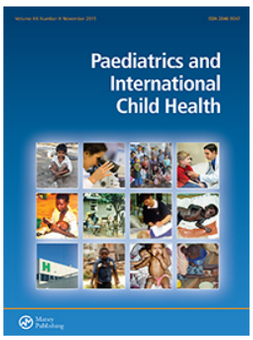

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# Nephrotic syndrome in infants and children: pathophysiology and management

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**ABSTRACT**

Nephrotic syndrome is defined by nephrotic-range proteinuria (≥40 mg/m$^2$/hour or urine protein/creatinine ratio ≥200 mg/mL or 3+ protein on urine dipstick), hypoalbuminaemia (<25 g/L) and oedema. This review focuses on the classification, epidemiology, pathophysiology, management strategies and prognosis of idiopathic nephrotic syndrome of childhood, and includes a brief overview of the congenital forms.

**Abbreviations:** NS: nephrotic syndrome; MCD: minimal change disease; FSGS: focal segmental glomerulosclerosis; SSNS: steroid-sensitive nephrotic syndrome; SRNS: steroid-resistant nephrotic syndrome; FRNS: frequently relapsing nephrotic syndrome; KDIGO: Kidney Disease Improving Global Outcomes; ESRD: end-stage renal disease; VPF: vascular permeability factor; CLC-1: cardiotrophin-like cytokine 1; suPAR: soluble urokinase-type plasminogen activator receptor; AKI: acute kidney injury; DVT: deep vein thrombosis; LCAT: lecithin-cholesteryl acyltransferase; RAAS: renin-angiotensin-aldosterone system; ENaC: epithelial sodium channel; ANA: antinuclear antigen; anti-dsDNA: anti-double stranded DNA; ANCAs: anti-neutrophil cytoplasmic antibodies; ASOT: anti-streptolysin titres; CNIs: calcineurin inhibitors; MMF: mycophenolate mofetil; CNS: congenital nephrotic syndrome; CMV: cytomegalovirus; uPCR: urine protein:creatinine ratio

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## Introduction

Nephrotic syndrome (NS) is a common paediatric kidney disease characterised by leakage of protein from the blood into the urine through damaged glomeruli. It is classically defined by nephrotic-range proteinuria (≥40 mg/m$^2$/hour or urine protein/creatinine ratio ≥ 200 mg/mL or 3 + protein on urine dipstick), hypoalbuminaemia (<25 g/L) and oedema [1]. Childhood NS can be congenital, presenting within the first 3 months of life, and in these children there is usually a genetic mutation affecting either the podocyte or the glomerular basement membrane, although rarely it can be associated with congenital infections, such as cytomegalovirus. Apart from the congenital form of nephrotic syndrome, many different underlying aetiologies can cause nephrotic syndrome, including glomerular disorders, vasculitides, infections, toxins, malignancy, genetic mutations and, most commonly, unknown. This review focuses on the classification, pathophysiology, management strategies and prognosis of idiopathic NS and includes a brief overview of the congenital forms.

Typically, the histological classifications corresponding with idiopathic childhood NS are described either as minimal change disease (MCD) or focal segmental glomerulosclerosis (FSGS) — the quintessential podocyte diseases, or podocytopathies [2]. MCD is more common in childhood NS than FSGS and refers to glomeruli which appear normal on light microscopy with evidence of podocyte foot process effacement by electron microscopy. FSGS has a similar appearance on electron microscopy, but, unlike MCD, on light microscopy demonstrates segmental destruction of the glomerular capillaries with adhesions/synechiae forming between the sclerosed segments and Bowman's capsule. Damage to these foot processes causes a change in podocyte shape and rearrangement of their cellular cytoskeleton, which results in loss of serum protein through the glomerulus [3]. This change in shape can usually be reversed with corticosteroid therapy in MCD, but is often resistant and progressive in the setting of FSGS. More recently, MCD and FSGS are beginning to be considered histological descriptions within a spectrum of disease, with MCD representing an earlier stage that is more responsive to treatment and FSGS considered a more advanced and resistant stage of disease [4].

Idiopathic NS is clinically classified based on response to corticosteroid therapy. Between 80% and 90% of children over 1 year of age presenting with NS respond to treatment with steroids within 4 weeks [steroid-sensitive nephrotic syndrome (SSNS)], while the remaining

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10–20% are non-responsive and classified as having steroid-resistant nephrotic syndrome (SRNS) [5]. In children with SSNS, the subsequent course of illness can be quite variable, with the majority of children having at least one episode of relapse, and up to 50% having either frequently relapsing nephrotic syndrome (FRNS) (≥2 relapses in first 6 months or ≥4 relapses in any 1-year period) or steroid-dependent nephrotic syndrome (SDNS) (relapse, while on steroid therapy or within 2 weeks of steroid cessation) [6–8]. It is of note that South Asian and South-east Asian children have significantly lower odds of FRNS than European children [9]. SRNS is more likely to be associated with FSGS histology, and has an increased likelihood of progressing to end-stage renal disease (ESRD) [10]. In children with SSNS, although rare, relapses may continue beyond adolescence into adulthood, with the number of relapses in childhood and administration of steroid-sparing medication, such as cyclophosphamide, calcineurin inhibitors (CNIs) or rituximab, being the two most important risk factors [10–13].

Although these classifications of idiopathic NS based on histology description and response to corticosteroid therapy shed little light on the true understanding of the disease, they do guide management strategies and prediction of long-term outcomes. This review describes what is currently known about the pathophysiology of idiopathic childhood NS, as well as current understanding of how underlying cause influences management strategies and overall outcomes.

## Definitions

The current definitions for idiopathic NS are outlined in Table 1 and are adapted from the 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines [1].

**Table 1.** KDIGO definitions of nephrotic syndrome in children.

| Classification | Definition |
|---|---|
| Nephrotic syndrome | Oedema, uPCR ≥200 mg/mmol or 3+ protein on urine dipstick, hypoalbuminaemia ≤25 g/L |
| Complete remission | uPCR <20 mg/mmol or <1+ on urine dipstick for 3 consecutive days |
| Initial responder (SSNS) | Attainment of complete remission within initial 4 weeks of corticosteroid therapy |
| Initial resistance (SRNS) | Failure to achieve complete remission after 8 weeks of corticosteroid therapy |
| Relapse | uPCR ≥200 mg/mmol or ≥3+ protein on urine dipstick for 3 consecutive days |
| Frequent relapse | >2 relapses within 6 months of initial relapse, or ≥4 relapses in any 12-month period |
| Steroid dependence | Two consecutive relapses during corticosteroid therapy or within 14 days of ceasing therapy |

Note: uPCR, urine protein:creatinine ratio.

## Epidemiology

The incidence of childhood NS is reported as 4.7 (range 1.15–16.9) per 100,000 children worldwide, with substantial variability according to ethnic background and geographical location [9,14]. In several European studies, South Asian children were reported to have a higher incidence of NS than the European population [15–17], and historical data from USA studies demonstrates a higher incidence in African-American children than in children of European decent [18,19]. African-American children also have an increased likelihood of having FSGS on kidney biopsy (42–72%) and overall are more likely to progress to ESRD than European children [20–23]. Likelihood of having SRNS also varies by ethnicity and geographical location, with 20% reported in Europeans, 16–27% in Africans, 27–54% in Asians and 20–39% in South Asians [21,24–26]. Most of these studies are retrospective or cross-sectional, however, and therefore, true causative factors explaining these differences in steroid response cannot be determined; they can perhaps be explained by variations in clinical practice between regional centres as well as differing definitions of outcomes around the world. In order to address these limitations, several prospective registries are on-going worldwide which aim to identify the clinical, histological, ethnic and genetic predictors influencing NS outcomes [27–30].

## Aetiology

In a recent prospective, longitudinal, multicentre study in the USA of children and adults (NEPTUNE, Nephrotic Syndrome Study Network), the causes of NS were as follows: MCD 27%, FSGS 32%, membranous nephropathy 15% and other glomerulonephropathy 27%. The distribution of pathology varied with patient age, younger children more commonly displaying MCD and adults more commonly showing membranous nephropathy [31]. Aetiologies of childhood NS are outlined in Table 2.

## Pathophysiology

### *Podocyte and glomerular filtration barrier defects*

Podocytes are highly differentiated cells that function to support and maintain the kidney's glomerular basement membrane filtration mechanism. These cells are composed of a cell body that extends many foot processes that wrap around glomerular capillaries. Foot processes interdigitate with special cell–cell junctions called the slit diaphragm which together form the glomerular filter. A complex cytoskeleton supports the structure of the podocyte cell body and foot processes to allow changes in hydrostatic pressures in response to different molecular movement across the glomerular membrane. Podocytes' cells have a limited ability to divide and regenerate and are therefore vulnerable to injury [32]. Destruction of podocytes above a critical mass also leads to irreversible glomerular damage, with podocyte

**Table 2.** Aetiologies of nephrotic syndrome.

| | |
|---|---|
| Idiopathic | Minimal change disease |
| | Focal segmental glomerulosclerosis |
| | Membranoproliferative glomerulonephritis |
| | Membranous nephropathy |
| | IgM nephropathy |
| | C1q nephropathy |
| | Thin basement membrane disease |
| Systemic diseases | Henoch–Schönlein purpura |
| | Systemic lupus erythematosis |
| | Diabetes mellitus |
| | Sarcoidosis |
| Infections | Hepatitis B and C |
| | HIV |
| | Malaria |
| | Schistosomiasis |
| | Syphilis |
| | Toxoplasmosis |
| Haematological diseases | Leukaemia |
| | Lymphoma |
| | Sickle cell disease |
| Drugs | Non-steroidal anti-inflammatory drugs |
| | Gold |
| | Penicillamine |
| | Angiotensin converting enzyme inhibitors |
| | Pamidronate |
| | Interferon |
| | Mercury |
| | Heroin |
| | Lithium |

depletion of >20% driving the development of glomerulosclerosis and progressive loss of kidney function [33].

Genetic mutations in podocyte structure and function result in kidney dysfunction, presenting most often as either congenital or SRNS. Some of the earliest recognised genetic disorders involved genes encoding slit diaphragm proteins nephrin (NPHS1) and podocin (NPHS2) [34]. Mutations in genes encoding the podocyte actin cytoskeleton, including CD2AP and INF2, are also associated with SRNS phenotypes. Finally, podocyte nuclear proteins (WT1), glomerular basement membrane proteins (LAMB2) and mitochondrial proteins (COQ2) are responsible for glomerular filtration dysfunction, leading to these more severe forms of progressive podocytopathies.

### *Immune dysregulation*

As immunosuppression with corticosteroids is the mainstay of treatment of nephrotic syndrome, it is logical to suspect immune dysregulation plays a pathogenic role in disease development. This hypothesis of immune dysregulation was initially postulated from clinical observations of NS occurring after exposure to allergens [35]. Furthermore, there is evidence that Hodgkin's and other T-cell lymphomas may trigger nephrotic syndrome, and chemotherapy can subsequently induce remission [36]. Measles infection may also induce a temporary spontaneous remission in NS by depression of cell-mediated immunity and T-cell subsets [37]. Although no particular cytokine triggers nephrotic syndrome, clinical patterns of disease occurrence certainly suggest that there is a role for T-cell dysregulation in the pathophysiology of disease. More recently, CD80 (B7-1), a T-cell co-stimulatory molecule expressed in diseased podocytes, is a possible target for inhibitory therapy in the treatment of NS [38]; however, the results of various trials are inconclusive [39,40].

### *Systemic circulating factors*

Circulating permeability factors may also play a role in the pathogenesis of nephrotic syndrome, as evidenced by the recurrence of proteinuria after renal transplantation in the setting of FSGS [41,42], and with induced remission of FSGS after plasma exchange, particularly in the early post-transplant period [43]. Furthermore, serum from patients with FSGS has induced proteinuria in rat kidneys and increased glomerular permeability to albumin *ex vivo* [44,45], FSGS has been transmitted from mother to child [46], and implantation of a kidney with FSGS into a recipient without the disease has induced remission [47].

Many types of circulating factors are reported in MCD and FSGS, notably vascular permeability factor (VPF) and haemopexin which are both postulated to change glomerular permeability in the setting of MCD [48,49]. Haemopexin is thought to alter the podocyte cytoskeleton, thereby increasing the albumin diffusion across the glomerular membrane [50]. It has been identified in the urine of children with steroid-responsive NS and then shown to disappear during remission [49]. It has also been postulated that the circulating factor might bind to galactose residues in the glycocalyx [51].

In FSGS, additional circulating factors include cardiotrophin-like cytokine 1 (CLC-1) which was isolated from the serum in patients with active FSGS and leads to increased glomerular permeability to albumin, as well as decrease nephrin expression in the glomeruli in *ex vivo* models [52]. More recently, soluble urokinase-type plasminogen activator receptor (suPAR) has received much attention as a proposed circulating factor causing FSGS. Again, suPAR was a substance isolated from patient serum and was thought to act by deforming the podocyte cytoskeleton. In initial observational studies, suPAR was elevated in 70% of FSGS patients (significantly higher than in patients with MCD), and post-transplant levels were higher in those with recurrent FSGS than in those without [53]. Several subsequent studies, however, report that suPAR levels depend on the degree of renal dysfunction, do not correlate with degree of proteinuria and are elevated in other kidney conditions, not only FSGS [54–57].

## Clinical features

The characteristic presenting symptom in NS is oedema, with periorbital, labial/scrotal and lower extremity swelling [58]. In more severe clinical scenarios, anasarca can develop, leading to ascites and pleural/pericardial

effusions. This, in turn, can lead to abdominal pain from hypoperfusion and ileus, dyspnoea and cool extremities. Presence of abdominal pain should also trigger further investigation to rule out spontaneous bacterial peritonitis, a known and serious complication of nephrotic syndrome. In general, children with NS are at high risk of serious bacterial infections, such as peritonitis, sepsis and pneumonia owing to T-cell dysfunction and loss of immunoglobulins in the urine. Infection is the leading cause of morbidity, and, historically, mortality in children with NS [59].

Oliguria and intravascular volume depletion may also develop, sometimes leading to acute kidney injury (AKI), another important complication of nephrotic syndrome. Concomitant infections, use of nephrotoxic medications and SRNS add to the risk of developing AKI, especially in hospitalised patients with NS [60].

It is well recognised that NS is a hyper-coagulable state with a risk of developing deep vein thrombosis (DVT), cerebral sinus venous thrombosis, pulmonary embolism, renal vein thrombosis and, more rarely, arterial thromboses [61]. The pathophysiology of the hypercoagulability is multifactorial and includes increased circulating prothrombotic factors (factor V and VIII and fibrinogen), dysfunction in platelet aggregation, urinary loss of anticoagulant factors (protein C and S, and antithrombin III) and intravascular volume depletion [62].

Hyperlipidaemia is a common consequence of nephrotic syndrome, known to be a result of several underlying mechanisms: (i) increased synthesis of cholesterol, triglycerides and lipoproteins in the liver, (ii) hypoalbuminaemia itself as albumin transports cholesterol in the bloodstream, (iii) decreased activity of lipoprotein lipase that normally facilitates the maturation of LDL from VLDL, and (iv) acquired lecithin-cholesteryl acyltransferase (LCAT) deficiency through urinary losses preventing the normal development of HDL [63]. The safety and efficacy of using lipid-lowering medications in very young children with NS is not yet established, and long-term cardiovascular outcomes in childhood NS is currently unknown and primarily limited to individual case reports of cardiovascular events [64,65].

## Oedema in nephrotic syndrome

Two hypotheses have been proposed for the aetiology of oedema in nephrotic syndrome: the underfill and the overfill hypotheses [66]. Neither hypothesis fully explains the pathophysiology of oedema in NS as there is probably some overlap of children presenting intravascularly volume depleted and 'under-filled', euvolemic, or volume overloaded and 'over-filled'. The underfill hypothesis proposes that high-grade proteinuria leads to hypoalbuminaemia that in turn decreases plasma oncotic pressure, causing fluid to leak into the interstitium. As a consequence of the intravascular volume depletion, tachycardia, hypotension and oliguria can develop and the renin-angiotensin-aldosterone system (RAAS) becomes activated. Not all clinical circumstances fit this hypothesis, however, as albumin replacement alone is often insufficient to stimulate diuresis without the addition of a diuretic. Some children respond to diuretic medication alone without albumin [67], and, as they enter remission, most will experience a diuresis well before normalisation of serum albumin level.

In contrast, the overfill hypothesis postulates that protein loss in the urine leads to consequent sodium retention, thereby causing intravascular volume expansion, leading to fluid overflow into the interstitium. The epithelial sodium channel (ENaC) in the distal segment of the nephron is the primary instrument of sodium reabsorption in NS [68]. Through an aldosterone-independent mechanism, ENaC is activated by plasmin, a metabolite of plasminogen present in the nephrotic ultrafiltrate. Plasmin cleaves the normally inhibitory subunit of the ENaC channel, thereby opening it and allowing influx of salt [69,70]. Amiloride is known to block ENaC activity, and, therefore, based on the 'overfill' theory, treatment of oedema in NS with amiloride seems logical. Although no study has examined the efficacy of amiloride monotherapy, combined amiloride and furosemide therapy achieves greater diuresis than either agent alone in children with NS [71].

Recent literature has also suggested that there may be a commonality in pathophysiology between the hypoalbuminaemic states in childhood NS and oedematous malnutrition, such as kwashiorkor [72,73]. There are conflicting views of the use of intravenous albumin in the setting of kwashiorkor to correct serum oncotic pressure, thereby mobilising fluid and correcting the oedema [74]. These theories outlined by the underfill and overfill hypotheses highlight the significant conundrum in understanding the pathogenesis of oedema in nephrotic syndrome.

Based on both hypotheses of oedema development, recommended strategies for management in NS are primarily salt and water restriction along with loop diuretic administration. The addition of intravenous albumin infusion combined with diuretic could be considered in the settings of intravascular volume depletion or severe oedema, threatening cardiac or respiratory compromise.

## Diagnostic investigations

Evaluation of NS at first presentation should include the following baseline investigations: (i) urinalysis and urine microscopy, (ii) quantified protein:creatinine ratio on a spot sample or on 24 h collection, and (iii) serum electrolytes, albumin, renal function, complete blood count and cholesterol. If there is suspicion of a combined nephritic picture, more directed investigations might also include

serum complement levels ($C_3$ and $C_4$), antinuclear antigen (ANA), anti-double stranded DNA (anti-dsDNA) if ANA is positive, anti-neutrophil cytoplasmic antibodies (ANCAs), immunoglobulins (IgG, IgA and IgM) and anti-streptolysin titres (ASOT). Infectious causes, such as hepatitis B and C, HIV, syphilis, schistosomiasis and tuberculosis should be considered if clinically warranted. Genetic testing should be considered under the following circumstances: (i) congenital nephrotic syndrome, (ii) SRNS, (iii) positive family history of NS or (iv) if there are clinical features of syndromic disease. Renal biopsy is usually not required at diagnosis but should be considered in the setting of several risk factors (see Table 3).

## Management

### *Corticosteroids*

The first-line therapy for NS is oral corticosteroids which, in the 1960s, were found to dramatically reduce mortality (to 3%) and to induce remission in approximately 80% of children with NS [5,75]. Corticosteroids are thought to work by several mechanisms, but overall their specific action is not fully understood. Their main effect is through regulation of cytokine gene expression through the glucocorticoid receptor, acting to induce genes coding for anti-inflammatory cytokines and suppress genes for pro-inflammatory cytokines. More recently, corticosteroids are reported to suppress T-cell function, as well as to stabilise the podocyte cytoskeleton [76].

Side-effects of long-term corticosteroid therapy in children with NS include growth impairment, development of cataracts and substantial weight gain [10,77,78]. In addition, behavioural and psychological consequences are common, including anxiety, depression and aggressive behaviour [79]. Given that they often require multiple courses throughout their lifetime, children with frequently relapsing and steroid-dependent NS are at increased risk of these adverse effects.

The current KDIGO guidelines for initial corticosteroid therapy recommend a single daily dose of oral prednisone at 60 mg/m$^2$/day to a maximum of 60 mg/day for 4–6 weeks. This daily dose should then be followed by alternate-day dosing with 40 mg/m$^2$/day, continued for 2–5 months with further tapering of the dose. Total therapy should be given for at least 12 weeks (see Table 4) [8]. Until recently, it was thought that treatment with corticosteroids for 6 *vs* 3 months achieved superior outcomes with significant reduction in the number of relapses [80]. However, several recent randomised-controlled trials demonstrated that treatment for 2–3 months is indeed the equivalent of treatment for 6 months, without increasing the risk of relapse, the development of SDNS or the need for second-line agents [81–83]. Therefore, the current KDIGO recommendations are in line with current evidence.

For relapse of SSNS, KDIGO recommends a customised approach based on whether the child has infrequent or frequent relapses (see Table 4) [8]. Corticosteroid protocols differ around the world as there is limited high-quality evidence that addresses tapering protocols [76]. Recently, several small trials have demonstrated that treatment with daily prednisone for 6 days at the onset of upper respiratory tract infections can reduce the risk of relapse in both frequently-relapsing and steroid-resistant nephrotic syndrome. Currently, a prospective large multicentre trial is ongoing to examine the safety and efficacy of this approach with a suggested dose of 15 mg/m$^2$ (maximum 40 mg) [84].

**Table 3.** Indications for early renal biopsy in childhood nephrotic syndrome.

| |
|---|
| Age <1 or >12 years |
| Persistent elevation in serum creatinine |
| Hypocomplementaemia |
| Gross haematuria |
| Infection with HIV, TB or hepatitis B/C |
| Steroid resistance |

### *Cyclophosphamide*

Cyclophosphamide is the most commonly used steroid-sparing agent worldwide and has been effective in multiple randomised-controlled trials for the treatment of frequently relapsing NS [85–87]. Although used in SDNS, cyclophosphamide has been shown more recently to produce less favourable results in this setting [88,89]. In a recent Cochrane review, cyclophosphamide was shown to decrease the incidence of relapse at 6–12 months when compared with corticosteroid alone [90], and, again in a meta-analysis, cyclophosphamide was demonstrated to induce longer duration of remission in FRNS compared with SDNS (72 *vs* 40% after 2 years) [59].

Cyclophosphamide is an alkylating agent with cytotoxic effects on lymphocytes by inhibiting DNA replication, leading to apoptosis. It therefore also has many important side-effects, including leucopenia, thrombocytopenia, alopecia, haemorrhagic cystitis and risk of infections [90]. Gonadal dysfunction and infertility, particularly in boys, are important sequelae after exposure to cyclophosphamide, and cumulative dosing further increases this side-effect [59]. In balancing the risks and benefits of this medication, KDIGO recommends a single 8–12 week course of cyclophosphamide for frequently relapsing SSNS, and advise against any repeat doses [8]. In addition, cyclophosphamide has no benefit for SRNS [91].

### *Levamisole*

Levamisole is another immunomodulatory agent used to spare treatment with steroids in the setting of SDNS and FRNS [90]. Also used as an antihelminthic agent, it

**Table 4.** KDIGO recommendations for corticosteroid treatment of childhood nephrotic syndrome.

| Classification | Treatment |
|---|---|
| Initial episode of SSNS | 60 mg/m$^2$/day (max 60 mg/day) as a single dose for 4–6 weeks<br>Then 40 mg/m$^2$/day as alternate-day dosing, tapered over 2–5 months<br>Total therapy minimum 12 weeks |
| Infrequently relapsing SSNS | 60 mg/m$^2$/day (max 60 mg/day) as a single dose until the child is in remission for >3 days<br>Then 40 mg/m$^2$/day as alternate-day dosing for at least 4 weeks, then tapered |
| Frequently relapsing/steroid-dependent NS | Daily prednisone until the child is in remission for >3 days<br>Then alternate day prednisone for at least 3 months<br>Maintain on lowest dose, alternate-day prednisone to maintain remissionDaily prednisone to be given during episodes of infections |

is thought to act by augmenting the type 1 immune response while down-regulating the type 2 response by inducing transcription of the cytokine, interleukin-18 [92]. Although, compared with placebo, it may reduce the risk of relapse [93,94], the data are limited and no conclusions can be drawn as to its efficacy as a steroid-sparing agent or its safety [90,95]. Levamisole has a more tolerable side-effect profile than cyclophosphamide; in many countries, however, its use is limited mostly by its availability. KDIGO guidelines recommend a dose of 2.5 mg/kg on alternate days for at least 12 months, as most children will relapse when levamisole is stopped [8].

### *CNIs*

Both cyclosporine and tacrolimus are effective in the treatment of FRNS and SDNS [96–99], although no trials have directly compared the two CNIs. Most of the evidence available has demonstrated the efficacy of cyclosporine; however, owing to the significant cosmetic side-effects of hypertrichosis and gum hyperplasia, tacrolimus is being used increasingly. Both medications may lead to hypertension, renal dysfunction and have a potential for diabetes mellitus which are often dose-related [99–101]. Chronic nephrotoxicity is an important and problematic side-effect and drug level should therefore be closely monitored. For cyclosporine, KDIGO suggests a starting dose of 4–5 mg/kg/day in two divided doses [8], with trough levels or 2 h post-dose levels monitored and adjusted within the target range (trough 60–100 ng/mL, 2 h post-dose 300–700 ng/mL) [96,102]. For tacrolimus, dosing starts at 0.1 mg/kg/day in two divided doses [8], with optimal trough levels ranging from 5 to 8 ng/mL [103]. In addition to drug level monitoring, the difficulty with CNIs is that many patients experience relapses after discontinuation of therapy (CNI dependence) [104,105] and the total length of treatment is controversial with some studies suggesting that therapy with CNIs should be restricted to 2 years because of the risk of nephrotoxicity [100].

CNIs are recommended as initial treatment for SRNS, as several randomised-controlled trials have shown that cyclosporine is significantly better than placebo at inducing partial or complete remission in this setting [106,107]. Again, optimal duration of therapy is controversial: KDIGO recommends a minimum of 12 months [8]. Combination therapy with CNI and corticosteroids can be used to induce remission of SRNS, although only in extreme cases [108,109].

### *Mycophenolate mofetil*

Mycophenolate mofetil (MMF) has inhibitory effects on T and B lymphocytes and cytokine gene expression [110]. Therapy with MMF is often used in FRNS or SDNS to spare the more significant side-effects of both calcineurin inhibitors and cyclophosphamide. In terms of efficacy, MMF performs less well than cyclosporine in preventing relapse in patients with FRNS; however, the nephrotoxic side-effects of CNIs are spared [111,112]. More recently, it was suggested that higher levels of mycophenolic acid (the active form of the drug), at a dose higher than 45 mg/h/L, may be more effective in reducing rates of relapse; however, this was a single-centre, retrospective study of only 15 patients [113].

### *Rituximab*

Rituximab, a monoclonal antibody that binds to the CD20 antigen on B-cells, is a newer therapeutic agent for more advanced SSNS. Studies have shown that it induces remission in FRNS and SDNS; however, there is no benefit in using it for SRNS [114–117]. Two recent randomised-controlled trials demonstrated the short-term (<1 year) safety of rituximab; they also demonstrated that rituximab combined with lower doses of corticosteroid and calcineurin inhibitors was not inferior to standard therapy in maintaining remission in FRNS, and that CNIs and steroids could eventually be weaned off with remission maintained [118,119]. Also, rituximab is not inferior to steroids in maintaining remission in SDNS patients who have never been exposed to calcineurin inhibitors [120]. These results were quite promising, but, similar to treatment with corticosteroids and steroid-sparing agents, children who initially benefited from rituximab therapy do eventually relapse, suggesting the effect is not permanent. Additionally, although rituximab is well tolerated by most children, it does have potentially serious side-effects, including pulmonary fibrosis, *Pneumocystis jiroveci* pneumonia, reactivation of hepatitis B virus, multifocal leucoencephalopathy, immune-mediated ulcerative colitis and agranulocytosis [121–126].

Dosing quantity and frequency, as well as appropriate monitoring of repopulation of CD20 B-cells and long-term consequences of therapy, have yet to be properly established.

## Congenital nephrotic syndrome

Congenital nephrotic syndrome (CNS) is defined as NS presenting in the first 3 months of life, compared with infantile NS (presenting between 3 and 12 months) and childhood NS (presenting after 1 year of age). The rationale for this division of classification is based on differences in aetiology, clinical features and treatment [127]. As mentioned previously, the main underlying aetiologies of childhood NS are minimal-change disease (MCD) and FSGS; treatment strategies for these types of childhood NS are outlined above. In contrast, the aetiology of CNS is heterogeneous, with genetic defects accounting for the majority of cases, and infections, inflammatory conditions and other rare causes accounting for the remainder.

Infectious causes of CNS include congenital syphilis, toxoplasmosis and cytomegalovirus (CMV) infections. Congenital syphilis is the most common infection causing NS, and most often presents with associated systemic features, such as fever, hepatic dysfunction and skin abnormalities, as well as membranous nephropathy on biopsy. Treatment with penicillin is often curative [128]. Congenital toxoplasmosis and CMV are much rarer causes of CNS, and proteinuria has been shown to be reversible by treatment with spiramycin and ganciclovir, respectively [129,130]. Rarer still, there are reports of CNS related to maternal systemic lupus erythematosus and mercury poisoning [131].

More commonly, CNS is caused by genetic defects in structural proteins that form the glomerular filtration barrier in the kidney. As discussed in the pathophysiology section of this review, the most common genetic pathogens include NPHS1, NPHS2, WT1, PLCE1 and LAMB2 [127,132]. Treatment of CNS initially revolves around ensuring there is no treatable cause such as a congenital infection [133], evaluating the eyes for associated abnormalities of syndromes associated with CNS, such as Pierson syndrome [134] and initiating a genetic work-up. Infants typically require daily albumin infusions which necessitates central intravenous access. Thrombotic complications are therefore almost inevitable and prophylactic anticoagulation is warranted. There needs to be monitoring for anaemia and thyroid dysfunction, common secondary effects of the protein losses [135,136]. Although they also often have agammaglobulinaemia and are at increased risk of infections, routine administration of prophylactic intravenous immune globulin is not advised [137]. Close attention to nutrition is also imperative to ensure adequate growth [138]. Thereafter, management strategies include (i) the use of medications, such as ACE inhibitors or indomethacin in an attempt to limit the number of albumin infusions required, (ii) unilateral nephrectomy, (iii) bilateral nephrectomies and commencement of peritoneal dialysis and finally, kidney transplantation when of an appropriate size [138].

## Conclusions and future perspectives

Overall, the prognosis for NS is excellent, with less than 5% rapidly progressing to end-stage renal disease. As outlined above, steroid resistance remains the most important risk factor for future development of CKD. Although there are significant side-effects from chronic use of steroids and steroid-sparing medications, current treatments are reasonably successful in inducing remission across the spectrum of disease. There remain many unanswered questions, including (i) who develops NS and why, (ii) what explains the individual variability in response to different treatments, and (iii) what are the specific triggers that provoke relapse. Further work is needed to clarify dosing and duration protocols for calcineurin inhibitors, mycophenolate mofetil and rituximab therapies. Lastly, there is a need to develop novel therapies for the treatment of steroid-resistant disease. This review outlines what is currently known about the pathophysiology of idiopathic childhood NS, as well as current understanding of how the underlying cause influences management strategies and overall outcomes of the disease. Further work is required to close the gaps in our understanding of the aetiological heterogeneity and diversity of the clinical course of this common and complex childhood disease.

## Authorship details

Mallory L. Downie drafted the manuscript, provided interpretation of results and approved the written manuscript. Claire Gallibois assisted in drafting the manuscript and approved the written manuscript. Rulan S. Parekh critically revised the manuscript and approved the written manuscript. Damien G Noone provided interpretation of results, critically revised the manuscript and approved the written manuscript.

## Disclosure statement

No potential conflict of interest was reported by the authors.

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