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REVIEW

Therapeutic trials in difficult to treat steroid sensitive nephrotic syndrome: challenges and future directions

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Abstract

Steroid sensitive nephrotic syndrome is a common condition in pediatric nephrology, and most children have excellent outcomes. Yet, 50% of children will require steroid-sparing agents due to frequently relapsing disease and may suffer consequences from steroid dependence or use of steroid-sparing agents. Several steroid-sparing therapeutic agents are available with few high quality randomized controlled trials to compare efficacy leading to reliance on observational data for clinical guidance. Reported trials focus on short-term outcomes such as time to first relapse, relapse rates up to 1–2 years of follow-up, and few have studied long-term remission. Trial designs often do not consider inter-individual variability, and differing response to treatments may occur due to heterogeneity in pathogenic mechanisms, and genetic and environmental influences. Strategies are proposed to improve the quantity and quality of trials in steroid sensitive nephrotic syndrome with integration of biomarkers, novel trial designs, and standardized outcomes, especially for long-term remission. Collaborative efforts among international trial networks will help move us toward a shared goal of finding a cure for children with nephrotic syndrome.

Keywords Nephrotic syndrome · Idiopathic nephrotic syndrome · Steroid sensitive nephrotic syndrome · Frequently relapsing nephrotic syndrome · Steroid resistant nephrotic syndrome · Children · Randomized controlled trials · Clinical trials · Steroid-sparing agents

Introduction

Childhood idiopathic nephrotic syndrome (NS) is one of the most common conditions encountered by pediatric nephrologists globally. Incidence of NS has remained stable over the past 60 years at approximately 2.92 per 100,000 children per year [1]. Based on response to steroids, NS is traditionally categorized into broad groups, with steroid sensitive nephrotic syndrome (SSNS) representing 90% of children presenting with this condition [2].

Approximately 25% of these children will be effectively cured and have no further relapses after an initial course of steroids. The remainder go on to have relapsing disease and are characterized based on the pattern of relapses as infrequently relapsing, frequently relapsing (FR) or steroid dependent (SD) [2, 3]. There is significant inter-individual variability in clinical course and treatment response that cannot be predicted based on demographics, relapse pattern, or previous treatment [2]. There are now several lines of evidence supporting various mechanisms leading to NS which may explain the heterogeneity seen in this condition.

Several therapeutic agents are now routinely used in the treatment of FR- and SD-NS including cyclophosphamide, calcineurin inhibitors, mycophenolate, levamisole, and rituximab. A clear advantage of any single agent over the others is lacking, and there are few head to head randomized trials directly comparing these agents [4]. Hence, pediatric nephrologists often

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move through the therapeutic agents in a stepwise fashion that is more often based on historical, institutional, or physician proclivities driven by medication side effect profiles, drug access, and patient preference, rather than by scientific rationale or evidence [5–7].

Long-term prognosis for children with FR- or SD-NS is excellent, with most achieving long-term remission in adolescence, and kidney failure is rare [2]. With the average age of onset of NS at 3 years, however, many children could endure a decade or more of relapsing disease with repeated exposure to corticosteroids, steroid-sparing therapeutics, and their associated side effects. This ultimately leads to a significant health care burden and reduced quality of life and children would benefit from induction of long-term remission early in the disease course [2, 8].

Many barriers have impeded our progress towards achieving long-term, treatment-free, remission, or "cure" in SSNS. The ever elusive pathogenesis that limits opportunities for targeted drug development, the scarcity of well-designed, randomized control trials, our focus on short-term outcomes over long-term remission, and the lack of a universally accepted definition of long-term remission are some of the barriers [4].

In this review, we highlight proposed pathogenic mechanisms that may lead to NS and how this heterogeneity can impact treatment response and clinical trials. We review clinical trials in SSNS focused on the treatment of frequently relapsing and steroid dependent disease, discuss their limitations and how we might strengthen future trials. We conclude by discussing future directions and incorporation of recent scientific advances and novel trial methodology to move us forward toward finding a cure for children with NS.

Potential pathways leading to nephrotic syndrome

Genetic susceptibility

Pathogenesis of nephrotic syndrome is not fully understood and likely results from complex interactions between genetic, immune, and environmental factors. Detailed reviews of SSNS pathogenesis [9] and SSNS genetics were recently published [10]. Human leukocyte antigen (HLA) risk alleles and mutations in immune regulatory genes increase the risk of SSNS but appear insufficient to cause disease alone. A multiple hit model is proposed with genetic risk alleles interacting with unknown environmental factors resulting in immune dysregulation leading to podocyte dysfunction and proteinuria [11]. Genes linked to the podocyte and slit diaphragm are also implicated in SSNS and exert direct effects on podocyte integrity. While no monogenic forms of NS are reported to exclusively cause SSNS, mutations in *PLCE1*, *NPHS1*, and genes associated with the Rho GTPase regulatory pathway (*MAG12*, *TNS2*, *DLC1*, *CDK20*, *ITSN1*, and *ITSN2*), essential for maintaining podocyte cytoskeletal structure, manifest variable phenotypes including both steroid resistant (SR) and SSNS [12]. Recent exome and genome-wide association studies have identified risk alleles for SSNS, mainly located in the *HLA-DQ* and *HLA-DR* regions, with some risk loci located near genes associated with immune function (Table 1) [13–16]. Imputation of HLA alleles has identified a number of deleterious and protective classical HLA alleles [13–17]. In European cohorts, the *HLA-DRB1*07:01-DQA1*02:01-DQB1*02:02* was most strongly associated with SSNS, whereas in Japanese cohorts, it was the *HLA-DRB1*08:02-DQB1*03:02* locus, suggesting different risk alleles may be at play in different ancestral populations [13–15].

Table 1 Genetic risk loci and study population associated with steroid sensitive nephrotic syndrome

HLA risk loci	Classical HLA alleles	Non-HLA risk loci
HLA-DQA1 *HLA-DQB1* *HLA-DRB1*	Deleterious: *HLA-DQA1*02:01* (European, South Asian) *HLA-DRB1*07:01* (European, South Asian) *HLA-DRB1*02* (European, South Asian) *HLA-DRB1*08:02* (Japanese) *HLA-DQB1*03:02* (Japanese) Protective: *HLA-DQA1*01* (European) *HLA-DQA1*01:03* (European)[a] *HLA-DRB1*13* (European)[a] *HLA-DRB1*13:02* (Japanese) *HLA-DQB1*06:04* (Japanese)	Immune mediated: *CALHM6/DSE* (European)[a] *TNFSF15* (Japanese) *BTNL2* (African) Other/unknown: *PARM1* (European) *CALHM6/DSE* (European)[a] *NPHS1* (Japanese, South Asian, African)[b] / *KIRREL2* (Japanese)[a]

[a]Not replicated to date

[b]Replicated in South Asian and African cohort but not in a European, Hispanic, Maghrebian, or independent African cohort

Immune dysregulation

The role of the immune system in nephrotic syndrome remains poorly understood. Most initial work centered around cell-mediated immunity and a role for T cells due to the spontaneous remission of nephrotic syndrome in children with measles, which is known to suppress cell-mediated immunity, and the remission of nephrotic syndrome in patients with Hodgkin's lymphoma after treatment [18]. Favorable response to cyclophosphamide and calcineurin inhibitors, known to primarily target cell–mediated immunity, also supports a role for T cells [19, 20].

Studies have found a relative imbalance of various T cell subsets with a reduction in CD4 + and an increase in CD8 + circulating T cells during relapse, as well as upregulation of Th2-related cytokines, elevated Th17 cells, and Th17-related cytokines and increased expression of IL-17 (interleukin-17) in kidney biopsies [21–23]. A role of regulatory T cells (Tregs) is suggested with reduced numbers of Tregs in children with active nephrotic syndrome, a protective effect of direct Treg infusion or stimulation by IL-2 in animal models, and the association of nephrotic syndrome with immunodeficiency, polyendocrinopathy, and enteropathy (IPEX) syndrome, an X-linked disease due to a mutation of *FOXP3* which inactivates Tregs [24–29].

B cells are also implicated with the success of rituximab in producing sustained remission, coupled with the finding of HLA genetic risk alleles, suggesting a role for the adaptive immune response. Reconstitution of switched memory B cells (cells that have undergone isotype switching from IgM to IgG antibody production) was the strongest predictor of relapse after rituximab in a study of 28 children, suggesting immune response to specific antigens may be responsible for relapses [30]. Relapses of nephrotic syndrome were also observed before reconstitution of circulating B cells [31]. Explanations for this phenomenon include failure to deplete B cells in all body compartments, such as the long-lived plasma cells residing in bone marrow, or a waning of alternative non-B cell–mediated modes of action such as rituximab's hypothesized direct effect on the actin cytoskeleton of podocytes via cross-reactivity with SMPDL-3b, a sphingomyelin phosphodiesterase expressed by podocytes [32]. Ofatumumab, a fully humanized anti-CD20 monoclonal antibody, which binds to a different CD-20 epitope, is also effective in nephrotic syndrome, which opposes the SMPDL-3b cross-reactivity theory [33]. Curiously, the measles virus does not just cause immunosuppression by depleting memory T cells, but also via B cells and long-lived plasma cells. It leads to immunological amnesia, a reset of the immune system, where a significant proportion of preexisting antibodies are lost, with an overall reduction in antibody diversity [34].

Circulating glomerular permeability factors

A circulating glomerular permeability factor has long been suspected to play a role in the pathogenesis of NS and focal segmental glomerulosclerosis (FSGS), but a single causative circulating factor has not been identified. A number of putative pathogenic circulating factors have been proposed including heparanase, hemopexin, angiopoietin-like 4 (ANGPTL4), cardiotrophin-like cytokine-1 (CLC-1), radical oxygen species, and soluble urokinase plasminogen activator receptor (suPAR) [35, 36]. Most recently, anti-nephrin antibodies were reported in 29% of 41 children and 21 adults with minimal change disease during relapses, and the antibodies were absent or significantly reduced during remission [37]. This finding requires validation in larger populations and earlier in the course of NS as it may only represent a subset of SSNS.

Gene-environment interaction and triggers

Environmental factors associated with nephrotic syndrome include respiratory viruses, EBV, other infections, and allergens. The most common trigger of nephrotic syndrome relapses is upper respiratory tract infections, which precede 50–70% of relapses in SSNS [38, 39]. EBV is also a pathogen of interest, with evidence of recent EBV infection found in approximately 50% of patients presenting with nephrotic syndrome in a French cohort [40]. Increasing evidence for the role of B cells in nephrotic syndrome, and the association with polymorphisms in *HLA-DQA1* and *HLA-DQB1* associated with the ability to produce anti-EBNA-1 antibodies, lends some strength to this hypothesis [41].

Aeroallergens, food allergies, and insect bites are reported to trigger nephrotic syndrome relapses, and small case series have reported improvement on elemental and oligoantigenic diets suggesting a pathogenic role of allergic disease [42, 43]. The lack of seasonality to relapses or a proven benefit of mast cell stabilizers in nephrotic syndrome casts doubts [42, 44].

The range of mechanisms proposed to lead to NS suggests NS is a heterogeneous group of disorders leading to a common clinical phenotype of NS via dysfunction of the glomerular filtration barrier. Due to this heterogeneity, the perceived effect of treatments from clinical trials may not be generalizable. Selection of participants in trials may also bias outcomes and lead to negative trials even though a subgroup, for example those with antibodies, may benefit depending on the treatment mechanism. Often pediatric trials are not powered for subgroup analyses, and these effects can be overlooked.

Defining long-term remission and long-term outcomes

A focus on short-term outcomes in SSNS clinical trials and a lack of a robust, standard definition of long-term remission to be used in clinical trials, limits our ability to identify treatments leading to long-term remission in children with NS. Defining long-term remission in SSNS

presents several challenges. Very few studies report the relapse-free duration that reliably predicts long term remission or "cure" in their cohorts. Among 63 patients with SSNS, the longer the period of remission, not unexpectedly, resulted in a lower risk of relapse. Even after 5 years of remission, however, the risk of relapse remained as high as 23%, and a relapse-free period that definitively protected from future relapse could not be identified [45]. While studies show a steady decrease in disease activity with increasing age, the historical notion of nephrotic syndrome resolving at puberty regardless of type of therapeutic intervention also remains unproven [46].

SSNS was once thought to almost universally remit in adolescence; however, long-term studies now dispute this, with 16 to 42% of patients going on to have relapses in adulthood [45–49]. Several factors proposed to be associated with increased risk of relapse in adulthood include, diagnosis before the age of 6, higher number of relapses per patient per year and cyclosporine use; however, no single factor consistently predicted relapse in adulthood across all long-term studies [45–48]. In our center, 631 children with NS (SSNS and SRNS) were followed for 2.1 to 6.6 years, and 80% achieved long-term remission and were discharged from the nephrology clinic before 18 years of age. Demographic or clinical factors, individually or in combination, could not predict the clinical course, need for second-line agents, or long-term remission [2]. Variation in factors associated with relapses in adulthood may be due to differences in disease severity leading to selection bias, definitions of "adulthood" and long-term remission, geographical location, and ethnicity.

Definitions of long-term remission are infrequently reported in studies. One study used a definition of remission as 3 years treatment-free [50]. At our own center, we typically discharge children from follow-up after 4 years of treatment-free remission; however, the duration likely varies by physician practice and clinical setting. A consistent definition of long-term remission for use in clinical and research settings will greatly enhance our ability to understand long-term efficacy of steroid-sparing agents.

Therapeutic trials in steroid sensitive nephrotic syndrome

Improving long-term remission rate after initial episode

Since the introduction of the 8-week steroid regimen, by the International Study of Kidney Disease in Children (ISKDC) in the 1970s, much effort was expended on determining the optimal steroid regimen at the initial presentation of NS. There was a move toward longer regimens of 12 weeks from the original ISKDC 8-week course after the 2007 Cochrane review found longer steroid courses resulted in higher rates of sustained remission at 12–24 months, without an increase in adverse effects [51]. Recent randomized control trials (RCTs) have called this into question, and some centers have returned to an 8-week prednisone course for the initial presentation of NS (see an in-depth review of the use of corticosteroids in NS [52]). The PREDNOS trial, with 237 children at first episode of SSNS, found no advantage of 16 weeks over 8 weeks of prednisolone. A multicenter trial of 255 children from Japan compared 2 months versus 6 months of prednisolone and also found no difference in time to first relapse or the incidence of frequently relapsing disease [53]. Although these findings provide evidence for the shorter 8-week steroid course, a study in 1988 by the Arbeitsgemeinschaft fur Padiatrische Nephrologie (APN) of 61 children presenting with INS found 4 weeks versus 8 weeks of steroids resulted in a significantly higher relapse rate and lower long-term remission suggesting further reduction of the initial course beyond 8 weeks is unlikely to be beneficial [54]. The recent updated 2020 Cochrane review has recommended no further resources should be invested in determining the optimal duration of the initial steroid course [55]. Nevertheless, questions remain whether certain subgroups, such as very young children before 4 years of age, who may be at higher risk of steroid dependency or frequent relapses, may benefit from longer courses of steroids at diagnosis [56]. A recent meta-analysis of 54 studies suggests, we have made only modest gains in achieving long-term remission after treatment of the initial presentation of nephrotic syndrome; the risk of relapses declined from 78.4% in 1945 to 66.2% in 2011 regardless of initial steroid treatment duration [1].

While steroid-only regimens are the backbone of treatment, the burden of steroid side effects can be significant. The Gesellschaft für Pädiatrische Nephrologie (GPN, formally APN) published a protocol for a non-inferiority trial comparing standard 12-week steroid course (prednisolone 60 mg/m^2 daily for 6 weeks followed by 40 mg/m^2 alternate days for 6 weeks) to a 12-week course of mycophenolate mofetil combined with a shorter course of prednisolone (60 mg/m^2 daily until remission and then 2-week course of prednisolone 40 mg/m^2 alternate days) for the initial presentation of NS and results are pending [57]. Three studies are also underway assessing the use of levamisole as an adjunct to corticosteroids for the treatment of the initial presentation of nephrotic syndrome (ClinicalTrials.gov #NCT02818738, EudraCT 2016–002,324-92, and 2017–001,025-41). A recent study in adults found tacrolimus monotherapy to be non-inferior to corticosteroids to induce remission in minimal change disease. While there are likely significant differences in the underlying pathophysiology of minimal change disease in adults compared to children, the success of a completely steroid free regimen remains noteworthy [58].

If alternate steroid-sparing treatment strategies at the initial presentation of nephrotic syndrome result in a larger proportion of children achieving long-term remission, this could be a significant step forward in management of SSNS. However, when 1 in 4 children achieve long-term remission with steroids alone, exposing this group to additional immunosuppression with potentially more serious adverse effects upfront, is difficult to justify. It is critical that we find ways to identify this group in advance to avoid additional unnecessary immunosuppression.

Relapses

The dose and duration of corticosteroids for NS relapses to optimize remission rates and minimize corticosteroid toxicities were recently reviewed [52]. While the optimal steroid regimen for relapse is yet to be identified, in the quest to achieve long-term remission for children with nephrotic syndrome, it is unlikely the dose or duration will substantially alter the course of NS [1]. Time and resources should be devoted to optimizing steroid-sparing regimens in order to increase the proportion with long-term remission.

Frequently relapsing and steroid-dependent SSNS

There are few head-to-head trials comparing steroid-sparing agents in FR- and SD-SSNS; thus, there is no clear benefit of any one drug over another (Table 2) as demonstrated in a systematic Cochrane review, which failed to identify difference in efficacy of calcineurin inhibitors, mycophenolate mofetil, levamisole, and alkylating agents. The authors highlighted the need for further studies [4].

Low-dose alternate day corticosteroids are another common approach to FR-SSNS. Only two controlled trials have been performed comparing this strategy to steroid-sparing agents. Both compared cyclophosphamide to the low-dose steroid strategy, with cyclophosphamide clearly the superior drug [62, 63].

Cyclophosphamide has been used in SSNS for over 50 years, but just five randomized controlled trials have compared cyclophosphamide to placebo, steroids alone, or other steroid-sparing agents. The first UK trial in 1970 was conducted in 30 children with FR-SSNS on maintenance prednisolone. Cyclophosphamide of 3 mg/kg/day for 8 weeks with prednisolone withdrawal compared to prednisolone withdrawal alone was associated with a significant reduction in relapse risk at 16 weeks (20% vs. 73%, $P=0.005$) [61]. Two subsequent trials in Canada and Europe compared cyclophosphamide to placebo demonstrating significant improvements in relapse rates up to 2 years [62, 63]. Only two RCTs compared cyclophosphamide to other steroid-sparing agents. In 1982, the APN compared cyclophosphamide to chlorambucil in 50 children and found no difference in sustained remission up to 2.5 years, and in 1993, an Italian group demonstrated no differences in relapses up to 9 months on cyclophosphamide 2.5 mg/kg/day for 8 weeks to cyclosporine 6 mg/kg/day [69, 84]. Recently, a non-randomized pilot study in Saudi Arabia compared rituximab to cyclophosphamide (rituximab 375 mg/m^2 two doses vs. cyclophosphamide 3 mg/kg/day for 8 weeks) as the first steroid-sparing agent in 46 children with FR- and SD-SSNS, and showed a non-significant increase in 1-year relapse-free survival in the rituximab group (84.2% vs. 58.6%, $P=0.1$).

Cyclophosphamide has the advantage of achieving long-term remission in approximately 30% of children after a single course and 58% will have ≤ 2 relapses, based on observational studies, over an average follow-up of 4 years [85]. There is a fear of potential serious long-term adverse events such as cancer and infertility after cyclophosphamide with limited data [86]. Nonetheless, physician preference due to these concerns limits its use [5]. There is, however, a distinct advantage over other second agents where relapses tend to recur after discontinuation of the drug.

Calcineurin inhibitors, despite their widespread use, have just three randomized control trials to support their use. Two studies used cyclosporine and were compared to cyclophosphamide and mycophenolate mofetil. Mycophenolate mofetil (1200 mg/m^2/day) was compared to cyclosporine A (trough level target 50–150ug/L) over 12 months, in a multi-center study in Belgium and the Netherlands in children with FR- and SD-SSNS. Although a greater percentage in the cyclosporine group were in remission at 12 months (91% vs. 58%), the study was underpowered with only 31 patients and the finding not statistically significant [71]. The primary outcome in the study was eGFR decline, which showed a small but significantly greater decline in eGFR at 1 year among those on cyclosporine vs. mycophenolate (14 vs. 6 ml/min/1.73 m^2). When we consider the additional mechanism of cyclosporine and risk of a small and reversible drop in GFR, the relevance of this finding to the long-term outcomes is unclear. One RCT included tacrolimus as the control arm and found it to be inferior to rituximab in maintaining sustained remission at 12 months [80].

Levamisole is also effective in reducing the risk of relapse at 12 months on meta-analysis (HR 0.22, 95% CI 0.11–0.43), although the time to first relapse is similar in the first 100 days on the therapy [68]. In six trials of levamisole, the most-studied steroid-sparing agent in trials, three compared levamisole to placebo or prednisolone withdrawal, one to low-dose prednisolone and two to other steroid-sparing agents (IV cyclophosphamide and mycophenolate mofetil). While effective compared to placebo and low-dose prednisolone, no difference in efficacy was found compared to cyclophosphamide or mycophenolate [64–68, 72]. Most trials assessing levamisole were performed in South Asia and the Middle East where the drug is readily available.

Table 2 Randomized control trials of steroid-sparing agents for frequently relapsing or steroid dependent nephrotic syndrome

Drug	Study	Country	Population	N	Intervention	Control	Outcome	Follow up
Chlorambucil	Grupe 1976 [59]	USA	FR or SD-SSNS Age 3.5 to 15.5 years	21	Chlorambucil 0.1–0.2 mg/kg/day increased every 2 weeks until WCC < 1000 cm^3 then stopped (av. dose 0.33 mg/kg, mean duration 9.7 weeks) + prednisolone as per control group continued until WCC > 5000/cm^3 then weaned	Prednisolone 80–120 mg on alt. days for 2 months tapered over 4–6 weeks	At 1 year, 0% had relapsed in the chlorambucil group vs 100% in the control group	1 year
	APN 1982 [60]	Germany (multi-center)	FR or SD-SSNS, Age 2 to 16 years Biopsy proven MCD	50	Oral chlorambucil 0.15 mg/kg/day for 8 weeks Both groups: Prednisone for 4 weeks	Oral CPA 2 mg/kg/day for 8 weeks	Overall, 6% of SD-SSNS and 75% of FR-SSNS in sustained remission at 2.5 years ($P < 0.001$). There was no difference between treatment groups	2.5 years
Cyclophosphamide	Barratt 1970 [61]	UK	FR-SSNS Age < 14 years On maintenance prednisolone	30	CPA 3 mg/kg/day + prednisolone for 8 weeks then weaned as per control group	Prednisolone withdrawal over 8 weeks	20% in CPA group vs 73% in control group relapsed at 16 weeks ($P = 0.005$)	16 weeks
	Chiu 1973 [62]	Canada	FR-SSNS Age 2 to 15 years Biopsy proven MCD	23	CPA 75 mg/m^2/day for 16 wks. + prednisolone as per control group	Prednisolone 60 mg/m^2/day (max 60 mg) until urine protein normal for 2 wks. then alt. days for 4 mos	16.7% vs 91% relapsed in CPA vs control group during follow up ($P < 0.01$).	2 years
	ISKDC 1974 [63]	Multicenter (23 sites, 12 countries)	FR-SSNS Age 12 weeks to 16 years	63 (53 in analysis)	Oral CPA 5 mg/kg/day to induce WCC 3000–5000/mm^3, then decreased to 1–3 mg/kg/day to maintain leukopenia (duration 6 weeks) + Prednisolone 10 mg/m^2/day for first 10 days	Prednisone 40 mg/m^2/day on 3 consecutive days out of 7 days for 180 days	48% in CPA group and 88% in control group relapsed (no p value quoted) over a mean follow up period of 22 months. Average time to first relapse 120 ± 39 days in CPA group vs 81 ± 17 days in control group ($P < 0.001$)	1.8 years

Table 2 (continued)

Drug	Study	Country	Population	N	Intervention	Control	Outcome	Follow up
Levamisole	BAPN 1991 [64]	UK	FR or SD-SSNS Age not specified (mean 8.3 ± 3.6 years)	61	Levamisole 2.5 mg/kg alt. days (max 150 mg)	Placebo	45% in levamisole group vs 13% in control group were in remission at 112 days ($P = 0.008$). Ten of the 14 in remission on levamisole relapsed within 3 months of stopping the drug	112 days
	Dayal 1994 [65]	India	SSNS, initial episode or relapse	61	Levamisole 2–3 mg/kg/day twice a week for 1 year + prednisolone as per control group	Prednisolone 60 mg/m^2/day for 4 weeks followed by 40 mg/m^2/day alt. days for 4 weeks	At 2.5 yrs. 63% vs 43% were in remission in levamisole and control group ($P = 0.11$). Longer time to first relapse in levamisole group (12 vs 10.5 months, $P = 0.10$)	2.5 years
	Donia 2005 [66]	Egypt	SD-SSNS in relapse Age 3 to 15 yrs Biopsy proven MCD	40	Levamisole 2.5 mg/kg on alt. days for 6 months Both groups: Prednisolone 2 mg/kg/day until remission, 1 mg/kg alt. days for 14 days then study medication started. Prednisolone weaned to 1 mg/kg alternate days for 14 days then weaned by 0.25 mg/kg ev. 14 days until stopped	IV CPA 500 mg/m^2/month. for 6 months	At end of therapy 50% vs 45% were in remission in the levamisole and CPA group (P value not stated). Post-treatment 25% in each group, 15% vs 5% and 5% in each group were in remission at 6 months, 2 years and 4 years respectively (NS)	4 years
	Al-Saran 2006 [67]	Saudi Arabia	FR or SD-SSNS Age < 14 years No previous non-steroid immunosuppressants	56	Levamisole 2.5 mg/kg alt. days for 1 year	Low-dose prednisolone (< 0.5 mg/kg) on alt. days	Greater reduction in relapse rate in levamisole group (0.29 vs 0.11/patient/month, $P < 0.01$). 62.5% vs 0% were relapse-free at 2 years in levamisole and control group	2 years
	Gruppen 2018 [68]	International multicenter (13 sites, 5 countries)	FR or SD-SSNS Age 2 to 18 years	103 (99 modified ITT analysis)	Levamisole 2.5 mg/kg alt. days (max 150 mg). Started 3 to 21 days after remission and continued for 12 mos. or until relapse	Placebo alt. days	Similar relapse-free survival until 100 days. After 100 days, relapse-free survival greater in levamisole group (HR 0.22, 95% CI 0.11–0.43, $P = 0.001$)	1 year
Calcineurin inhibitors	Ponticelli 1993 [69]	Italy (multicenter)	FR or SD-SSNS Age 2 to 15 years No treatment with cytotoxic agents in past 2 years (included adults > 15 years – results for children only reported here)	55	CsA 6 mg/kg/day for 9 mos. (dose adjusted to trough level 200–600 ng/ml), tapered by 25% every mo. until discontinued at 12 months	CPA 2.5 mg/kg/day for 8 weeks. Prednisone 60 mg/m^2/day until complete remission then 40 mg/m^2 every other day for 4 weeks	70% vs 68% in sustained remission at 9 months (NS) and 20% vs 68% at 2 years (P value not stated) in CsA and CPA group	2 years

Table 2 (continued)

Drug	Study	Country	Population	N	Intervention	Control	Outcome	Follow up
Mycophenolate	Gellermann 2013 [70]	Germany (15 sites)	FR ± SD-SSNS Biopsy proven MCD	60	MMF for 12 months followed by CsA for 12 months Cross-over RCT. Both groups: MMF 1000–1200 mg/m^2/day adjusted to trough level 1.5–2.5 ug/ml. CsA 150 mg/m^2/day adjusted to trough levels 80–100 ng/ml	MMF for 12 months followed by CsA for 12 months	Lower relapse rate and longer time to first relapse on CsA in 1st year (0.24 vs 1.10 relapses/pt/year, $P=0.03$) but not in 2nd year 85% vs 64% relapse-free during treatment with CsA vs MMF ($P=0.06$). Post hoc analysis: Pts with a MPA-AUC < 50 ug.h/ml had more relapses (mean 1.4 vs 0.27/year, $P<0.05$)	2 years
	Dorresteijn 2008 [71]	Netherlands, Belgium (6 sites)	FR ± SD-SSNS Age < 18 years Biopsy proven MCD	31 (24 in analysis)	MMF 1200 mg/m^2/day (max 1g bid) for 12 months. Dose reduced by 25% if adverse effects or infection occurred. Further 25% reduction if adverse effects persisted	CsA 4–5 mg/kg/day for 12 months. Dose adjusted to achieve trough levels of 50–150 ug/L	Greater decline in eGFR (primary endpoint) in CsA vs MMF group (14 vs 6 ml/min/1.73 m^2, $P=0.03$). Greater percentage in remission in CsA group at 1 year (91% vs 58%, $P=0.06$)	1 year
	Sinha 2019 [72]	India	FR or SD-SSNS Age 6 to 18 years Requiring prednisolone < 1 mg/kg alt. days No previous levamisole, MMF, CNI, azathioprine, or RTX treatment and no CPA in past 6 months	149	MMF 750 to 1000 mg/m^2/day for 1 year + prednisolone as per control group	Levamisole 2–2.5 mg/kg alt. days for 1 year Prednisolone 2 mg/kg/day until remission, then 1.5 mg/kg alt. days for 4 weeks, tapered by 0.25 mg/kg every 2 weeks (stopped at 12 to 14 weeks)	No difference in relapse rate (1.05 vs 1.34 relapses/person-year; $P=0.12$) or sustained remission at 1 year (40.8% vs 34.2%, $P=0.20$) in MMF vs levamisole groups In subset of 137 pts, followed for median of 43.0 months, no difference in long-term outcomes	1 year
	Iijima 2022 [73]	Japan (27 sites)	FR or SD-SSNS 2 to 18 years	78	RTX 375 mg/m^2 weekly × 4 weeks followed by MMF 1000–1200 mg/m^2/day for 17 months	RTX 375 mg/m^2 weekly × 4 weeks followed by placebo for 17 months	Non-significant increase in time to treatment failure (frequent relapses, SD or resistance, use of immunosuppressive agents, 784 vs 472.5 days, $P=0.07$) and time to relapse (654 vs 320 days, $P=0.07$) in MMF group	1.5 years

Table 2 (continued)

Drug	Study	Country	Population	N	Intervention	Control	Outcome	Follow up
Rituximab	Ravani 2011 [74]	Italy	SSNS dependent on prednisolone and CNIs for at least 1 year Age 1 to 16 years	54	RTX 375 mg/m^2 (1 dose only or if pt had signs of prednisolone or CNI toxicity 2 doses 2 weeks apart) At 30 days, prednisolone was tapered off by 0.3 mg/kg/week if proteinuria < 1 g/day. After 2 weeks, CNI decreased by 50% and withdrawn after a further 2 weeks	Prednisolone and CNI alone. Doses tapered as in the intervention group if proteinuria < 1 g/day	Less proteinuria (0.11 vs 0.36 g/day; $P = 0.003$) and lower risk of relapse (18.5% vs 48.1%, P=0.03) in RTX group at 3 months	1 year
	Iijima 2014 [75] Kamei 2017 (long-term data) [76]	Japan (9 sites)	Complicated FR or SD-SSNS (≥ 4 relapses in 12 months or SD in past 2 years) in relapse Diagnosed between age 1 and 18 years	52 (48 in analysis)	RTX 375 mg/m^2 (max 500 mg) weekly for 4 weeks Both groups: If on prednisolone at screening, 60 mg/m^2/day (max 80 g) for 4 weeks, if not on prednisolone, 60 mg/m^2/day until in remission for 3 days Prednisolone weaning for both groups: 60 mg/m^2/day alt. days for 2 weeks, 30 mg/m^2/day on alt. days for 2 weeks, 15 mg/m^2/day on alt. days for 2 weeks Other immunosuppressants weaned and stopped	Placebo IV infusion at same frequency as RTX	Longer relapse-free survival (267 vs 101 days, $P < 0.0001$) in RTX group At 1 year, 30% in RTX vs 5% in control group were in remission Ninety-four percent of RTX group relapsed during long-term follow up (mean follow-up 59 months)	1 year
	Ravani 2015 [77]	Italy (4 sites) non-inferiority trial	SDNS for 6–12 months In remission on high dose prednisolone (≥ 0.7 mg/kg/day) Age 1–16 years	30	RTX 375 mg/m^2 single dose. Prednisone tapered as per control group	Prednisone tapered by 0.3 mg/kg/week starting at 30 days and withdrawn if proteinuria < 1 g/m^3/day at the end of taper. Restarted if proteinuria ≥ 1 g/m^2/day. Steroid-sparing agents (CNI or CPA) used at discretion of local investigators	At 3 months, proteinuria lower (ratio of means 0.58; 95% CI, 0.18 to 1.95). At 6 and 12 months, respectively, 50% and 25% of RTX group were in sustained remission without prednisolone/CNI. 14 of 15 patients in control group relapsed during prednisone taper	3 months
	Ahn 2018 [78]	South Korea (8 sites)	SD-SSNS + CNI dependence > 2 yr Diagnosed < 18 and age < 24 yrs	61 (51 in analysis)	RTX 375 mg/m^2 (max 500 mg) single dose; second dose given if B cell depletion not achieved at 2 wks. (n = 9) + (steroids ± CNI)	Steroids ± CNI	At 6 mos. 74% vs 31% in remission in RTX and control group (P = 0.003). Longer median duration of remission in RTX (9.0 vs 2.9 mos., P = 0.004)	6 months
	NEPHRUTIX 2018 [79]	France (multicenter)	FR-SSNS + highly steroid/CNI and/or MMF-dependent	23	RTX 375 mg/m^2 × 2, 1 week apart. Other agents weaned as per control group	Placebo IV MMF stopped 1 week after first infusion, CNI tapered by 25% every 2 weeks after 2nd infusion, steroids decreased by 25% every 2 weeks until 5 to 7 mg alternate days	At 6 months, 90% vs 0% were in remission in RTX and control group (P value not stated)	6 months
	RITURNS 2018 [80]	India	SD-SSNS Age 3 to 16 years No previous corticosteroid-sparing agent	120	RTX 375 mg/m^2 (max 500 mg) 2 doses, 1 week apart + tapering doses of alt. day prednisolone	Tacrolimus 0.2 mg/kg/day (target trough level 5–7 ng/mL) + tapering doses of alt. day prednisolone	Ninety percent vs 63% in RTX and tacrolimus group were in sustained remission at 1 year. ($P < 0.001$). Median time to 1st relapse longer in RTX group (40 vs 20 weeks, $P < 0.001$)	1 year

Table 2 (continued)

Drug	Study	Country	Population	N	Intervention	Control	Outcome	Follow up
	Ravani 2021 [81]	Italy	SD-SSNS Age 2 to 24 yrs	30	RTX 375 mg/m^2 single dose Both groups: 45 day run in MMF 1200 mg/1.73 m^2/day + steroid withdrawal	MMF 350 mg/m^2 bid	Trial stopped due to high rate of relapse in MMF group. Risk of relapse at 12 months higher in MMF group (80% vs 13%, $P = 0.008$)	1 year
Ofatumumab	Ravani 2021 [82]	Italy	SD-SSNS + CNI dependent Age 2 to 24 yrs	140	Ofatumumab 1.50 mg/1.73m^2 single dose Both groups: steroid and CNI minimized during 1 mo run in period. CNI and steroids tapered and withdrawn within 60 days	RTX 375 mg/m^2 single dose	No difference in relapse rate at 1 or 2 years (53% vs 51% at 1 year, OR 1.06; 95% CI 0.55 to 2.06)	2 years
Mizoribine	Yoshioka 2000 [83]	Japan (57 sites)	FR-SSNS Age 2 to 19 years	197	Mizoribine 4 mg/kg/day for 48 week	Placebo Prednisolone 1–2 mg/kg for 28 days, then tapered and stopped by 12 weeks	Non-significant lower relapse rate in mizoribine group (0.0055 vs. 0.0067 relapses/day, P=0.12). Subgroup analysis of < 10 y.o., relapse rate significantly lower (ratio 0.66, 95% CI 0.44 to 0.94; P=0.017)	18 months

NB Studies published in abstract form only were not included

FR, frequently relapsing; *SD*, steroid dependent; *SSNS*, steroid sensitive nephrotic syndrome; *MCD*, minimal change disease; *CPA*, cyclophosphamide; *CNI*, calcineurin inhibitor; *CsA*, cyclosporine; *MMF*, mycophenolate mofetil; *eGFR*, estimated glomerular filtration rate; *RTX*, rituximab

Mycophenolate mofetil is the most common steroid-sparing drug used in Europe by physician preference as it is appealing for its lack of nephrotoxicity [6]. Three RCTs found mycophenolate mofetil less effective in reducing relapse rates and achieving sustained remission compared to cyclosporine; however, the recent Cochrane meta-analysis found no difference in relapse at 12 months (RR 1.9, 95% CI 0.66–5.46) [4]. A criticism of these RCTs is the use of standard dosing regimens (750–1200 mg/m^2/day) or trough levels to adjust mycophenolate mofetil doses which correlate poorly with mycophenolic acid area under the concentration–time curve (MPA-AUC). A post hoc analysis of an RCT of 60 children, which initially reported poorer outcomes in patients on mycophenolate mofetil vs. cyclosporine A, found patients with high mycophenolic acid exposure (MPA-AUC > 50 ug.h/ml) had fewer relapses compared to those with lower mycophenolic acid exposure (MPA-AUC < 50ug.h/ml) and similar relapse-free survival in those with higher mycophenolic acid exposure compared to those on cyclosporine A [70]. An MPA-AUC > 45 ug/h/ml was also associated with lower risk of relapse in two retrospective observational studies [87, 88]. This raises the question of whether the mycophenolate mofetil efficacy can be improved with therapeutic drug monitoring. Limited sampling AUC strategies using either Bayesian estimation or multiple linear regression are validated in patients with nephrotic syndrome, and prospective trials are needed to assess utility of integration into clinical practice [89]. Low-dose mycophenolate strategies have also been tried; however, a recent RCT comparing low-dose mycophenolate (350 mg/m^2 bid) to rituximab was stopped after randomization of just 30 patients due to unacceptably high rate of relapse in the mycophenolate group [81].

Rituximab has emerged as a very effective steroid-sparing agent in the short term. In an RCT of 120 children with SDNS, rituximab significantly improved 12-month relapse-free survival when compared to tacrolimus (90 vs. 63.3%; $P < 0.001$) [80]. However, the risk of recurrence after discontinuation and subsequent B cell repopulation is high, and in a multinational cohort study of 421 children, 81% relapsed after rituximab therapy (median relapse-free survival of 12.5 months) [30, 90]. Relapse-free survival may be increased with the adjunct of maintenance immunosuppression after rituximab, specifically mycophenolate [90]. A recent multicenter RCT compared rituximab followed by mycophenolate for 6 months to rituximab and placebo and found no significant difference in treatment failure (defined as development of frequent relapses, steroid dependent or resistance, or use of immunosuppressive agents or rituximab) or time to first relapse. Post hoc analysis did show a reduction in relapse rate during the mycophenolate course (HR 0.26; 95% CI 0.08 to 0.48) [73]. Rituximab was commonly used as a third- or fourth-line agent due to concerns of potential serious adverse effects including progressive

multifocal leukoencephalopathy and persistent hypogammaglobulinemia, but with increasing experience in its use, studies using rituximab earlier in the course of the disease are underway [91]. Research for other monoclonal antibodies is limited — a single RCT has been published assessing ofatumumab and found it was not superior to rituximab [82]. Whether other selected antibodies can change the natural history of nephrotic syndrome and achieve long-term remission remains unknown.

Limitations of current trials

Over the past 60 years, only 24 controlled trials investigated the seven most used medications in FR- and SD-SSNS (Table 2). Most trials were small with a median of 55 children. Small study population size only allows for detection of large treatment effects, and precludes the ability to identify subgroups of this heterogeneous disease that have either a beneficial effect, no consequence or harm from specific treatments [92]. Most trials are also limited to a single geographical area, which limits the generalizability of the findings due to the known geographical and genetic differences in SSNS, and the outcomes reported are not consistent, and hence, it is not possible to directly compare outcomes [85]. Trials also focus on short-term outcomes with the longest trial follow-up of a maximum of 2.5 years, although some trials report subsequent observational periods. Our focus on short-term outcomes is insufficient, and inclusion of long-term outcomes is needed to change the life course of disease. In the context of high cost and large time commitment to conduct RCTs, observational studies have a role in informing practice but remain vulnerable to selection bias, even after the use of rigorous statistical techniques to reduce potential bias (i.e. propensity methods).

Future directions

RCTs remain the gold-standard in assessing efficacy of therapeutics, and we must commit to improving the availability of quality randomized evidence in NS. We have highlighted the challenges to performing these trials in SSNS, including (1) unknown pathogenic mechanisms limiting targeted drug discovery; (2) high degree of heterogeneity in the SSNS population; (3) inadequate sample sizes; and (4) a lack of standardized outcomes. Nephrology as a whole lags behind other specialties in quantity and quality of clinical trials, but strategies are available to advance NS trials [93].

Addressing heterogeneity and identifying biomarkers

The ability to identify subgroups of SSNS that are similar in either underlying pathological mechanisms or prognosis will provide opportunities to enrich clinical trials through selection of participants that are most likely to benefit from a specific drug, increasing the likelihood of detecting a drug effect [94]. There are early examples of using genomics to predict response in SSNS. In 1997, a German retrospective study of 54 children with FR-NS +/− SD-NS found *HLA-DR7*-positive children were less likely to remain in remission after cyclophosphamide or chlorambucil than *HLA-DR7*-negative children (36% vs. 81% in remission at 3 years). *HLA-DR7* status was better at predicting a favorable response to alkylating agents than the rate of previous relapses [95]. This allele was identified as a risk factor for SSNS in European and South Asian cohorts, suggesting a role in the pathogenesis and response to treatment [13, 14, 17]. A study of 113 children with NS found the GR-9 polymorphism of the glucocorticoid receptor gene, related to impaired glucocorticoid sensitivity, was associated with a higher risk of steroid dependence. These studies illustrate the need to consider an individual's responsiveness to treatment, and its influence on outcomes, in clinical trials. To date, neither HLA typing nor pharmacogenetics have been incorporated into prospective therapeutic trials in SSNS.

Genomics, transcriptomics, metabolomics, and proteomics in combination with machine learning show promise in defining homogeneous subgroups within glomerular disorders. Recently, researchers were able to categorize adults and children with FSGS or minimal change disease (MCD) into 3 clusters associated with complete remission and eGFR decline using a digital pathology scoring system and unsupervised machine learning techniques [96]. The glomerular transcriptome data found a cluster associated with poorest clinical outcome showed downregulation of podocyte specific gene expression and an increase in monocyte/macrophage specific gene expression, laying the groundwork to identify potential biomarkers and therapeutic targets [96].

A number of nephrotic syndrome cohort studies are in process with many incorporating multi-omic approaches. The Nephrotic Syndrome Study Network (NEPTUNE) study in North America, a study of children and adults with MCD, FSGS, and membranous nephropathy, has already published several studies using these techniques [97]. Other cohort studies are ongoing, such as the Canadian childhood nephrotic syndrome (CHILDNEPH) study and the insight into nephrotic syndrome (INSIGHT) study in Canada and the European Rare Kidney Disease Registry (ERKReg) in Europe [98, 99]. With a greater understanding of the molecular mechanisms, and identification of biomarkers that predict clinical course and treatment response in SSNS, we can aim for precision medicine, where treatment is tailored to the individual child's genomic, molecular and pharmacogenetic profile (Fig. 1A).

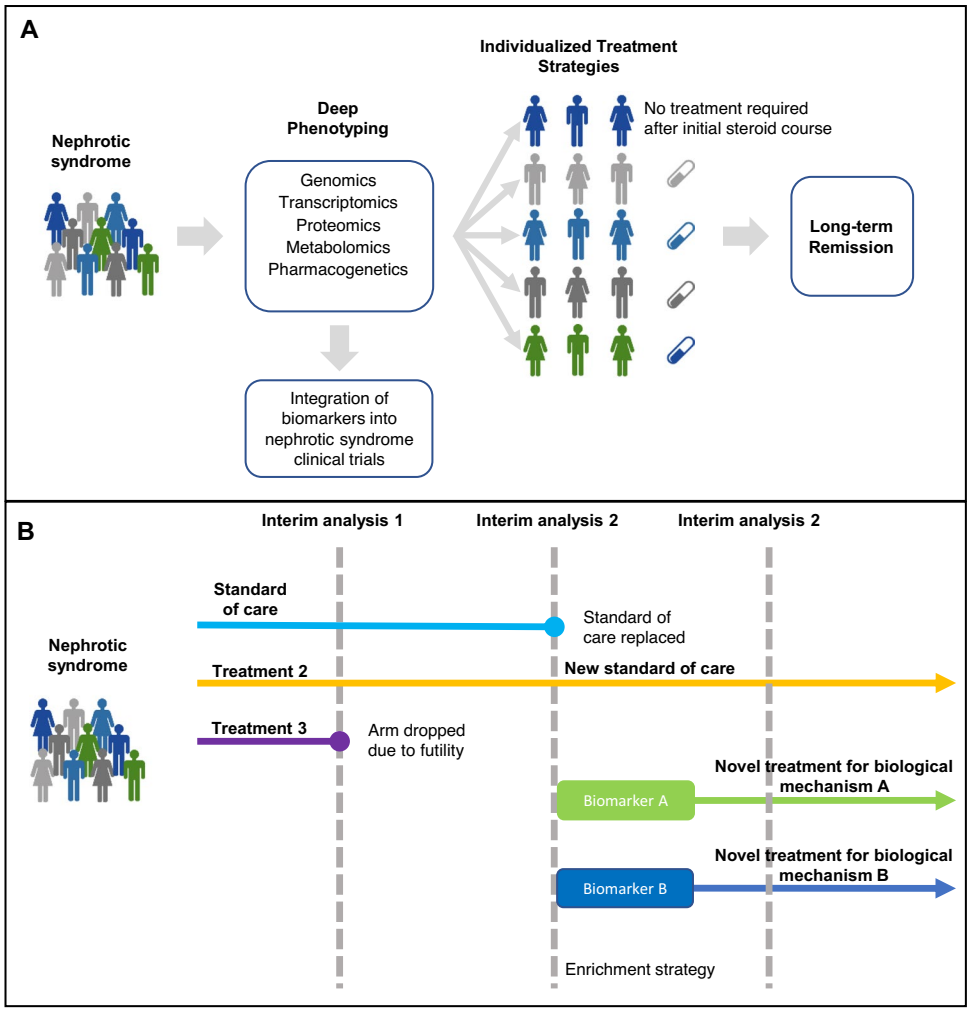

Fig. 1 **A** Potential precision medicine model for steroid sensitive nephrotic syndrome. Current phenotyping of steroid sensitive nephrotic syndrome is limited to clinical features. In the future, deep phenotyping may be available based on genetic variants and biomolecular profiles. Biomarkers can be incorporated into clinical trials to identify children who will benefit most from existing and new therapies, ultimately leading to a precision medicine approach where treatment is personalized to achieve the optimal outcome for each individual child. **B** Graphical example of an adaptive platform trial with integration of biomarkers. Prespecified changes can be made during planned interim analyses of trial data. Treatment arms may be dropped due to futility, a superior treatment can replace the standard of care, and new treatment arms can be introduced as novel agents become available and biomarker enrichment strategies can be used

Novel trial designs

Traditional RCTs are expensive and time consuming, which has led to the development of novel, more efficient trial designs. Master protocol trials test multiple interventions in one or multiple diseases, in a single protocol, and are a more efficient trial design [100]. They encompass umbrella trials that assess multiple interventions in a single disease, basket trials that assess a single intervention within multiple diseases, or disease subtypes, and platform trials that assess multiple interventions in a disease (often within biomarker- and clinically defined subgroups) in a perpetual manner [100, 101]. Adaptive platform trials allow iterative adjustments to the master protocol when pre-specified criteria are met and can include changes in sample size, enrichment strategies, and addition of treatment arms when new drugs are available, or cessation if treatments are deemed futile (Fig. 1B).

The COVID-19 pandemic highlighted the value added from novel trial designs. The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial is an adaptive platform trial assessing multiple interventions for patients hospitalized with COVID-19 in the UK. The trial began in early 2020 and has identified several effective (dexamethasone, tocilizumab and casirivimab/imdevimab) and six ineffective treatments [102–104]. This is a remarkable achievement in 2 years and illustrates the potential of platform trials to rapidly produce high-quality data and adapt to new medications as they become available. During the pandemic, broad data–sharing policies and collaborative research team models involving industry, scientists, patients, and researchers demonstrated the value in collaboration to reduce inefficiencies, find innovative solutions, and enhance knowledge translation of research findings.

Standardized trial outcomes

The use of a standard set of outcomes in SSNS research allows comparison across trials and reduces research waste. The Standardised Outcomes in Nephrology (SONG) initiative is working toward establishing a set of validated core outcomes, through input from both clinicians and patients.

Core outcome measures are under development for children with chronic kidney disease and for patients with glomerular disease, both of which will inform standard outcomes measures for NS research [105, 106]. We also advocate for the inclusion of a standard definition of long-term remission to ensure we remain focused on this important outcome.

Trial networks and patient engagement

Strong trial networks facilitate patient recruitment, build clinical trial capacity, and minimize research waste by reducing duplication. The National Institute of Cancer–sponsored Children's Oncology Group (COG) is an example of an extremely successful trial network in pediatrics. It includes centers from North America, Australia, New Zealand, and Europe, and over 90% of children with cancer in the USA are treated at a COG center. COG has an enviable trial participation rate, peaking at 50–70% of all US pediatric cancer patients enrolled in clinical trials in 1990s [107]. Their research efforts have been largely responsible for improving survival rates in childhood cancer, from an almost incurable disease, to over 80% 5-year survival [108].

In response to the deficiency of high-quality clinical trials in nephrology, the International Society of Nephrology formed the Advancing Clinical Trials initiative (ISN-ACT 2013) to support clinical trial capacity–building worldwide [109, 110]. Nephrology clinical trial networks now exist across the world and include the UK Renal Trials Network, Canadian Nephrology Trials Network, Australasian Kidney Trials Network, and the Global Kidney Patient Trials Network started by the George Institute. Leveraging these existing resources can help accelerate research, but greater gains are likely if strong international collaborations can be developed in NS research, to ensure trial results are generalizable given the known geographical and genetic differences in this disease [85]. Also, NS is a rare disease and requires patient advocacy to engage patients and increase trial participation and selection of relevant patient outcomes such as long-term remission [111, 112].

Conclusion

Children with difficult to treat SSNS, despite good long-term outcomes, can endure a decade or more of medical intervention. Steroid-sparing agents available to treat this condition lack well-designed and sufficiently powered controlled trials to guide treatment choice. There is not a single steroid-sparing agent shown to be superior and choice is often dependent on region, clinical practice, and physician preference. Heterogeneity in pathogenic mechanisms, genetics, and environment influences in SSNS can impact trial design and treatment response. Integration of biomarkers, use of novel trial design, and standardized outcomes including a standardized definition of long-term remission have the potential to improve clinical trials and outcomes in NS. Further collaborative international trial networks are needed to work toward a shared goal of finding a cure for children with nephrotic syndrome.

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Declarations

Competing interest Rulan Parekh is the principal investigator for the INSIGHT study. Ashlene McKay and Damien Noone declare no conflicts of interest.

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