Childhood nephrotic syndrome

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Idiopathic nephrotic syndrome is the most common glomerular disease in children. Corticosteroids are the cornerstone of its treatment, and steroid response is the main prognostic factor. Most children respond to a cycle of oral steroids, and are defined as having steroid-sensitive nephrotic syndrome. Among the children who do not respond, defined as having steroid-resistant nephrotic syndrome, most respond to second-line immunosuppression, mainly with calcineurin inhibitors, and children in whom a response is not observed are described as multidrug resistant. The pathophysiology of nephrotic syndrome remains elusive. In cases of immune-mediated origin, dysregulation of immune cells and production of circulating factors that damage the glomerular filtration barrier have been described. Conversely, up to a third of cases of steroid-resistant nephrotic syndrome have a monogenic origin. Multidrug resistant nephrotic syndrome often leads to kidney failure and can cause relapse after kidney transplant. Although steroid-sensitive nephrotic syndrome does not affect renal function, most children with steroid-sensitive nephrotic syndrome have a relapsing course that requires repeated steroid cycles with significant side-effects. To minimise morbidity, some patients require steroid-sparing immunosuppressive agents, including levamisole, mycophenolate mofetil, calcineurin inhibitors, anti-CD20 monoclonal antibodies, and cyclophosphamide. Close monitoring and preventive measures are warranted at onset and during relapse to prevent acute complications (eg, hypovolaemia, acute kidney injury, infections, and thrombosis), whereas long-term management requires minimising treatment-related side-effects. A subset of patients have active disease into adulthood.

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Clinical presentation

The diagnosis of nephrotic syndrome is based on the presence of nephrotic-range proteinuria and hypoalbuminaemia (table 1). Oedema is often present and distributed in gravity-dependent areas, such as the periorbital area (thus leading to frequent misinterpretation as allergy), the lower extremities, and scrotal or labial areas. Ascites and pleural oedema can develop and lead to abdominal discomfort and dyspnoea, and families or patients might describe the urine as foamy or frothy. Acute presentation can be complicated by acute kidney injury, secondary to renal hypoperfusion following low oncotic pressure due to severe hypoalbuminaemia, severe infections due to excessive urinary loss of immunoglobulins and complement opsonins, and venous thrombosis following massive loss of anticoagulants in the presence of hyperlipidaemia and hyperviscosity. Between 15% and 20% of children with nephrotic syndrome have microscopic haematuria or hypertension.

Epidemiology

Although idiopathic nephrotic syndrome is the most common glomerular disease in children, it is nonetheless rare, with an incidence of 1·4–6·1 per 100 000 children depending on ethnicity.[1] A meta-analysis of 27 studies reported an average incidence of 2·92 per 100 000 children per year.[1] The incidence was higher in southeast Asia and east Asia than in Europe, North America, and Oceania (6·1 *vs* 2·15, 2·4, and 1·4 per 100 000 children per year, respectively) and did not appear to change between 1929 and 2011 (p=0·39).[1]

Most children with idiopathic nephrotic syndrome respond to a standard course of oral corticosteroids, and are therefore classified as having steroid-sensitive nephrotic syndrome. Most patients tend to have disease relapses throughout childhood, but the disease course varies, with 35–40% of patients having a single episode or one to two relapses, and 55–60% having more frequent relapses.[2] Steroid resistance is observed in 5–15% of cases, and usually occurs at disease onset (primary or initial resistance), or occasionally later in the disease course (secondary steroid resistance).[3] Table 1 summarises the current definitions and disease classification.

Pathophysiology

The underlying cause of nephrotic syndrome differs depending on age at first presentation (figure 1). In adults, a renal biopsy is done at presentation, most frequently revealing membranous nephropathy and focal segmental glomerulosclerosis, and less frequently minimal change disease or other glomerular diseases. By contrast, more than 85% of children older than 1 year with a classic presentation of nephrotic syndrome have steroid-sensitive nephrotic syndrome, and if a biopsy sample is taken, it

Search strategy and selection criteria

We searched the Cochrane Library for publications published in a 5-year period until Nov 1, 2022, and MEDLINE in a 50-year period until Nov 1, 2022, with no language restrictions. We used the search terms "nephrotic syndrome", "minimal change disease", and "focal segmental glomerulosclerosis" in combination with "childhood" or "pediatric" or "children". We largely selected publications in the past 5 years but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Review articles and book chapters are cited to provide readers with additional details and references.

	Definition
Nephrotic-range proteinuria	UPCR ≥200 mg/mmol (2 mg/mg) in a spot urine sample, 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 hypoalbuminaemia (serum albumin <30 g/L) or oedema when serum albumin is not available
Complete remission	UPCR based on either first morning void (≤20 mg/mmol [0·2 mg/mg]) or 24 h urine sample (<100 mg/m² per day), or negative or trace dipstick on 3 or more consecutive days
Partial remission	UPCR (based on first morning void) >20 mg/mmol, but <200 mg/mmol (>0·2 mg/mg but <2 mg/mg) and serum albumin ≥30 g/L
Steroid-sensitive nephrotic syndrome	Complete remission within 4 weeks of taking prednisone or prednisolone at standard dose (60 mg/m² per day or 2 mg/kg per day at a maximum of 60 mg/day) at disease onset
Steroid-resistant nephrotic syndrome	Complete remission not observed within 4 weeks of treatment with prednisone or prednisolone at standard dose at disease onset
Confirmation period	Time period between 4 weeks and 6 weeks from prednisone or prednisolone initiation, during which time responses to further oral prednisone or prednisolone, with or without pulses of intravenous methylprednisolone and renin-angiotensin system inhibitors, are seen in patients for whom partial remission is observed at 4 weeks; if complete remission is not observed by 6 weeks, these patients are defined as having steroid-resistant nephrotic syndrome
Steroid-sensitive nephrotic syndrome late responder	A patient for whom complete remission is observed during the confirmation period (ie, between 4 weeks and 6 weeks of prednisone or prednisolone therapy)
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 oedema in a child who had previously reached complete remission
Infrequently relapsing nephrotic syndrome	Less than two relapses in the 6 months following remission of the initial episode, or fewer than three relapses in any subsequent 12 month period
Frequently relapsing nephrotic syndrome	More than or equal to two relapses in the first 6 months following remission of the initial episode, or more than or equal to three relapses in any 12 month period
Steroid-dependent nephrotic syndrome	A patient with steroid-sensitive nephrotic syndrome who has two consecutive relapses during recommended prednisone or prednisolone therapy for first presentation, relapse, or within 14 days of its discontinuation
Multidrug resistant steroid-resistant nephrotic syndrome	Absence of complete remission after 12 months of treatment with two mechanistically distinct steroid-sparing agents (eg, a calcineurin inhibitor and rituximab or mycophenolate mofetil) at standard doses
Secondary steroid resistant nephrotic syndrome	Steroid-sensitive nephrotic syndrome in which complete remission is not observed within 4 weeks of taking prednisone or prednisolone at standard dose after a subsequent relapse
Congenital nephrotic syndrome	Nephrotic syndrome with onset within the first 3 months of age
Infantile nephrotic syndrome	Nephrotic syndrome with onset between ages 3 months and 12 months

UPCR=urinary protein:creatinine ratio

Table 1: **Definitions of childhood nephrotic syndrome (adapted from International Pediatric Nephrology Association guidelines)[3,47]**

often shows minimal change disease.[7,8] A kidney biopsy is therefore only done if there is not a complete response to oral prednisone at 4–6 weeks (defined as steroid-resistance) or if there are atypical features (panel 1). In the absence of a biopsy being done, and given our incomplete understanding of the underlying mechanisms, typical cases of nephrotic syndrome are considered idiopathic.

The majority (>80%) of congenital forms (ie, presenting within the first 3 months of life)[9] and up to 30% of initial steroid-resistant forms of nephrotic syndrome are caused by pathogenic variants in genes encoding for proteins of the glomerular filtration barrier scaffolding.[10] These variants cause structural alterations that disrupt the integrity of the glomerular filtration barrier, leading to proteinuria that is non-responsive to immunosuppressive drugs. Figure 2 shows genetic and immune-mediated alterations that lead to nephrotic syndrome in children.

The pathophysiology of idiopathic nephrotic syndrome in childhood is not clearly understood. The disappearance of proteinuria following immunosuppression with prednisone and other agents indirectly indicates a pivotal role for immune cells and circulating immune factors in damaging the glomerular filtration barrier, but the exact mechanism is not known. Kidney biopsies show little or no evidence of inflammatory infiltrate or immune-complex deposition in the glomeruli. Historically, T cells were thought to have a leading role in the pathogenesis of nephrotic syndrome based on indirect evidence, such as sensitivity to prednisone and cyclophosphamide, the association of steroid-sensitive nephrotic syndrome with T-cell lymphomas, and spontaneous remission after measles infection, which suppresses T cell activity.[11] Shalhoub's hypothesis[11,12] of a T cell-derived permeability factor prompted numerous studies yielding conflicting results, probably due to heterogenous disease severity and the confounding effect of concomitant immunosuppression. Studies in the past two decades suggest an imbalance of T-helper-17 cell (Th17) and T regulatory cell (Treg) responses, indicated by an increase in circulating Th17 cells and Th17-related cytokines, IL-17 deposition in kidney biopsies, and a decrease in $CD4^+$, $CD25^+$, and $FOXP3^+$ Tregs.[13–15]

In the past 15 years, the effective use of B cell-depleting monoclonal antibodies, mainly rituximab, in relapsing forms of steroid-sensitive nephrotic syndrome has raised interest in the pathogenic role of B cells. Alterations in B-cell subsets, mainly a prevalence of memory B cells over other subsets, have been reported in treatment-naive patients at disease onset and during relapse.[16] Reconstitution of memory B cells following treatment with anti-CD20 antibodies precedes and predicts relapse.[14,17,18] A 2022 study described anti-nephrin antibodies in serum and kidney biopsies in a subset of patients,[19] and anti-podocyte UCHL1 antibodies had previously been identified in plasma of children with nephrotic syndrome in relapse.[20] Circulating factors are present in multidrug-resistant nephrotic syndrome, usually characterised by focal segmental glomerulosclerosis, which progresses to kidney failure and recurs post-transplantation in the allograft. The presence of circulating factors is indicated both by clinical observation that immediate recurrence post-transplant is reversed by the allograft being removed and reimplanted in another recipient,[21] and by experimental animal models in which serum from patients with recurrent focal segmental glomerulosclerosis induced proteinuria and podocyte foot process effacement.[22] The identity of these circulating

factors remains elusive. Putative agents that have been proposed are haemopexin (a protease; HPX),[23,24] cardiotrophin-like cytokine factor 1 (CLCF1; a cytokine of the IL-6 family) and calcium/calmodulin-dependent serine protein kinase (CASK).[25,26] Elevated concentrations of suPAR, the soluble form of urokinase plasminogen activator receptor expressed by immune cells, endothelial cells and podocytes, are found in many conditions associated with kidney injury, and can induce foot process effacement. However, suPAR injection alone is insufficient to induce proteinuria in experimental models.[27] Increased serum concentrations of soluble CD40 ligand and of anti-CD40 immunoglobulins have been found in some patients with focal segmental glomerulosclerosis.[28,29]

Genetics and risk factors

A monogenic origin for steroid-resistant nephrotic syndrome is identified in up to 30% of cases (higher in consanguineous families), and is caused by pathogenic variants in more than 50 different podocyte-related genes.[30,31]

Clinical findings signalling a genetic origin include syndromic features, a family history of nephrotic syndrome, early age at presentation, non-response to immunosuppressive drugs, progression towards kidney failure, and the absence of recurrence after renal transplantation. As the monogenic forms of steroid-resistant nephrotic syndrome are caused by a structural defect of the podocyte, they are not expected to be responsive to immunosuppression, and do not recur after transplantation of a healthy kidney.[30,32,33]

The prevalence of genetic causes of nephrotic syndrome decreases with age, from greater than 80% in congenital nephrotic syndrome and 50% in infantile nephrotic syndrome (aged 4–12 months), to 25% in individuals aged 13 months to 6 years, 18% in individuals aged 7–12 years, and 11% in adolescents (aged between 12 years and 18 years).[9,10] The pattern of underlying genetic defects also depends on age. *NPHS1* bi-allelic pathogenic variants account for most cases of congenital nephrotic syndrome,[34] although it can be due to bi-allelic variants of *NPHS2, PLCE1, LAMB2,* or monoallelic variants of *WT1* in rare cases.[9] *NPHS2* variants are the leading cause of congenital nephrotic syndrome and steroid-resistant nephrotic syndrome in individuals older than 1 month at diagnosis, followed by *NPHS1* variants.[32,34,35] *WT1* variants show a biphasic distribution with a first peak in individuals aged 4–12 months, and a second peak in individuals aged older than 18 years.[36] Other dominant gene variants (mainly *INF2* and *TRPC6*) are most often detected in individuals aged between 11 years and 30 years, although they have been detected in individuals aged between 5 years and 70 years. Altogether, variants in *NPHS1, NPHS2, PLCE1, LAMB2, WT1* and *TRPC6* genes cover around 25% of the genetic causes of childhood-onset steroid-resistant nephrotic syndrome.[10] Since 2015, pathogenic variants in the *COL4A3–5* genes, also known to underlie Alport syndrome, have emerged as important causes of steroid-resistant nephrotic syndrome with isolated proteinuria. These pathogenic variants are now identified in 2·5% of children and 10% of adults with steroid-resistant nephrotic syndrome or focal segmental glomerulosclerosis, thereby accounting for half of identified monogenic cases in adults.[35,37] Between 1% and 5% of the identified genetic variants concern genes involved in the coenzyme Q10 biosynthesis pathway (ie, *COQ2, COQ6, COQ8B,* and *PDSS2*). *COQ8B* variants are particularly frequent in Asia,[10,38–40] and are the only variants that have a potential specific treatment (ie, COQ10).[41] These genes, and others, can cause isolated or syndromic steroid-resistant nephrotic syndrome, and their association with non-renal manifestations can further suggest genetic causes (appendix p 1). Variants in *WT1,* for instance, are associated with Denys-Drash syndrome and Frasier syndrome.[36] These forms are associated with an increased neoplastic risk (eg, Wilms tumour and dysgerminoma), warranting close follow-up by abdominal ultrasound.

See Online for appendix

Comprehensive genetic screening, including all steroid-resistant nephrotic syndrome-related genes by a gene panel or whole exome sequencing is indicated in two subsets of patients. These subsets are children with primary steroid-resistant nephrotic syndrome after exclusion of differential diagnoses by renal histology, and children with congenital nephrotic syndrome, infantile nephrotic syndrome, or syndromic nephrotic syndrome[3] (panel 1, figure 3).

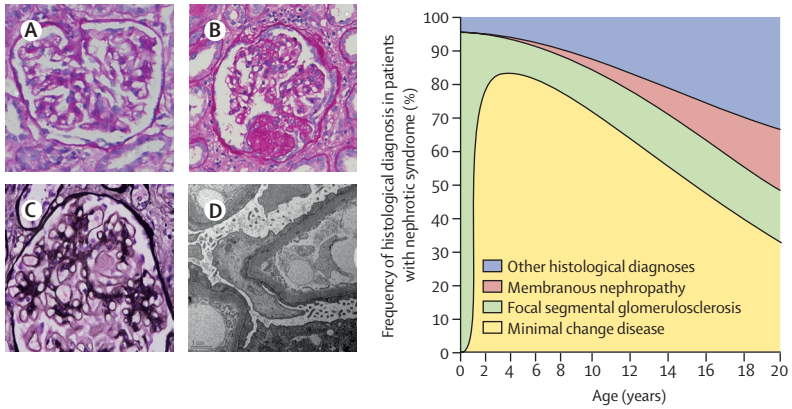

Figure 1: **Approximate distribution of underlying causes of nephrotic syndrome according to age, and representative histological images**

Data that comprise the graph are derived from previously published studies[4-6] modified from a review on minimal change disease.[7] (A) Minimal change disease: a morphologically unremarkable glomerulus (Periodic acid–Schiff stain; magnification 20×). (B) Focal segmental glomerulosclerosis: the sclerotic segment in the bottom middle section of the image is crowned by epithelial cells with an irregularly thickened Bowman capsule (Periodic acid-Schiff stain; magnification 20×). (C) Membranous nephropathy: silver methenamine stained glomerulus indicates prominent glomerular basement membrane with stiff capillary walls, and a spike appearance caused by the projections of basement membrane matrix towards the urinary space (magnification 30×). (D) Transmission electron microscopy showing diffuse foot process effacement, actin condensation, and microvillous transformation, the ultrastructural hallmarks of podocyte injury underlying proteinuric renal diseases (Uranyl acetate-lead citrate; magnification 2550×). Histological biopsy images provided by Geetika Singh (Department of Pathology, All India Institute of Medical Sciences, New Delhi, India).

Panel 1: Diagnostic investigations of childhood nephrotic syndrome

Clinical evaluation

Relevant patient history

- Presence of gravity-dependent oedema, recent weight increase
- Fever, pain, abdominal discomfort, or fatigue
- At onset: search for risk factors for secondary causes (eg, sickle cell disease, HIV, systemic lupus erythematosus, hepatitis B, cytomegalovirus, malaria, parvovirus B19, and medications)
- Screen for tuberculosis in patients from endemic areas before starting immunosuppressant medications
- During follow-up: screen for symptoms of PDN*-related toxicity† (infection and increased appetite, weight gain, sleep disturbances, behavioural changes)

Physical examination

- Blood pressure, and assess blood volume status and the extent of oedema (ascites, and pericardial and pleural effusions); lymphadenopathy
- Signs of infection (the respiratory tract, skin, urinary tract, and for peritonitis)
- At onset: search for extrarenal features, such as dysmorphic features, ambiguous genitalia, eye abnormalities (eg, microcoria or aniridia), rash, or arthritis
- During follow-up: signs of PDN-related toxicity:‡ striae rubrae, Cushingoid features, acne, or skeletal or muscular pain

Anthropometry

- Growth chart: height or length, weight, and head circumference (in children younger than 2 years), compare data with appropriate national standards or WHO-multicentre growth reference study charts
- During follow-up, for patients on corticosteroids for longer than 12 months: body-mass index and annual height velocity, compare data with appropriate national standards or WHO-multicentre growth reference study charts

Vaccination status

- Check and complete before starting steroid-sparing agents, according to national standards
- Vaccines include pneumococcal, meningococcal, *Haemophilus influenzae*, hepatitis B, SARS-CoV-2, influenza, varicella, and measles

Family history (at onset)

- Kidney disease in family members
- Extrarenal manifestations
- HIV or tuberculosis in endemic regions
- Consanguinity

Biochemistry†

- Spot urine sample in the morning, recommended at least once before starting treatment for the first episode, and at each visit: protein:creatinine ratio and urinalysis, including haematuria
- Complete blood count; concentrations of creatinine, electrolytes, urea, and albumin; and estimated glomerular filtration rate (eGFR)§
- At onset: complement C3, complement C4, antinuclear antibodies, antistreptococcal antibodies, and antineutrophil cytoplasmic antibodies, as needed, especially if haematuria is present

Imaging and other specialised assessments

Kidney ultrasound

- Consider exclusion of renal malformations and venous thrombosis in patients with reduced eGFR, haematuria, or abdominal pain
- Done to exclude solitary kidney before taking a biopsy

Kidney biopsy

- Perform when atypical features are present, including macroscopic haematuria, persistent microscopic haematuria, low concentrations of complement C3, sustained hypertension, systemic symptoms (eg, arthritis, rash), for all children with steroid-resistant nephrotic syndrome, and if there is an acute kidney injury not attributed to hypovolaemia
- Consider for patients older than 12 years at disease onset and subsequently in patients who have received treatment with a calcineurin inhibitor for longer than 2–3 years.

Genetic testing

- By gene panel or whole exome-sequencing
- Perform in all patients with congenital nephrotic syndrome and primary steroid-resistant nephrotic syndrome, particularly if the patient has extrarenal features, family history suggesting syndromic or hereditary steroid-resistant nephrotic syndrome, onset in infancy (<12 months), or a non-response to immunosuppression with a calcineurin inhibitor

Dual-energy x-ray absorptiometry scan

- To be considered in follow-up, every 12–18 months if the patient is on a prolonged course or a high cumulative dose of corticosteroids

Ophthalmological evaluation

- For glaucoma and cataracts in follow-up, yearly if the patient is on a prolonged course or a high cumulative dose of corticosteroids

Home monitoring

- Dipstick assessment daily until remission, then at least twice weekly after, daily if the dipstick score is 1 or more, or during episodes of fever, infections, or suspected relapse (oedema)
- Blood pressure and bodyweight during relapse twice weekly

*Commonly written to mean either prednisone or prednisolone, dpeending on what is available at the time and location. In individuals with normal hepatic function they are considered equivalent in terms of efficacy. †See table 2 for required evaluations in children taking different immunosuppressive agents. ‡See table 2 for symptoms and signs of toxicity related to other immunosuppressive agents. §eGFR (mL/min per 1·73 m^2) measured as k × height (cm)/serum creatinine (mg/dL), where k is 0·413, or as k × height (cm)/serum creatinine (μmol/L), where k is a constant 36·5.[44,45]

No definite genetic cause has been identified in children with steroid-sensitive nephrotic syndrome, including familial forms,[46] and genetic testing is not recommended.[3] Familial clustering and interethnic variability suggest that genetic susceptibility might play a role in some cases; however, the pattern of inheritance of steroid-resistant nephrotic syndrome is complex, with multiple variants interacting with one another and with environmental factors. Genome-wide association studies done in transethnic cohorts have highlighted the central role of the immune system in steroid-sensitive nephrotic syndrome.[47] The strongest and most consistent association in these studies is located within the *HLA-DR* and *DQ* region, specifically in and around *HLA-DQA1* and *HLA-DQB1*.[48,49] Ethnicity also plays an important role because risk haplotypes are often different between study populations. For example, steroid-resistant nephrotic syndrome associated with two *APOL1* risk-alleles (G1 or G2) is prevalent in populations of sub-Saharan African ancestry, and is associated with fast progression to kidney failure.[50–52]

Triggering events, such as upper respiratory tract infections, other infections, and allergic reactions (eg, food allergens or environmental allergens such as pollen, dust, and mould) often lead to the onset and relapse of idiopathic nephrotic syndrome. Although some patients with nephrotic syndrome present with elevated IgE concentrations, numerous studies attempting to link atopy and nephrotic syndrome have not identified a specific allergen or allergic disorder that induces the disease.[53] A 2021 study described gut dysbiosis leading to increased oxidative stress and quantitative and qualitative Treg cell impairment in children with relapsing forms of steroid-sensitive nephrotic syndrome.[15] Reports of dietary interventions (eg, gluten-free or dairy-free diets) altering gut microbiota, Treg–Th17 imbalances, and reducing proteinuria in some children with multidrug resistant forms of steroid-resistant nephrotic syndrome need to be confirmed in larger studies.[54]

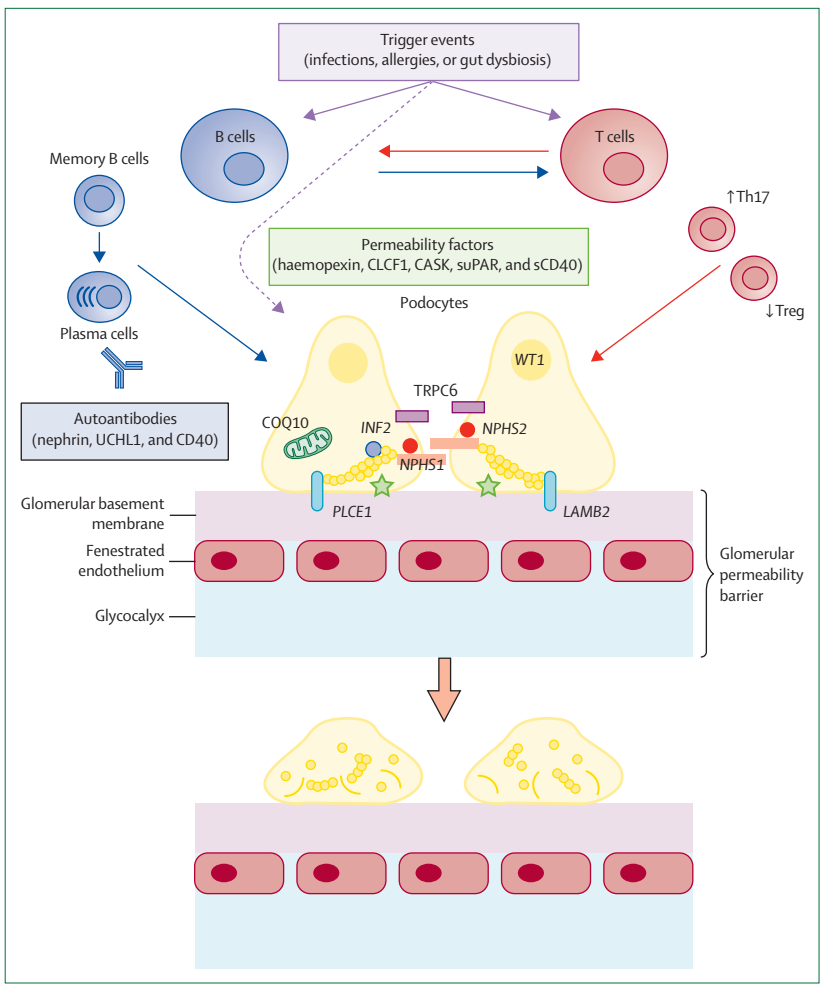

Figure 2: **Pathophysiology of childhood nephrotic syndrome (immune system and genetic)**
Adapted from Vivarelli et al.[7] In forms of nephrotic syndrome that respond to immunosuppression, alterations in immune cells can lead to disruption of the glomerular filtration barrier. This mechanism is unknown and probably varies within different forms of the disease. However, T cells and B cells crosstalk, imbalances in T-cell subpopulations with an increase in the T-helper-17:T regulatory cell ratio, increased B-cell subsets (particularly some forms of memory B cells), the presence of circulating autoantibodies (eg, antinephrin, anti-UCHL1, and anti-CD40 in other forms), and other circulating factors (eg, haemopexin, CLCF-1, suPAR, and sCD40) in some forms of steroid-resistant nephrotic syndrome have been identified. In monogenic forms of nephrotic syndrome, pathogenic variants in genes encoding proteins of the podocyte scaffolding (eg, *NPHS1, NPHS2, WT1, LAMB2, PLCE1, INF2, TRPC6*, and *COQ10*) determine damage to the filtration barrier. CLCF1=cardiotrophin-like cytokine factor 1. CASK=calcium/calmodulin-dependent serine protein kinase. suPAR=soluble form of urokinase plasminogen activator receptor. Th17=T-helper-17 cells. Tregs=T regulatory cells.

Clinical investigation and differential diagnosis

The differential diagnosis of children with nephrotic syndrome is driven by their age at onset (figure 1) and steroid responsiveness (table 1, appendix p 2). In children younger than 12 months, monogenic forms of nephrotic syndrome caused by podocyte mutations are prevalent. Particularly in cases of steroid-resistant nephrotic syndrome, a careful history noting family members with nephrotic syndrome, extrarenal manifestations not limited to dysmorphic features, ambiguous genitalia or eye conditions, such as microcoria, hypoplasia of the iris, lenticonus, posterior cataracts, strabismus, nystagmus, optic atrophy, or blindness, or a history of consanguinity should prompt the consideration of genetic testing (panel 1, appendix pp 1, 2).

In addition to urinalysis to confirm the presence of proteinuria, the initial biochemical tests done for a child with suspected nephrotic syndrome should include a quantitative assessment of proteinuria alongside blood collection to measure serum albumin, creatinine, and electrolytes. Measurement of complement C3 and C4 concentrations, antinuclear antibodies, antistreptococcal antibodies, and antineutrophil cytoplasmic antibodies should be considered in patients with concurrent haematuria (panel 1).

Children presenting with idiopathic nephrotic syndrome should receive a standard course of oral PDN (table 2 and appendix p 2; PDN is commonly written to mean either prednisone or prednisolone, depending on

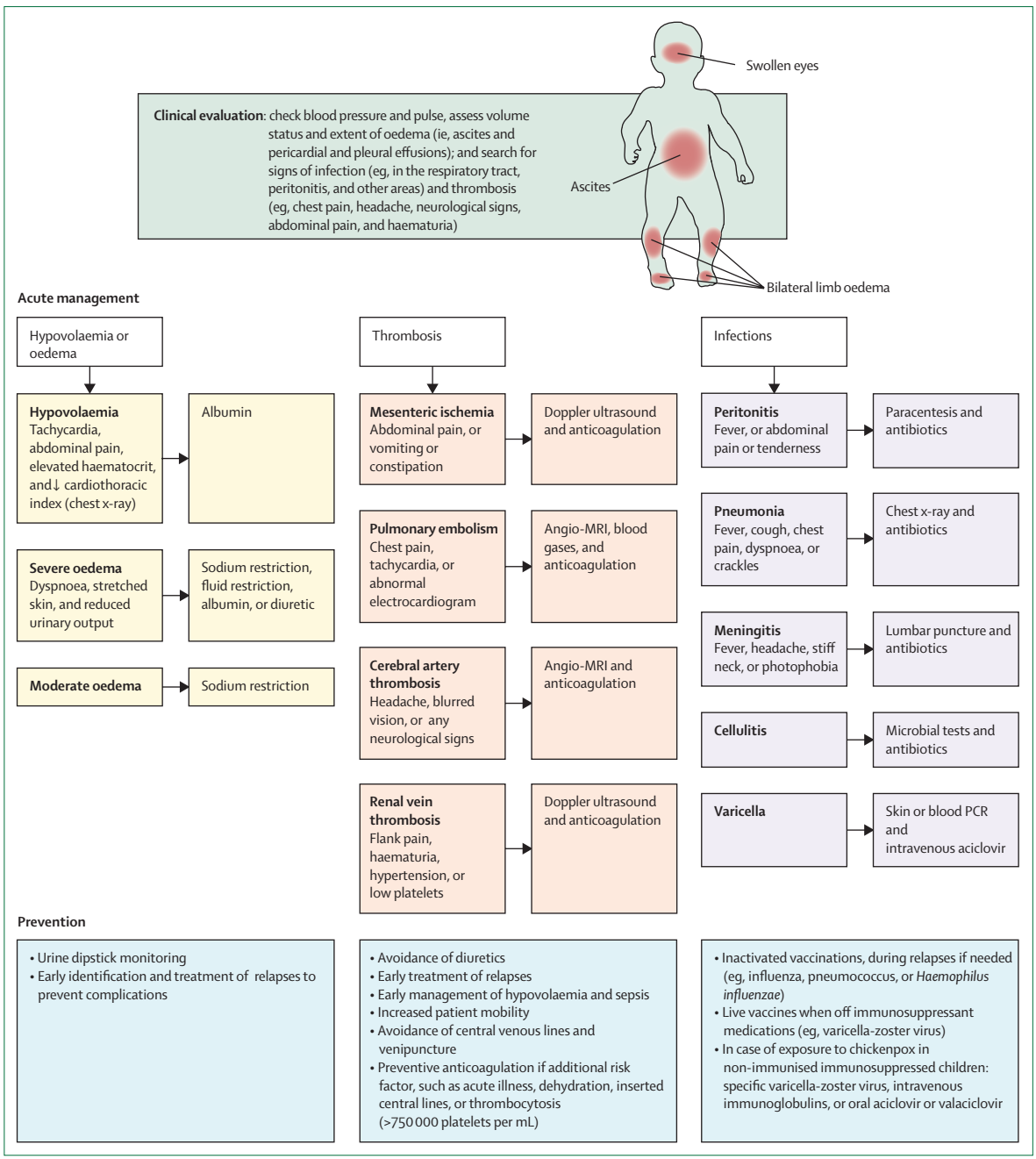

***Figure 3*: Evaluation, management, and prevention of nephrotic syndrome complications in children**
In the presence of any acute symptom, the main nephrotic syndrome complications (ie, hypovolaemia, infections, and thromboses) should be investigated and treated promptly if appropriate. Prevention mostly relies on monitoring proteinuria with dipstick tests, early treatment of relapses, and vaccination.

what is available at the time and location. In individuals with normal hepatic function they are considered equivalent in terms of efficacy). Steroid sensitivity is expected for 75–90% of children presenting with idiopathic nephrotic syndrome. If done, kidney biopsy is likely to reveal minimal change disease with podocyte foot process effacement on electron microscopy[8] (figure 1, panel D). As previously mentioned, renal biopsy is not recommended as part of the initial tests for children with idiopathic nephrotic syndrome, because it does not affect initial management of the disease.[43] However, kidney biopsy is warranted for any patient found to have steroid-resistant nephrotic syndrome.[3] Additionally, kidney biopsy should be considered as part of the initial tests for children presenting with atypical features, such as macroscopic haematuria or hypocomplementaemia

	Dose	Monitoring	Adverse effects
Oral PDN*	Treatment of first episode: 60 mg/m² (2 mg/kg, max 60 mg) daily for 4 weeks or 6 weeks followed by 40 mg/m² (1·5 mg/kg, max 40 mg) alternate day for 4 weeks or 6 weeks. If steroid-resistant nephrotic syndrome is diagnosed, taper and discontinue within 6 months; treatment of relapse: 60 mg/m² (2 mg/kg, max 60 mg) daily until 3–5 daily negative dipstick test results, followed by 40 mg/m² (1·5 mg/kg, max 40 mg) alternate day for 4 weeks	Quarterly: blood pressure, height, weight, BMI; yearly: height velocity, 25-hydroxy vitamin D concentration in patients receiving oral PDN for at least 6 months, aiming for >20 ng/mL (>50 nmol/L); frequency of ophthalmological assessment and DEXA scan to be established on an individual basis	Weight gain, hypertension, hyperglycaemia, behavioural disorders, sleep disruption, linear growth delay, Cushingoid features, glaucoma, cataracts, and reduced bone mineral density
Low dose alternate day PDN	≤0·5 mg/kg per alternate day, max 20 mg alternate day	Quarterly: blood pressure, height, weight, and BMI; yearly: height velocity, 25-hydroxy vitamin D concentrations in patients receiving oral PDN for at least 6 months, aiming for >20 ng/mL (>50 nmol/L); frequency of ophthalmological assessment and DEXA scan to be established on an individual basis	Weight gain, hypertension, hyperglycaemia, behavioural disorders, sleep disruption, linear growth delay, Cushingoid features, glaucoma, cataracts, and reduced bone mineral density
Intravenous methylprednisolone†	Three boluses at 500 mg/m² (15 mg/kg) at the end of the first 4 weeks of oral PDN in non-responsive forms	Blood pressure during infusion, and fasting blood glucose	Weight gain, hypertension, hyperglycaemia, behavioural disorders, sleep disruption, linear growth delay, Cushingoid features, glaucoma, cataracts, and reduced bone mineral density; acutely, hypertension and hyperglycaemia are the most noticeable adverse effects
Ciclosporin (calcineurin inhibitor)	Start: 3–5 mg/kg per day (maximum dose 250 mg) in two divided doses; steroid-sensitive nephrotic syndrome: C_0 60–100 ng/mL or C_2 300–550 ng/mL (aiming for the lowest possible dose to maintain remission); steroid-resistant nephrotic syndrome: C_2 600–800 ng/mL if possible, then lower once or if remission is attained; discontinue if no partial remission at 6 months with adequate levels	Quarterly: blood pressure, CBC, creatinine, eGFR, potassium, LFTs, lipids, uric acid, drug levels; consider discontinuation or a kidney biopsy after 2–3 years to avoid or detect toxicity	Acute and chronic nephrotoxicity, hypertension, seizures, tremor, posterior reversible encephalopathy syndrome, hirsutism, and gum hyperplasia; consider risk of toxicity due to drug interactions (eg, macrolide antibiotics, certain antiepileptic agents, and grapefruit juice increase drug concentrations by competing for cytochrome P450 metabolism)
Tacrolimus (calcineurin inhibitor)	Start: 0·1–0·2 mg/kg per day (maximum dose 10 mg) in two divided doses; steroid-sensitive nephrotic syndrome: C_0 3–7 ng/mL (aiming for the lowest possible dose to maintain remission); steroid-resistant nephrotic syndrome: C_0 6–9 ng/mL if possible, then lower once or if remission is attained; discontinue if no partial remission at 6 months with adequate levels	Quarterly: blood pressure, CBC, creatinine, eGFR, potassium, LFTs, lipids, magnesium, fasting glucose, drug levels; consider discontinuation or a kidney biopsy after 2–3 years to avoid or detect toxicity	Tacrolimus drug concentrations can increase in cases of intense diarrhoea; hyperglycaemia; consider risk of toxicity due to drug interactions (eg, macrolide antibiotics, certain antiepileptic agents, and grapefruit juice increase drug concentrations by competing for cytochrome P450 metabolism)
Cyclophosphamide (only for steroid-sensitive nephrotic syndrome)	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 total cumulative dose 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	CBC every 14 days during therapy	Leukopenia, severe infections, alopecia, nail discoloration, seizure, infertility, abdominal pain, diarrhoea, haemorrhagic cystitis, and jaundice; fertile individuals must be warned of the need to avoid unplanned pregnancy due to possible fetal malformation
Levamisole (only for steroid-sensitive nephrotic syndrome)	2–2·5 mg/kg per alternate day (maximum dose 150 mg); levamisole is usually initially alternated with oral PDN	Every 4–6 months: CBC, LFTs; yearly: antineutrophil cytoplasmic antibody titres (also at baseline)	Arthritis, vasculitic rash, neutropenia, and abnormal LFTs
Mycophenolate mofetil or mycophenolic sodium	Mycophenolate mofetil: 1200 mg/m² per day in two divided doses every 12 h (maximum dose 3000 mg); to optimise tolerance, start with half dose for 1–2 weeks; mycophenolic sodium: 360 mg corresponds to 500 mg of mycophenolate mofetil; therapeutic drug monitoring using a limited sampling strategy: the most effective mycophenolic acid area under the curve, 0–12 h, is above 50 mg h/L	Every 4–6 months: CBC and LFTs	Abdominal pain, diarrhoea, anorexia (might be improved with mycophenolic sodium), leukopenia, anaemia, toxic hepatitis (rare), and verrucae; fertile individuals must be warned of the need to avoid unplanned pregnancy due to possible fetal malformations; concomitant tacrolimus can elevate levels of mycophenolic acid, reduce dose to about 600 mg/m² per day
Rituximab	375 mg/m² for one to four doses per course (maximum single dose 1000 mg) at weekly intervals; aim for CD19 depletion (<5 cells per mm³ or <1% total lymphocytes); premedication is often used with antihistamines, acetaminophen, and steroids; repeated courses can be given; administer in remission whenever possible, after appropriate premedication under close supervision and monitoring; exclude hepatitis B, hepatitis C, HIV, and any active infection; in children with concomitant immunosuppression, prophylactic antibiotics might be useful to prevent *Pneumocystic carinii* pneumonia	Quarterly: CBC, LFTs; CD19 counts and total IgG (at baseline, quarterly in the first year, then yearly)	Infusion reactions, activation of latent viruses, transient or persistent IgG deficiency; serious adverse effects: tuberculosis, hepatitis B, John Cunningham virus infection, and myocarditis

Adapted from Kidney Disease: Improving Global Outcomes (chapter 4)[42] and International Pediatric Nephrology Association guidelines.[3,43] DEXA=dual-energy x-ray absorptiometry. C_0=trough level. C_2=2 h postadministration level. CBC=complete blood count. eGFR=estimated glomerular filtration rate. LFT=liver function tests. *Commonly written to mean either prednisone or prednisolone, depending on what is available at the time and location. In individuals with normal hepatic function they are considered equivalent in terms of efficacy. †Optional treatment; eGFR (mL/min per 1·73 m²) is calculated as k × height (cm)/serum creatinine (mg/dL), where k is a constant 0·413, or as k × height (cm)/serum creatinine (μmol/l), where k is a constant 36·5.[44,45]

Table 2: **Doses and practical tips for immunosuppressive treatments for different forms of nephrotic syndrome**

(often prevalent in glomerulonephritis), and for children older than 12 years, where different causes of nephrotic syndrome are more prevalent (panel 1, figure 1, appendix p 2). For congenital nephrotic syndrome, kidney biopsies might be done if genetic testing is not available. Biopsies can also confirm specific histopathological findings, such as diffuse mesangial sclerosis with *WT1* variants, which confer a high risk of Wilms tumour.[36]

Acute management

Complications of idiopathic nephrotic syndrome can be life-threatening and occur during 1–4% of flares (onset and relapses), especially when albumin concentrations are less than 20–25 g/L.[43] Despite visible oedema and weight gain, children are rarely volume overloaded.[55,56] Hypovolaemia follows urinary loss of proteins, and can be aggravated by diuretics or sepsis, resulting in acute kidney injury, thrombosis, or shock. Shock warrants urgent volume resuscitation and albumin infusion (figure 3). The other indications for albumin infusions are severe oedema or functional acute kidney injury, although supporting evidence is scarce.[43,56] A 2022 systematic review found that urinary output was greater after treatment with furosemide and albumin compared with furosemide alone.[56] Albumin infusion can lead to severe complications, including pulmonary oedema,[56] and requires close monitoring. Diuretics should be used with caution and only in the most severe forms of oedema and after hypovolaemia has been corrected. Salt restriction is advised during relapses for management of oedema and during high doses of glucocorticoid therapy to prevent hypertension. Fluid restriction is recommended for hyponatraemia of less than 130 mEq/L, after excluding false hyponatraemia due to hyperlipidaemia.[43]

Arterial or venous thromboembolic events occur in 3% of children with idiopathic nephrotic syndrome, less often in steroid-sensitive nephrotic syndrome (1·5%) than steroid-resistant nephrotic syndrome (3·8%), and far less frequently in children than in adults (27%).[57,58] Prevention of arterial or thromboembolic events includes increasing patient mobility, correcting hypovolaemia, avoiding central venous catheters, and early treatment of sepsis. Preventive anticoagulation is not routinely indicated during relapses, but should be considered in patients with identified inherited predisposition for thromboembolic complications, indwelling central venous lines, or past history of thrombosis.[59]

Infections are a major concern not only during steroid-sensitive nephrotic syndrome relapses due to urinary losses of IgG and complement opsonins, but also in remission due to immunosuppressive therapy.[60] 30–50% of infections are caused by *Streptococcus pneumoniae*, with the remainder due to gram-negative bacteria, primarily *Escherichia coli*.[61] These infections can be severe, and as of 1985, caused 60% of steroid-sensitive nephrotic syndrome-related deaths.[62] However, prophylactic antibiotics are not indicated because they do not reduce the frequency or severity of sepsis.[63,64] Peritonitis is reported during 1·5–16% of relapses.[65] Exposure to varicella, or overt varicella, in non-immunised, immunosuppressed children requires immediate treatment and reduction of immunosuppression.[43] Expert clinicians recommend reviewing the child's vaccination status at disease onset and completing all vaccinations without delay. At diagnosis, vaccination against encapsulated bacteria (*Streptococcus pneumoniae, Neisseria meningitidis,* and *Haemophilus influenzae*) must be updated, even during ongoing nephrosis and under steroid treatment.[66] All other inactivated vaccines are recommended, including annual influenza vaccines, and SARS-CoV-2 vaccines. A 2022 review reported excellent efficacy and safety profile of vaccines, with no statistically significant risk of vaccine-induced relapse, and good efficacy in remission or relapse, except with rituximab (anti-CD20) therapy.[67] If possible, vaccines should be administered at least 3 weeks before the first rituximab infusion. Live vaccines are generally not recommended for children receiving immunosuppressive drugs because of the risk of vaccine-induced infectious disease, albeit very low.[68] Experts recommend that non-immunised children be vaccinated against chickenpox and measles at the end of the first course of steroids and either before the introduction of steroid-sparing agents, or after their withdrawal and B-lymphocyte repletion.[43]

Transient conditions that resolve in remission, such as hypothyroidism or hyperlipidaemia, should not be treated during relapses of steroid-sensitive nephrotic syndrome, but rather if they persist in steroid-resistant nephrotic syndrome.[3,43]

Long-term management

Steroid-sensitive nephrotic syndrome

Patients with steroid-sensitive nephrotic syndrome present over the course of their disease with phases of remission and relapses that require iterative courses of steroids. Cumulative use of steroids can induce side-effects. To prevent them, steroid dose and duration should be minimised, and approaches to management should be considered (appendix p 3). In cases of infrequent relapse, steroid therapy can be given in short courses at the time of relapse (table 2, appendix p 3), without maintenance therapy. Maintenance with low-dose (≤0·5 mg/kg) PDN on alternate days is a reasonable first option in children with frequently relapsing nephrotic syndrome.[69–71] To maintain prolonged remission with minimal adverse effects, frequent assessment of these children for steroid toxicity is warranted (table 2).

Steroid-induced bone fragility should be prevented by minimising steroid exposure, ensuring adequate dietary calcium intake, and administering vitamin D supplementation in remission at a dose appropriate for age, ethnicity, and geographical latitude.[72] Although the quality of the evidence is low, and there are only a few pieces of evidence, we suggest considering a dual-energy

x-ray absorptiometry scan every 12–18 months if patients are on a prolonged course of steroids, or have received a high cumulative dose of steroids.[43]

Almost 50% of relapses are precipitated by minor infections, usually upper respiratory tract infections. Three studies done in south Asia and the Middle East found that giving a daily dose of PDN for 5–7 days from infection onset reduced the risk of relapse in patients with frequently relapsing nephrotic syndrome already receiving PDN on alternate days.[73–75] However, the large placebo-controlled PREDNOS 2 trial found no reduction in risk of relapse when prednisolone was administered following onset of an infection to patients with frequent or infrequent relapses on or off low-dose prednisolone.[76] The 2023 International Pediatric Nephrology Association (IPNA) guidelines suggest that PDN can be administered daily during episodes of upper respiratory tract infection in patients with frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome who are already on alternate-day PDN maintenance.[43]

In cases of steroid toxicity in children with frequently relapsing nephrotic syndrome and in all children with steroid-dependent nephrotic syndrome, steroid-sparing agents are indicated. Available evidence is insufficient to establish a single treatment sequence suitable for all children. Thus, the choice of agent should be individualised after informing the family, considering side-effect profiles, severity of the condition, age (young or pubertal peak growth), comorbidities, adherence to treatment, cost, and availability. The different steroid-sparing agents used for steroid-sensitive nephrotic syndrome are presented in table 2, which provides clinical tips and recommended dosing.[3,42,43] On introduction of a steroid-sparing agent, if remission for at least 3–6 months is obtained, steroids should be tapered and discontinued. All steroid-sparing agents require periodic monitoring for potential side-effects at least every 6 months and at each visit; if remission is persistent (≥12 months), treatment discontinuation should be considered.

Levamisole

Levamisole is an antihelminthic drug with immunomodulatory properties. It is inexpensive, has few adverse effects, and is effective in preventing relapses in a high proportion of children with frequent relapses.[66] Meta-analyses of randomised studies show that the risk of relapse is reduced by a third during therapy with levamisole on alternate days.[77] The efficacy of levamisole appears to be lower in patients who are steroid dependent compared with those who have frequent relapses.[78] Levamisole is a popular first-choice steroid-sparing drug, especially in Asia. Two rare adverse effects associated with levamisole use are neutropenia[78,79] and antineutrophil cytoplasmic antibody-associated vasculitis.[80] Hence, children receiving levamisole should have periodic testing for full blood count and antineutrophil cytoplasmic antibodies (table 2).

Mycophenolate mofetil and mycophenolate sodium

Mycophenolate mofetil inhibits de novo synthesis of guanine nucleotides and thereby the proliferation of B cells and T cells. Enteric-coated mycophenolate sodium has the same mechanism of action as mycophenolate mofetil, but delays mycophenolate acid release until the drug enters the small intestine. There is extensive documentation of the successful and safe use of mycophenolate mofetil or mycophenolate sodium in children with relapsing steroid-sensitive nephrotic syndrome and numerous observational studies have reported that these drugs are more effective than steroids in maintaining remission in children with frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome.[77] These studies showed an approximate reduction of 50% in the relapse rate when taking mycophenolate mofetil or mycophenolate sodium, enabling a reduction in dose or cessation of prednisone in most children. However, relapses are frequent after cessation of treatment. The most common adverse effects of mycophenolate mofetil are abdominal pain and diarrhoea, which are less likely to occur with mycophenolate sodium. Other rare adverse effects of mycophenolate mofetil and mycophenolate sodium are transient and mild leukopenia, anaemia, and rare cases of toxic hepatitis.[81] Mycophenolate mofetil and mycophenolate sodium are contraindicated during pregnancy. Complete blood count and liver function should be assessed every 4–6 months during treatment, and therapeutic drug monitoring with area under the curve calculations might be useful to adjust the dose in patients not controlled on therapy, or in case of side-effects.[82] Mycophenolate mofetil given at an adequate dose appears similarly effective to calcineurin inhibitors, without the nephrotoxicity.[82] Therefore, despite its relative expense, mycophenolate mofetil might have the most advantageous profile of safety and efficacy for patients with frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome, when available.

Calcineurin inhibitors

Calcineurin inhibitors inhibit the synthesis of interleukins, particularly IL-2, which is essential for the autoactivation and differentiation of T cells. Calcineurin inhibitors, such as ciclosporin and tacrolimus, are highly effective in the treatment of frequently relapsing nephrotic syndrome and steroid-dependent nephrotic syndrome, and allow for the tapering and discontinuation of steroids in the majority of patients.[83–85] Two small randomised controlled trials combined in a Cochrane meta-analysis suggested that the number of patients relapsing by 12 months might not differ between mycophenolate mofetil and ciclosporin (risk ratio 1·90, 95% CI 0·66–5·46).[77,82,86] Three large observational studies found calcineurin inhibitors had a higher efficacy in maintaining remission compared with

mycophenolate mofetil, although adverse effects were more common with calcineurin inhibitors.[87–89] Many patients become calcineurin inhibitor-dependent (ie, relapse when dose is tapered or after treatment withdrawal).[90,91] Side-effects include nephrotoxicity, which is associated with dose and duration of treatment and can develop without any appreciable decline of the glomerular filtration rate,[92] infections, hypertrichosis, gum hypertrophy, hypertension, and posterior reversible encephalopathy syndrome. The side-effect profile with regards to nephrotoxicity is similar between ciclosporin and tacrolimus, but gingival hyperplasia and hypertrichosis are more prevalent with ciclosporin and can reduce adherence to treatment, although glucose intolerance occurs more frequently with tacrolimus. The dose of calcineurin inhibitors should be adjusted on the basis of regular blood concentration monitoring, aiming for the lowest possible dose to maintain remission. Monitoring of kidney function, liver function, and complete blood count is mandatory. It is recommended to avoid prolonging calcineurin inhibitor treatment beyond 12–24 months to prevent nephrotoxicity if an alternative is available,[93,94] and to complete the tapering treatment within a 3-month period. If discontinuation is not feasible, a kidney biopsy is indicated after 2–3 years (table 2).

Rituximab

Since 2004, rituximab has been identified as a steroid-sparing agent for the treatment of frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome.[95] Rituximab is a chimeric mouse–human monoclonal antibody that targets CD20, which induces B cell apoptosis.[96] The observation that nephrotic syndrome enters sustained remission following B-cell depletion[95] challenged the long-held idea that nephrotic syndrome is primarily a T cell-mediated disorder.[97] Multiple case series and clinical trials have shown the effectiveness of rituximab in preventing relapses and enabling discontinuation of steroids and other immunosuppressive medications, including calcineurin inhibitors.[98–100] Therapy with two to four doses in uncontrolled studies postponed relapses by a median of 5–11 months.[96] However, benefits of therapy wane over time. A meta-analysis of randomised studies found that the risk of relapse is reduced by 75% at 6 months after beginning treatment, but most children relapse within 1 year after beginning treatment.[77] In direct or indirect comparisons, rituximab was non-inferior to cyclophosphamide,[101] and had a similar or greater initial effectiveness than tacrolimus.[102]

Although dose strategies vary, the most common practice is to administer one to two doses of rituximab 1 week apart during disease remission, after excluding active infections. The infusion is given slowly over several hours following premedication to prevent infusion reactions. Relapses usually recur once B cells repopulate, which has led to regimens involving redosing at occurrence of relapse, redosing at B-cell recovery, or use of additional immunosuppression (especially mycophenolate mofetil)[103] to sustain remission by prolonging B-cell depletion.[104] Although repeated courses of rituximab to maintain B-cell depletion appears to be safe, this approach should be considered only in patients who cannot be stabilised with calcineurin inhibitors or mycophenolate mofetil following the first course of treatment.[105] Systematic reviews indicate that therapy with rituximab is associated with a statistically significant risk of infusion reactions, reactivation of hepatitis B virus infection, and delayed adverse events, including serum sickness, serious infections, and hypogammaglobulinaemia.[77,106,107] Due to the risk of hypogammaglobulinaemia in young children,[108] rituximab might be preferred mainly for patients older than 9–10 years non-responsive to one steroid-sparing agent.[43,109]

Alkylating agents

Oral cyclophosphamide is one of the longest-used steroid-sparing agents to treat nephrotic syndrome.[110] Therapy with chlorambucil is no longer recommended due to its association with frequent adverse events of grade 3 or worse, including seizures. Meta-analyses indicate that the risk of relapses is reduced by more than 50–86% between 6 months and 12 months following therapy with cyclophosphamide.[111] Most children show sustained remission for several months after therapy, and sometimes the disease remits for life. Cyclophosphamide appears to be more effective in children with frequently relapsing nephrotic syndrome compared with steroid-dependent nephrotic syndrome, and less effective in young (age younger than 7 years) children.[77,110] Although neutropenia requires frequent monitoring of blood counts (table 2), the risk of gonadal toxicity is an important consideration when prescribing the medication, particularly in boys, due to an increased frequency of dose-dependent gonadal toxicity. Given this concern and a small risk of malignancy, therapy should not exceed a single course of 8–12 weeks, such that the cumulative dose does not exceed 168 mg/kg.[110]

Steroid-resistant nephrotic syndrome

Calcineurin inhibitors

In patients with steroid-resistant nephrotic syndrome, the evidence-based first-line therapeutic approach requires calcineurin inhibitors, including ciclosporin or tacrolimus.[112] A 2012 randomised trial showed an improved remission rate in patients with steroid-resistant nephrotic syndrome when treated with calcineurin inhibitors compared with cyclophosphamide (approximately 52·4% *vs* 14·8%).[113] Differences in efficacy between ciclosporin and tacrolimus have not been found, yet the body of literature for ciclosporin is more extensive. In addition to immunomodulation, antiproteinuric effects of ciclosporin might be mediated by haemodynamic effects that reduce renal blood flow. Calcineurin inhibitors might also induce remission by inhibiting calcineurin-mediated degradation of synaptopodin and by stabilising the podocyte actin cytoskeleton.[114]

The IPNA guidelines recommend starting calcineurin inhibitors as soon as the diagnosis of steroid-resistant nephrotic syndrome is confirmed, followed by a progressive tapering of corticosteroids.[3] Some evidence of the benefit of three methylprednisolone boluses at calcineurin inhibitor initiation has been shown.[115] The efficacy of calcineurin inhibitor treatment should be reassessed after 6 months, and if complete remission is obtained, the treatment should be continued for at least 12–24 months to avoid relapses. Partial remission warrants continuing treatment and reassessing after 6 months. The absence of at least partial remission after 6 months defines calcineurin inhibitor-resistance, and other therapies should be introduced. In the absence of remission with two distinct agents after 12 cumulative months of treatment, the nephrotic syndrome is defined as multidrug resistant (table 1). If a monogenic form of steroid-resistant nephrotic syndrome is identified and no response has been observed, immunosuppression should be discontinued.[3]

Rituximab

The efficacy of rituximab in children with steroid-resistant nephrotic syndrome is not well established, due to a paucity of studies and the heterogeneity of underlying cause, with a large proportion of monogenic forms of the disease. Approximately 30% of children with non-monogenic forms of steroid-resistant nephrotic syndrome might respond to rituximab treatment,[112] which should, therefore, be limited to patients for whom complete remission is not observed following at least 6 months of treatment with a calcineurin inhibitor at an adequate dose.[3]

Mycophenolate mofetil and mycophenolate sodium

In steroid-resistant nephrotic syndrome, mycophenolate is mainly used in two scenarios. First, for children with steroid-resistant nephrotic syndrome who are responsive to calcineurin inhibitors and who have entered prolonged remission, after approximately 2 years, to avoid nephrotoxicity.[3] Second, for children with steroid-resistant nephrotic syndrome and an estimated glomerular filtration rate of less than 30 mL/min per 1·73 m², in whom use of a calcineurin inhibitor is hazardous. For all other patients with steroid-resistant nephrotic syndrome, calcineurin inhibitors appear considerably more effective in inducing and maintaining remission.[112]

Antiproteinuric agents

Renin-angiotensin-aldosterone system blockade with angiotensin-converting enzyme (ACEI) inhibitors and angiotensin-receptor blockers (ARBs) has been shown in numerous trials to reduce proteinuria in children and adults with glomerular diseases.[116–118] The antiproteinuric effects of ACEIs and ARBs are due to their ability to reduce glomerular capillary plasma flow rate, decrease transcapillary hydraulic pressure, and alter the permselectivity of the glomerular filtration barrier.[119] The addition of an aldosterone blockade with ACE inhibition has been shown to reduce protein excretion by 30–58% in patients with both diabetic and non-diabetic kidney disease.[120] Another mechanism of action could be related to inhibition of fibrosis by aldosterone in several organs, including the kidneys.[119]

Clinical trials

For children with persistent proteinuria or multiple relapses despite optimal management, consideration for entry into clinical trials evaluating novel therapies should be strongly considered. In a phase 2 randomised double-blind trial, sparsentan, a dual endothelin and ARB, was found to decrease proteinuria by 45%, compared with 19% for those treated with irbesartan, with no differences in serious adverse events between the groups.[121] A phase 3 multicentre trial is in progress (NCT03493685). A small post-approval study for LDL apheresis for children with steroid-resistant nephrotic syndrome has shown increased responsiveness to treatment and an improved or stable estimated glomerular filtration rate over the follow-up period.[122]

Follow-up and outcomes

Patients with either steroid-sensitive or steroid-resistant nephrotic syndrome require frequent follow-ups to monitor the disease course and biochemical responses, so that complications can be managed quickly (panel 1, appendix p 3).

80% of patients with steroid-sensitive nephrotic syndrome have a self-limiting illness that abates by puberty.[123] Although multiple retrospective and prospective series indicate reduction in disease relapses as children get older,[2,124–128] the disease persists into adulthood in 5–42% of patients.[124,129] A young age at onset for frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome SDNS is associated with relapsing illness once patients are older than 18 years.[130–132]

Morbidities associated with steroid-sensitive nephrotic syndrome include infections and toxicity due to repeated courses of corticosteroids. Morbidity secondary to severe infections has declined with improved socioeconomic conditions, decreased time to diagnosis, and the use of vaccines. However, 10–15% of patients with steroid-sensitive nephrotic syndrome require admission to hospital for major infections, usually during disease relapses or with intense immunosuppression.[63] Repeated or prolonged use of corticosteroids is responsible for a high prevalence of hypertension (6–46%), mineral bone disease (osteoporosis or fractures; 9–63%), short stature (2–20%), obesity (2–17%) or overweight (15–35%), ocular complications (2–20%), infertility (0–75%), and diabetes (2–3%), particularly in patients with frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome.[129,133] Growth and bone mineral density appear to be negatively correlated with the cumulative dose of corticosteroids.[134]

Panel 2: **Questions, controversies and uncertainties around nephrotic syndrome**

Can genetic testing replace the need for kidney biopsy in patients with initial steroid-resistant nephrotic syndrome?
This question touches on resource-related issues: in a setting where genetic results by panel screening can be obtained in weeks, performing a renal biopsy can be limited to non-genetic forms of steroid-resistant nephrotic syndrome, including secondary steroid-resistant nephrotic syndrome. This is especially relevant for children in whom a genetic cause is the most probable (eg, those with infantile onset of nephrotic syndrome, family history, or syndromic features, or a combination of these). In non-genetic steroid-resistant nephrotic syndrome, a biopsy sample might be valuable in guiding management, or to indicate prognostic value or proliferative lesions.

When is it appropriate to use albumin infusions for a child with nephrotic syndrome?
The chief indication for albumin is in management of hypovolaemia, and to assist diuretics in oedema management while preventing thrombotic events. Detecting hypovolaemia is tricky and thrombosis is difficult to predict on the basis of the degree of hypoalbuminaemia alone.

How early should steroid-sparing agents be introduced in the management of steroid-sensitive forms of nephrotic syndrome?
Second-line immunosuppressive agents are not necessarily always preferable in terms of cost and safety profile, compared with low-dose maintenance with oral prednisone. However, if this regimen is selected, periodic reassessment of possible tapering and discontinuation of steroids, and careful monitoring of toxicity must be performed at least every 6 months.

What should be the order of use of steroid-sparing agents in patients who frequently relapse or are steroid dependent?
There are few direct comparisons of therapies. The disease often lasts longer than a decade in patients with frequently relapsing or steroid-resistant disease, and most agents do not have a disease-modifying effect.

Can relapses of steroid-sensitive disease be treated with a short course of prednisone, or lower doses?
Recent studies[138] have tried to address this issue; however, the lower dose and short course might lead to more frequent relapses, and any change would have implications for definitions of the disease course.

Panel 3: **Outstanding research questions**

- The duration of oral prednisone treatment for the first episode of nephrotic syndrome: can it be shortened to less than 8 weeks (four weeks of full daily doses and four weeks of alternate-day doses) in children who are steroid sensitive? Can it be tailored to individuals, and if so, which predictive factors could be used (eg, age and time to remission)?
- Concomitant use of steroid-sparing agents (ie, levamisole or mycophenolate mofetil) during the first episode of steroid-sensitive nephrotic syndrome on remission: can it delay relapses and improve long-term outcomes?
- The use of repeated doses of rituximab in children with severe forms of steroid-dependent nephrotic syndrome: what is the optimal regimen in terms of dose and timing?
- Biomarkers of disease prognosis or severity: at onset, what predicts prognosis? Are there any specific immune phenotypes that indicate steroid resistance? Are there ancestry-related differences in immune phenotypes?
- The genetic background of steroid-resistant nephrotic syndrome: how does it differ in European and non-European ancestries?
- What is the most appropriate management for multidrug resistant, non-genetic steroid-resistant nephrotic syndrome? Additionally, what is the most appropriate strategy to manage recurrent forms of this disease on the renal allograft post-transplantation?

Responses to immunosuppression in patients with steroid-resistant nephrotic syndrome appear to be higher in randomised studies than in longitudinal reports, which could reflect treatment adherence and short-term observation during clinical trials. Pooled data from five large multicentre studies on 1107 patients with steroid resistance indicate complete remission in 26·7% (95% CI 24·2–29·4), partial remission in 18·4% (16·2–20·8), and non-response in 54·8% (51·9–57·7).[135]

Although kidney failure is uncommon (<1%) in patients with steroid-sensitive nephrotic syndrome, patients with steroid-resistant nephrotic syndrome are at risk of kidney failure, particularly in patients with monogenic disease or patients with a poor response to immunosuppression. However, although monogenic forms almost never relapse, relapse on renal allograft is a significant concern for patients with steroid-resistant forms—particularly if they have secondary resistance—and relapse can occur in up to 50% of patients.[33]

Other morbidities in nephrotic syndrome include common psychosocial concerns, including dropping out of school, adult unemployment, and unstable relationships.[129] Patients who continue to show disease relapses, persistent proteinuria, or decline in renal function into adulthood require transition of care to nephrologists who specialise in adult care.[136]

Conclusions and future perspectives

Despite significant challenges deriving mainly from its rarity and heterogeneity, the past few years have seen a large improvement in the quality of available data guiding

management of different forms of nephrotic syndrome. Randomised controlled trials have shown how to optimise corticosteroid treatment of the initial episode and first relapse of nephrotic syndrome, and how to react when a relapse is triggered by an acute infection, leading to steroid-sparing and to simple and clear steroid protocols.[76,137,138] Moreover, randomised controlled trials have proved the safety and efficacy of levamisole, particularly for frequently relapsing nephrotic syndrome, and should promote advocacy for global distribution of this inexpensive, but often unavailable, drug.[78] Other randomised controlled trials have confirmed the efficacy of rituximab in frequently relapsing nephrotic syndrome and steroid-dependent nephrotic syndrome and provided key evidence on its optimal use in combination with mycophenolate mofetil for severe forms of steroid-dependent nephrotic syndrome.[99,103] A global effort has led to the formulation of international guidelines that aim to promote uniform evidence-based management with awareness of resource disparity in different geographical regions.[3,9,43] Moreover, our understanding of the underlying pathogenesis has evolved due to genetic studies revealing multiple monogenic forms, genome-wide association study cohorts and immunological studies leading to the discovery of pathogenic autoantibodies (ie, antinephrin antibodies), and the identification of B-cell subpopulations predicting relapse.[16,17,19,139,140] In panels 2 and 3 we summarise current controversies and outstanding research questions that should be investigated in the coming years.

Contributors

All authors contributed to writing and revision of drafts, data visualisation, and concur with the final submission and revisions of the Seminar.

Declaration of interests

MV provides scientific advice or participates in sponsored clinical trials for Novartis, Travere, Apellis, Roche, Biocryst, Chemocentrix, Bayer, Alexion, GlaxoSmithKline, and Purespring. OB provides scientific advice or participates in sponsored clinical trials for Alexion, Alnylam, Biocodex, Bristol-Myers Squibb, GlaxoSmithKline, Purespring, Roche, Sanofi, Takeda, and Travere/Vifor. KG provides scientific advice or receives research support for Travere, Aurinia, and Genentech. AS declares no competing interests.

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