodies: Maternal variant in the some metallomembrane endopeptidase gene (MME) may be found in some fetus with CNS which encodes the

podocyte protein NEP (neutral endopeptidase)., crosses placenta sensitizes the mother with anti-NEP. NEP is present on the podocytes and the brush border of the renal tubules. The mother had truncating mutations in the MME gene, leading to the absence of NEP. Consequently, anti-NEP antibodies were produced by the use of maternal steroid and/or chlorpheniramine during pregnancy and are transferred to her fetus during the last trimester, inducing neonatal membranous nephropathy (MN). Anti-NEP antibodies damage the podocyte of the fetus leading to proteinuria. (538)

Non-genetic forms of CNS: Genetic defects account for the great majority of CNS cases, but especially in developing countries, infections are the most possible etiology. (539). In addition to infections, CNS has been associated with maternal systemic lupus erythematosus and more recently with neonatal alloimmunization against neutral endopeptidase present on podocytes (538)

Congenital syphilis: Congenital syphilis has long been known to cause nephritic or nephrotic syndrome in the newborn. Proteinuria and hematuria are present, but severe NS is less common. Kidney biopsy shows membrnous nephropathy. Antimicrobial therapy with penicillin is curative provided that irreversible renal lesions have not developed. (539)

Cytomegalovirus infection: An association of neonatal cytomegalovirus infection (CMV) and CNS has also been reported . CMV infection is common during the first weeks of life, and detection of this virus in an infant with NS does not exclude an underlining genetic defect. This should be searched especially if ganciclovir therapy is not helpful. (540)

Other infections: Toxoplasmosis has been associated with CNS, together with neurologic or ocular features . In one report, it was found that toxoplasmosis responded well to spiramycin therapy. (541)

Congenital rubella can cause CNS due to membranous glomerulonephritis . While acquired immunodeficiency syndrome caused by the human immunodeficiency virus may be associated with nephropathy, including nephrotic syndrome that presents in older children, no patients with CNS caused by this infection has been reported (542,543)

Hepatitis B virus commonly causes membranous nephropathy in children and adults, but has not been reported to cause CNS. Other infections that might be rarely associated with CNS include measles, pertussis, herpes simplex and herpes zoster.

We suggest following to an infant with congenital nephrotic syndrome should be evaluated in the following way (Grade A, strong recommendation).

Initial work-up for a child with CNS

- Family history: consanguinity, ethnicity, history of CNS, early infantile death, or miscarriage and Early onset neurological and kidney diseases, autoimmune diseases.
- Prenatal and perinatal history: enlarged prenatal nuchal translucency, increased amniotic fluid alpha-fetoprotein, fetal edema, oligohydramnios and placental weight >25% of birth weight of newborn, maternal infections
- Patient history: fever episodes, pain, abdominal discomfort, swelling, fatigue.

Initial evaluation

- Assessment of Growth: height or length, weight, head circumference if aged <2 years, calculation of BMI and annual height velocity.
- Blood pressure.
- Physical examination: volume status, signs of edema (e.g. ascites, pleural and pericardial effusions), features of complications like sepsis, thrombosis, hypothyroidism.
- Blood biochemistry: blood count, electrolytes, albumin, magnesium, creatinine, urea, protein, albumin, cholesterol, fasting triglycerides and glucose.
- Thyroid-stimulating hormone and free thyroxine (T4) hormone level.

- Serum IgG level.
- Serum levels of ionized calcium, phosphate, alkaline phosphatase, parathyroid hormone (PTH), 25(OH) vitamin D3.
- Ultrasound scan of abdomen and pleural space to see the kidney echogenicity and size, ascites, effusions and thrombosis.
- Cardiac evaluation – cardiac hypertrophy and mild pulmonary stenosis found in 25% of CNS. Few can have pulmonary and aortic stenosis.

Extended evaluation

- Evaluation of dysmorphic features and skeletal abnormalities, genital examination, ophthalmological examination, hearing test.
- Full neurological examination and standardized assessment of cognitive status with or without brain MRI.
- Serology for syphilis, toxoplasmosis, Cytomegalovirus (CMV), rubella, measles, Hepatitis B virus (HBV), Hepatitis C virus (HCV), Herpes simplex virus type 1 (HSV1), Herpes simplex virus type 2(HSV2), Herpes zoster virus (HZV), Human immune-deficiency virus (HIV) and pertussis
- Further screening in selected patients in endemic areas or in the case of clinical suspicion: malaria, anti-nuclear antibodies, serum complement (C3 and C4), anti-neutral endopeptidase (NEP) antibodies, amino acids (for diagnosis of glutaric aciduria type I or sialic acid storage disease) and/or mercury levels).

Genetic tests: Genetic testing is highly warranted in primary CNS. A gene panel that includes at least NPHS1, NPHS2, WT1, LAMB2 and PLCE1 is preferred primarily. If negative, whole exome sequencing is recommended as it provides the diagnosis of another 5% of genetic CNS cases. (544,545)

Table 13 Genes associated with CNS with key phenotypic features (509)

Gene (Syndrome)	Associated feature
PODXL (podocalyxin)	Renal malignancy Omphalocele microcoria
OCRL defect	Oculocerebrorenal syndrome (Lowe syndrome)
PMM2	Hypotonia Developmental delay Strabismus Pericardial effusion Abnormal fat distribution Characteristic facies
CD2AP	FSGS Hypertension

Prenatal diagnosis:

Prenatal diagnosis in families with a known risk for CNS should be based on genetic testing whenever possible. The results can be obtained fast if the mutations are known in advance. In case of no family history or if the mutations in the affected child were not identified, prenatal genetic testing is a challenge, since sequencing the NPHS1 (29 exons) and NPHS2 (eight exons) genes is time consuming and usually not possible within the short time frame available. NPHS1 especially can still be suspected prena tally based on elevated alpha-fetoprotein (AFP) levels in maternal serum and amniotic fluid. If the AFP concentration in amniotic fluid is very high and the ultrasound examination does not reveal fetal

anencephaly or other malformations, NPHS1 is a probable diagnosis. However, heterozygous fetal carriers of NPHS1 gene mutations may have temporarily elevated AFP levels in amniotic fluid and maternal serum, and repeated measurement of amniotic fluid AFP before the 20th week of pregnancy is recommended in cases with high AFP levels (546)

Renal histology

Kidney biopsy is indicated if all other screening is negative, indicating non-infectious, non-genetic CNS. Histological examination should include light microscopy, immunofluorescence and/or immunohistochemistry and electron microscopy.

Renal biopsy does not reveal the etiology of CNS. As pointed out, the genetic defects may cause several types of glomerular lesions, such as mesangial expansion, FSGS, MCNS, and DMS, and the findings overlap in different entities (510). CNS was historically defined by histopathological appearance, with five discrete patterns described; Finnish type, diffuse mesangial sclerosis (DMS), focal segmental glomerulosclerosis (FSGS), membranous glomerulopathy and minimal change disease. The non-glomerular findings, such as tubular dilatations and interstitial fibrosis and inflammation, can be seen in all forms of proteinuric diseases (509). Thus, the indications for renal biopsy are not quite clear. Hence, kidney biopsy may be done in following situations

- Failure to establish genetic diagnosis with certainty
- Substantial reduction of eGFR <30ml/min/1.73m2
- Rare diagnosis eg. Anti-neutral endopeptidase (NEP)
- For prognostication purpose. (94)

The knowledge of severity of glomerular sclerosis and interstitial fibrosis may help in the assessment of treatment strategies. On the other hand, the lesions are focal, and the biopsy findings may be misleading. If immunohistochemistry for nephrin and podocin is available, analysis of their expression in a biopsy sample is useful. Total lack of either protein speaks for a severe disorder not responding to antiproteinuric therapy. (510)

Table 14 Histological pattern of CNS

Histology	Gene
Diffuse mesangial sclerosis	WT1 PLCE1 LAMB2
Irregular microcystic dilatation of proximal tubule	NPHS1 (CNS of the Finnish type)
Membranous nephropathy	Congenital infection Neonatal lupus nephritis Nephropathy due to anti NEP antibodies

Histological confirmation either by percutaneous renal biopsy or by examination of nephrectomy material would then confer a confirmed diagnosis. Histologically, Finnish-type NS is associated with expansion of the mesangial matrix and hypercellularity leading to progressive glomerulosclerosis. Microcystic dilatation of the proximal tubules is a classical feature. There is an absence of immune complex deposition on immunofluorescence.(547) Conversely, diffuse mesangial sclerosis more typically demonstrates small condensed glomeruli with collagen deposition in the mesangium, a feature absent in the Finnish type (548) Immunofluorescence may demonstrate mesangial IgM and C3 deposition. In membranous nephropathy,

localised inflammation causes an increase in the thickness of the capillary mem brane. Deposition of immune complexes with the associated inflammation leads to podocyte effacement. FSGS shows sclerosis of segments of the glomerular tuft. These lesions are best demonstrated with PAS and silver-methenamine staining highlighting the increased collagen deposition. They will often abut normal glomeruli highlighting its focal nature. However, the undertaking of percutaneous renal biopsy is not without risk. Though it can confirm the presence of histological features consistent with a diagnosis of CNS, the correlation between mutational analysis and histology is less definitive than originally believed. Unless there is significant diagnostic uncertainty, awaiting genetic analysis is often more prudent. Furthermore, nephrectomy often forms a part of the subsequent management, providing a wealth of histological tissue to support the diagnosis later on (547,548).

Imaging:

The kidneys may be of normal size or larger than normal in ultrasound scanning, and the renal cortex is often hyperechogenic. Search for possible non-renal malformations is important, especially since they may give clues to the etiologic diagnosis. These include genital abnormalities (WT1), eye defects (LAMB2), and neurological disorders (Mowat–Galloway). Cardiac evaluation often reveals ventricular hypertrophy but no structural defects. (515)

Management

Nutrition

- Adequate nutrition – hypercaloric diet 120-150 kcal/kg/day; Protein 3-4 g/kg/day.
- Low salt content (<0.5 g per day in babies aged <6 months, <1 g per day in infants aged 7–12 months, <2 g per day in children aged 1–3 years and <3 g/day in children aged >3 years)
- Breast milk and cow's milk based infant formula are first used and the excess protein is given as whey and casein-based protein product. (549)
- Glucose polymers and fat emulsion are given to increase energy intake
- Lipid supplementation
- Multivitamin: calcium (500-1000 gm/day), magnesium (50 md/day), and potassium supplementation
- Nasogastric tube or gastrostomy often required for proper feeding.
- Modification of diet is needed if renal function deteriorates. (550)

Albumin infusion

- Albumin infusions are indicated in unstable patients with severe edema with complications
- Initial 20% albumin dose 0.2-1 g/kg, up to three infusion a day, each over 2 hr
- Maintenance 20 % albumin dose is 1-4 g/kg/day (over 6h; at night)
- During albumin infusion, 1-2 doses of frusemide 0.5-2 mg/kg (510,551)

The use of albumin infusions in children with CNS varies between centers. Some centers administer intravenous albumin only when deemed clinically indicated, whereas others use regular albumin infusion protocols (1–4 g/kg/day). Potential advantages of regular albumin infusions are replacement of lost protein to support growth and psychomotor development, stabilization of intravascular volume and minimization of oedema. The disadvantages of regular albumin infusions are the need for a central line, which increases the risk of infection and/or thrombosis of large vessels, which endangers future hemodialysis access, the need for prolonged hospitalization and the associated costs. Retrospective studies show no difference in long-term outcomes with these two strategies. (545,552)

Diuretics

- Diuretics should be used in patients with signs of intravascular fluid overload (as evidenced by good peripheral perfusion and high blood pressure in combination with oedema) and preserved kidney function. (553,554)

- If albumin infusions are given, administration of a dose of furosemide (0.5–2 mg/kg) at the end of each infusion, unless the patient has marked hypovolemia and/or hyponatremia.
- In severely oedematous patients, the commencing dose of furosemide is 0.5–2 mg/kg per dose, intravenously or orally up to six times daily; maximum 10 mg/kg per day) dependent on the degree of oedema and achieved diuresis unless the patient has evidence of intravascular hypovolemia. Dosages >6 mg/kg per day should not be given for periods longer than 1 week. We recommend administering infusions over 5–30 min to avoid ototoxicity. (555)
- IV frusemide is preferred in very oedematous patient and orally can be given in more stable patients along with thiazide or spironolactone.
- The preference of potassium-sparing diuretics are directed to epithelial sodium channel (ENaC) inhibitors such as amiloride over mineralocorticoid inhibitors such as spironolactone. This is due to the fact that ENaC activation is independent of mineralocorticoid receptor action. (556)

Antiproteinuric agents

- RAAS-blocking therapy such as ACE inhibitors or ARBs used in children with CNS aged >4 weeks.

When possible, RAAS inhibition should not be used before a post-term age of 4 weeks to avoid interfering with physiological RAAS functions in early postnatal tissue growth and/or long-lasting hypotension and oliguric acute kidney injury (AKI). (557)

- ACE inhibition should be started with the short-acting ACE inhibitor captopril, escalating the dosage from 0.01 to 0.5 mg/kg per dose in children younger than 3 months (maximum dosage of 2 mg/kg/day). Older infants should receive 0.15–3 mg/kg per dose (maximum dosage of 6 mg/kg/day). (558)
- Combining ACE inhibitors and ARBs is avoided owing to the potentially increased risk of acute kidney injury (AKI).(559)
- In the case of poor responsiveness to RAAS blockade, consider the use of prostaglandin inhibitors as an add-on treatment (indomethacin dosed incrementally from 0.5 to 3 mg/kg/day).
- Prostaglandin inhibitors should be stopped if no clinical benefit (that is, increase in serum albumin levels and/or reduction in oedema) is apparent after 2–4 weeks.(560)
- In the case of non-kidney volume losses such as vomiting and diarrhea, routine treatment with RAAS inhibitors, prostaglandin inhibitors and diuretics must be discontinued owing to the high risk of intravascular volume depletion and AKI. (561)

Additional medications

- Thyroxin substitution, dosed according to thyroxine stimulating hormone levels
- Parenteral antibiotics if systemic bacterial infection is suspected (550)
- Intravenous immunoglobulin considered in recurrent severe infection. (43)
- If nutritional deficiencies have been excluded, growth hormone (0.045–0.05 mg/kg/day subcutaneously) may be administered from the age of 6 months in children whose height is <3rd percentile, height velocity is <25th percentile and eGFR is ≤60 ml/min/1.73 m2 (562)
- Monitoring of ionized calcium, 25(OH)D3 and parathyroid hormone (PTH) levels in children with CNS and supplementing with oral D3 vitamin (cholecalciferol) or 25-OH-D3 vitamin (calcifediol) and calcium (250–500 mg/day) in those with low 25-OH-D3 and/or low ionized calcium and/or elevated PTH levels. (510)
- Consider use of statins when fasting LDL cholesterol is persistently >160 mg/dl (4.1 mmol/l)84,85 or >130 mg/dl (3.4 mmol/l) in patients with additional cardiovascular risk factors such as hypertension and obesity. (113,563,564)

Vaccination

- Vaccination should follow the recommended schedule for healthy children, including vaccinating against encapsulated bacteria (especially Meningococcal, Haemophilus influenzae and Pneumococcal) and Varicella-zoster virus (565–567)
- We also recommend annual vaccination against influenza

Recommendations for nephrectomies

- Unilateral nephrectomy in selected cases to reduce proteinuria
- Routine preemptive nephrectomy is not necessary in stable patients
- Consider preemptive bilateral nephrectomy in refractory severe nephrotic state with complications that are difficult to manage (repeated infections, undernutrition and development delay, thrombosis (568)
- Before transplant: Consider bilateral nephrectomy in patients with persisting nephrotic syndrome and/or a WT1-dominant pathogenic variant.
- At 1 yr after nephrectomy the benefit waves up compared to conservative management. Dialysis has independent morbidity. Though bilateral kidney transplant is standard, reduced needs for albumin, improve quality of life, and growth, preemptive transplant is advised. (569)

Renal replacement therapy

- Indication for dialysis: ESKD or after bilateral nephrectomy
- Median age of ESRD 45-50 month of conservative care.
- To optimize treatment bilateral nephrectomy and commence peri¬toneal dialysis or haemodialysis when the infants weigh about 7 kg. The mortality of these infants on dialysis is low (6–11%) (568,569)
- Peritoneal dialysis preferred; hemodialysis if peritoneal dialysis contraindicated, or caregiver preference.
- Transplantation May be preemptive, provided nephrotic state has resolved.
- Extraperitoneal grafting is preferred (95)

In autosomal recessive conditions, parents (heterozygous carriers) are suitable donors

Renal transplantation

- Renal transplantation is curative therapy for most patients with CNS.
- May be preemptive, provided nephrotic state has resolved.
- Extraperitoneal grafting is preferred when > 10-15 kg
- In autosomal recessive conditions, parents (heterozygous carrier) are suitable donors.(570)
- In children with post-transplant proteinuria, consider antibody-mediated disease and antibody reduction strategies (i.e. plasmapheresis and immunosuppressive drugs). (571)
- Prior to transplantation, non-nephrotic state with normal serum albumin reduce risk of thrombosis in graft.

Pushing child to CKD by CNI, NSAID, in attempt to reduce or stop proteinuria , may be an option, because renal replacement therapy treatment is easier than continuous long time albumin infusion (medical nephrectomy). (90)

- Mild proteinuria after kidney transplantation is not rare and can be related to several conditions including graft rejection, recurrence of primary glomerulopathy, de novo glomerulopathy, infection or drug toxicity (549).
- Recurrence of nephrotic range proteinuria after kidney transplantation have a homozygous NPHS1 variant (known as Fin-major) with total absence of nephrin .
- Post-transplant de novo glomerulopathy occurs in 25–35% of these patients and at least 70% of those with post-transplant glomerulopathy have detectable anti-nephrinantibodies caused by allo-immunization against the nephrin molecule in the kidney graft. (571,572)

Thrombosis prophylaxis

Patients with CNS are at risk of developing potentially life-threatening venous or arterial thromboembolic complications, including of the kidney, cerebral and/ or pulmonary vessels. In CNS, the thrombotic risk is multifactorial and includes a disease-related hypercoagulability, underlying thrombophilic predisposition and risks related to treatment (such as CVLs or diuretics).(573) In CNS, hypercoagulability is related to an imbalance between procoagulant and anticoagulant factors .(574–576) Urinary leakage of anticoagulant circulating factors (antithrombin III and plasminogen) and low molecular weight procoagulant factors (factor IX and factor XI) results in compensatory liver synthesis of high molecular weight procoagulant factors (fibrinogen, factor V, factor VII, factor VIII and factor X) resulting in hypercoagulability .(577)

Moreover, patients with CNS are deficient in pituitary adenylate cyclase-activating poly peptide, which is a major inhibitor of megakaryopoiesis and of platelet activation, owing to urinary losses of pituitary adenylate cyclase-activating polypeptide bound to ceruloplasmin (578). These findings theoretically justify the administration of platelet aggregation blockers in patients with CNS.

Preventive anticoagulation should be considered in patients with CNS during states of increased thrombosis risk (owing to acute illness, risk of dehydration, inserted central lines and/or thrombocytosis >750,000/ml) and/or in patients with a previous thrombosis.

Infusion of antithrombin III (ATIII; 50 units/kg) before the placement of a central venous catheter is recommended. Agents that have been used for anti thrombotic prophylaxis in nephrotic syndrome include heparin, vitamin K antagonist and aspirin (575,576)

Anemia prevention and management

- Treatment of iron deficiency anemia and consider administration of erythropoietin in patients who have anemia despite iron supplementation. Recombinant human EPO has been reported to be safe and efficacious for the treatment of anaemia in children.
- Close monitoring of the reticulocyte count as a marker of erythropoiesis and response to therapy. Persistent anemia after 4 weeks of iron and erythropoietin therapy requires further evaluation for other possible contributing factors, such as copper, ceruloplasmin or vitamin B12 deficiency, and appropriate treatment.(579,580)

Management of non-genetic CNS

- If comprehensive genetic testing and screening for secondary forms of CNS yield negative results, kidney biopsy and a trial of immunosuppressive therapy may be considered in selected cases.
- Consider congenital membranous nephropathy owing to anti-NEP antibodies in patients who have kidney failure at presentation, transient proteinuria that resolves spontaneously or siblings with transient proteinuria at birth. (581). ACE inhibitors can be used , which can reduce proteinuria (582,583)
- Patients with infection-related CNS should be treated with specific antimicrobial agents and performing genetic screening in these patients.(584)
- Immunosuppressive drugs to treat children with CNS are not recommended. Moreover, spontaneous remission has been reported in some patients with CNS
- Negative genetic testing, negative infection screening results and a kidney biopsy sample excluding diffuse mesangial sclerosis should be obtained before considering immunosuppression (501,583).

Role of immunosuppressive in CNS

Primary CNS, being genetic in most cases, usually does not respond to immunosuppressive agents like prednisolone or calcineurin inhibitors. Accordingly, only one of 45 patients with CNS and no known genetic defect achieved prolonged remission with steroid therapy (98). There are few case reports of patients with pathogenic variants in WT1 and PLCE1 who show improvement in proteinuria after immunosuppressive therapy (585). While the mechanism is not clear, there is data to suggest direct effects of immunosuppressive medications on the podocytes (586). In CNS infants with no identified genetic defects, a trial with steroids or calcineurin inhibitors has been suggested (565)

Table 15 Complications

Acute complications	Chronic
• hypovolemic and hypervolaemic crisis, intermittent hypertensive • thromboembolic events • bacterial and viral infections	• Hypertension, • Dyslipidaemia, • hypothyroidism, • hypomagnesaemia, • hypocalcaemia, • vitamin D deficiency, • bone disease, • growth failure and progressive CKD • Adverse effects of medications • complications of prematurity (such as hyperbilirubinaemia)

Adopted from (94)

Table 16 Follow up for a child with CNS

Assessment	Frequency during follow-up
A. Clinical	
Patient history (fever episodes, pain, abdominal discomfort, swelling, fatigue, adherence to medication)	At every visit
Physical examination including signs of oedema (e.g. ascites, pericardial and pleural effusions), tetany, skeletal status and extrarenal features	At every visit
Blood pressure	At every visit
Full neurological examination and standardized assessment of cognitive status	Monthly for 3 months, yearly Thereafter
Growth chart: height or length, weight, head circumference if age <2 years, calculation of BMI and annual height velocity	Monthly for 3 months, every 3 months thereafter
B. Biochemistry	
Blood: complete blood cell count, sodium, chloride, ionized calcium, phosphate, magnesium, creatinine, urea, protein, albumin, cholesterol, fasting triglycerides and glucose	Monthly for 3 months, every 3 months thereafter or as appropriate
eGFR (Schwartz formula)	Every 3 months (more frequently in CKD stage 4)
ALP, PTH	Every 3 months, more frequently in advanced CKD (stages 4–5)
25(OH) vitamin D3	Every 6 months, yearly after age 12 months
TSH, free T4	Monthly for 3 months, thereafter every 3 months or as appropriate
IgG	• Trough levels as appropriate
Diet Assessment and advice from a dietician including salt, K, calorie and protein intake	Monthly in infants, thereafter every 3 months

(94)

Table 16	Follow up for a child with CNS (Cont'd)
V. Imaging Ultrasound of abdomen and pleural space (kidney echogenicity and size, ascites, effusions, thrombosis) X-ray of the left knee: mineralization and left wrist for bone age assessment in children aged >5 years	Every 3 months until the age of 7 years in children with exonic WT1 variant Yearly or as appropriate
Extrarenal involvement Assessment depending on the underlying disease	As appropriate
Preparation for kidney replacement therapy Referral to dialysis and/or transplant centre; preparation for dialysis including fistula creation and transplantation	Around 6 months of age and not later than when eGFR is <30 ml/min/1.73 m^2

Adopted from (94)

Prognosis:

The course of the congenital nephrotic syndrome of the Finnish type is progressive, leads to end-stage renal disease by 2-3 years of age (587). Prognosis is worse in NPHS1 gene mutations compared with NPHS2 gene mutations. Prognosis vary with different ethnic backgrounds. Female patients with NPHS1 mutations have longer survival than male (542). Kidney transplantation is the only curative treatment in most cases. Overall, the results of kidney transplantation in congenital nephrotic syndrome are quite good. The patient's 5-year survival rate is over 90%, and the graft survival rate is over 80% (552) A great majority (72%) of those of transplanted survivor reach the school, attend a normal class. Chronic allograft nephropathy is a major problem second transplantation may needed.

ADJUNCTIVE MEASURES

EDEMA:

Greek word: oidēma, fromoidein, means "to swell."

- Massive proteinuria, hypoalbuminemia and hypovolemia which causes two counter working system – underfill and overfill hypothesis (588–591)
- The "Underfill" hypothesis suggests that an initial decrease in oncotic pressure (induced by significant proteinuria and resultant hypoalbuminemia) leads to excess loss of fluid from intravascular space to interstitial space, causing edema (591–593). This also results in intravascular hypovolemia and kidney hypoperfusion (which may present as hypotension, tachycardia, postural hypotension, and/or oliguria), and this ultimately activates the renin–angiotensin–aldosterone system and arginine vasopressin (AVP) causing secondary water and sodium retention. Most children with idiopathic NS fall into this category.
- The "Overfill" hypothesis, on the other hand, proposes that edema in NS is caused by primary renal sodium retention resulting in an "intravascular overfill" state and a rise in capillary hydrostatic pressure(553,591,594–597)
- Edema mechanisms can vary between patients and also vary at different times in the same patient. Early studies showed that the collecting ducts are the main segment of the kidney tubules involved in primary

Na retention in NS (598), which was initially thought to be mainly induced by increased activity of the basolateral Na+ /K+ ATPase pump (599). A major advance in our understanding of primary Na retention in NS was the discovery that proteinuria can activate the ENaC channels on the principal cells of the collecting ducts. This mechanism is likely present in all patients with active NS, to some degree, regardless of their intravascular volume status, since most studies show that the majority of patients with NS have urine FeNA < 1% (600–602). Renin, angiotensin II, aldosterone, sympathetic nervous system, vasopressin, and atrial natriuretic peptide ANP causes salt retention and edema (590,603,604).

- ENaC activation occurs via the effects of plasminogen that is filtered by nephrotic glomeruli into the urinary filtrate. This plasminogen is eventually converted to plasmin by urokinasetype plasminogen activator in cortical collecting duct cells. Plasmin then proteolytically removes the C inhibitory domain of ENaC, resulting in its activation and subsequent Na retention through an aldosterone-independent process. This mechanism suggests that ENaC suppression through amiloride can be an effective method to treat edema in NS.
- Angiotensin II is known to have a direct effect on sodium retention independent of glomerular filtration rate, while vasopressin results in insertion of ENaC into the apical membrane of the collecting duct cells, thus promoting Na retention. Both Angiotensin II and vasopressin are elevated in patients with active NS, especially when underfill pathophysiology dominates.
- ANP on the other hand stimulates sodium and water excretion at the level of the collecting duct thus alleviating interstitial edema; however, its natriuresis effect is blunted in NS. This dampening could be caused by multiple mechanisms such as increased activity of the sympathetic system of kidneys or enhanced cyclic GMP–phosphodiesterase.

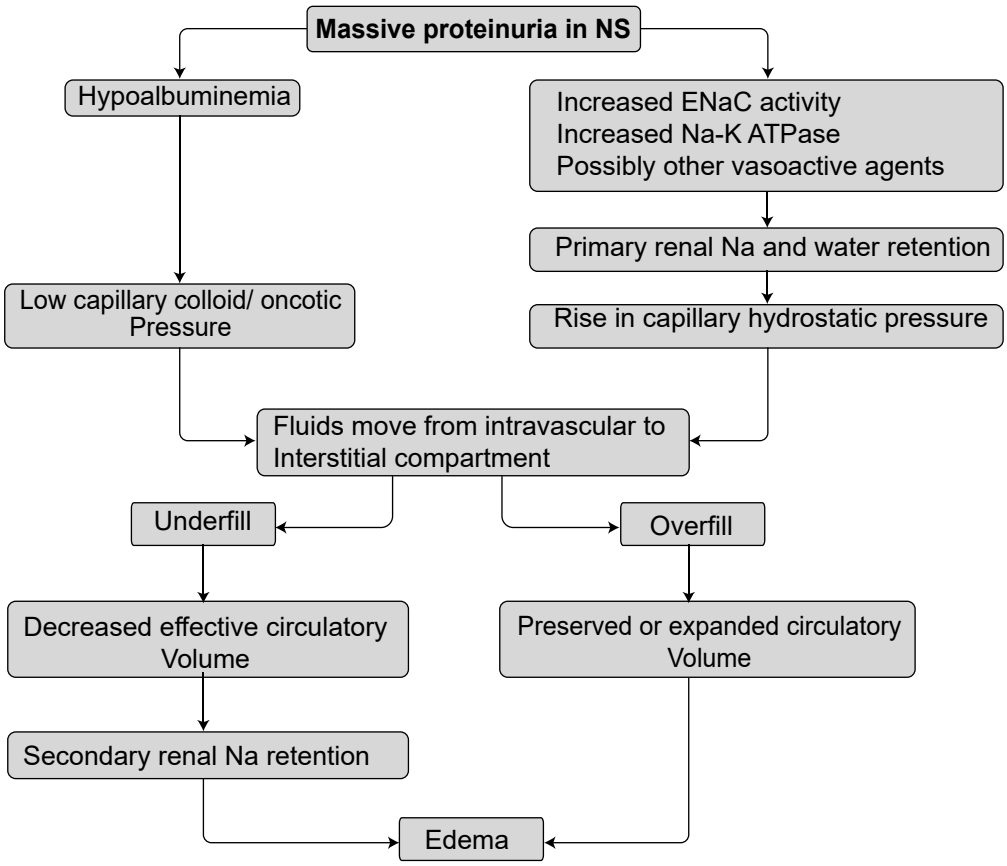


Figure 8 : Clinical and laboratory findings that support overfill vs. underfill mechanisms of edema formation in children with nephrotic syndrome. Adopted from (604b)

Table 17 **Contribution of volume and blood pressure regulatory hormones and channels which mediate or participate in renal Nat and edema formation in NS.**

Hormones and channels	Function
RAAS activation	Direct stimulation of active Na- reabsorption in the PCT by AT II; aldosterone-mediated Nat retention
Non-osmotic ADH/vasopressin release	Water retention in CD, vasoconstriction
Norepinephrine (NE) release	α-Adrenergic stimulation of renal tubular Na+ reabsorption; vasoconstriction
Atrial natriuretic peptide (ANP) release	Promotes natriuresis and diuresis in DCT and CD, but tubular epithelium is resistant to these effects in NS
Urodilatin activation	Promotes natriuresis and diuresis in DCT and CD, but tubular epithelium is resistant to these effects in NS
Phosphodiesterase activation	Promotes degradation of ANP and urodilatin
Sodium-hydrogen exchanger 3 (NHE3) activation	Mediates Na+ reabsorption in PCT
Epithelial sodium channel (ENaC) activation by plasmin loss in nephrotic urine	Stimulates Na+ reabsorption in the DCT and CD
Sodium potassium ATPase (Na+/K+ ATPase) activation	Provides energy for pumps involved in active Nat transport and facilitates peritubular uptake of Na+ by exporting Na+ out of cells in the anti-lumenal side of CCT

RAAS, renin angiotensin aldosterone system; AT II, angiotensin II; Na+/K+ ATPase, sodium potassium adenosine tri-phosphatase: DCT, distal convoluted tubule: CD. collecting duct; PCT, proximal convoluted tubule; CCT, cortical collecting tubule.

Table 18 **Assessment of underfill and overfill theory**

Underfill mechanism	Overfill mechanism
Clinical features	
Weakness, pallor, cool extremities, tachycardia, orthostatic hypotension, abdominal pain (gut wall edema, ischemia), delayed capillary refill	Normal or elevated BP without tachycardia or orthostatic changes; warm extremities
Oliguria	Lack of oliguria
Laboratory	
Lack of hematuria/cellular casts (pointing away from glomerulonephritis)	Hematuria and cellular casts (pointing to glomerulonephritis, which may be associated with impaired water excretion)
FENa < 0.2% (605)	FENa > 0.2–0.5% (605)
UK/UK + Na > 60% (increased TTKG index) (606,607)	UK/UK + Na < 60% (decreased TTKG index) (606,607)
Very low serum albumin (< 2.0 g/dl) (591,608)	Low serum albumin but >2.0 g/dl (591,608)
Estimated kidney function > 75 mL/min/1.73 m2 (591)	Estimated kidney function ≤ 75 mL/min/1.73 m2 (591)
Low ANP (605)	High ANP (605)
High circulating renin, aldosterone, vasopressin levels (605)	Decreased circulating renin, aldosterone, vasopressin levels (605)

Adopted from (604b)

Presentation:

- Patients with volume contracted state present with abdominal pain, nausea, vomiting, dizziness, lethargy, tachycardia, pallor, cold peripheries, delayed capillary refill, low blood pressure, postural hypotension, which may progress to hypovolemic shock.

- Hypovolemic shock is defined by blood pressure less than 5th centile in presence of other evidence of hypovolemia. Patients in volume expanded state usually show refractory edema, hypertension, bloating and dyspnea (590).
- Two reliable biochemical markers of intravascular volume are fractional excretion of sodium (FENa), and potassium index i.e., ratio of urinary potassium to sodium plus potassium [UK+/(UK+ UNa+)] .
- In patients with nephrotic syndrome and edema, the observed value of FENa is less than 1%; it is less than 0.2–0.5% in volume contracted state. Therefore FENa value of <0.2–0.5% can reliably identify children with hypovolemia (605,607,609). Similarly, potassium index >0.6 is a marker of increased aldosterone activity in the distal nephron and suggests intravascular volume contraction (189,607,609).
- Other parameters for identifying hypovolemia are rise in hematocrit (>8–10%), high blood urea to creatinine ratio, and hyponatremia
- Very small number of patients have been evaluated, and the results do not support the use of ultrasonography as a reliable bedside tool for fluid volume assessment (610,611). Bioelectrical impedance analysis has also been used for assessment of fluid volume in childhood nephrotic syndrome (612,613).

The grading of edema is determined by pit depth (measured visually) and recovery time from grade 0-4 (514). The scale is used to rate the severity and the scores are as follows:

- Grade 0: No clinical edema
- Grade 1: Slight pitting (2 mm depth) with no visible distortion that rebounds immediately.
- Grade 2: Somewhat deeper pit (4 mm) with no readily detectable distortion that rebounds in fewer than 15 seconds.
- Grade 3: Noticeably deep pit (6 mm) with the dependent extremity full and swollen that takes up to 30 seconds to rebound.
- Grade 4: Very deep pit (8 mm) with the dependent extremity grossly distorted that takes more than 30 seconds to rebound.

Table 19 Features of hypovolemia during relapse of nephrotic syndrome

Clinical features	Abdominal pain, vomiting, lethargy Prolonged capillary refill time; cold extremities Tachycardia, low volume pulses Low blood pressure; postural hypotension
Biochemical indices[a]	Elevated hematocrit Fractional excretion of sodium <0.2% Urinary potassium index [urine K+/urine Na+ + K+] >0.6 High levels of plasma renin, aldosterone, vasopressin Ultrasonography: Decreased inferior vena cava diameter, increased collapsibility index

$$\text{Fractional excretion of sodium} = \frac{\text{urine Na+ x serum creatinine}}{\text{serum Na+ x urine creatinine}} \times 100$$

[a]When analyzing urine electrolytes, the patient should be off diuretics, and on normal salt and water intake

Management:

General measures to control edema with NS:

- Reduce dietary salt intake.
- Fluid restriction is not usually recommended as it may worsen hypovolemia-
- Regular monitoring of the individual's volume status (urine output, blood pressure, heart rate, and capillary refill), electrolytes, and kidney function, especially when children are sick and/or are in the hospital.

- Providing adequate nutrition with normal protein intake (RDI) for age, as lower protein intake is a risk for a negative nitrogen balance, malnutrition, and poor growth. High-protein diet should be avoided as this may cause progression of the kidney disease.
- Elevation of extremities and the use of compression socks can reduce discomfort and leg pain.
- Avoidance of nephrotoxic medications including NSAIDs.
- Avoidance of central catheter insertion (if possible) as this increases risk of thrombotic events.
- Use of angiotensinogen convertase enzyme inhibitors (ACEis) and/or angiotensin-receptor blockers (ARBs) can be pursued/considered in patients with NS and edema (these should not be viewed as contraindicated), but should be done with caution and regular safety monitoring.
- Active lifestyle as tolerated, as this can help edema mobilization and minimize risk of thrombosis.

Indications for adding specific medical interventions (diuretics, diuretic + albumin, other medical therapies):

- Pulmonary edema, pleural effusions, and/or hypoxia
- Congestive heart failure
- Volume-related hypertension
- Oliguria—concern for evolving AKI
- Skin infection/cellulitis
- Significant ascites with discomfort
- Severe scrotal/labial edema
- Sleep difficulties related to edema . Generalized discomfort (body ache and /or feeling unwell because of significant body edema)

Based on results of urine FeNa, patients with FeNa < 0.2% were treated with IV albumin and furosemide. Patients with FeNa ≥0.2% received IV furosemide and oral spironolactone. This study showed that the children with FeNa <0.2% had, on average, higher serum BUN, BUN/creatinine ratio, serum renin, aldosterone, and AVP compared with patients with FeNa ≥ 0.2% (605).

Diuretics:

- Loop and osmotic diuretics are highly potent resulting in almost ~25% glomerular filtrate being excreted as urine. Thiazides are moderately efficacious, while ENaC blockers and aldosterone antagonists are less effective. Frusemide is the most commonly used diuretics followed by hydrochlorothiazide and metolazone . Both drugs have satisfactory oral bioavailability (60–70%) and require once daily dosing. Furosemide, a loop diuretic, which is tightly bound to blood albumin, is actively secreted through organic acid pumps in the ascending limb of Henle (615) Furosemide is usually started at a dose of 1–2 mg/kg/dose in children up to 20 kg and at a 20–40-mg dose in older children, and can be given every 6–12 h orally. Intravenous infusion can increase loop diuretic efficacy (616). Patients with moderate (8%–15% weight gain from baseline weight) to severe edema (>15% weight gain from baseline) require diuretic treatment (602). In severe hypoalbuminemia, this tubular secretion is hampered resulting in resistance to loop diuretics and albumin followed by furosemide at the end of albumin infusion is beneficial in this case (617).
- In children with nephrotic syndrome having moderate to severe edema, diuretics are indicated after assessment of volume status. Diuretics should be avoided in settings of persistent vomiting and/or diarrhea, as they may cause hypovolemia. Although diuretics are the cornerstone for the management of edema, their prolonged use is associated with adverse effects. Prolonged diuretic therapy causes acute kidney injury (AKI), hyponatremia, hypokalemia, and metabolic alkalosis. Therefore, children receiving prolonged furosemide for >48 h should receive spironolactone, a potassium sparing diuretic

(618). In addition, furosemide can cause hypersensitivity reaction and reversible ototoxicity. It also displaces warfarin from the protein binding site, resulting in its increased anticoagulation effect. Diuresis following furosemide administration lasts for 6–8 h then fades away; during post diuretic phase there is compensatory increase in sodium retention from distal segment of nephron .

- Torasemide is pharmacologically superior to furosemide in terms of longer half life, and better and predictable oral bioavailability. However this agent is not approved for use in children

Na+-K+-2Cl− Cotransport Inhibitors: This class of drugs acts by blocking sodium reabsorption through Na+-K+-2Cl− cotransporter (NKCC2) in the thick ascending limb of Henle. NKCC2 blockers are organic anions which bind to chloride binding site of this transporter at the luminal side. They are highly bound to albumin (~90%) in the blood, which limits their filtration through glomerulus. Hence to act from luminal surface, these agents are secreted in proximal tubules through organic anion transporters present on basolateral (OAT1) and apical surfaces (OAT3) of proximal tubular epithelial cells. . Once the drug reaches the thick ascending limb, they increase sodium and chloride excretion (upto 25–30% of total filtered sodium load) in the urine by blocking salt transport through NKCC2. Increase in delivery of sodium in the distal segment results in increased secretion of potassium and hydrogen ions in cortical collecting ducts, and hypokalemic metabolic alkalosis. Interruption of sodium reabsorption by NKCC2 inhibitors also impairs the concentrating ability, resulting in massive diuresis.

Na+-Cl− Cotransport Inhibitors: Inhibitors of Na+-Cl− cotransporter (NCC) were derived from benzothiadiazine, hence medications in this group are known as thiazide diuretics. Some agents have different structure, but similar mechanism of action and are called thiazide-like (i.e., metolazone). Similar to NKCC2 inhibitors, drugs in this class are organic anions and highly albumin bound that restricts their filtration from glomeruli. Two commonly used agents are **hydrochlorothiazide and metolazone**. Both drugs have satisfactory oral bioavailability (60–70%) and require once daily dosing. Adverse effects are similar to loop diuretics, except for higher risk of hyponatremia and .hypomagnesemia. Metabolic complications (hyperuricemia, hypertriglyceridemia, glucose intolerance) are more common with NCC inhibitors than NKCC2 inhibitors.

Epithelial Sodium Channel Inhibitors: These are less effective diuretics, and used for their potassium sparing effect. Amiloride and triamterene are used in clinical practice.

Mineralocorticoid Receptor Antagonists: Mineralocorticoid receptors are located on basolateral surface of the tubular epithelial cells in late distal tubule and collecting duct. When aldosterone binds to these receptors, it regulates gene expression and increased production of ENaC, Na+-K+ ATPase and its migration to epithelial surface. This leads to reabsorption of sodium coupled with augmented secretion of potassium and hydrogen. Overall aldosterone antagonists are weak diuretics; their efficacy however depends on the endogenous level of aldosterone. Spironolactone and eplerenone are used in practice. Their chief side effect is hyperkalemia, other adverse effects, includes gynecomastia, impotence, hirsutism, menstrual irregularity, gastritis and peptic ulcer.

Osmotic Diuretics: Osmotic diuretics are pharmacologically inert; they are freely filtered by the glomeruli and undergo limited reabsorption in tubules. Presence of osmotic agents within tubular lumen inhibits water reabsorption from proximal tubule and descending limb of Henle, which decreases sodium concentration in fluid reaching thin ascending limb, limiting passive reabsorption of sodium as well. Commonly use drug is Mannitol. Mannitol is administered through the IV route, and its half life is short, requiring frequent dosing or continuous IV infusion.

Table 20 Diuretic for edema in nephrotic syndrome

Diuretic class, name, mechanism, and site of action	Bioavailability %	PO/iv ratio	Route of elimination	Onset of action (min) PO/iv	Duration of action (h)	Dose	Interval, hour	Route	Dose in adults
Loop diuretics: Inhibit the $Na^+/K^+/2Cl^-$ cotransport system in the thick ascending limb of Henle's loop (ALH)									
Furosemide	60	1.5	65% renal	40/5	6	Neonates: 1-4 mg/kg/dose	12–24	IV, oral	40–80 mg QD daily or alternate days
						Infants/children: 1–4 mg/kg/day 1–2 mg/kg/dose	 6–12 6–12	 Oral IV	
						Infuse at 0.1–0.4 mg/kg/h	Infusion	IV	
Bumetanide	85	1		40/5	4	Children: p.o./iv/im 1–2 mg/kg/dose q 6–12 h			
Torsemide, ethacrynic acid	80	1	20% renal	20–40/5	6–12	5-10mg/d			
Thiazide diuretics: Inhibit NaCl cotransport in the early distal convoluted tubule (DCT)									
Trichlormethiazide						Infants: 0.04 mg/kg/dose	12–24	Oral	2–8 mg/day at 1–2 doses
Chlorothiazide	11–20			120	24	<6 months: p.o. 20–40 mg/kg/day divided bid iv 2–8 mg/kg/day divided bid >6 months: p.o. 20 mg/kg/day divided bid iv 4 mg/ kg/day			
Hydrochlorothiazide	60–75		95% renal	120	12–24	<6 months: p.o. 2–3.3 mg/kg/dose divided bid >6 months: p.o. 2 mg/kg/day divided bid Infants: 1–2 mg/kg/day	12–24	Oral	
Metolazone						0.2–0.4 mg/kg/day			
Mefruside						Infants: 15 mg/day for 3 years old	12–24	Oral	25–50 mg once (morning)
Thiazide-like: Similar to thiazides but also proximal tubular inhibition of sodium uptake									
Metolazone	40–60/**80%**		95% renal	60	24	Children: 0.2–0.4 mg/kg/day divided q 12–24 h	12–24	Oral	2.5–10 mg QD
Aldosterone antagonists									
Spironolactone	65%		No renal excretion		3	Preterm infants (<32 weeks): 1 mg/kg/day	24	Oral	50–100 mg/day divided doses
						Mature infants: 1–2 mg/kg/day	12	Oral	
						Infants/children: 1–3 mg/kg/day	6–12	Oral	
Potassium canrenoate						Infants: 1–4 mg/kg/day	12–24	IV	100–200 mg IV once or twice daily, Not exceed 600 mg/day, Treatment period within 2 weeks
Triamterene						Infants: 1–2 mg/kg/day	8–12	Oral	90–200 mg/day, 2–3 doses
Carbonic anhydrase inhibitor: *inhibits absorption of Na, HC03, CI in proximal tubule*									
Acetazolamide	85%	1	100% renal excretion	90–120/2	3–6	Child: PO/IV 10 to 30 mg/kg/day (max: 1000 mg/day) divided QD-QID			
ENaC inhibitors: *inhibits Na reabsorption in distal convoluted tubule and collecting ducts*									
Amiloride	50%		100% renal	120	6–12	Child: 2.5–10 mg/day, Q day		Oral	
Mannitol	Negligible		80% renal		2	Child: 0.25-1 g/kg/dose		IV	

PO: orally, IV: intravenous, IM: intramuscular, NB: newborn, Q Day: once daily, BID: twice daily, QID: four times daily.

Diuretic Resistance:

Furosemide is often the initial diuretic of choice for weight reduction in patients with moderate to severe edema. A proportion of patients fail to achieve clinically desired reduction in weight despite maximum dose of diuretic; these patients are considered as diuretic resistant. (Ref)

Table 21 Mechanisms of furosemide resistance and their management

Mechanisms of resistance	Management
Poor adherence	Ensure compliance to salt restriction and therapy with furosemide
Poor oral bioavailability due to gut edema	Shift to intravenous route; use of diuretics with better bioavailability (torasemide)
Impaired furosemide secretion in proximal tubules due to low serum albumin	Coadministration of furosemide with 20% albumin
Compensatory increase in sodium reabsorption from distal nephron	Sequential nephron blockade using combination of furosemide and thiazides; administer thiazides 30 min before furosemide.

Albumin infusion:

Albumin infusion is used to correct hypoalbuminemia, since it is the chief contributing factor for edema. While initial studies reported that albumin infusion enhances diuresis in patients with diuretic refractory edema (619,620), others have contradicted these findings (621). The goal of the infusion is to replenish serum albumin.

Indications of albumin infusion:

- Tense ascites with abdominal compartment syndrome limiting diaphragmatic
- excursion, lymphatic flow, and venous return
- Severe pleural effusions compromising breathing
- Oliguria with incipient acute kidney injury (AKI)
- Marked eyelid edema compromising vision
- Severe scrotal or labial edema, risking skin breakdown

Dosing of salt-poor albumin (25%; 25 g/dl) 0.5–1 g/kg infused over 1–4 h and can be given 1–3 times/day. This can be considered in cases of significant body edema, severe hypoalbuminemia and / or significant underfill. On the other hand, albumin 5% is often used in settings when volume expansion is needed during active NS. Slower infusion may lead to more equilibration and thus less effect; faster infusion may lead to more hypertension and / or pulmonary edema

Concerns

- Potential side effects: hypertension, pulmonary edema, heart failure, electrolyte abnormalities
- Expensive
- Low supply
- Obtained from multiple blood donors (hypersensitivity reactions) – allo-sensitization

Combination Therapy of Furosemide and Albumin

Several mechanisms are proposed to explain the improved efficacy of combined therapy, the most accepted being that IV albumin enhances the secretion of furosemide in proximal tubules, with increased delivery at its primary site of action.

A metaanalysis performed in patients with nephrotic syndrome, to assess the efficacy of combined therapy with furosemide and albumin, compared to furosemide therapy alone (620–625). Six studies, involving 69 patients were included in this meta-analysis. Of these studies, only one trial included children, and most had small sample size and high risk of bias. The meta-analysis showed that combination therapy was more effective in augmenting diuresis than furosemide therapy alone (Fig. 9).

However in a recent Cochrane review authors failed to draw any conclusion, regarding use of human albumin infusion, due lack of studies as they excluded cross-over randomized trials (626)

(Duffy et al. reviewed several well-defined studies and trials of the use of albumin/ furosemide in NS. This included one randomized trial in children (16 patients) and five randomized trials in adults (total of 58 patients) (627) and found that giving albumin and furosemide together was more effective than using furosemide alone in terms of fluid excretion. However, there was significant variability in the doses employed and timing for each of the agents in these trials)

Fresh frozen plasma (FFP)

FFP cost half than albumin and same duration required to reduce edema but with double number of infusion and it is safe in pediatric patients with NS presenting with moderate to severe edema. The cost-effectiveness may place FFP as a better choice especially in developing countries of the world. One study showd that dry weight was achieved in albumin group in 6.66± 3.710 days and in FFP group in 6.66± 3.038 days in albumin group number of infusion required was 1.44±0.697 and in FFP group number of FFP infusion required was 3.11± 1.5 (628). We recommend use of FFP for treating edema in low socioeconomic countries.

Angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers:

Angiotensin-converting enzyme inhibitors (ACEis) or Angiotensin-receptor blockers (ARBs) are often used, along with immunosuppressive, to control proteinuria and hypertension in patients with complicated forms of NS. By lowering proteinuria and increasing serum albumin ,these agents can help to minimize edema. The main mechanism for ACEis and ARBs to reduce proteinuria is their effect on relaxing the efferent arteriole of the glomerulus, thus reducing intra-glomerular pressure and ultimately reducing proteinuria by limiting movement of serum proteins from the glomerular capillary into the urinary space. ACEis and ARBs have also been demonstrated to impact fibrosis through inhibition of transforming growth factor-beta (TGF-beta 1) in the kidney (629).

Vasopressin Receptor Antagonists (Aquaretics)

Tolvaptan is an oral vasopressin receptor antagonist (V2RA) with high affinity that increases urine volume. This drugs increases urine volume by augmenting free water excretion. Vasopressin acts through type 2 receptors (V2R) located on basolateral surface of the epithelial cells in the collecting duct. Binding of vasopressin to V2R leads to increased density of aquaporin channels (AQP2 and AQP4), resulting in water reabsorption. Aquaresis begins 2–4 h following oral administration of tolvaptan, and peak effect is observed at 4–8 h. In children although these agents should be used carefully since they can cause significant hypernatremia, and may worsen intravascular underfill with subsequent risk of AKI and/or thrombosis (630).

Water immersion:

Water immersion is not a recent development in management of edema in NS. This method is not widely used for edema management and it is not a current standard of treatment of edema in NS.

Newer drugs:

Aquaretics

- Vasopressin 2 receptor antagonist - Tolvapatan
- Somatostatin analog (octreotide) and urea channel blockers

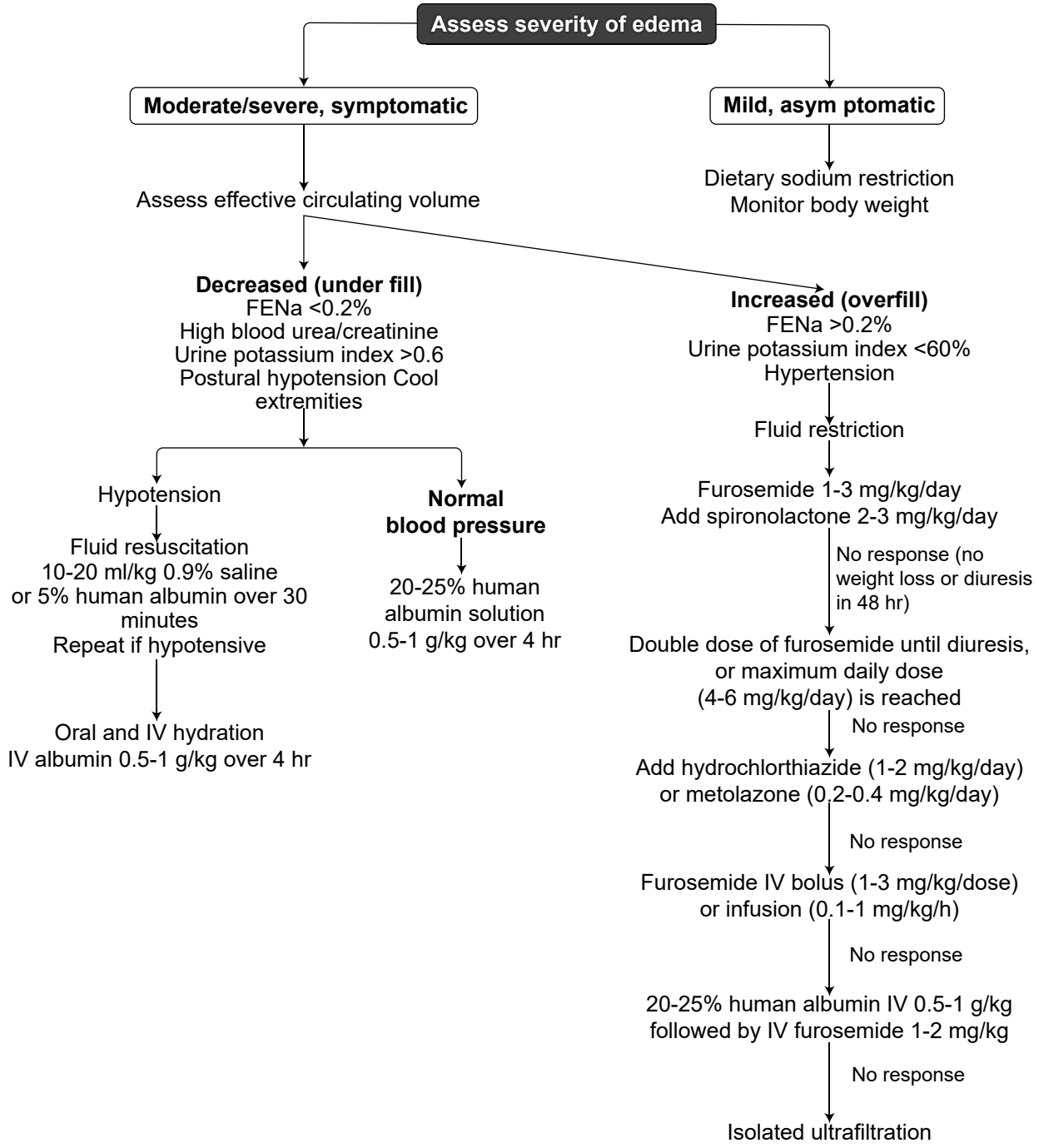


Figure 9 : Management of edema in nephrotic syndrome. Patients with mild edema are managed with salt restriction; prednisone therapy is associated with spontaneous diuresis. Hypovolemia should be excluded (Table 4) before considering therapy with diuretics. Oral furosemide is the diuretic of choice; patients receiving therapy with furosemide for >48 h should additionally receive a potassiumsparing diuretic. Edema refractory to furosemide therapy may be treated with additional thiazide diuretics or IV furosemide, as bolus and/or infusion. Combination therapy with IV albumin (20%) and furosemide enables diuresis in patients refractory to the above measures. IV albumin carries the risk of fluid overload and pulmonary edema in patients with renal dysfunction. Patients with features of hypovolemia require bolus(es) of normal saline if hypotensive, followed by oral and IV hydration, and IV albumin (20%) infused over 2–4 h. FENa fractional excretion of sodium; urine potassium index UK+/UK+ + UNa+ (Modified from Indian Pediatrics 2021)

Novel agents:

1. Particulate-guanylyl-cyclase A receptor activator (trial name ZD100): this agent activates cGMP to promote natriuresis, inhibit aldosterone and reduce BP (631). There are no reports on its use for management of edema in NS.
2. Relaxin (an endogenous neurohormone): this agent increases expression of epithelial and endothelial endothelin B receptors (ETB) to indirectly stimulate ETB to inhibit Na+/K+-ATPase and vasopressin effects. This promotes natriuresis and diuresis without changes in levels of aldosterone (632). There is some experience with this agent in adults with heart failure (633), but no reports in management of edema in NS.
3. Synthetic human ANP (carperitide): atrial natriuretic peptide promotes natriuresis through increasing cardiac output but more directly through effects on medullary collecting duct cells, in particular sodium channels on both the apical (ENaC) and basolateral Na+/K+-ATPase sides (634). ANP also increases glomerular filtration rate and glomerular permeability through direct dilation of the afferent arteriole and blocking norepinephrine induced vasoconstriction of the afferent arteriole. Combined, these effects result in reducing edema in subjects with NS while preserving GFR. There are small series of their effectiveness in adult patients with NS reported by Ueda (635) (Japan) but no studies reported yet in children.
4. Luteolin: this phenolic compound with anti-inflammatory and anti-allergic effects also stimulates muscarinic acetylcholine receptors to increase natriuresis and diuresis in rats (636). There are no human studies reported to date.
5. Epicatechin: these flavonoids in food and plant extracts induce diuresis and K, Na, and Cl excretion in rats (637). Again, there are no human studies to date.

ANTI HYPERTENSIVE MEDICATION

Table 22 Oral anti-hypertensive drug doses in children and adolescents

Drug	Dose	Maximum Dose	Maximum Adult Dose	Comments
ACE inhibitors and Angiotensin II receptor blockers				
Captopril Infants: Children:	0.05 mg/kg/ dose 6–24 hourly 0.5 mg/kg/ dose 8 hourly	6 mg/kg/day 6 mg/kg/day	 50 mg 8 hourly to 450 mg/day	
Enalapril ≥1 month:	0.08 mg/kg/ day 12–24 hourly	0.6–1 mg/kg/ day 12–24 hourly	40 mg/day 12–24 hourly	Teratogenic. Check potassium and creatinine within 1 week regularly. FDA approval for child ≥6 years and creatinine clearance ≥30 ml/min/1.73m2.
Lisinopril ≥6 years	0.07 mg/kg/ day 24 hourly (up to 5 mg)	0.6 mg/kg/ day 24 hourly	40 mg/day 24 hourly	
Ramipril	1.6 mg/m2/ day 24 hourly	6 mg/m2/day 24 hourly	10 mg/day 24 hourly	
Losartan potassium	0.5–0.7 mg/ kg/dose 24 hourly	1.4 mg/kg/ dose 24 hourly	100 mg/day 24 hourly	
Candesartan 1–5 years ≥6 years <50 kg ≥50 kg	 0.02 mg/kg/ day 12–24 hourly (up to 4 mg) 4 mg/day 12–24 hourly 8 mg/day 12–24 hourly	 0.4 mg/kg/ day 12–24 hourly 16 mg/day 12–24 hourly 32 mg/day 12–24 hourly	 16 mg/day 12–24 hourly 32 mg/day 12–24 hourly 32 mg/day 12–24 hourly	

Table 22 **Oral anti-hypertensive drug doses in children and adolescents (Cont'd)**

Drug	Dose	Maximum Dose	Maximum Adult Dose	Comments
Irbesartan 6–12 years ≥13 years	 75 mg/day 24 hourly 150 mg/day 24 hourly	 150 mg/day 24 hourly 300 mg/day 24 hourly	 300 mg/day 24 hourly	
Telmisartan	1 mg/kg/day 24 hourly	2 mg/kg/day 24 hourly	80 mg/day 24 hourly	
Lisinopril ≥6 years	0.07 mg/kg/ day 24 hourly (up to 5 mg)	0.6 mg/kg/ day 24 hourly	40 mg/day 24 hourly	
Valsartan ≥6 years	1.3 mg/kg/ day 24 hourly	2.7 mg/kg/ day 24 hourly	160 mg/day 24 hourly	
Beta-blockers				
Atenolol	0.5–1 mg/kg/ day 12–24 hourly	2 mg/kg/day 12–24 hourly	100 mg/day	Contraindicated in asthma, heart failure, and diabetes mellitus. Discontinue treatment in event of severe (heart rate 80/ minute) or symptomatic bradycardia.
Propranolol	0.2–0.5 mg/ kg/dose 6–12 hourly	1.5 mg/kg/ dose 6–12 hourly	640 mg/day 6–12 hourly	
Labetolol	1–2 mg/kg/ dose 12 hourly	10 mg/kg/ dose 6 hourly	600 mg/ dose 6 hourly	
Carvedilol	0.1 mg/kg/ dose 12 hourly Increase by 0.1 mg/kg/ dose every 1–2 weeks	0.8 mg/kg/ dose 12 hourly	25 mg 12 hourly	
Calcium channel antagonists				
Amlodipine 1–5 years ≥6 years	 0.1 mg/kg/ day 2.5 mg/day	 0.6 mg/kg/day (up to 5 mg) 10 mg/day	 10 mg/day	Contraindicated in patients with heart failure and reduced ejection fraction.
Nifedipine	0.04–0.25 mg/kg/dose 4–6 hourly	1–2 mg/kg/ day 4–6 hourly	10 mg 4–6 hourly	
Nifedipine Extended Release	0.25–0.5 mg/ kg/day 12–24 hourly	3 mg/kg/day 12–24 hourly	120 mg/day	
Peripheral alpha-antagonists				
Prazosin	Test dose: 5 µg/kg (maximum 0.25 mg); 0.025 mg/kg/ dose 6–12 hourly	0.5 mg/kg/ day 6–12 hourly	40 mg/day 6–12 hourly	Hypotension or syncope may occur especially after first dose.
Terazosin	Test dose: 0.02 mg/kg/ dose; 0.04 mg/kg/ day 12–24 hourly	0.4 mg/kg/ day	20 mg/day	If hypotension occurs at 2–4 hours following dose, change to 12-hourly dosing.

Table 22 **Oral anti-hypertensive drug doses in children and adolescents (Cont'd)**

Drug	Dose	Maximum Dose	Maximum Adult Dose	Comments
Clonidine	2–5 µg/kg/ dose 6–12 hourly	10 µg/kg/ dose 6–12 hourly	2.4 mg/day	Drowsiness.
6 years	0.1 mg/24 hourly patch applied every 7 days (= total oral daily dose after titration)	0.3 mg/24 hourly patch applied every 7 days	0.3 mg/24 hourly patch applied every 7 days	Beta-blockers may potentiate bradycardia and may increase rebound hypertension during withdrawal.
Diuretics				
Hydrochloro- thiazide	1 mg/kg/day 12–24 hourly	2 mg/kg/day 12–24 hourly	50 mg/day 12–24 hourly	Check electrolytes and creatinine within 1 week and regularly. Potassium supplementation may be required.
Furosemide	0.5–1 mg/kg/ dose 6–24 hourly	12 mg/kg/day	240 mg 4–6 hourly (maximum 600 mg/ day)	
Bumetanide	0.015 mg/kg/ dose 6–24 hourly	0.1 mg/kg/ dose 6–24 hourly	10 mg/day	
Vasodilators				
Minoxidil	0.1–0.2 mg/ kg/dose 8–24 hourly	10 mg/dose 8–24 hourly		
Hydralazine	0.25 mg/kg/ dose 6–12 hourly	25 mg/dose 6–12 hourly		

Table 23 **Anti-hypertensive medications in hypertensive urgencies or emergencies**

Drug	Dosage	Onset	Duration	Advantages	Caveats
Nifedipine	Oral or sublingual 0.25 – 0.50 mg/kg q30 mins. Increase dose if ineffective (maximum dose 20 mg).	15–20 mins	2–5 hours		Only if patient is conscious. Contraindicated in heart failure with reduced ejection fraction.
Glyceryl trinitrite	Continuous IV infusion 1–10 µg/kg/min (maximum dose 400 µg/ min)	At once	3–5 mins	Rapid onset and cessation. Relieves coronary spasm. Reduces preload and to a lesser extent afterload.	Bradycardia. Tachycardia. Headache. Methemoglobinemia. Vomiting.
Sodium nitroprusside	Continuous IV infusion 0.25–8.0µg/kg/min. Increase the dose by 25% every 5–10 mins until the desired BP control is obtained. Maximum final concentration: 200 µg/ml. If maximum dose is used for >10 mins without good BP control, stop the drug because of toxicity risk.	2 mins	1–10 mins		Contraindicated: • Coarctation of aorta. • Closed head injury. • High ICP. • Intracranial emorrhage. Chronic use may cause cyanide and thiocyanate accumulation. Do thiocyanate levels if used >48 hours. Toxicity risk increases with decreased kidney or liver function.

Table 23 **Anti-hypertensive medications in hypertensive urgencies or emergencies (Cont'd)**

Drug	Dosage	Onset	Duration	Advantages	Caveats
Labetalol	IV 0.2 mg/kg over 2 mins. If no response in 5–10 mins, increase to 0.4–1.0 mg/kg (maximum bolus dose 20 mg) OR continuous IV infusion 0.4–1.0 mg/kg/hour (maximum dose 3mg/kg/ hour).	5 mins	0.3–23 hours	Favorable cardiac effect. Favorable CNS effect: Use in patients with raised intracranial pressure.	Contraindicated in acute heart failure. Adverse effects: • Reactive airway disease • Heart failure • Heart block • Paradoxical hypertension • Postural hypotension • Hepatitis • Muscle weakness • Urinary retention • Scalp tingling • Burning in throat.
Furosemide	IV 1–5 mg/kg/dose 6 hourly (ma ximum dose 240 mg) OR continuous IV infusion 0.1–1.0 mg/kg/hour	2–5 mins	0.3–23 hours	Drug of choice in acute glomerulo- nephritis with fluid overload.	Hyponatremia. Hypokalemia.
Hydralazine	0.1–0.3 mg/kg (maximum 10 mg) slow IV over 3–5 mins. Repeat every 4–6 hours OR continuous infusion 4–6 μg/kg/min (maximum 300 μg/min)	10–20 mins	3–8 hours	Effective and doses can be repeated if necessary.	Increases ICP. May cause non-homogeneous cerebral perfusion. Tachycardia. Severe headache. Fluid retention.
Nicardipine	Continuous IV infusion 1–3 μg/kg/min (maximum 250 μg/min)	1–2 hours	2–4 hours	Similar to nifedipine without the deleterious risk of depressing myocardial function. Promotes natriuresis.	• Elevation of ICP (avoid in those at risk of raised ICP). • Tachycardia. • Flushing. • Headache. • Hypotension. • Peripheral edema. • Gastrointestinal disturbance.
Esmolol	IV 0.5 mg/kg over 1 min, repeat every 5–10 mins if required. IV infusion of 1.5–18 mg/kg/hour (undiluted 10 mg/ml)	1–2 mins	10–20 mins	Useful during anesthesia to prevent post-intubation hypertension and tachycardia. Useful in acute aortic dissection.	Hypotension. Nausea. Rarely given for 48 hours. *Avoid in patients where the cause of hypertension is unknown.
Phentola-mine	0.5–0.1 mg/kg stat (maximum dose 5 mg), THEN 5–50 μg/kg/min.	1–2 mins	3–10 hours	Drug of choice in catecholamine excess.	• Postural hypotension. • Tachycardia. • Cerebral vascular spasm. • Nausea.

*Avoid pure beta-blockers prior to adequate alpha-blockade in patients with hyperadrenergic states (pheochromocytoma, metamphetamine overdosage).

ASTHMA IN NEPHROTIC SYNDROME

The reported frequency of asthma and allergic conditions in nephrotic syndrome ranges from as low as 10% to as high as 50% (638). Another report stated the frequency as 30-60%.(639)

Asthma is characterized by cough,dyspnea,worse at night ,relieved with bronchodilators,may or may not associated with rhonchi and prolonged expitation on lung auscultation.We believe these description would pick up all cases of asthma.(Grade A:strong recommendation.)

Asthma causes respiratory symptoms such as fast breathing, wheezing, shortness of breath, chest tightness, that vary over time including in their frequency and intensity. These symptoms are variable expiratory airflow limitation that is airway narrowing,airway thickening and increased mucus.

Allergies are often ascribed as triggers for relapses, but treatment for allergies with dietary restrictions, skin desensitization, or mast cell stabilizers has demonstrated little benefit in preventing relapsing disease. (640).

Immune dysfunction, or dysregulation, of T-lymphocytes is suspected as the pathogenesis of nephrotic syndrome because of the success with immunosuppression in inducing remission (641). Two-thirds of children with nephrotic syndrome have asthma and allergies, with wheezing as the most commonly reported condition. Despite the high prevalence of lifetime allergies and history of allergies 12 months prior to diagnosis of nephrotic syndrome, there is a consistent null association with various measures of relapsing disease including initial relapse-free period, relapse rates, and frequently relapsing disease (642)

The cause of childhood nephrotic syndrome is still unknown, however, the combination of asthma, allergies, and nephrotic syndrome at disease presentation underscores the action of immune dysregulation (643). There may be a common immune mechanism leading to the high prevalence of coexistent disease (644). In a population-based cohort among children, the incidence of nephrotic syndrome is 3.36-fold greater in those with asthma than without. Asthma as one of the most common allergic diseases in childhood is another Th2- mediated disease. Various Th2 associated cytokines, interleukin (IL)-4, and IL-13, are also elevated in relapsing nephrotic syndrome. IL-4 and IL-13 regulate IgE or light chains of immunoglobulin production, both products of B-cells, which stimulates a cytokine cascade culminating in the development of atopy 645). Children with relapsing nephrotic syndrome, a polymorphism in the IL-12B promoter region, encoding IL-12 (a Th2 process), is associated with steroid dependence (646).

- In addition, podocytes play a key role in maintaining the structural integrity of the glomerular filtration barrier by preventing proteinuria (647). Podocytes express IL-13 receptors (CD80), and CD80 induction by T-cell co-stimulation leads to possible actin rearrangement of podocyte structure and damage to filtration barrier resulting in proteinuria (648).
- The higher rates of recur¬rence in children with FSGS receiving living related kidneys suggests that there may be a degree of HLA restriction of response and this is also supported by HLA linkage studies showing that increased incidence of disease is tied to cer¬tain alleles such as HLA B8, B13, DWQ2, DQB10301 and DR7 (93).
- Clinicians should do a rapid visual survey of the child assessing the child's general appearance,rate of breathing,adequacy of breathing,distinguishing between normal,comfortable respirations and respiratory distress.

Table 24 **Formal evaluation of asthma exacerbation severity in the urgent or emergency care setting**

	Mild	Moderate	Severe	Subset: Respiratory Arrest Imminent
Symptoms				
Breathlessness	While walking Can lie down	While at rest (infant—softer, shorter cry, difficulty feeding) Prefers sitting	While at rest (infant—stops feeding) Sits upright	
Talks in	Sentences	Phrases	Words	
Alertness	May be agitated	Usually agitated	Usually agitated	Drowsy or confused
Signs				
Respiratory rate	Increased	Increased Guide to rates of breathing in awake children: *Age* <2 months 2–12 months 1–5 years 6–8 years	Often >30/minute *Normal rate* <60/minute <50/minute <40/minute <30/minute	
Use of accessory muscles; suprasternal retractions	Usually not	Commonly	Usually	Paradoxical thoracoabdominal movement
Wheeze	Moderate, often only end expiratory	Loud; throughout exhalation	Usually loud; throughout inhalation and exhalation	Absence of wheeze
Pulse/minute	<100	100–120 Guide to normal pulse rates in children:: *Age* 2–12 months 1–2 years 2–8 years	>120 *Normal rate* <160/minute <120/minute <110/minute	Bradycardia
Pulsus paradoxus	Absent <10 mmHg	May be present 10–25 mmHg	Often present >25 mmHg (adult) 20–40 mmHg (child)	Absence suggests respiratory muscle fatigue

Table 25 **Stepwise management of intermittent asthma.**

Intermittent	
Step 1	SABA: nebulized or inhaled, whenever cough until free of symptoms
Intermittent	
Step 2	SABA+ low dose ICS (50 µgm of fluticasone)/montelukast
Step 3	SABA+ medium dose ICS (125 µgm of fluticasone)/low dose ICS+LABA/LTRA
Step 4	SABA+ medium dose ICS+LABA/LTRA
Step 5	SABA+ high dose ICS + LABA/LTRA (250 µgm of fluticasone) >12 year if indicated omalizumab
Step 5	SABA+ high dose ICS+ LABA/LRTA+OCS For >12year ± omalizumab if indicated, rare

SABA: Short acting β2-agonist (0.15 -0.3 mg per kg every 3-8 hours)

ICS: Inhaled/nebulized corticosteroid

LABA: Long acting β2-agonist

LTRA: Leukotriene receptor antagonist

OCS: Oral corticosteroid GINA(Global Initiative for Asthma) guideline 2023.

- Short acting inhaled β2 agonist (salbutamol, albuterol, terbutaline) has rapid onset of action and last for 4-6 hours. Asthma worsens at midnight to 8:00 AM can be managed with morning dose of SABA. Step down if good control achieved for at least 3 mo with close monitoring.(649)
- OCS can be used at any stage as rescue therapy if SABA rescue fails nebulizer are needed to deliver medication to lung. Used in exacerbation of very severe disease usually in oral form- prednisolone 1-2 mg/kg/day for 3-7 days, rarely in IV form in equivalent amount of other steroids can be used for rescue, some use it earlier stages of disease.(650)
- Noncompliance of preventer medication is around 50%. It may be unintentional (forgetfulness, cost, misunderstanding) and or intentional (not perceiving the need, laziness, fear of side effect, cost, cultural issues, no valid reason): adherence intervention is needed.(651) It has greater impact in management of nephrotic syndrome in term of relapse and financial burden. ICS are available in metered dose inhalers (MDIs) using hydrofluoroalkane (HFA) as propellant. Bronchodilators are anti-inflammatory and reduce allergen induced bronchoconstriction.(639)
- We suggest same management except ICS is replaced by nebulized salbutamol and nebulized corticosteroids (NCS).
- Montelukast is approved for >6 month – 5 year at 4 mg/day, 5 mg for 6-15 year and 10 mg for >15 year. FDA approved both montelukast and zafirlukast (>5year age group).LRTAs are less effective than ICS.(652)

Asthma treatment for all patients should include ICS: either regularly or (in mild asthma) as needed whenever symptom reliever is taken. (653)

Table 26 **Daily doses in this table are shown as metered doses. See product information for delivered doses.**

Inhaled corticosteroid (alone or in combination with LABA) Total daily ICS dose (mcg) – see notes above	Low	Medium	High
Adults and adolescents (12 years and older)			
Beclometasone dipropionate (pMDI, standard particle, HFA)	200–500	>500–1000	>1000
Beclometasone dipropionate (DPI or pMDI, extrafine particle, HFA)	100–200	>200–400	>400
Budesonide (DPI, or pMDI, standard particle, HFA)	200–400	>400–800	>800
Ciclesonide (pMDI, extrafine particle, HFA)	80–160	>160–320	>320
Fluticasone furoate (DPI)	100		200
Fluticasone propionate (DPI)	100–250	>250–500	>500
Fluticasone propionate (pMDI, standard particle, HFA)	100–250	>250–500	>500
Mometasone furoate (DPI)	Depends on DPI device – see product information		
Mometasone furoate (pMDI, standard particle, HFA)	200–400		>400
Children 6–11 years – see notes above (for children 5 years and younger, see Box 6-7, p.184)			
Beclometasone dipropionate (pMDI, standard particle, HFA)	100–200	>200–400	>400
Beclometasone dipropionate (pMDI, extrafine particle, HFA)	50–100	>100–200	>200
Budesonide (DPI, or pMDI, standard particle, HFA)	100–200	>200–400	>400
Budesonide (nebules)	250–500	>500–1000	>1000
Ciclesonide (pMDI, extrafine particle*, HFA)	80	>80–160	>160
Fluticasone furoate (DPI)	50		n.a.
Fluticasone propionate (DPI)	50–100	>100–200	>200
Fluticasone propionate (pMDI, standard particle, HFA)	50–100	>100–200	>200
Mometasone furoate (pMDI, standard particle, HFA)	100		200

DPI Dry-powder inhaler, HFA Hydrofluoroalkane propellant, pMDI Pressurized metered-dose inhaler, LABA Long-acting-beta2 agonist

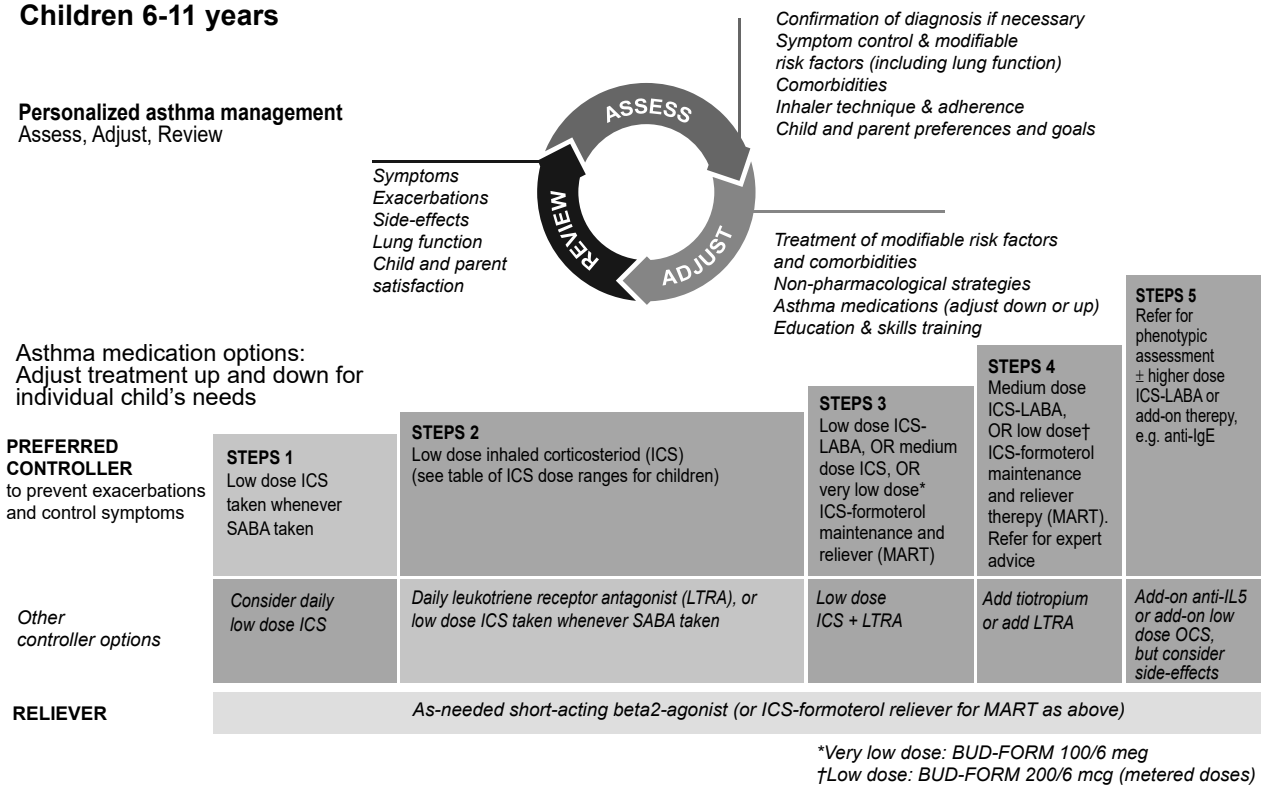


Figure-10: Personalized management for children 6-11 years to control symptoms and minimize future risk

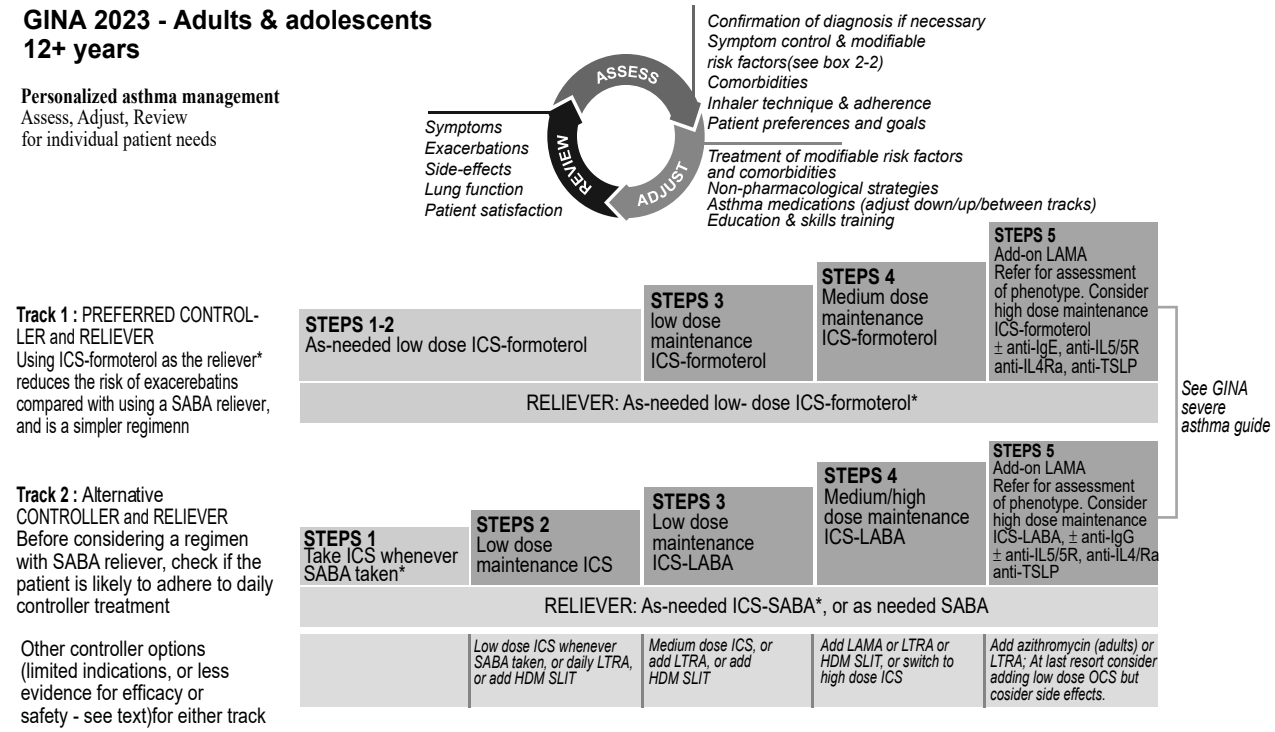


Figure-11: Personalized management for adults and adolescents to control symptoms and minimize risk

Optimization of asthma treatment includes education and skills training for inhaler technique and adherence, and provision of a written/pictorial asthma action plan.(654) Respochamber and spacer use in inhalation is recommended to optimize inhaled particle entry into bronchial tree and alveoli.

Failure to successfully optimize care in people with difficult-to-treat asthma should prompt reassessment—if available, by a specialist with appropriate facilities for diagnosis and interdisciplinary treatment.(655)

Poor compliance to medications and health-related advices have diverse effects including frequent relapse,drug toxicity, higher rates of complications and hence increased healthcare cost.Remote location,ignorance and idiopathic causes are major contributing factors behind non-compliance issue.All intrusiveness control issues including patients as well as parental education should be addressed in intervention efforts to improve compliance in patients with nephrotic syndrome.(656)

Financial burden with outpocketing has greatest impact on the livelihood of patients in a resource constraint area.Cost of non compliance and outpocketing is much higher in developing nation.Drug toxicity,disease response,drug response and complications are also higher in this group of people.We recommend repeated counseling and candid discussion to the patients and their family to prevent non adherence.

COMPLICATIONS

A. Nephrotic syndrome-related complications (657)

Immediate complication

- Infections: pneumonia, primary peritonitis, sepsis, cellulitis, chickenpox
- Thromboembolic tendency: venous thromboembolism, pulmonary embolism
- Hypovolemic crisis
- Acute renal failure

Long term complication

- Cardiovascular complication due to hypertension, hyperlipidemia, vasculitis
- Anemia
- Hormonal and mineral alterations: hypothyroidism, hypocalcemia, bone disease

B. Drug-related complications (657)

- Corticosteroids: obesity, growth retardation, hypertension, osteoporosis, cataract, glaucoma, and behavioral changes, etc.
- Alkylating agents: bone marrow suppression, alopecia, nausea, vomiting, hemorrhagic cystitis, infections, infertility, secondary malignancy
- Cyclosporin A: nephrotoxicity, neurotoxicity, gingival hyperplasia, hirsuitism, and hypertension, etc.
- Mycophenolate mofetil: nausea, vomiting, bone marrow suppression
- Tacrolimus: diabetes, hypertension, nephrotoxicity, tremor, headache, etc.
- Rituximab: bronchospasm, myocardial infarction, progressive multifocal leukoencephalopathy, and reactivation of viruses

INFECTION

Nephrotic Syndrome with Pneumonia

Pneumonia is a lower respiratory tract infection due to microorganism. Pneumonia is the leading cause of death in children under 5 years of age. In many hospitals in low-income countries, even with the World Health Organization (WHO) recommended standard treatment using antibiotics, oxygen, and other supportive

measures, the case fatality rate from childhood severe pneumonia ranged from 6% to 20% (658).

Tachypnoea is the consistent useful sign of pneumonia with sensitivity of 64-81%,and specificity of 54-70%. (659) Clinically cough, fever, fast breathing (>40/min in 0-10 years and >30/min in 10-18years, toxicity, coarse crackles are prominent lung finding, wheeze and vesicular with prolonged expiration may be associated. Congested throat and concomitant asthma is common.

Children with pneumonia may present with fever with or without chills, cough, fast breathing, and in severe cases chest retractions, nasal flaring, lethargy or irritability and inability to feed (660). Very severe cases of pneumonia may present with cyanosis and respiratory failure. Among these the fever and fast breathing are the consistent symptoms (661). Commonest organisms are S.pneumoniae, S. aureus, H.influenzae, Influenza H1N1, M. tuberculosis, atypical organisms (665). Severe pneumonia requires hospitalization and injectable antibiotics (662).

Table 27 Normal Respiratory Rate

Age	Respiratory rate (breaths/min)
0-3months	35-55
3-6 months	30-45
6-12 months	25-40
1-3 yr	20-30
3-6 yr	20-25
6-12 yr	14-22
12+ yr	12-18

Table 28 Respiratory rate according to severity of pneumonia.(664)

Age	Pneumonia Respiratory rate (breaths/min)	Severe pneumonia	Very severe pneumonia (+ danger sign)	Danger sign
0-3 month	<60	≥60	≥60	Lower chest indrawing, unable to feed/drink, reduced level of consciousness, cyanosis, grunting, convulsion and sepsis in infants. (663)
3-12 month	<50	≥50	≥50	
1-6 year	<40	≥40	≥40	
6-12 year	<30	≥30	≥30	

Adopted from 664

Investigations:

CBC, Chest X-ray, blood culture, sputum for gram stain and culture, throat swab for H1N1 by PCR, for M.tuberculosis Tuberculin test, plural tap, gastric aspirate. (666)

Treatment:

Pneumonia is treated with per oral antibiotic, severe pneumonia is by intravenous antibiotics and very severe pneumonia is to be hospitalized where it is treated by IV antibiotic and other supportive measures even intensive care.(667)

Oral: (RR < 40 breaths/min and Nephrotic syndrome in remission) : Amoxicillin, co-amoxiclav, cefuroxime for 10-14 days. In case of penicillin allergy : Clarithromycin, azithromycin, clindamycin or vancomycin. (668)

Parenteral: (RR > 40 breaths/min and nephrotic syndrome in relapse) : Ceftriaxone or ampicillin and amikacin, ceftipime or ceftazidime or meropenem until severe pneumonia or fast breathing persists according to current local sensitivity pattern and then switch to oral antibiotics.

Oseltamivir for days in case of influenza H1N1.(666)

M.tuberculosis therapy as per guideline.

It is expected that PCV introduction will have shifted pneumonia epidemiology such that a greater proportion of cases have viral disease, with altered risk profiles of patients, including a lower mortality and potentially a different response to continuous positive airway pressure (CPAP). (669)

A recent study from Dhaka hospital of(International center for diarrhoeal disease research Bangladesh) ICDDRB found the low prevalence of pneumococcal pneumonia ,but multidrug resistant gram-negative bacteria causing community acquired pneumonia was associated with high case fatality rates.(670)

Bangladesh needs to continue to keep its highly achieved 8.1% average annual rate of reduction in pneumonia-related deaths.In a study in ICDDRB,the children from 4 to 59 months of age who were immunized according to theExpanded program of immunization(EPI)schedule and hospitalized for pneumonia and severe pneumonia had significantly lower case-fatality-rate, compared to those who were not immunized. (671)

The immunized children also had a lower risk of developing severe pneumonia, anemia, and diarrhea than their contemporaries.(672) The overall results underscored the importance of increasing the national immunization coverage as high as 100%, scrupulously following the expanded program immunization (EPI) schedule in order to reduce morbidities and pneumonia-related mortality in children, especially in resource-constrained settings. (673)

URINARY TRACT INFECTION IN NEPHROTIC SYNDROME

Urinary tract infection (UTI) is the most common and serious bacterial infection in the pediatric age group. It is more prevalent in girls than in boys, except in early infancy. It is more common in boys (3.7%) when compared with girls (2%) in the first year of life.(674) Beyond infancy, the condition is reversed as it is more prevalent in girls. The incidence in girls is 3% and it is 1% in boys during prepubertal age (675). Under 3 months of age, uncircumcised boys had a 20% higher risk of UTI compared with circumcised boys (2.4%). In both the groups, the prevalence tends to lower as the age increases (676).

Clinical experience suggests that UTI in childhood nephrotic syndrome is frequently diagnosed incorrectly and managed inadequately , leading to poor outcome. Because UTI symptoms are not evident precisely in immunocompromised child of nephrotic syndrome who are also on immunosuppressive medication. It leads to suboptimum investigation and hence undiagnosed with untreated.

Urinary tract infection (UTI) is a common infection in children with nephrotic syndrome (NS) and needs to be looked for and treated aggressively before starting steroid therapy (677)

Significant lower serum albumin level, immunoglobulin loss in urine (678), defective T cell function, corticosteroids therapy, reduced perfusion of the spleen and loss of properdin (a complement factor that opsonizes certain bacteria) in the urine,(679) presence of ascites or relative malnutrition (680) associated with NS make the outcome worse in the presence of this infection.

Escherichia coli is responsible for 80–90% of cases of pediatric UTI (681). The occurrence and severity of this illness are largely mediated by bacterial virulence factors and host defense mechanism.(682) Other common uropathogens are Klebsiella, Proteus, Enterococcus, and Enterobacter species.(683)

The clinical manifestations of UTI in children are highly heterogeneous, and improper method of collection of urine sample to diagnose the condition accurately is quiet challenging for young pre-continent children.(684)

Proteus infection is more common in uncircumcised boys probably due to its presence under the foreskin.(685) It also predisposed to the formation of phosphate stone by splitting urea to ammonia causing alkalinization of urine and subsequently develops UTI.(686)

Organisms such as Pseudomonas, Group B Streptococcus, and Staphylococcus aureus are the causative agents of UTI in children with congenital anomalies of kidney and urinary tract(CAKUT), genitourinary surgery, catheter, and recent antibiotic treatment (687)

1. According to site

Upper UTI: Pyelonephritis (PN) and ureteritis;

Lower UTI: Cystitis and urethritis.

2. According to severity

Mild UTI: When symptoms are mild and children are able to take oral fluid and medications;

Severe UTI: When symptoms are more severe such as fever >39°C, persistent vomiting, and dehydration present.

3. According to episode

Recurrent UTI: Two or more episodes of UTIs with acute pyelonephritis(APN) or one episode of APN plus one or more episodes of cystitis or three or more episodes of cystitis (688);

Relapse : UTI with the same strain of organism;

Reinfection: UTI with a different strain or species of organism;

Breakthrough UTI: UTI occurring in patients receiving antimicrobial prophylaxis.

4. According to symptoms

Febrile UTI : UTI associated with temperature ≥38°C (100.4 F);

Symptomatic UTI: UTI associated with fever and/or urinary symptoms;

Asymptomatic bacteriuria (ABU): Presence of significant bacteria in urine without any symptom of UTI.

Fever may be absent in immunocompromised nephrotic syndrome on steroid therapy.

5. According to complicating factors

Uncomplicated UTI: UTI occurs in a patient with normal upper and lower urinary tract, normal renal function, competent immune system, and patients can be managed on outpatient basis.

Complicated UTI: UTI in newborns, kidney and urinary tract anomaly, urosepsis, organism other than E. coli, atypical clinical course, absence of clinical response to antibiotic within 72hour, renal abscess, abdominal and/or bladder mass, raised serum creatinine. Septic feature symptoms are not always pointing to urinary tract and infants and children may fail to describe all the symptoms.

Complicated cystitis: children with comorbid medical conditions, underlying bladder pathology,indwelling bladder catheter, and atypical clinical course. (688)

There are 3 screening methods of urinalysis (676):

1. Dipstick
2. Microscopy
3. Flow imaging analysis technology

The leukocyte esterase test on urine dipstick is a widely available screening test. Most but not all uropathogens (including Klebsiella and Enterococcus) convert nitrates into urinary nitrites.(689) None of them is fully sensitive or specific for UTI.

They are considered as a useful screening tool when used in combination. RBC and/or protein on urine dipstick is not specific for UTI, (688) but dipsticks have a good negative predictive value to exclude the diagnosis of UTI.(690) Urine culture is the gold standard technique for the diagnosis of UTI.(691)

The colony count threshold varies between methods of collection and recommendations of guidelines.(692) While samples are obtained by catheterization, the threshold is 50,000 CFU/mL. For clean catch urine and suprapubic aspiration(SPA), it is 100,000(105) and 1000(103) CFU/mL, respectively (688). According to AAP(American Academy of Pediatrics) UTI guidelines 2024, urinalysis positivity and >50,000 CFU/mL of a single uropathogen found in the specimen obtained from bladder catheterization suggest true urine infection (668). Any growth on SPA constitutes a positive culture, suggested by many guidelines.(693)

In febrile children <4 months of age, a cut-off value of 10^3 CFU/mL can be considered depending on clinical and laboratory findings as well as a correct sampling method.(694) The choice of empirical antibiotic therapy must be guided by local guidelines and current sensitivity patterns, as it can vary significantly between countries and hospitals.(690)

In the clinical experience, it has been noticed that UTI is frequently misdiagnosed and inadequately treated in general practice.(695) Only 44.8% of the times the patients are given correct diagnosis by the primary care physician.(696) Though in the paediatric settings, the proportion of providing correct diagnoses of the disease is better,possible in 64.3% but in family care setting and walk in clinics its only 17.2% and 16.7%, respectively.(695)

Most of the UTI in NS are asymptomatic in children,(697) very often is under diagnosed and important cause of prolonged hospital stay.(698) This leads to propensity for long term renal damage(699). UTI reported to be adversely influences the response of patient with NS to corticosteroids,(700) which is the mainstay of treatment of nephrotic syndrome in children.

if treating physician or pediatrician in primary care setting is encountered with a child having suspected NS, especially in active phase, it is essential to have high index of suspicion of existence of UTI even in absence of urinary symptoms and should perform urine cultures and ultrasonography (USG) must be advised to rule out underlying cause and complication of UTI.(701) About one fifth of children with nephrotic syndrome have UTI at admission.(702) Therefore in a primary care setting, UTI should be ruled out in every case of nephrotic syndrome before starting any specific therapy to prevent long term morbidity and mortality and to have good outcome.

PERITONITIS:

Primary peritonitis is a well-described infectious complication of nephrotic syndrome. Peritonitis has been reported with an incidence of 1.5–16% in nephrotic children (703).

Peritonitis should be suspected when abdominal pain, fever, sluggish or absent bowel sound are are found and in some cases severe systemic septic features are found. Peritonitis has been suspected by suggestive symptoms and signs and was confirmed with the presence of >100 WBC/mm3 in peritoneal fluid.We recommend peritoneal fluid aspiration (paracentesis)for culture and sensitivity to confirm peritonitis (Level 1 :strong recommendation) by gram stain and culture sensitivity of peritoneal fluid.

Relatively more severe hypoalbuminemia and low serum total protein levels are known to predispose serious infections in NS (235).

Severity of hypoalbuminemia may reflect increased urinary excretion of some immunological factors and/or may increase capillary permeability to peritoneal defense. In many cases of peritonitis, a diagnostic paracentesis can not be done only when paralytic ileus (absent bowel sound) is present, and patients may be treated empirically with broad-spectrum antibiotics. This approach has disadvantages of antibiotic resistance and increased risk for fungal infections (704) also underdiagnoses of peritonitis.

It has been reported that the frequency of infections was higher in nephrotic children who were frequent relapsers or steroid dependent and subsequent non-responders (705) .However, besides steroid introduction, these patients may have defective humoral and non-specific immunity parameters.

Urinary loss of small molecular proteins such as IgG fractions, factor I, and factor B may alter opsonization, phagocytosis, and killing of bacteria (706)

After suspecting peritonitis,patients should be kept nothing per oral,with parenteral antibiotics according to local contemporary available sensitive antibiotics.

Although chemoprophylaxis with penicillin is shown to reduce the incidence of pneumococcal infections in children with sickle cell disease, there are no controlled trials on the use of penicillin prophylaxis in children with NS (707). Penicillin prophylaxis has been used sporadically in nephrotic children, and peritonitis was reported in children both with and without penicillin.

There are some studies about the efficacy of pneumococcal vaccination in healthy and immunocompromised children.(708) A population-based surveillance study from the USA revealed that administration of pneumococcal conjugate vaccine to children younger than 2 years of age and selective administration to 2–5 years of age has resulted in a significant decline in invasive pneumococcal disease (IPD) (709).

Studies are lacking to identify whether immunization with PCV7 provide protection against IPD for the patients with traditional risk factors such as hemoglobinopathies, splenic dysfunction, chronic cardiac and pulmonary diseases, diabetes mellitus, human immunodeficiency virus infection, chronic renal failure, or nephrotic syndrome.(710) Some efficacy studies have used levels of circulating pneumococcal antibody as a surrogate for protection against pneumococcal disease (711). Response to polysaccharide pneumococcal vaccine is poor in all children under 2 years of age, in contrast to older children with SSNS who respond to polysaccharide, similar to healthy controls (712,713) prophylaxis.

VARICELLA:

Viral infection also poses a significant hazard to children with INS. Varicella zoster virus (VZV), measles or influenza can have devastating consequences in immunosuppressed children with INS, including severe pulmonary disease, multi-organ failure and even death(714). Several studies found that when a VZV naïve (according to the above criteria) immunosuppressed child is exposed to VZV, passive immunoprophylaxis and/or acyclovir should be considered (715). Significant exposure to varicella may be defined as “residing in the same household, face-to-face indoor play for more than 1 h and hospital contact with an infectious individual (same 2- to 4-bed room or in adjacent beds or a visit in room by contagious person for more than 1 h)”. (716)

Unimmunized patients with nephrotic syndrome:

If not immunosuppressed should receive the vaccine within 5 days of exposure.The risk of post exposure varicella was reduced to one third of children who were vaccinated following exposure compared to those unimmunized.(717)

In patients whom vaccination is contraindicated,administration of varicella zoster immunoglobulin(VARIZIG 125 IU per 10kg is recommended within 10 days of exposure preferably <4days of exposure.

If VARIZIG is not available oral acyclovir 10-20mg/kg/day or valacyclovir if ≥3months 60mg/kg/day for 7 days within 6-10 days of exposure corresponding to the period of secondary viraemia (718).

IVIG 400mg/kg less than 10 days after exposure can be an alternative if VARIZIG is not available.(719)

We recommend that children who develop VZV infection should receive intravenous aciclovir (1500 mg/m2 /day in 3 divided doses) or oral aciclovir (80 mg/kg/day in 4 divided doses) for 7–10 days.(strong recommendation,Grade A). The guidelines also recommend that the dose of prednisolone should be tapered to 0.5 mg/kg/day or lower during the infection.(720)

VZIG is given by intramuscular (IM) injection, but children with bleeding disorders who cannot receive IM doses should be given intravenous normal immunoglobulin. (721)

Following vaccination,the antibody response is, however, variable and a second dose was necessary before seroconversion is achieved .(722)

VACCINE GUIDELINE IN CHILDREN WITH NEPHROTIC SYNDROME

- All children should review their vaccination status at disease onset.
- All inactivated vaccine recommended for healthy children, like Pneumococcus, Meningococcus and Haemophilus influenza should be completed .
- Covid-19 vaccine in children with steroid sensitive nephrotic syndrome should follow the national recommendation.
- Vaccinating the household against
- Influenza-annually (<8year after 1month 2nd dose)
- Live vaccines: e.g. mumps, measles, rubella, varicella(MMRV,MMR),oral polio. (if live vaccine contraindicated in child with SSNS)
- Live vaccines should generally be avoided in immunocompromised children (723,724).
- The risk of vaccine-induced relapses has been shown to be low in numerous studies (567,725–727)

Patients with nephrotic syndrome suggested to received

- Age appropriate killed subunit of inactivated vaccine (728,729)
- Live vaccine should be given according to table 30
- Vaccine against Pneumococcus varicella, Influenza & Hepatitis B

Pneumococcal vaccines: Two categories of vaccines are available. (i) The polysaccharide vaccine (PPSV-23) is poorly immunogenic <2 yrs of age.

Conjugate vaccine (PCVJ-10 and 13 valent) Superior and sustained antibody response and immune memory even in infants (730). Both PCV 7/10/13 and PPSV23 elicit satisfactory serological response, even when given during relapse or while on immune suppressive agents. Nevertheless suggestion is that the vaccine preferably be given during remission and while on low or no immune suppression. As antibody response is ill sustained in patient with recurrent relapse 2nd dose of PPSV2 should be given after 5 years.

Varicella vaccine: Patients with nephrotic syndrome recommend to receive 2 dose of varicella vaccine 4-8 weeks apart (565). Two doses results in seroconversions 95%, breakthrough varicella might occur in 2.2%-7.3% of children (731). Vaccination should be given to non-immunized siblings and parents against Varicella Zoster.

Influenza vaccine: Influenza vaccine is given 2nd dose after 1st dose in under 8year old child and then annual revaccination. Influenza accounts for 13% of all pneumonia and 7% of severe pneumonia in children <5 years (732,733). Influenza causes pneumonia particularly in immunosuppressed individual. Annual administration of the inactivated influenza vaccine is recommended (567,734,735). Household contacts will also receive yearly influenza vaccine.

Hepatits B vaccine:

Vaccination rate in Bangladesh is 94%. Seroprotection is lower in nephrotic syndrome children compared to healthy children (736). Seroprotection is lower in SRNS and those on non steroidal therapy (88). To overcome vaccine failure, we advise an accelerated schedule using twice the age-appropriate dose and assessment of serological response to administer booster dose (737).

Table 29 Principles of immunization with live vaccines in patients with nephrotic syndrome

Immunosuppression Advice	Immunosuppression Advice
Receiving high dose prednisolone (≥2 mg/kg/day; ≥20 mg/day if >10 kg) for <14 days	Vaccinate immediately after discontinuing treatment
Receiving high dose prednisolone (≥2 mg/kg/day; ≥20 mg/day if >10 kg) for >14 days	Vaccinate 1 month after discontinuing corticosteroids
Receiving low moderate dose prednisolone (<2 mg/kg/day or equivalent; <20 mg/day)	No live vaccines, until discontinuation of steroid therapy
Low dose alternate day prednisolone and pressing need for vaccine	Live vaccine may be administered
Patients receiving cyclophosphamide	Avoid live vaccines until off therapy for 3 months
Patients receiving calcineurin inhibitors, levamisole, or mycophenolate mofetil	Avoid live vaccines until off therapy for 1 month
Therapy with rituximab	Avoid live vaccines until after B cell recovery (~6-9 months)
Immunocompetent siblings and household contacts	Do not administer oral polio vaccine; may receive measles mumps rubella, rotavirus and varicella vaccines
Household contacts older than 1 year	Administer influenza vaccine annually

Adopted from (738)

We suggest that patients with nephrotic syndrome receive: (i) age appropriate killed, subunit or inactivated vaccines; (ii) live vaccines following principles outlined in Table 1; (iii) vaccines against pneumococcus, varicella, influenza, and hepatitis B [Table 30].

Killed, inactivated, or subunit vaccines are not contraindicated but may have reduced efficacy during immunosuppression (739,740). The schedule for administration of specific vaccines that are relevant to patients with nephrotic syndrome is summarized in Table 2. The risk of relapse following vaccination is negligible.

Influenza accounts for 13% of all pneumonia and 7% of severe pneumonia in children <5 years (732,733). Influenza causes pneumonia particularly in immunosuppressed individual. Annual administration of the inactivated influenza vaccine is recommended (567,734,735). Household contacts will also receive yearly influenza vaccine.

Hepatits B vaccine:

- Vaccination rate in Bangladesh 94%.
- Seroprotection is lower in nephrotic syndrome children compared to healthy children (736).
- Seroprotection is lower in SRNS and those on non steroidal therapy (88).
- To overcome vaccine failure, we advise an accelerated schedule using twice the age-appropriate dose and assessment of serological response to administer booster dose (737).

Table 30 **Specific vaccines for patients with nephrotic syndrome**

Vaccine	Age	Previously received	Vaccine	Schedule
Pneumococcal: Conjugate (PCV, 13 valent preferred to 10 valent) Polysaccharide, (23 valent, PPSV23)	6-72 Months	Completely immunized (3 doses at 6, 10, 14 weeks; booster at 12-15 months)	PCV13/10 PPSV23	One dose ≥2 year old One dose when ≥2 year old and ≥8 week after last PCV13/10 doseb
		No, or incompletely immunized	PCV13/10 PPSV23	Two doses, ≥8 weeks apartc One dose when ≥2 year old and ≥8 weeks after last PCV13/10 doseb
	≥72 Months	Completely immunized	PPSV23	1 doseb
		No, or incompletely immunized	PCV13/10 PPSV23	1 dose 1 dose, ≥8 week after last PCV13/10 doseb
Varicella	>15 Months	No evidence of immunitye	Live attenuated	Two doses 4-8 week apart
Influenza	>6 Months		Inactivated	Annually
Hepatitis B	Any	No, or anti HBs antibody <10 mIU/mL	Subunit (10 µg/0.5 mL)f	3 doses at 0, 1 and 6 months; or in an accelerated schedule with ≥4 weeks gap between doses 1 and 2, ≥8 weeks between doses 2 and 3, and ≥16 week between doses 1 and 3f

Addpted from (738)

Table 31 **Postexposure management of unimmunized patients with nephrotic syndrome exposed to varicella**

Contraindication to live vaccine	Strategy	Timing after exposure	Level of evidence
No	Administer varicella vaccine	As soon as possible, <5 days	A
Yes	Options (in order of preference) VARIZIG, 125 IU per 10 kg body weight (maximum 625 IU) intramuscular	<10 days; preferably <4 days	B
	Oral acyclovir, 80 mg/kg in 4 divided doses (maximum 3.2 g) daily for 7 days OR oral valacyclovir (if ≥3-month-old), 60 mg/kg (maximum 3g) daily in 3 divided doses for 7 days	Begin 6-10 days after exposure	C
	IV immunoglobulin, 400 mg/kg	<10 days	X

Addpted from (741-745)

AKI

Acute kidney injury (**AKI**) is due to hypovolemia, acute tubular necrosis (**ATN**), acute cortical necrosis (AcN), interstitial edema, renal vein thrombosis (**RVT**).

Acute prerenal causes has hypovolemic features as describe earlier, Renal causes and drug toxicities (CNI, diuretics) has its own features

Thromboembolism

The risk of thromboembolism is variable, ranging from ~3% in children to ~20% in adults; children older than 12 years have a comparatively higher risk (746) .

Venous thrombosis is more common than arterial thrombosis, and deep venous thrombosis, cerebral venous thrombosis, and pulmonary embolism account for the majority. The complication is chiefly observed in patients with frequent relapses, steroid dependence or steroid resistance. However, many patients show this complication early in the course of illness, more commonly during relapse than in remission (746).

The risk of thromboembolic events in children with nephrotic syndrome is estimated to be 1.8–5% with a higher risk reported in children with SRNS compared with those with SSNS (747,748). Factors contributing to an increased risk of thrombosis during nephrotic syndrome include abnormalities of the coagulation cascade, such as increased clotting factor synthesis in the liver (factors I, II, V, VII, VIII, X, and XIII) and loss of coagulation inhibitors such as anti-thrombin III in the urine. And also loss of protein S & C

Other prothrombotic risks present in these children include increased platelet aggregability (and sometimes thrombocytosis, hyperviscosity resulting from increased fibrinogen levels, hyperlipidemia, prolonged immobilization, and the use of diuretics. In one series, the use of diuretics was the major iatrogenic risk factor for thrombosis (748) and hypovolaemia. Protein C & S in the serum remain inactive because of increase in the hepatic synthesis of hepatic bimding protein S & C (749). Platelet disorders predispose to arterial, and the latter two to venous thrombosis. Prolonged bed rest, hypovolemia with hemoconcentration, infections, nephrotic range proteinuria, central venous catheters, and genetic variations favoring coagulation further increase the risk. Patients with marked hypoalbuminemia (<2 g/dL), low anti-thrombin-III (<70%), and high fibrinogen (>600 mg/dL) should be observed for the complication (746,750). Hypercoagulable states can be classified as acquired, for example, if they arise as a consequence of the heavy proteinuria, or inherited, if only causally associated to NS.

Acquired thrombophilia: Several studies have focused on the abnormalities of the coagulation pathways in NS patients. The TEC in NS have been attributed to low plasma ATIII levels. Plasma ATIII levels have been shown to correlate with albumin levels and degree of proteinuria in NS (751) . However, the excess thrombin generation played a part in the development of the acquired deficiency of ATIII in NS (752).

Table 32 Acquired and inherited thrombophilia in children with NS.

Acquired thrombophilia	Conditions	Pathophysiology
ATIII	Serum reduction	Urinary loss
Protein S	Serum reduction	Urinary loss
Protein S	Raised activity	Increased hepatic synthesis
Protein C	Raised activity	Increased hepatic synthesis
Fibrin network	Hypofibrinolysis	Abnormal conformation
Proteins S and C levels	Serum reduction	Increased binding proteins
Platelets	Dysfunctional, Increased activation	Increased number, increased synthesis of thromboxane
tPA, PAI-1	Increased concentration	Cyclosporine A
Inherited thrombophilia		
Protein C, protein S, ATIII		Defect
Lipoprotein (a)		Raised
Coagulation factors V and II		Gene mutations
Factor V Leiden		Presence
Prothrombin variant (20210G-A)		Presence
MTHFR gene		Gene mutation

The majority of episodes of thrombosis are venous in origin. The most common sites for thrombosis are the deep leg veins, ileofemoral veins, and the inferior vena cava. In addition, use of central venous catheters can further increase the risk of thrombosis.

Renal vein thrombosis (RVT) can also occur and may manifest as gross hematuria with or without acute renal failure. Development of these features should prompt either renal Doppler ultrasonography or magnetic resonance angiography to rule out RVT.

Pulmonary embolism is another important complication that may be fatal if not recognized early. Rarely, cerebral venous thrombosis, most commonly in the sagittal sinus, has also been reported (753) . In addition to imaging studies, development of thrombosis should prompt an evaluation for possible inherited hypercoagulable states

Management

If a thrombus is detected in a medium or large vessel, anticoagulation measures are instituted. Unfractionated or low-molecular weight heparin is administered initially, followed by warfarin for 3–6 months. There is insufficient evidence for primary prophylaxis against venous thromboembolism in children with relapsing nephrotic syndrome.

The typical acute management of thrombosis in children with nephrotic syndrome includes initial heparin infusion or low molecular weight heparin, followed by transition to warfarin for 6 months. Children with a history of prior thrombosis and patients with severe proteinuria should also receive prophylactic anticoagulation therapy during future relapses.

DYSLIPIDEMIA

Nephrotic syndrome is associated with dyslipidemia. Hypoalbuminemia increases hepatic synthesis of lipoproteins, particularly low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) that increase total cholesterol, triglycerides, LDL cholesterol, and lipoproteins (564). In SSNS, dyslipidemia rapidly normalizes during remission and is therefore unlikely to have long term consequences, except for anecdotal reports on atherosclerosis and coronary artery disease. Since some patients might have additional cardiovascular risk factors (hypertension, obesity, insulin resistance), the potential risk of dyslipidemia cannot be ignored (189) . Use of lipid-lowering agents for dyslipidemia is not recommended, unless there is persistent proteinuria with extremely high levels of LDL cholesterol and triglycerides. Therapy with statins may be instituted in specific patients over 8-year-old, with monitoring of liver functions and creatinine kinase (564,754).

Dyslipidemia, cardiovascular health, and renal injury in nephrotic syndrome

While children having frequent relapses experience prolonged periods of hypercholesterolemia (755) , the long-term clinical consequences of this remain unclear. In contrast, NS in adults is known to confer a six-fold increased risk for myocardial infarction and three-fold increased risk for cardiovascular mortality (756). A study of 37 children with SRNS showed evidence of subclinical cardiovascular disease in 5–22% of patients, assessed by abnormal aortic pulse wave velocity, elevated carotid intima medial thickness (cIMT), and increased left ventricular mass index (757). This increased risk was independently associated only with higher LDL-C levels (757). Dyslipidemia is an important modifiable risk factor that may also aggravate glomerulosclerosis and contribute to the progression of renal injury (758,759). In the Chronic Kidney Disease in Children (CKiD) cohort, the presence of dyslipidemia was associated with a 40% shorter time to the composite outcome of requirement of renal replacement therapy or 50% reduction in estimated GFR in patients with non-glomerular disease (760). Dyslipidemia may also induce direct cellular injury to both renal proximal tubular epithelial cells and podocytes in NS (761). Another important clinical consequence of dyslipidemia in refractory NS is its contribution to the known increased risk for thromboembolism. Levels of oxidized LDL and markers of oxidative stress have been shown to be significantly elevated in children with active NS (762).

Screening and monitoring for dyslipidemia in nephrotic syndrome

The National Heart, Lung and Blood institute (NHLBI) guidelines recommend universal screening of children for hyperlipidemia at ages 9 and 11 years and earlier (between 2 and 8 years) in at-risk children including those with NS (763). Two fasting lipid profiles 2 weeks to 3 months apart are recommended, with abnormal tests confirmed on a repeat measurement.

Table 43 shows cutoffs of lipid levels that have been adopted by the NHLBI guidelines and are widely accepted in clinical practice. However, fixed thresholds that ignore cholesterol variations by age and sex may be problematic. Whereas hyperlipidemia is invariably present in refractory NS, lipid abnormalities are

unlikely to be abnormal during sustained remission in children with steroid-sensitive NS. Total cholesterol levels are routinely obtained in children with NS, although a complete lipid profile is recommended in those with SRNS. The baseline lipid profile for children with SRNS should include total cholesterol, triglyceride, HDL-C, LDL-C, and non-HDL-C. When available, apoB and Lp(a) may also be assessed (764). While obtaining a lipid profile following a 10–12-h fast is standard, current guidelines suggest that nonfasting lipid levels can be utilized for screening because they show comparable results for total cholesterol, LDL-C, and HDL-C, with only a small increase (± 20%) in triglycerides.

In clinical practice, LDL-C is either estimated directly or calculated by the Friedewald formula as follows (765): [LDL cholesterol (mg/dl) = Total cholesterol−HDL cholesterol−plasma triglyceride/5].

Direct measurement of LDL-C does not require a fasting sample but does incur additional costs (764). The Friedewald formula has significant limitations; errors in LDL-C become magnified with triglycerides > 200 mg/dl and the calculation is not valid for samples having triglycerides > 400 mg/dl (764).

A modification of this equation was published by Martin and colleagues (764b) to improve the accuracy of estimating LDL-C: [LDL cholesterol = Total cholesterol−HDL cholesterol−plasma triglyceride/adjustable factor].

The potential usefulness of hydroxymethylglutaryl CoA (HMG CoA) reductase inhibitors (statins) in children with SRNS has been reported in a few uncontrolled trials. One study reported a 41% reduction in cholesterol and 44% reduction in triglyceride levels within 6 months of treatment (766). A second study found significant reductions within 2–4 months in total cholesterol (40%), LDL cholesterol (44%), and triglyceride (33%) levels, but no significant changes in HDL cholesterol levels (767). Treatment was found to be very safe in these studies, with no associated adverse clinical or laboratory events. Although the long-term safety of statins in children has not yet been established, these medications appear to be generally well tolerated in adults with nephrotic syndrome, with only minor side effects such as asymptomatic increases in liver enzymes, creatine kinase, and rarely diarrhea (754).

Table 33 **Cut-off values (mg/dl) for abnormal lipid levels and targets during therapy according to NHLBI guidelines [4]**

	Acceptable	Abnormal	Targets during therapy	
			Without risk factors	≥2 risk factors
Total cholesterol	<170	≥200		
LDL cholesterol	<110	≥130	≤130	≤100
Non-HDL cholesterol		≥145	<140	< 120
Triglycerides				
<9 years	<75	≥100		
10-19 years	<90	≥130	<130	<90
HDL cholesterol	>45	<40		

HDL, high-density lipoprotein; LDL, low-density lipoprote in

*Risk factors include estimated glomerular filtration rate <60 ml/min/1.73m^2 for 3 months, stage I hypertension, body mass index ≥95th percentile, fasting glucose > 100 mg/dl or positive family history (parent, grandparent, aunt, uncle, sibling with history of cardiovascular disease before age of 55 years in males and 65 years in females)

Treatment of dyslipidemia in nephrotic syndrome

This review focuses primarily on the screening and management of dyslipidemia in patients with NS, which is an integral part of a comprehensive strategy for cardiovascular risk reduction including the following (768):

- Minimize proteinuria (specific therapy; renin angiotensin aldosterone system blockade)
- Control of blood pressure, preferably ambulatory blood pressure to < 50th centile for age and sex; assess for left ventricular hypertrophy and cardiac dysfunction
- Weight reduction to achieve body mass index (BMI) <85th centile for age and sex
- Achieve target lipid levels (Table 43)
- Achieve fasting glucose levels (< 100 mg/dl and HbA1c < 7%)
- Minimize tobacco exposure

Lifestyle modifications

Dietary modification: The NHLBI recommends Cardiovascular Health Integrated Lifestyle Diet (CHILD-1) as the first step as dietary modification in children > 2 years of age with dyslipidemia. This diet includes restricting saturated fat intake to < 10% of the total caloric intake and cholesterol to < 300 mg/day, with sufficient calories to maintain normal growth and development. Dietary fat is not restricted for children ≤ 2 years of age, and breast feeding is allowed for infants. In children with hypercholesterolemia, the CHILD-2 intervention is recommended, which further limits dietary fat to < 7% of total caloric intake and cholesterol to < 200 mg/day. Trans fats should also be avoided as much as possible.

Fiber, omega 3 fatty acids, and plant stanols and sterols may have an additional benefit (769). For total cardiovascular risk reduction, a diet as per local food habits including fruits, vegetables, legumes, nuts, and whole grain cereal foods should be encouraged, and trans or saturated fat intake (hard margarines, tropical oils, fatty or processed meat, sweets, cream, butter, regular cheese) should be discouraged or replaced with monounsaturated fat (extra virgin olive oil) and polyunsaturated fat (nontropical vegetable oils) (770). Salt intake should be reduced to < 2.3 g/day in children with hypertension by choosing fresh or frozen unsalted food, since many processed and convenience foods are high in salt (771). The intake of beverages and foods with added sugars, particularly soft drinks, should also be limited, and tobacco exposure avoided (770). To facilitate adherence with these guidelines, a leaflet on healthy eating detailing these guidelines should be made available to patient and their families (772).

Enhanced physical activity

There is strong evidence to suggest that increased physical activity reduces cardiovascular risk factors such as blood pressure, BMI, and blood glucose and might also improve levels of HDL-C and triglycerides in children (763,769,773). The NHLBI guidelines recommend limiting leisure screen time (computer, video games, television, etc.) to < 2 h/day, moderate-tovigorous activity for at least 1 h/day, and vigorous activity for at least 3 days/week for children > 5 years of age (763).

Pharmacological treatment

Due to the lack of good quality evidence, there are no clear recommendations on pharmacotherapy for hyperlipidemia in pediatric NS. The Kidney Disease Improving Global Outcomes (KDIGO) guidelines note that hyperlipidemia in NS be treated according to the guidelines for high-risk individuals for developing cardiovascular disease, particularly when the disease cannot be ameliorated. It also suggests that dietary restrictions have only modest effects and suggests drug therapy be used (121). The indications for pharmacotherapy in children with NS are shown in Fig. 11. While there are well-designed studies demonstrating that drug therapy reduces cholesterol levels in children, there are no data from randomized controlled trials in children with NS demonstrating these long-term benefits. Therapy to lower lipid levels would likely be indicated as long as children continue to have active nephrotic syndrome, raising concerns for long-term safety of drugs and issues with adherence to recommended therapy. An important potential concern with lipid lowering drugs is the long-term impact on neurological development and puberty, since lipids are necessary for brain development and are also building blocks for steroid hormones such as estrogen and testosterone.

Statins

Statins inhibit hepatic HMG-CoA reductase. They inhibit cholesterol synthesis and upregulate LDL receptors, leading to clearance of atherogenic LDL-C and apoB-containing lipoproteins from the circulation (774). Statins have demonstrated longterm safety and efficacy to reduce LDL-C by 25–35% in children with familial hypercholesterolemia (FH) (775,776). Beneficial effects on endothelial dysfunction, reflected by reduced progression of cIMT and improved flow-mediated dilation (FMD) of the brachial artery, have also been reported in patients with both FH (776) and NS (777) treated with statins. Statins and their doses approved for use in children after 8 to 10 years of age by the United States Food and Drug administration.

Experience in the pediatric age group is limited to only two prospective uncontrolled studies demonstrating declines in triglycerides, LDL-C, and total cholesterol by 30–40%, occurring by 6–12 months, in 19 patients over a period of 6–60 months (766,767).

While American and Japanese guidelines on childhood NS and the American Academy of Pediatrics Dyslipidemia Guidelines recommend considering statins in NS with persistently high fasting LDL cholesterol (113,563,763). In a prospective, randomized, double-blind, placebo controlled trial, Indian study

examined whether a fixed dose of 10 mg atorvastatin was effective in improving dyslipidemia, cIMT, and brachial artery FMD in children 5–18 years of age with refractory NS (778).

Changes in serum albumin levels were negatively associated with changes in serum LDLC, very low-density lipoprotein cholesterol, total cholesterol, triglyceride, and apo B ($P < 0.001$), irrespective of receiving atorvastatin, age, gender, body mass index, and serum creatinine, suggesting that therapy to raise serum albumin (i.e., induce partial or complete remission) may instead be useful (778). Our recommendation is also in corollary to all published international data's and recommendations.

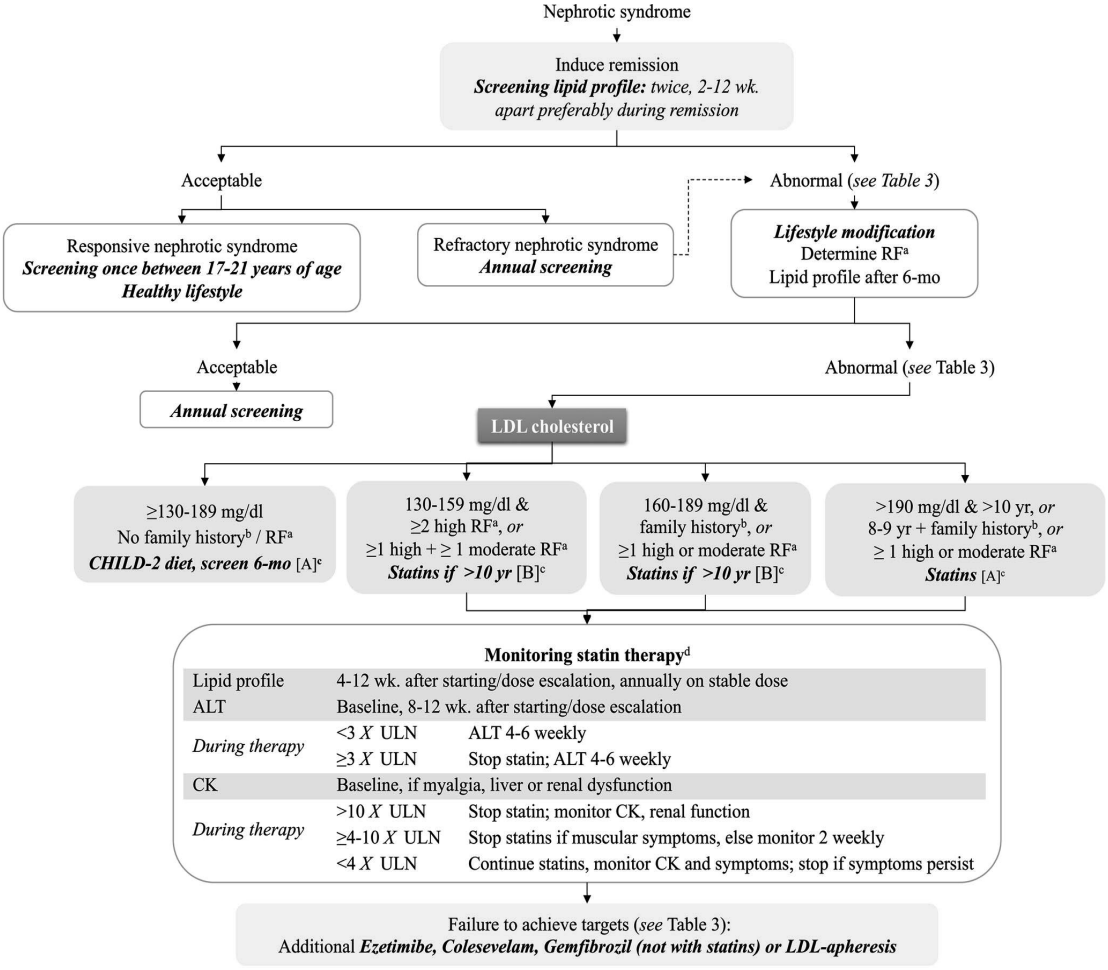


Figure-12: Adapted from "Pankaj Hari 'Dyslipidemia and cardiovascular health in childhood nephrotic syndrome,'" (564). Proposed interventions for dyslipidemia in refractory nephrotic syndrome. [a]High-risk factors: chronic kidney disease stages 3 or more, stage 2 hypertension and body mass index (BMI) ≥ 97th centile; moderate risk factors: stage 1 hypertension and BMI > 95–97th centile (in addition to nephrotic state that itself imposes a moderate risk). [b]Family history: parent, grandparent, aunt, uncle, sibling with a history of cardiovascular disease before 55 years of age in males and 65 years of age in females. [c]Grade of recommendations (in parenthesis) is based on the National Heart, Lung, and Blood Institute guidelines. [d]Monitoring of lipid profile and statin therapy is adopted from the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) 2016 guidelines (ALT, alanine aminotransferase; BMI, body mass index; BP, blood pressure; CK, creatinine kinase; ECHO, echocardiography; HDL, high-density lipoprotein; LDL, low-density lipoproteins; RF, risk factor; ULN, upper limit of normal).

Table 34 Lipid-lowering drugs used in children

Class	Mechanism of action	Therapeutic effect in randomized controlled trials in FH	Drug	Age (years)	Dose range
Statins[a]	Reduce cholesterol synthesis in the liver, upregulate LDL receptors causing increased clearance of lipoproteins	20–40% reduction in total cholesterol and LDL cholesterol; 5–17% reduction in triglycerides	Atorvastatin	10–17	10–20 mg
			Lovastatin	10–17	10–40 mg
			Pravastatin	8–13 14–18	20 mg 40 mg
			Simvastatin	10–17	10–40 mg
			Fluvastatin	10–16	20–80 mg
			Rosuvastatin	10–17	5–20 mg
Cholesterol absorption inhibitors	Inhibit absorption of biliary and dietary cholesterol by blocking Niemann-Pick C1-like protein in the intestine	20–30%[b] reduction in total cholesterol; 26–28% in LDL cholesterol	Ezetimibe[a]	10–17	10 mg
Bile acid sequestrants	Bind to bile salts preventing its absorption in the ileum; increased uptake and conversion of cholesterol to bile in the liver	6–13% reduction in total and LDL cholesterol; 5–6% increase in triglycerides	Colesevelam[a]	10–17	1.87 mg twice daily or 3.75 mg/day
		10–20% decline in LDL cholesterol	Colestipol	7–18	10–15 g/day
		10–17% decline in LDL cholesterol	Cholestyramine	6–18	240 mg/kg/day or 8 g/day
Fibric acid derivatives	Upregulate lipoprotein lipase and increase degradation of cholesterol and triglycerides, decrease hepatic triglyceride synthesis	22–34% reduction in total cholesterol, 23–53% in triglycerides	Benzafibrate Gemfibrozil	4–15 5–15	10–20 mg/day
Niacin	Inhibits the release of free fatty acid from adipose tissues; decreases LDL, triglyceride, and VLDL production	No randomized controlled trial	Niacin	4–14	500–2200 mg/day
Omega 3 fatty acid	Decreases hepatic free fatty acid and triglyceride synthesis, increases fatty acid oxidation	Insignificant reduction in total, LDL, HDL cholesterol, and triglycerides as compared to placebo	Omega 3 fatty acid	10–19	1–4 g/day
Combination drugs		38% reduction in total cholesterol; 49% in LDL cholesterol	Simvastatin + ezetimibe		10–40 mg 10 mg
		13% reduction in total cholesterol; 17% in LDL cholesterol	Pravastatin + colestipol		10 mg 5 mg

FH, familial hypercholesterolemia; *HDL*, high-density lipoprotein; *LDL*, low-density lipoprotein; *VLDL*, very low-density lipoprotein

[a] Recommended by the US Food and Drug Administration

[b] Uncontrolled studies. Adopted from (564)

CARDIOVASCULAR COMPLICATIONS

An increased risk of cardiovascular disease exists in patients with NS because of hyperlipidemia, increased thrombogenesis, and endothelial dysfunction (779). Hypercholesterolemia is strongly associated with severity of hypoalbuminemia, and persistent proteinuria or renal insufficiency also contributes to cardiovascular disease (780).

There is little or no risk of cardiovascular disease in children with MCNS who are responsive to CS because hyperlipidemia is intermittent and of short duration. The risk of premature atherosclerosis is increased due to hyperlipidemia. The duration of nephrotic hyperlipidemia appears to be critical to initiating vascular damage, and patients with unremitting proteinuria and hypoalbuminemia are the most at risk (781).

Very low-density lipoprotein (VLDL), low-density lipoprotein (LDL) and lipoprotein (a) are elevated in children with longstanding and frequently relapsing NS (779). Elevated VLDL and LDL should place patients at increased risk for developing atherosclerosis. Hyperlipidemia contributes to the development of glomerular and interstitial renal disease. Endothelial damage from hyperlipidemia may favor influx of lipoprotein into the mesangium, leading to proliferation and sclerosis (780).

ANEMIA

Mild anemia is observed on occasion in patients with NS. Anemia is usually microcytic and hypochromic, typical of iron deficiency, but is resistant to therapy with iron because of large loss of serum transferrin in the urine of some nephrotic patients30). Vaziri31) reported some data on the metabolism and regulation of erythropoietin (EPO) and transferrin, which are essential for erythropoiesis in nephrotic children. Urinary loss of EPO causes EPO-deficiency anemia and transferrinuria, and increased transferrin catabolism induces hypotranferrinemia and iron-deficiency anemia in some cases. Subcutaneous administration of recombinant EPO and iron supplementation can be used for the treatment of EPO- and iron-deficiency anemia, respectively (579). However, correction of the underlying proteinuria will be the ideal approach to reversing these complications.

HORMONAL, MINERAL ALTERATIONS

Urinary loss of hormone-binding proteins contributes to various hormonal abnormalities in patients with NS. While thyroid function tests are in the normal range in most nephrotic patients, the mean values for triiodothyronine (T3) and thyroid-binding globulin (TBG) are lower than those in non-NS children because of a significant increase in urinary excretion of T3, T4 and TBG (782). Routine thyroid screening and early replacement therapy of thyroid hormone are necessary for infants with severe NS and clinical hypothyroidism.

Hypocalcemia in NS is also attributed to the decreased albumin level, which results in reduced bound and ionized calcium in 50 to 80% of NS cases ((783)). Children with NS often have hypocalciuria due to decreased gastrointestinal absorption of calcium and increased renal tubular reabsorption of calcium. These suggest the possibility of an abnormality in vitamin D metabolism. The abnormalities are due to increased filtration of vitamin D metabolites bound to vitamin D-binding globulin (784). However, bone disease is rarely shown in NS patients, and therefore, routine treatment with vitamin D is not recommended. Nevertheless, special concern should be given to subclinical mineral bone disorder like secondary hyperparathyroidism. Prednisolone used to treat nephrotic syndrome binds with vitamin D receptor at intestine and proximal tubules and hence reduces its absorption (ref – vit D)

Measurement of bone mineral density (BMD) using dual-energy X-ray absorptiometry is recommended for children with FRNS or SDNS (785,786). Collectively, there is insufficient evidence on bisphosphonates, vitamin D,

NUTRITION

Several recommendations supported by observational data exist regarding nutrition in pediatric patients with nephrotic syndrome. Specifically, children with nephrotic syndrome and edema should be evaluated for malabsorption and subsequent malnutrition due to bowel wall edema.

In edematous patients, long-term sodium restriction is appropriate with a maximum goal of approximately 2500 mg/day.

Drug related complications are discussed details in table 05.

TRANSITION FROM PEDIATRIC TO ADULT RENAL SERVICES

Transition is a process that involves purposeful, planned efforts to prepare the pediatric patient to move from caregiver-directed care to disease self management in the adult unit.

Now a days the number of young patients reaching from pediatric to adult renal care has progressively increased due to improvement in medical science and survival rates of 85–90% (787). It is recognised that there are substantial risks of nonadherence at the time of transfer from pediatric to adult care. For children with a chronic conditions, a comprehensive, multiprofessional team of clinicians, nurses, dietitians, social workers, play therapists, psychologists and educators is the most effective way to minimise disabilities and maximise the potential of each child. Support for children and familiesis are needed during transition. In the most desirable format, therefore, transfer is an event that takes place at the end of a transition process designed to be a more purposeful and concerted effort to prepare the young person with a chronic condition to accept responsibility for his/her disease management. Wherever managed, young people in the 14- to 24-year age group need special consideration, and it is important that their view points are considered when transfer does take place between pediatric and adult units.

Timing:

When a patient reaches 14 years of age, the doctor and the psychologist inform them and their family about the transition process, the healthcare professionals involved, and the medical appointments they will need to attend. When the patient reaches 16 years of age, a multidisciplinary appointment is organized during which the pediatric team introduces the patient to the adult nephrologist and psychologist responsible for the transition process (788).

The process of transfer to adult services begins when the patient is 14 and is complete by the time they reach 18 years of age. During this period, all the patients in transitional care receive continuous medical care and psychological support and their families are involved throughout the entire process.

The psychological interviews which take place between 16 and 18 years of age include psychometric evaluation, which is repeated in cases where significant psychological suffering .

The adult nephrologist in the transition team initially takes charge of the patient, irrespective of their type of kidney disease. Only subsequently will the patient be assigned to the appropriate out-patient clinic based on their specific nephropathy. Within the first year after transfer to the adult service, the patient is asked to undergo a psychological-psychometric evaluation.

Table 35 Timing of transition

When	14 yrs	16 yrs	18 yrs
Where	Pediatric Nephrology Clinic	Transition Clinic	Adult Nephrology Clinic
Who	Pediatric team	Pediatric and adult team	Adult team

Consensus statement

Where appropriate, components are marked with an A for essential and a D for desirable.

1. Transition to transfer: Transfer should occur from pediatric to adult nephrology services only after efforts to assess and prepare the adolescent/young adult have occurred and necessary patient care information has been delivered to the receiving adult service (A).
2. Transfer from pediatric to adult nephrology should:

a) Be individualised for each patient after he/she has completed a transition plan; this will depend upon completion of physical growth and, where possible, educational, social and psychological attainment (A)

b) Be agreed upon jointly by the patient and his/her family/carers in conjunction with the pediatric and adult renal care teams (A);

c) Take place during a period without crises, especially if there is unstable social support (A);

d) Take place after completing school education (A);

e) Take into account treatment plans by other subspecialties, with particular reference to urological supervision (A);

f) Take place with due consideration of financial factors and not be done abruptly without adequate preparation as a result of financial pressures (A).

3. Transition process

The most effective time to transfer an adolescent/ young adult from a pediatric to adult renal service occurs after a transition process. Hence, young people should be:

a) Introduced to the concept of transition in early adolescence (12–14 years) (A);

b) Given information about transition in a gradual manner appropriate to his/her developmental stage and intellectual ability (A);

c) Directed by identified lead clinicians (transition champions) in pediatric and adult units to coordinate and educate on transition issues (A);

d) Assigned to a nominated key worker responsible for coordinating transition from both the pediatric and adult renal service (A); support professionals (nurses, youth workers, social workers etc) can be very effective in facilitating transition by providing access to ongoing support groups, providing practical aid and advice to the transitioning young person .

e) Provided with a generic transition plan that then can be individualised for each patient . (A); most transition plans have certain competencies to be achieved at a certain age (see example in Table 1). Feedback from young people indicates that some like to follow a plan through different stages and some like to do it all in a short period prior to transfer;

f) Include parents, other family members and even boyfriends/girlfriends (if the young person agrees), as more information lessens anxiety (A);

g) Be offered the opportunity of an informal visit to the nominated adult service before transfer occurs (A)

h) Be given the opportunity to participate in group sessions with other young people who are about to transition for peer-support experience (A); peer support can be complemented by establishing a local e-mail and social networking group;

i) Be able to receive tools to aid in the acquisition of disease self-management skills, such as the transition medical passport, a self-administered transition, readiness survey and the TRxANSITION Scale, which are useful adjuncts (D).

4. Transition or transfer clinic

a) A transfer clinic in either the adult or pediatric renal unit with both adult and pediatric nephrologist in attendance is the optimal minimum standard (A);

b) An internal medicine specialist or nephrologist in each adult service should take a special interest and be trained in managing young people with CKD 4–5 (D);

c) Specialist nurses for adult patients who liaise with specialist nurses from the paediatric unit can ensure continuity of care (A);

d) Transfer to adult renal care should include a comprehensive written and verbal summary of all the multidisciplinary aspects of the young person's care; this should include medical, nursing, dietary, social and educational information (A);

e) The young person should be prepared through a transition pathway to assert their autonomy and help provide the relevant information about themselves (A);

5. Continuity of care

A recurring point raised by young people who have transferred is the lack of continuity of care and build up of trust that they experienced in the paediatric unit. It is appreciated that many transition issues raised in these statements are aspirational, but two options could be considered:

Option 1: An ideal method to promote successful transition is to preserve continuity of care through the efforts of a small team of specific professionals responsible for assuring the care of the transferred young person. This may involve an adult nephrologist, nurse specialist and one or more support staff (youth worker, social worker, etc) in the adult service. This dedicated team should have training in managing teenagers and young adults and have knowledge of paediatric renal diseases (D). The potential availability of such a team will vary according to country and facilities resourced.

Option 2 Adult renal centres could establish young adult clinics that would incorporate both patients transferred from paediatric care and adolescents and young adults (aged <24) who may have presented with CKD 4–5 directly to the adult renal unit (D) . A recent survey of US internists found that many felt the need for better training in congenital and childhood-onset conditions, and expressed concerns about psychosocial.

Transition from pediatric to adult renal services is an individualised process that provides the young person with appropriate self-management skills and assesses support structures. As young people are in transition from 14 to 24 years, it is vital that there is good communication between pediatric and adult services, especially at the point of transfer. Support for this age group should be developed on both paediatric- and adult-focused sides. The consensus statements highlight developments that are necessary to ensure a successful health care transition process.

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