Consensus Guidelines on Management of Steroid-Resistant Nephrotic Syndrome

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Justification: The management of steroid resistant nephrotic syndrome (SRNS) is challenging. These guidelines update existing 2009 Indian Society of Pediatric Nephrology recommendations on its management. **Objective:** To frame revised guidelines on diagnosis and evaluation, treatment and follow up, and supportive care of patients with the illness. **Process:** The guidelines combine evidence-based recommendations and expert opinion. Formulation of key questions was followed by systematic review of literature, evaluation of evidence by experts and two face-to-face meetings. **Recommendations:** Fourteen statements provide updated advice for managing steroid resistance, and underscore the importance of estimating proteinuria and baseline kidney function, and the need for kidney biopsy and genetic screening. Calcineurin inhibitors are recommended as most effective in inducing remission of proteinuria, the chief factor associated with long-term renal survival. Advice on managing allograft recurrence, congenital nephrotic syndrome, and monitoring and supportive care, including transition of care, are described. This revised practice guideline is intended to improve management and patient outcomes, and provide direction for future research.

Keywords: *Calcineurin inhibitors, Congenital nephrotic syndrome, Focal segmental glomerulosclerosis, Minimal change disease.*

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The prevalence of idiopathic nephrotic syndrome, characterized by proteinuria, hypoalbuminemia and edema, varies from 12-16 per 100000 children [1]. Majority of patients achieve remission of proteinuria following 4-6 weeks therapy with prednisolone. However, 10-15% patients do not achieve complete remission, and are termed steroid-resistant nephrotic synd-rome (SRNS) [2]. Renal histology shows focal segmental glomerulosclerosis (FSGS), minimal change disease and mesangioproliferative glomerulonephritis. Other patterns, including C3 glomerulopathy, membranous nephropathy and IgA nephropathy, and secondary causes of nephrotic syndrome are uncommon. The management of patients with SRNS is challenging. The illness is associated with unsatisfactory patient-reported quality of life, morbidity due to infectious and non-infectious illnesses, and side effects of therapy [2,3]. Patients with persistent proteinuria are at risk for progressive kidney failure [4].

Guidelines from the Indian Society of Pediatric Nephrology (ISPN) were first published in 2009 [5]. In view of recent evidence, the ISPN has proposed revision of these recommendations. The revised guidelines refer to patients with SRNS due to minimal change disease, mesangioproliferative glomerulonephritis and FSGS. These guidelines also address management of patients with post-transplant recurrence of FSGS and congenital nephrotic syndrome. Clinical practice recommendations, from the International Pediatric Nephrology Association (IPNA), on the illness were published recently [6].

PROCESS

Three work-groups were constituted to evaluate evidence on: (*i*) diagnosis and evaluation, (*ii*) treatment and follow up, and *(iii)* supportive care of patients with SRNS. The groups developed key questions, and reviewed and analyzed published studies. Quality of evidence was assessed and rated from A-D following the GRADE model [7], and is provided with each guideline. Each statement was assigned one of the two levels of guidance, recommendation or suggestion, indicating strength of the advice **(Web Table I)**. Ungraded statements (X) are like practice points, not supported by sufficient evidence.The work-groups discussed the evidence, through alternating break-out and plenary sessions, in New Delhi on 5 April 2019. Draft guidelines were discussed with members of the ISPN in Pune on 21 December 2019.

GUIDELINES

Table I compares the current and previous guidelines [5] and recent recommendations from the IPNA [6]. Given the challenges in management, we advise that a pediatric nephrologist be responsible for the diagnosis and management of children with SRNS.

Guideline 1: Diagnosis of Steroid-Resistant Nephrotic Syndrome (SRNS)

1.1 We recommend that steroid-resistance be defined in patients not showing complete remission of proteinuria, despite 6-weeks daily treatment with prednisolone. (1B)

1.2 We suggest similar definitions for initial and late (secondary) steroid-resistance (**Box I**). (X)

Rationale

Approximately 85-90% patients with idiopathic nephrotic syndrome respond to treatment with prednisolone, with complete remission of proteinuria and normalization of serum albumin [1]. There is lack of consensus regarding the minimum duration of daily prednisolone treatment before defining steroid-resistance. The International Study of Kidney Disease in Children (ISKDC) reported that, of patients who achieved remission, 94% did so within 4-weeks daily treatment and the rest during 4-weeks' alternate-day therapy [8]. Others found that 4-weeks and 6-8 weeks initial therapy results in remission in 90-92% and 87-93% patients, respectively [9-12]. While few experts suggest additional therapy with 3-doses of IV methyl pre-dnisolone before labeling steroid-resistance, this is not uniformly practiced [6,13,14].

Table I Guidelines on Steroid-Resistant Nephrotic Syndrome (SRNS): Current Indian Society of Pediatric Nephrology (ISPN), ISPN 2009 and International Pediatric Nephrology Association (IPNA) 2020

	Current ISPN	*ISPN 2009 [5]*	*IPNA 2020 [6]*
Definition: Duration of prednisone therapy	6 weeks daily	4 weeks daily	4 weeks daily; if partial remission, 2 weeks additional therapy (confirmation period)
Kidney biopsy	All; except if monogenic SRNS identified	All patients	All; except if monogenic SRNS identified
Genetic testing	Specific subsets of initial SRNS, congenital NS; not in late SRNS	Specific forms of initial SRNS	All patients with initial SRNS; not in late SRNS
Immunosuppression in monogenic SRNS	Not advised; may continue after counseling if partial remission	Not discussed	Not advised; may continue after counseling
Estimated GFR, mL/min/1.73 m^2	At diagnosis; q 3-6 months Avoid immunosuppression if eGFR<60	At diagnosis	At diagnosis; q 3 months Prefer MMF if eGFR <30 mL/min/1.73 m^2
First line: Calcineurin inhibitors (CNI)	Duration of therapy at least 2-year	Duration: 2-3 year	Duration: 1-2 year
Cyclophosphamide	IV cyclophosphamide may be used; oral not advised	IV therapy has low efficacy; oral not used	IV or oral cyclophosphamide
Indications for mycophenolate mofetil	(*i*) Prolonged CNI use and disease relapses; (*ii*) CNI-resistant SRNS	No recommendation	(*i*) eGFR<30 mL/min/1.73 m^2; (*ii*) CNI therapy for 1-yr; (*iii*) steroid sensitive relapses
Use of rituximab	(*i*) Prolonged CNI use and disease relapses; (*ii*) CNI-resistant SRNS; (*iii*) allograft recurrence	No recommendation	(*i*) CNI-resistant SRNS; (*ii*) allograft recurrence
Prednisone alternate day	Taper over 6-9 months	Taper over 1-1.5 yr	Taper and stop by 6 months
Statins; in addition to dietary advice	LDL cholesterol >160 mg/dL; >130 mg/dL if cardiovascular risk factors	Total cholesterol >200 mg/dL or LDL >130 mg/dL	LDL cholesterol >160 mg/dL; >130 mg/dL if cardiovascular risk factors
CNI-resistant disease	Rule out monogenic cause; consider rituximab or addition of MMF	Not discussed	Switch to MMF or rituximab; enroll in clinical trials
Renal transplantation	Evaluation of recipient, donor; managing recurrent FSGS	Not discussed	Evaluation of recipient, donor; managing recurrent FSGS

eGFR-estimated glomerular filtration rate; FSGS-focal segmental glomerulosclerosis; LDL-low density lipoprotein; MMF-mycophenolate mofetil; NS-nephrotic syndrome.

Box I Definitions Related to Nephrotic Syndrome

Nephrotic syndrome

Nephrotic range proteinuria (40 mg/m^2/h or > 1000 mg/m^2/day; spot Up/Uc ≥ 2 mg/mg; 3-4+ by dipstick); hypoalbuminemia (albumin < 3.0 g/dL); and edema

Steroid sensitive nephrotic syndrome

Complete remission within 6-weeks' treatment with prednisolone at a dose of 60 mg/m^2/day (2 mg/kg/day; maximum 60 mg/day)

Initial steroid-resistance

Failure to achieve complete remission after 6-weeks initial therapy with prednisolone (as defined above)

Late (secondary) steroid-resistance

Initially steroid-sensitive; steroid resistance in a subsequent relapse

Complete remission

Urine protein nil-trace by dipstick for 3 consecutive days, Up/Uc < 0.2, or 24-h protein < 100 mg/m^2/day

Partial remission

Urine protein 1+/2+ (dipstick), Up/Uc between 0.2-2, or 24-h urine protein 100-1000 mg/m^2/day; serum albumin ≥ 3.0 g/dL; and absence of edema

Non-response

Urine protein 3+/4+ (dipstick), Up/Uc ≥ 2, or 24-h urine protein > 1000 mg/m^2/day; albumin < 3.0 g/dL or edema

Relapse

Urine albumin 3+/4+ for 3 consecutive days, Up/Uc ≥ 2, or 24-h protein > 1000 mg/m^2/day, in a patient previously in partial or complete remission

Monogenic disease

Pathogenic or likely pathogenic variation, defined by American College of Medical Genetics and Genomics, in a gene associated with steroid-resistant nephrotic syndrome (Web Table II)

CNI-resistant disease

Non-response to cyclosporine or tacrolimus, given in adequate doses and titrated to optimal blood trough levels, for 6-months

Allograft recurrence of nephrotic syndrome

Persistent proteinuria (Up/Uc > 1) if previously anuric; or increase of Up/Uc by >1 if proteinuria at time of transplant (in absence of other apparent causes)

CNI-calcineurin inhibitor; Up/Uc-urine protein to creatinine ratio (mg/mg).

The previous version of this guideline defined SRNS as lack of complete remission despite 4-weeks therapy with prednisolone at a daily dose of 60 mg/m^2 [5]. The ISKDC and Kidney Disease: Improving Global Outcomes (KDIGO) proposed that steroid-resistance be defined following 8-weeks therapy [8,15]. Recent IPNA and KDIGO guidelines propose confirming steroid-resistance following 4-6-weeks' therapy with predniso(lo)ne, with or without additional therapy with three-doses of IV methylprednisolone [6,16].

In order to balance the benefits of extending therapy with steroid adverse effects, we recommend defining SRNS in patients who fail to show complete remission of proteinuria despite 6-weeks therapy with prednisolone at daily dose of 60 mg/m^2. Patients with steroid adverse effects may receive daily prednisolone for 4-weeks, followed by alternate-day therapy for the next 2-weeks. We do not advise therapy with IV methylprednisolone before making the diagnosis of SRNS.

We suggest similar definitions for initial (primary) and late (secondary) steroid-resistance (**Box I**). Initial resistance is lack of remission at the first episode of nephrotic syndrome. Patients who are steroid-sensitive initially but show steroid-resistance during subsequent relapse have late resistance. Systemic infections may be associated with persistent proteinuria and should be treated appropriately.

Guideline 2: Evaluation of Patients

We recommend the following in all patients with SRNS: Quantitation of proteinuria; serum creatinine; estimated glomerular filtration rate (eGFR); and kidney biopsy (***Box* II**). (1A)

Rationale

Nephrotic syndrome is characterized by nephrotic range proteinuria: ≥ 3+ by dipstick, proteinuria ≥ 40 mg/m^2/hr (> 1000 mg/m^2/day), urine protein to creatinine ratio (Up/Uc) ≥ 2 mg/mg; hypoalbuminemia (<3 g/dL); and edema [6]. All patients should be evaluated appropriately (**Box II**). Estimation of proteinuria, by Up/Uc in morning specimen or 24-hr protein excretion, at diagnosis and 6-monthly follow-up, helps determine response to therapy. Since 24-hr collection of urine is difficult to implement, Up/Uc is preferred. Parents are counseled regarding the importance of urinary dipstick analysis for home monitoring of proteinuria.

Response of proteinuria to therapy is an important determinant of renal survival [4,17,18]. Data from the PodoNet Registry on 1354 patients with SRNS shows that 10-year renal survival was highest (94%) in complete remission, 72% with partial remission and 43% with non-response [19]. Assessment of creatinine and eGFR at baseline and follow-up identifies acute kidney injury (AKI) secondary to hypovolemia, fluid loss, infections and drug toxicity, and CKD [20,21].

History and examination might help identify genetic and secondary forms of SRNS. History of deafness, developmental delay, seizures, family history of similar disorder and consanguinity, and syndromic features or extrarenal anomaly (e.g., genitourinary abnormality,

Box II Initial Evaluation of Patients with Steroid-Resistant Nephrotic Syndrome

Urinalysis, including microscopy

Spot urine protein to creatinine ratio; 24-h urine protein excretion

Complete blood counts

Blood creatinine, albumin, electrolytes, fasting glucose, glycosylated hemoglobin (HbA1c)

Total, low density and high-density cholesterol; triglycerides

Calcium, phosphate, alkaline phosphatase

Hepatitis B surface antigen; hepatitis C and human immunodeficiency virus antibodies

Ultrasonography of kidneys

Kidney biopsy (light, immunofluorescence, electron microscopy); avoided in selected patients*****

Investigations in selected children

Complement C3, C4; antinuclear antibody

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

Biopsy may be avoided in patients with familial steroid-resistance or with extrarenal features, where genetic diagnosis is preferred; a biopsy is also not required in patients with congenital nephrotic syndrome (Web Box II).

microcoria, dystrophic nails and microcephaly) suggest a genetic etiology. History of joint pain, weight loss, alopecia, jaundice, rash or palpable purpura indicates a secondary cause.

All patients with SRNS should undergo a kidney biopsy before instituting specific treatment. Biopsies are examined by light, immunofluorescence and electron microscopy. An adequate biopsy should include the corticomedullary junction and have ~20 glomeruli to identify focal pathology like FSGS [22]. A biopsy is useful for: (*i*) identifying pathology, extent of interstitial fibrosis and glomerulosclerosis for diagnosis and prognosis; and (*ii*) excluding differential diagnosis and secondary causes of nephrotic syndrome. Repeat biopsy is required to assess calcineurin inhibitor (CNI) toxicity, progression of disease or change in pathology.

Chief histological diagnoses in children with SRNS include FSGS (40-50%), minimal change disease (25-40%) and mesangioproliferative glomerulonephritis (5-8%) [23]. Histology suggestive of FSGS is considered a risk factor for progression to CKD [15-17,24]. Around 10-15% patients show membranous nephropathy, IgA nephropathy or proliferative glomerulonephritis, which requires additional evaluation. A kidney biopsy is not necessary in patients with well described monogenic form of SRNS, known to be unresponsive to immunosuppression, e.g., congenital nephrotic syndrome, familial disease, or if a known genetic cause is already identified.

Screening for viral infections: Patients should be evaluated for hepatitis B and C, and HIV infections. Collapsing FSGS may be associated with HIV or parvovirus infection [25]. Those with positive serology are evaluated for viral load and extent of disease. Active infection may require the use of antiviral therapy.

Guideline 3: Indications for Genetic Studies

We recommend genetic studies in the following patients: congenital nephrotic syndrome; initial resistance during infancy; nephrotic syndrome with extrarenal features; familial steroid-resistance; non-response to therapy with CNI; and prior to transplantation. (1B)

Rationale

Approximately 20-30% patients with SRNS have pathogenic variations in genes encoding proteins of podocyte structure and function **(Web Table II)** [2]. Mutations in *NPHS1, NPHS2, WT1, COQ2, PLCE1* and *LAMB2* account for 50-60% of monogenic disease in children [26-28]. Genetic testing is useful as follows:

- Identification of causal variant enables diagnosis of monogenic disorders, and occasional phenocopies (e.g., Alport syndrome, Dent disease, cystinosis). Specific diagnosis allows counseling regarding progression of kidney disease and monitoring for extrarenal complications, e.g., patients with *WT1, LMX1B,WDR73* and *SMARCAL1* mutations [29].
- Patients with monogenic etiology have 4-fold risk of non-response to therapy with CNI (odds ratio, OR 4.00; 95% CI 2.52-6.51) and 3-fold risk of kidney failure (OR 2.87; 95% CI 2.22-3.72) **(Web Table III)** [18,26,28,30].
- Certain mutations respond to targeted therapy, e.g., coenzyme Q10 for defects in CoQ pathway, and eplerenone for *ARHGDIA* mutations [31,32].
- Compared to patients with no identifiable genetic cause, those with monogenic etiology have significantly lower risk for allograft recurrence [18,27,33].
- Diagnosis of a monogenic etiology assists in counseling for future pregnancies and antenatal diagnosis, and facilitates screening of live related renal transplant donors [34-36].

While IPNA guidelines suggest comprehensive genetic evaluation in all children with initial steroid-resistance [6], we suggest a focused approach. The likelihood of detecting a genetic cause is inversely related to age at onset of the illness. A monogenic etiology was seen in 69%, 50%, 25%, 18% and 11% with disease presenting during the first 3 months, 4-12 months, 1-6 years, 7-12 year and 13-18 years, respectively [26]. Syndromic forms of the illness may be associated with specific mutations and characteristic phenotype (**Web Table II**). Family history of similar illness or consanguinity suggests a genetic cause in ~50-70% cases [26,27]. Although patients with an underlying genetic etiology are less likely to respond to therapy with CNI, few patients may occasionally show partial remission [37].

Siblings of patients with a monogenic cause may be screened for proteinuria by dipstick. There is no role for genetic screening in healthy children with family history of the disease. Since pathogenic mutations are not identified in patients with late steroid-resistance, genetic testing in these children is also not indicated [18,27].

The precise prevalence of monogenic variations in Indian patients with SRNS is unclear as studies are limited to small cohorts [38,39]. A nationwide study is in progress to determine the genetic basis of SRNS, and indications for testing may be revised in future.

Method of Genetic Testing

Causal variants in ~90 genes are associated with monogenic SRNS **(Web Table II)**. Most genes do not show a clear phenotype-genotype correlation. Next-generation sequencing (NGS) panels, incorporating multiple genes relevant to the phenotype, are feasible and less expensive, and provide higher diagnostic yield than Sanger sequen-cing. These panels include genes associated with other renal diseases that may have phenotype similar to SRNS. Clinical exome sequencing (Mendeliome gene panel), which includes all exons of genes listed in Online Mendelian Inheritance of Man (OMIM) database, facili-tates targeted gene analysis. In case a causative variant is not identified in the gene-panel, search for variants may be extended to remaining genes in the clinical exome. Whole exome sequencing might be considered for novel disease-causing genes. Sanger sequencing is preferred if a disease-causing mutation is highly likely in a specific gene, in context of extrarenal features or positive family history with known genetic cause. Sanger sequencing is essential to confirm variants detected on NGS, to screen parents to confirm segregation and for antenatal counseling.

Parents should be advised regarding risks and benefits of NGS, including limitation of insurance cover. Referral to genetic counselors might be necessary. Testing must be performed by certified and experienced laboratories, and pathogenicity of variants determined based on criteria proposed by the American College of Medical Genetics and Genomics [40].

Guideline 4: Therapy of Patients with SRNS

4.1 We recommend calcineurin inhibitors (CNI) as first-line therapy for patients with initial or late steroid-resistance. (1A)

4.2 We suggest continuing therapy with CNI for at least 24-months if partial or complete remission is achieved. (2C)

4.3 We suggest that CNI therapy should be withheld or discontinued for patients with AKI stage 2-3 or estimated glomerular function rate (eGFR) persistently below 60 ml/min/1.73m^2. (2C)

Rationale

Therapy aims to induce complete or partial remission, while avoiding medication-related toxicity. Long-term renal outcome in patients who achieve remission is significantly better when compared to non-responders [17-19,41]. Randomized controlled trials (RCT) and case series show that therapy with CNI (cyclosporine, tacrolimus) results in complete remission in 30-40% and complete or partial remission in 60-80% patients [2,3,18,41,42]. A Cochrane meta-analysis that compared cyclosporine to no treatment showed increased likelihood of complete or partial remission with the former (2 RCT; relative risk RR 3.50; 95% CI 1.04-9.57) at 6-months [43]. Similarly, therapy with CNI, compared to IV cyclophosphamide, was associated with higher rates of complete or partial remission (3 RCT; RR 1.98; 95% CI 1.25-3.13) [43]. While most reports do not show different outcomes between initial and late steroid-resistance [44-46], better outcomes in the latter have been reported [18]. The efficacy of tacrolimus and cyclosporin is comparable (2 RCT; RR 1.05; 95% CI 0.87-1.25), with no difference in nephrotoxicity or hypertension [43,47].

Similar to the IPNA and KDIGO guidelines, we recommend first-line use of CNI for patients with SRNS [6,16]. Tacrolimus is preferred to cyclosporine except in children who are unable to swallow tablets (cyclosporine is available as suspension), and patients with seizures or at risk for diabetes. Doses of tacrolimus and cyclosporine are titrated to achieve recommended trough levels, keeping in mind interaction with other medications **(Table II** and **Web Table IV)**. Low levels are associated with non-response and relapse, while high levels increase the risk for nephrotoxicity [48]. Lower levels may be targeted once sustained remission is achieved for 6-9 months [49,50]. **Fig. 1** provides an outline of the approach to management of SRNS.

Table II Dosing and Monitoring of Immunosuppressive Therapy

Medication	*Dose*	*Adverse effects*	*Monitoring*
First line therapy			
Tacrolimus	0.1-0.2 mg/kg/day in 2-divided doses; maximum initial dose 4 mg/day; trough level 4-8 ng/mL[a]	*Both:* Acute kidney injury, nephro-toxicity, hyperkalemia, hepatotoxic *Tacrolimus*: tremors, seizures, headache; diarrhea; glucose intolerance; hypomagnesemia	Screen for cosmetic side effects, tremors, diarrhea, hypertension Creatinine, potassium at 2-4 wk, then q 3-6 months
Cyclosporine	3-5 mg/kg/day in 2-divided doses; maximum initial dose 200 mg/day; trough level 80-120 ng/mL[a]	*Cyclosporine:* Gingival hyperplasia, hypertrichosis; hypertension; dyslipidemia	Liver function tests, glucose, uric acid, magnesium, lipids q 3-6 months
Prednisolone on alternate days	1.5 mg/kg for 4-wks; 1 mg/kg for 4-wks; taper to 0.3-0.5 mg/kg for ~6-9 months	Weight gain, Cushingoid features, glucose intolerance, hypertension, raised intraocular pressure, cataract, myopathy, osteoporosis	Blood pressure, screen for cosmetic effects; eye evaluation q 12 months Blood glucose q 6-12 months
Other agents[b]			
Cyclophosphamide	500-750 mg/m^2 IV; every month for 6-months	Leukopenia, hemorrhagic cystitis, vomiting, alopecia, risk of infections; gonadal toxicity, malignancies	Blood counts prior to infusion; withhold if total leukocyte count <4000/mm^3 Ondansetron, mesna prevent adverse effects
Rituximab	375 mg/m^2 every wk for 2-4 doses	Infusion reactions: Chills, fever, serum sickness, bronchospasm Neutropenia; *P. jirovecii* pneumonia; reactivation of hepatitis B, JC virus; acute lung injury; hypogamm-aglobulinemia	*Pre dose*: Blood counts, transaminases; hepatitis & HIV serology; IgG level *Post dose:* Monitor CD19, blood counts, IgG level
Mycophenolate mofetil	600-1200 mg/m^2/day in 2-divided doses	Leukopenia; liver dysfunction; pain abdomen, nausea, diarrhea; headache; warts; weight loss	Blood counts, liver functions q 3-6 months

[a]Dose titrated to blood trough level obtained 12-h after last dose; measure 2-wks after initiating therapy. Subsequently, if: (i) suspected drug toxicity, (ii) medications that affect levels (Web Table IV), or (iii) unsatisfactory response or relapses while on therapy. [b]Patients on intense immunosuppression (combination of calcineurin inhibitors and rituximab or mycophenolate mofetil) should receive prophylaxis with trimethoprim (5 mg/kg; 150 mg/m^{2}on alternate days).

Most patients who respond to CNI do so within the first 6-months of treatment [44,45,47,51]. Non-response to CNI is therefore considered in patients who continue to show nephrotic-range proteinuria, hypoalbuminemia or edema despite 6-months therapy. Patients showing non-response should be screened for significant genetic variations (see above), and considered for alternate management (Guideline 6).

Therapy with CNI is initially combined with prednisolone, administered at a dose of 1-1.5 mg/kg on alternate days for 4-6 weeks, and tapered over 6-9 months [6,44-46]. Following CNI-induced remission, ~60% patients may have steroid-sensitive relapses [44,45,52]. Relapses are treated with prednisolone (2 mg/kg/day until remission; tapered on alternate-days). Stoppage of steroid therapy might not be possible in patients with multiple relapses.

The duration of treatment with CNI for patients with partial or complete remission is not clear, with guidelines recommending minimum 12-months' therapy [6,16]. An RCT comparing continued therapy with tacrolimus vs switching to mycophenolate mofetil (MMF) at 6-months, found the former twice as effective in maintaining remission (90% vs 45%) [45]. In a retrospective study on 23 patients, therapy with cyclosporine for mean duration of 1.7 years could be successfully switched to MMF in 79% cases [52]. In view of the risk of relapse with early cessation of therapy, we suggest continuing therapy with CNI for 24 months or longer (**Fig. 1**), ensuring adequate dose and trough levels [49,51].

About 10-25% patients receiving prolonged CNI treatment are at risk of nephrotoxicity [53]. Risk factors for nephrotoxicity include presence of initial resistance, dose of CNI used, duration of heavy proteinuria, and hyper-

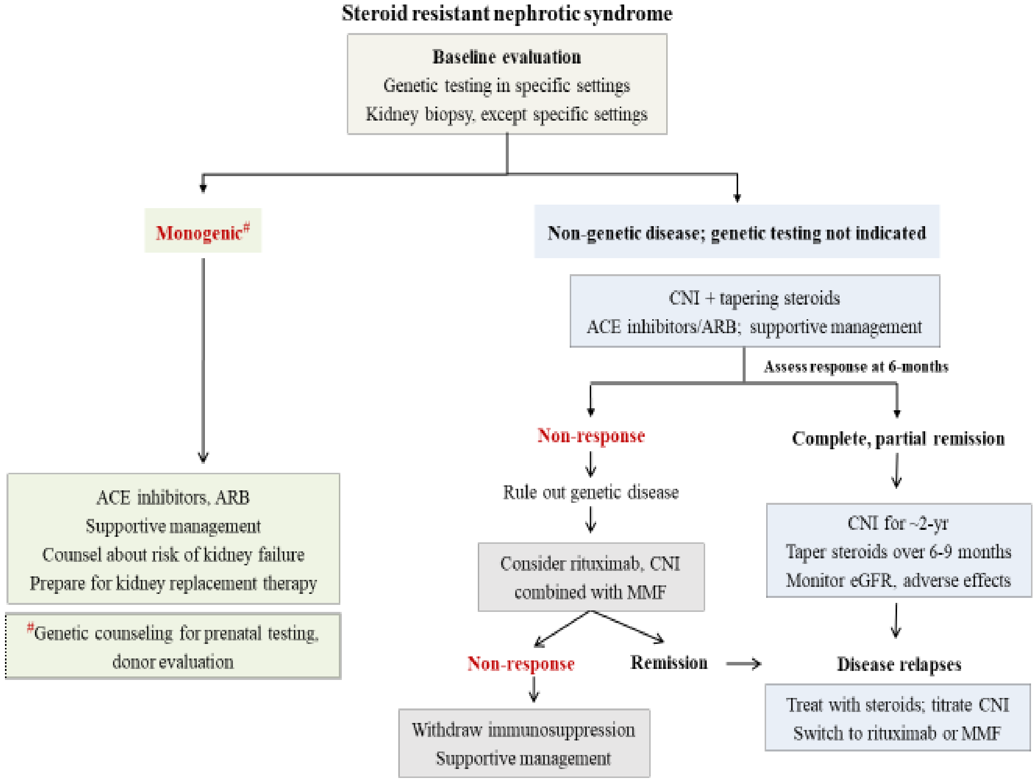

Fig. 1 Management of steroid-resistant nephrotic syndrome. Kidney biopsy is necessary, except in patients where genetic testing may obviate the need for biopsy (Box II). Patients with monogenic cause for steroid-resistance should not receive immunosuppression and are managed with angiotensin converting enzyme (ACE) inhibitors and supportive therapy. Patients with likely non-genetic disease are initiated on therapy with a calcineurin inhibitor (CNI) along with supportive care. Lack of remission despite adequate therapy with CNI for 6-months is an indication for genetic screening, if not performed earlier. Patients with CNI-resistant disease who do not show a monogenic defect may be treated with IV rituximab or combined therapy of CNI and mycophenolate mofetil (MMF). Immunosuppression is withdrawn in patients with continued non-response.

tension during therapy [48,53]. In order to balance the benefits and toxicity of CNI, we suggest individualizing therapy in children with partial or complete response at 24-months. Options include: *i*) discontinue therapy if patient has been in sustained remission; *ii*) continue CNI therapy; perform kidney biopsy if treatment is prolonged beyond 30-36 months, or if restarting treatment; *iii*) switch to IV rituximab or oral MMF in patients with CNI or steroid toxicity or steroid-sensitive relapses.

Risk factors for AKI in nephrotic syndrome include volume depletion, infections, nephrotoxic injury and steroid resistance [21,54,55]. We suggest withholding CNI during AKI [16,55,56]; treatment is restarted following recovery of kidney function. Therapy with CNI is avoided if eGFR is persistently <60 mL/min/1.73 m^2.

Guideline 5: Alternate Immunosuppressive Therapy

5.1 We suggest treatment with IV cyclophosphamide in patients with non-availability of CNI, either due to its cost or adverse effects. (2B)

5.2 We do not suggest the use of oral cyclophosphamide for therapy of patients with steroid-resistance. (2A)

Rationale

Studies utilizing IV cyclophosphamide (every month for 6-months) and tapering prednisolone show complete or partial remission in 10-50%, but with significant adverse effects [46,57,58]. Compared to CNI, IV cyclophosphamide is associated with lower rates of sustained remission (RR 0.50; 95% CI 0.37-0.68) at 6-months [43]. A multicenter study compared the efficacy of cyclosporine (150 mg/m^2/day) for 48-weeks with IV cyclophosphamide (500 mg/m^2; 7-doses over 36 weeks) in patients with SRNS. While complete remission was low, 47% patients treated with cyclosporine and 6% with IV cyclophosphamide had partial response [57]. Another multicenter trial on 131 patients showed 6-month complete remission rates of 14.8% and partial remission rates of 31.1% with IV cyclophosphamide, as against 52.4% and 30.1%, respectively with tacrolimus [44].

Two RCT showed similar efficacy and safety of oral and IV cyclophosphamide in 61 children with steroid-resistance (RR 1.58; 95% CI 0.65-3.85) [58,59]. However, two other RCT found no difference in rates of remission in patients receiving oral cyclophosphamide with prednisone compared to prednisone (*n*=84; RR 1.06, 95% CI 0.61-1.87) [60,61]. Based on the above, we do not advise use of oral cyclophosphamide in patients with SRNS.

Guideline 6: Treatment of CNI-Resistant Nephrotic Syndrome

In patients with non-genetic forms of SRNS and non-response to therapy with CNI, we suggest additional treatment with either IV rituximab or oral MMF (**Fig. 1**). (2C)

Rationale

Approximately 25-35% patients with non-genetic forms of SRNS do not show complete or partial remission following 6-months' therapy with CNI [43]. The management of patients with non-response to CNI therapy is difficult, since they are at high risk of kidney failure [17-19]. Patients with initial steroid- and CNI-resistance should be screened for an underlying monogenic disorder. Those with no pathogenic or likely pathogenic variants in podocyte genes may be considered for additional immunosuppressive therapy, administered under close supervision.

While rituximab has shown promising results in patients with steroid-sensitive nephrotic syndrome, its efficacy in CNI-resistant SRNS is less satisfactory. In a systematic review (7 case series, one RCT; *n*=226) on efficacy of rituximab in steroid and CNI-resistant nephrotic syndrome, the mean number of rituximab doses was 3.1. Complete or partial remission was observed in 46.4%, with better response in minimal change disease (63.2%) than in FSGS (39.2%), and late-resistance (52.8%) compared to initial-resistance (40.8%) [62]. Similar findings of satisfactory response to rituximab in patients with late resistance are reported in a series from United Kingdom [18] and in a systematic review [63]. While less favorable outcomes were reported in a study from India, with remission in 29.3% of 58 patients with CNI-resistance, there was trend for better response in minimal change disease and late-resistance [64].

We suggest administering 2-doses of IV rituximab at a dose of 375 mg/m^2 at weekly interval, targeting CD19 count <5/µl or ≤1% of lymphocyte count. If CD19 target is not met, 1-2 additional doses may be repeated at weekly intervals (maximum 4 doses). In patients achieving complete or partial remission, repeat dose(s) of rituximab may be given following B-cell reconstitution, which typically occurs after 6-9 months. There is limited guidance regarding redosing with rituximab, and benefits should be balanced by the risk of side effects, including infusion reactions, serum sickness, neutropenia and hypogammaglobulinemia. Therapy with rituximab may be associated with reactivation of hepatitis B, *Pneumocystis jirovecii* pneumonia, severe lung injury and rarely, progressive multifocal leukoencephalopathy [65].

The efficacy of MMF in patients with SRNS is less satisfactory than in steroid-sensitive disease. In the PODONET cohort, monotherapy with this medication was not effective in 83% patients [19]. The efficacy of combination of CNI and MMF (600 to 1000 mg/m^2/day) has been reported in patients with CNI-resistant disease. Three case-series (*n*=168) on combined therapy for 6-12 months, show complete remission, partial remission and non-response in 11.8-47.7%, 8.7-38.2% and 43.5-58.8%, respectively [66-68]. There is limited data on the efficacy of treatment with adalimumab, abatacept, ofatumumab and adrenocorticotrophic hormone, oral galactose and LDL apheresis in patients with CNI-resistant SRNS. These therapies should only be used in context of clinical trials [69-71].

Intense immunosuppression is associated with risk of systemic infections. Patients receiving combined therapy with CNI and either rituximab or MMF should receive prophylaxis with cotrimoxazole (5 mg/kg trimethoprim on alternate days) for 3-6 months. **Table II** summarizes dosing, side effects and monitoring of children receiving immunosuppressive agents.

Guideline 7: Immunosuppressive Therapy With Pathogenic or Likely Pathogenic Variants

We do not recommend that patients with monogenic disease receive therapy with calcineurin inhibitors or other immunosuppressive agents. (1B)

Rationale

Patients with SRNS with pathogenic or likely pathogenic variations (monogenic disease, **Box I**) usually do not show complete or partial remission following therapy with CNI. Analysis of pooled data (**Web Table III**; *n*=867) shows that compared to non-genetic disease, those with genetic forms of SRNS are not likely to respond to CNI (RR 4.00; 95% CI 2.52-6.51). Patients with monogenic forms of SRNS, irrespective of response are more likely to progress to kidney failure than those with non-genetic illness (RR 2.87; 95% CI 2.22-3.72).

The recent IPNA guidelines do not recommend that patients with monogenic disease receive immuno-suppressive medications [6]. However, some patients with a genetic cause for steroid-resistance, especially those with *WT1* variants, might show partial remission following treatment with CNI [37]. The decision to continue therapy in such patients should follow counseling of parents regarding anticipated benefits (relief of edema, higher blood albumin) *vs* risks (therapy-related toxicity, infec-tions) and cost of therapy. Targeted therapy is possible for specific mutations, e.g., coenzyme Q10 for defect(s) in CoQ10 pathway, eplerenone for *ARHGDIA*, and cortico-steroids for mutations in genes of Rho/Rac/Cdc42 network [31,32].

Guideline 8: Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

We recommend that all patients with SRNS should receive therapy with angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) (**Table III**). (1B)

Rationale

Since proteinuria is a risk factor for progressive kidney disease, its reduction is important for renoprotection [72]. Use of ACE inhibitors is associated with 30-40% reduction in proteinuria in a dose- and time-dependent manner (16,43). ARB may be used as effectively **(Table III)** [73]. Dual blockade with ACE inhibitors and ARB further reduces proteinuria, but is associated with side effects such as hypotension, AKI and hyperkalemia, and is not recommended [74]. ACE inhibitors or ARB are avoided in patients with eGFR < 25 mL/min/1.73 m^2, and discontinued during vomiting, diarrhea or reduced oral intake. In patients with FSGS, sparsentan, that combines endothelin receptor type A blockade with angiotensin II inhibition, reduces proteinuria and hypertension more effectively than irbesartan [75]. We do not advise therapy with other medications that target the renin-angiotensin axis, including aliskrein, eplerenone and vitamin D analogs.

Table III Antihypertensive and Anti-proteinuric Medications

Medication	*Initial (maximum) daily dose*	*Interval*
ACE inhibitors		
Enalapril	0.08 (0.6) mg/kg	1-2 doses
Fosinopril	0.1 mg/kg (40 mg)	Once daily
Lisinopril	0.07 (0.6) mg/kg	Once daily
Ramipril	1.6 (6) mg/m^2/day	Once daily
Angiotensin receptor blockers		
Irbesartan	65 (150) mg; 150 (300) mg/day if ≥13-year	Once daily
Losartan	0.7 (1.4) mg/kg	Once daily
Olmesartan	10 (20) mg; 20 (40) mg if ≥35 kg	Once daily
Valsartan	1.3 (2.7) mg/kg	Once daily
Telmisartan	1 (2) mg/kg	Once daily
Sparsentan	200 (800) mg	Once daily
Calcium channel blockers		
Amlodipine	0.1 (0.6) mg/kg	1-2 doses
Nifedipine ER	0.2 (3) mg/kg	1-2 doses
Felodipine	2.5 (10) mg	Once daily
Thiazides		
Hydrochlorothiazide	1 (2) mg/kg	1-2 doses
Beta blockers		
Atenolol	0.5 (2) mg/kg	Once daily
Metoprolol	1 (6) mg/kg	1-2 doses
Labetalol	1 (12) mg/kg	2-3 doses
Alpha blockers		
Prazosin ER	0.05 (0.5) mg/kg	1-2 doses
Central alpha agonist		
Clonidine	5-7 (25) mcg/kg/day	2-3 doses

ER extended release.

SUPPORTIVE CARE AND MONITORING

Important aspects of supportive care are summarized in **Table IV**. Principles of management of edema, systemic infections and immunization are discussed in the revised ISPN guidelines on steroid-sensitive nephrotic syndrome, published recently [76].

Guideline 9: Thrombotic Complications

We do not recommend routine thromboprophylaxis in children with SRNS. (1C)

Rationale

The risk of thromboembolic complications in nephrotic syndrome is ~3% in children, compared to 25% in adults, with most events within the first 3-months of illness [77]. Risk factors for thrombosis include congenital nephrotic syndrome, heavy proteinuria, membranous nephropathy,

Table IV Supportive Care of Children with Steroid-Resistant Nephrotic Syndrome

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

HPA: hypothalamo-pituitary axis. [a]Risk factors: chronic kidney disease stage 3-5; blood pressure >90th centile for age; body mass index > 95th centile; family history of cardiovascular disease.

central venous catheters and coexisting heart disease [77]. Sites of thrombosis include the deep veins, cerebral sinus(es), renal veins and occasionally, arteries [78].

Routine use of prophylactic anticoagulants is not recommended [77]. Aspirin is less effective and is associated with risk of AKI [79]. Non-pharmacological measures such as ambulation, hydration and use of compression stockings are encouraged; central venous catheters and arterial punctures should be avoided [79,80].

Therapy aims to prevent extension of thrombi and reduce the risk of embolism. Thrombolysis followed by anticoagulation is considered in patients with life or limb-threatening thrombosis. While anticoagulation may be initiated with unfractionated heparin, this requires IV access and close laboratory monitoring, has less predictable pharmacokinetics and is associated with the risk of adverse effects (thrombocytopenia, anaphylaxis and osteoporosis) [80]. Use of low-molecular weight heparin is preferred [79,81]. Therapy is initiated with enoxaparin at a dose of 1.5 mg/kg/dose (<2-months age) or 1 mg/kg/dose (>2-months) subcutaneously, every 12-hr [81]. Long-term therapy may continue either with enoxaparin or warfarin (0.2 mg/kg/dose started concurrently with enoxaparin) for 3-months or until remission [80]. For warfarin the international normalized ratio (INR) for prothrombin time is targeted between 2.0 and 3.0. Children with recurrent throm-botic events require long-term anticoagulation [77,80].

Guideline 10: Cardiovascular Morbidity

We recommend strategies to minimize cardiovascular risk in patients with SRNS (X).

Rationale

Steroid resistance is associated with multiple cardiovascular risks, including hypertension, dyslipidemia, hypoalbuminemia, hypercoagulable state and steroid-induced obesity. Strategies to reduce this risk include minimizing residual proteinuria, managing hypertension, weight reduction to achieve BMI <85th centile for age, non-exposure to tobacco, and achieving target levels of lipids, fasting glucose (<100 mg/dL) and HbA1c (< 5.7%) [82].

Hypertension: Blood pressure should be measured at each visit. A study on Indian children with frequently relapsing disease showed clinic hypertension in 64%, ambulatory hypertension in 33%, white coat hypertension in 30% and increased left ventricular mass in 21% [83]. Systolic and diastolic blood pressures are targeted between 50-75th percentile for age and sex [84]. Lifestyle changes include increased intake of vegetables, fresh fruits, low-fat milk, legumes and nuts, and reduced salt and sweets. Pharmacotherapy is initiated with ACE inhibitor or ARB, in view of additional benefit of reducing proteinuria **(Table III)**.

Dyslipidemia: Children with nephrotic syndrome show high blood levels of cholesterol, triglycerides, apoB-containing lipoproteins (LDL, VLDL, IDL) and lipoprotein (*a*). While abnormalities resolve during remission, these might persist in patients with SRNS. Dyslipidemia aggravates glomerulosclerosis and proximal tubular damage and is associated with progression of CKD. Screening for dyslipidemia is advised in patients with SRNS, and those with steroid-sensitive disease and cardiovascular risk factors [82,85].

We advise reduced intake of trans-fats or saturated fats and sugar, and increased consumption of fruits, vegetables, legumes and whole grain cereals [85]. The CHILD-1 diet is the first step in children with dyslipidemia or risk factors for cardiovascular disease and includes restricting intake of saturated fat and cholesterol to <10% of daily calories and 300 mg, respectively. In case this is not effective, the respective restrictions are enhanced to 7% and 200 mg in the CHILD-2 diet [82,85]. Limiting leisure screen time to <2-hr/day, ensuring moderate physical activity for 1-hr/day, and vigorous physical activity at least 3 days a week are advised [85].

If lifestyle measures fail to correct dyslipidemia, therapy with statins is advised, especially if associated with risk factors for cardiovascular disease [85]. Therapy in children 8-year or older may begin with atorvastatin at 10 mg/day, with monitoring for adverse effects.

Guideline 11: Stress Dosing of Glucocorticoids

We recommend that patients, who have received oral corticosteroids for more than 2-weeks within the past one-year, should receive additional steroid dosing during conditions associated with physiological stress. (1D)

Rationale

Therapy for nephrotic syndrome involves high-dose prednisolone for 12-weeks for the first episode, 5-6 weeks for relapse, and prolonged alternate-day for frequent relapses and steroid-resistance. A systematic review reported that 269 of 487 (55.2%) children receiving corticosteroids for varied indications for more than 14-days had biochemical evidence of suppressed hypothalamo-pituitary axis (HPA) [86]. The duration of HPA suppression might last up to two years, and vary with dose and duration of treatment [87].

We recommend additional steroids in situations where physiological stress is expected (fever ≥38°C, inadequate oral intake, lethargy, dehydration, invasive surgery, dental surgery, trauma and large burns). Conditions such as uncomplicated viral infections, acute otitis media and fever post-immunization do not require stress dosing. In case of critical illness or surgery, hydrocortisone is administered parenterally at 100 mg/m^2, initially or preoperatively followed by 25 mg/m^2 every 6-hr. With less serious illness, hydrocortisone 30-50 mg/m^2/day or prednisolone 0.3-1.0 mg/kg in a single daily dose is given during stress and tapered thereafter [88].

Guideline 12: Monitoring of Patients

Children with SRNS are at risk for progression to stage 5 CKD, complications of the disease and adverse effects of medications [89-91]. Managing immunosuppressive therapies is a challenge due to the risk of infections, non-compliance and presence of co-morbidities. Patients require regular monitoring and careful follow up, and counseling regarding need for compliance with medications **(Table V)**.

Guideline 13: Transplantation

13.1 We recommend that kidney transplant be considered in all patients with SRNS and stage 5 CKD. (1B)

13.2 We recommend that genetic testing be performed before transplant to assist in donor selection and predict the risk of recurrence in allograft. (1B)

13.3 In a patient with prior allograft recurrence, the decision for retransplantation should be taken after discussing the risks and benefits with treating physicians, patient and family. (2C)

13.4 In patients with allograft recurrence, we suggest initiation of plasma exchanges, increasing the dose of CNI, with or without additional use of rituximab. (2B)

Table V Monitoring of Patients with Steroid-Resistant Nephrotic Syndrome

Parameter	*Frequency*
Home urine dipstick for protein	Daily for 1-2 weeks; 2-3 times/week until remission; once-weekly thereafter
Spot urine protein/creatinine ratio*	Baseline; 2-4 weeks; then every 6-12 months
Weight, height; growth velocity; body mass index	Every 3-6 months (frequent in infants and stage 3-5 chronic kidney disease)
Blood pressure Ambulatory blood pressure monitoring 2-D echocardiography	At each hospital visit Every 1-2 yr Annually, if hypertensive
Blood creatinine, electrolytes, albumin, eGFR	Baseline; 2-4 weeks; then every 3-6 months
Hemoglobin, glucose, calcium, phosphate, alkaline phosphatase, 25-hydroxyvitamin D; thyroid profile	Every 6-12 months with partial remission or non-response; every 12 months with complete remission; additional investigations may be required for stage 3-5 chronic kidney disease
Monitoring drug toxicity	See Table II
Fasting lipid profile	Every 6-12 months
Eye examination (cataract, glaucoma)	Annually, if receiving long-term steroids
Repeat renal biopsy	Calcineurin inhibitor therapy beyond 30-36 months; recommencing therapy for second course Non-recovery from acute kidney injury
Nutritional status and advice	Every 6 months; more frequent in infants, malnourished children, stage 3-5 chronic kidney disease
Immunization	Check and complete every 12 months, as appropriate

**24-hr urine protein estimation may be considered instead. eGFR estimated GFR (mL/min per 1.73 m²)* $= \frac{0.413 \times \text{height (cm)}}{\text{creatinine (mg/dL)}}$

Rationale

Kidney transplantation is the definitive option for patients with SRNS and stage 5 CKD. Careful pre-transplant evaluation of recipient and donor is required. Genetic screening of the recipient is necessary, particularly if there is initial resistance or equivocal course of the illness, since it stratifies the risk for allograft recurrence and helps in donor screening. If inheritance pattern is autosomal recessive, a heterozygous carrier (parent) may be accepted as a donor with negligible risk of recurrence, except Afro-Caribbean donors with *APOL1* risk variant, or heterozygous R229Q variants in *NPHS2* [35,92]. Heterozygous carriers of pathogenic variants in *COL4A3* and *COL4A4* and women with variants in *COL4A5* should not be accepted as donors since they are at risk of kidney failure [93]. For autosomal dominant inheritance, individuals with same variant are not accepted as donors since they might show variable penetrance with late onset of disease.

FSGS recurs in the allograft in ~30% (range 6-50%) patients [94,95]. Recurrence is associated with allograft dysfunction and its loss in 40-60% patients, especially in those with persistent nephrotic range proteinuria [33,96]. Recurrence risk is highest in patients with late steroid resistance or recurrent nephrotic syndrome in a prior transplant (~80%), moderate with initial resistance and no identified genetic cause (~50%), and lowest with confirmed genetic mutation underlying SRNS (<5%) [18,97-100]. Patients with FSGS and kidney failure should be counseled about these risks.

Living-related transplantation is associated with better graft survival and is preferred for children in our country. While the risk of recurrence is minimally higher in children receiving live-related grafts, this is balanced by reduced risk of rejection and lower need for immunosuppression [100,101]. Live-related transplantation is therefore the first choice, except in patients with moderate to high risk of recurrence.

Nephrotic syndrome might recur occur within hours to days after transplant and is characterized by nephrotic range proteinuria and progressive hypoalbuminemia. Patients are monitored for recurrence by screening for proteinuria (Up/Uc ratio), initially daily and then with reduced frequency **(Web Box I)**. Recurrence is considered in patients with proteinuria and Up/Uc ≥1 mg/mg if anuric prior to transplant or increase of ratio by ≥1 in those with proteinuria at transplantation [6]. Early onset graft dysfunction may be a feature of recurrent FSGS. Where feasible, an allograft biopsy is recommended to detect podocyte foot process effacement or segmental sclerosis that supports the diagnosis of recurrence. A biopsy may also help exclude other diagnosis in patients with lower degree of late-onset proteinuria or allograft dysfunction.

Multiple therapies have been used to prevent recurrence of nephrotic syndrome, including pre-transplant plasma exchanges, rituximab and lipoprotein apheresis. There is limited evidence that any of these strategies prevent allograft recurrence in the first kidney transplant [102,103]. Strategies for managing patients with allograft recurrence include combination of plasma exchanges with high-dose CNI and corticosteroids, with or without cyclophosphamide [104-107] **(Web Box I)**. Multiple reports show benefit from additional therapy with rituximab (2-4 doses of 375 mg/m^2, administered once every 1-2 weeks) [65,104]. Using these strategies, 60-70% patients with recurrent FSGS show complete or partial remission.

Guideline 14: Transition of Care

A significant proportion of patients continue to have active disease into adulthood [89]. These children will need to be cared for by ‘adult’ physicians and nephrologists, keeping with the policy of the Indian Academy of Pediatrics of caring for children upto 18 years [108]. Parallel to the change in medical caregiver, patients need to transition from care by parents to self-care. Transition should occur smoothly, without affecting patient health. Institution-specific protocols for transition of care should be based on standard guidelines [109].

Congenital Nephrotic Syndrome

Patients with congenital nephrotic syndrome present at birth or in first 3-months of life. Infants are born prematurely with large placenta, and show massive proteinuria, hypoalbuminemia and anasarca. Antenatal ultrasonography may show hyperechoic kidneys; amniocentesis reveals high alpha-fetoprotein. There may be dysmorphic features or comorbidities. Most patients develop kidney failure by the age of 2-8 years. Recommendations on genetic aspects and management were published recently [110,111].

Almost 70-80% patients with congenital nephrotic syndrome have a genetic cause; mutations in *NPHS1, NPHS2, WT1, LAMB2* and *PLCE1* account for ~90% cases [110,112]. Exome sequencing using an extended SRNS gene panel **(Web Table II)** is recommended. Results of screening have implications for genetic counseling. Rarely, the condition is secondary to intrauterine infec-tions with cytomegalovirus, rubella, toxoplasma and syphilis [111]. The role of kidney biopsy is limited and may be considered if a genetic diagnosis is not established.

Evaluation aims to confirm the diagnosis and identify complications, including poor growth, hypothyroidism, systemic infections and thromboembolism (**Web Box II**) [111]. Infants with *WT1* variants are monitored by ultrasonography for Wilms tumor every 3-6 months.

Management includes maintaining euvolemia, optimizing nutrition, and therapy of complications. Patients should receive high energy (110-120 Cal/kg) and protein (3-3.5 g/kg/d) diet, orally or by feeding gastrostomy. Supplements of thyroxine, vitamin D and calcium are required. Albumin infusions (0.5-1.0 g/kg) are advised in presence of hypovolemia (oliguria, prolonged capillary refill, tachycardia) or anasarca. IV furosemide (0.5-2 mg/kg) is given at the end of infusion, unless patient has features of hypovolemia. Monitoring of fluid status, creatinine, electrolytes and blood pressure are necessary during diuretic therapy [111].

After 4-weeks of life, judicious use of ACE inhibitors (**Table III**) with or without prostaglandin inhibitors (indomethacin, celecoxib) is effective in reducing the severity of proteinuria. Therapy with these agents and diuretics should be withheld during episodes of hypovolemia. Since infections are the chief cause of death, infants should receive all primary immunization and bacterial infections are treated promptly. Therapy with anticoagulants is considered in patients with history of thrombosis.

Unilateral or bilateral nephrectomies are not proposed routinely, and may be considered in patients with repeated episodes of hypovolemia or refractory edema, thrombosis and malnutrition [112]. Bilateral nephrectomy is advised, prior to kidney transplantation, in patients with *WT1* mutations or persistent nephrotic

Box III Research Priorities in Steroid-Resistant Nephrotic Syndrome

Determine genetic burden and genotype-phenotype correlation in Indian patients; models for evaluating functional significance of variants

Pathogenesis of non-genetic forms of the illness

Duration of therapy with calcineurin inhibitors; switching to less toxic medications

Treatment for patients who are non-responsive to therapy with calcineurin inhibitors

Prevention and therapy for recurrent focal segmental glomerulosclerosis

Improving quality of life and patient-centered outcomes.

range proteinuria. Kidney transplantation is the definitive treatment, but has ethical, technical and immunologic challenges.

CONCLUSIONS

Recommendations on management of SRNS, first proposed by the ISPN in 2009, have been revised based on systematic reviews, published studies and expert opinion. While there is better understanding regarding the genetic basis and management, important clinical issues require to be examined **(Box III)**. The management of the disease continues to be challenging, and patients not responsive to treatment with CNI are at risk of progressive kidney disease. We hope that the present guidelines will standardize therapies and improve the quality of care for these patients.

Note: Supplementary material related to this study is available with the online version at www.indianpediatrics.net

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REFERENCES

1. Noone DG, Iijima K, Parekh R. Idiopathic nephrotic syndrome in children. Lancet. 2018;392:61-74.
2. Tullus K, Webb H, Bagga A. Management of steroid-resistant nephrotic syndrome in children and adolescents. Lancet Child Adolesc Health. 2018;2:880-90.
3. Gipson DS, Trachtman H, Kaskel FJ, et al. Clinical trial of focal segmental glomerulosclerosis in children and young adults. Kidney Int. 2011;80:868-78.
4. Troyanov S, Wall CA, Miller JA, Scholey JW, Cattran DC. Focal and segmental glomerulosclerosis: Definition and relevance of a partial remission. J Am Soc Nephrol. 2005;16:1061-8.
5. Indian Society of Pediatric Nephrology, Gulati A, Bagga A, Gulati S, Mehta KP, Vijayakumar M. Management of steroid resistant nephrotic syndrome. Indian Pediatr. 2009;46:35-47.
6. Trautmann A, Vivarelli M, Samuel S, et al. IPNA clinical practice recommendations for the diagnosis and management of children with steroid-resistant nephrotic syndrome. Pediatr Nephrol. 2020;35:1529-61.
7. American Academy of Pediatrics Steering Committee on Quality Improvement and Management. Classifying Recommendations for Clinical Practice Guidelines. Pediatrics. 2004;114: 874-7.
8. The primary nephrotic syndrome in children. Identification of patients with minimal change nephrotic syndrome from initial response to prednisone: A report of the International Study of Kidney Disease in Children. J Pediatr. 1981;98:561-4.
9. Sinha A, Saha A, Kumar M, et al. Extending initial prednisolone treatment in a randomized control trial from 3 to 6 months did not significantly influence the course of illness in children with steroid-sensitive nephrotic syndrome. Kidney Int. 2015;87:217-24.
10. Nakanishi K, Iijima K, Ishikura K, et al. Two-year outcome of the ISKDC regimen and frequent-relapsing risk in children with idiopathic nephrotic syndrome. Clin J Am SocNephrol. 2013;8:756-62.
11. Bagga A, Hari P, Srivastava RN. Prolonged versus standard prednisolone therapy for initial episode of nephrotic syndrome. Pediatr Nephrol. 1999;13:824-7.
12. Hoyer PF, Brodeh J. Initial treatment of idiopathic nephrotic syndrome in children: Prednisone versus prednisone plus cyclosporine A: A prospective, randomized trial. J Am Soc Nephrol. 2006; 17:1151-7.
13. Murnaghan K, Vasmant D, Bensman A. Pulse methylprednisolone therapy in severe idiopathic childhood nephrotic syndrome. Acta Paediatr Scand. 1984;73:733-9.
14. Letavernier B, Letavernier E, Leroy S, Baudet-Bonneville V, Bensman A, Ulinski T. Prediction of high-degree steroid dependency in pediatric idiopathic nephrotic syndrome. Pediatr Nephrol. 2008;23:2221-6.
15. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO Clinical Practice Guideline for Glomerulonephritis. Kidney Int Suppl. 2012;2:139-274.
16. Rovin BH, Caster DJ, Cattran DC, et al; Conference Participants. Management and treatment of glomerular diseases (part 2): Conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2019; 95:281-95.
17. Gipson DS, Chin H, Presler TP, et al. Differential risk of remission and ESRD in childhood FSGS. Pediatr Nephrol. 2006;21:344-9.
18. Mason AE, Sen ES, Bierzynska A, et al. Response to first course of intensified immunosuppression in genetically stratified steroid resistant nephrotic syndrome. Clin J Am Soc Nephrol. 2020;15:983-94.
19. Trautmann A, Schnaidt S, Lipska-Ziêtkiewicz BS, et al. Long-term outcome of steroid-resistant nephrotic syndrome in children. J Am Soc Nephrol. 2017;28:3055-65.
20. Stevens PE, Levin A; Kidney Disease: Improving Global Outcomes (KDIGO) Chronic Kidney Disease Guideline Development Work Group Members. Evaluation and management of chronic kidney disease: Synopsis of the Kidney Disease: Improving Global Outcomes 2012 Practice Guideline. Ann Intern Med. 2013;158: 825-30.
21. Kushwah S, Yadav M, Hari P, Meena J, Sinha A, Bagga A. Incidence and determinants of acute kidney injury in patients with nephrotic syndrome. Asian J Pediatr Nephrol. 2019; 2:75-81.
22. Corwin HL, Schwartz MM, Lewis EJ. The importance of sample size in the interpretation of the renal biopsy. Am J Nephrol. 1988;8:85-9.
23. Gulati S, Sengupta D, Sharma RK, et al. Steroid resistant nephrotic syndrome: Role of histopathology. Indian Pediatr. 2006;43:6.
24. D'Agati VD, Fogo AB, Bruijn JA, Jennette JC. Pathologic classification of focal segmental glomerulosclerosis: A working proposal. Am J Kidney Dis. 2004;43:368-82.
25. Wenderfer SE. Viral-associated glomerulopathies in children. Pediatr Nephrol. 2015;30:1929-38.
26. Sadowski CE, Lovric S, Ashraf S, et al. A single-gene cause in 29.5% of cases of steroid-resistant nephrotic syndrome. J Am Soc Nephrol. 2015;26:1279-89.
27. Bierzynska A, McCarthy HJ, Soderquest K, et al. Genomic and clinical profiling of a national nephrotic syndrome cohort advocates a precision medicine approach to disease management. Kidney Int. 2017;91:937-47.
28. Trautmann A, Lipska-Ziêtkiewicz BS, Schaefer F. Exploring the clinical and genetic spectrum of steroid resistant nephrotic syndrome: The PodoNet Registry. Front Pediatr. 2018;6:200.
29. Landini S, Mazzinghi B, Becherucci F, et al. Reverse phenotyping after whole-exome sequencing in steroid-resistant nephrotic syndrome. Clin J Am Soc Nephrol. 2020;15:89-100.

30. Nagano C, Yamamura T, Horinouchi T, et al. Comprehensive genetic diagnosis of Japanese patients with severe proteinuria. Sci Rep. 2020;10:270
31. Montini G, Malaventura C, Salviati L. Early coenzyme Q10 supplementation in primary coenzyme Q10 deficiency. N Engl J Med. 2008;358:2849-50.
32. Gee HY, Saisawat P, Ashraf S, et al. ARHGDIA mutations cause nephrotic syndrome via defective RhoGTPase signaling. J Clin Invest. 2013;123:3243-53.
33. Morello W, Puvinathan S, Puccio G, et al. Post-transplant recurrence of steroid resistant nephrotic syndrome in children: The Italian experience. J Nephrol. 2020;33:849-57.
34. Hildebrandt F, Heeringa SF. Specific podocin mutations determine age of onset of nephrotic syndrome all the way into adult life. Kidney Int. 2009;75:669-71.
35. Lentine KL, Kasiske BL, Levey AS, et al. KDIGO Clinical Practice Guideline on the evaluation and care of living kidney donors. Transplantation. 2017;101:S1-S109.
36. Lipska BS, Iatropoulos P, Maranta R, et al. Genetic screening in adolescents with steroid-resistant nephrotic syndrome. Kidney Int. 2013;84:206-13.
37. Malakasioti G, Iancu D, Tullus K. Calcineurin inhibitors in nephrotic syndrome secondary to podocyte gene mutations: A systematic review. Pediatr Nephrol. 2021;36:1353-64.
38. Siji A, Karthik KN, Pardeshi VC, Hari PS, Vasudevan A. Targeted gene panel for genetic testing of south Indian children with steroid resistant nephrotic syndrome. BMC Med Genet. 2018;19:200.
39. Ramanathan ASK, Vijayan M, Rajagopal S, Rajendiran P, Senguttuvan P. WT1 and NPHS2 gene mutation analysis and clinical management of steroid-resistant nephrotic syndrome. Mol Cell Biochem. 2017;426:177-81.
40. Richards S, Aziz N, Bale S, et al. Standards and Guidelines for the Interpretation of Sequence Variants: A Joint Consensus Recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405-24.
41. Troost JP, Trachtman H, Nachman PH, et al. An outcomes-based definition of proteinuria remission in focal segmental glomerulosclerosis. Clin J Am Soc Nephrol. 2018;13:414-21.
42. Hamasaki Y, Yoshikawa N, Nakazato H, et al. Prospective 5-year follow-up of cyclosporine treatment in children with steroid-resistant nephrosis. Pediatr Nephrol. 2013;28:765-71.
43. Liu ID, Willis NS, Craig JC, Hodson EM. Interventions for idiopathic steroid-resistant nephrotic syndrome in children. Cochrane Database Syst Rev. 2019;11:CD003594.
44. Gulati A, Sinha A, Gupta A, et al. Treatment with tacrolimus and prednisolone is preferable to intravenous cyclophosphamide as the initial therapy for children with steroid-resistant nephrotic syndrome. Kidney Int. 2012;82:1130-5.
45. Sinha A, Gupta A, Kalaivani M, Hari P, Dinda AK, Bagga A. Mycophenolate mofetil is inferior to tacrolimus in sustaining remission in children with idiopathic steroid-resistant nephrotic syndrome. Kidney Int. 2017;92:248-57.
46. Mantan M, Sriram CS, Hari P, Dinda A, Bagga A. Efficacy of intravenous pulse cyclophosphamide treatment versus combination of intravenous dexamethasone and oral cyclophosphamide treatment in steroid-resistant nephrotic syndrome. Pediatr Nephrol. 2008;23:1495-502.
47. Choudhry S, Bagga A, Hari P, Sharma S, Kalaivani M, Dinda A. Efficacy and safety of tacrolimus versus cyclosporine in children with steroid-resistant nephrotic syndrome: A randomized controlled trial. Am J Kidney Dis. 2009;53:760-9.
48. Kim JH, Park SJ, Yoon SJ, et al. Predictive factors for ciclosporin-associated nephrotoxicity in children with minimal change nephrotic syndrome. J Clin Pathol. 2011;64:516-9.
49. Inaba A, Hamasaki Y, Ishikura K, et al. Long-term outcome of idiopathic steroid-resistant nephrotic syndrome in children. Pediatr Nephrol. 2016; 31:425-34.
50. Jahan A, Prabha R, Chaturvedi S, Mathew B, Fleming D, Agarwal I. Clinical efficacy and pharmacokinetics of tacrolimus in children with steroid-resistant nephrotic syndrome. Pediatr Nephrol. 2015;30:1961-7.
51. Büscher AK, Beck BB, Melk A, et al. Rapid response to cyclosporin A and favorable renal outcome in nongenetic versus genetic steroid-resistant nephrotic syndrome. Clin J Am Soc Nephrol. 2016;11: 245-53.
52. Gellermann J, Ehrich JHH, Querfeld U. Sequential maintenance therapy with cyclosporin A and mycophenolate mofetil for sustained remission of childhood steroid-resistant nephrotic syndrome. Nephrol Dial Transplant. 2012;27:1970-8.
53. Sinha A, Sharma A, Mehta A, et al. Calcineurin inhibitor induced nephrotoxicity in steroid resistant nephrotic syndrome. Indian J Nephrol. 2013; 23:41-6.
54. Sharma M, Mahanta A, Barman AK, Mahanta PJ. Acute kidney injury in children with nephrotic syndrome: A single-center study. Clin Kidney J. 2018;11:655-8.
55. Rheault MN, Zhang L, Selewski DT, et al. AKI in children hospitalized with nephrotic syndrome. Clin J Am Soc Nephrol. 2015;10: 2110-8.
56. Lombel RM, Gipson DS, Hodson EM; Kidney Disease: Improving Global Outcomes. Treatment of steroid-sensitive nephrotic syndrome: New guidelines from KDIGO. Pediatr Nephrol. 2013;28: 415-26.
57. Plank C, Kalb V, Hinkes B, et al. Cyclosporin A is superior to cyclophosphamide in children with steroid-resistant nephrotic syndrome: A randomized controlled multicentre trial by the Arbeitsge-meinschaft für Pädiatrische Nephrologie. Pediatr Nephrol. 2008;23: 1483-93.
58. Elhence R, Gulati S, Kher V, Gupta A, Sharma RK. Intravenous pulse cyclophosphamide - A new regime for steroid-resistant minimal change nephrotic syndrome. Pediatr Nephrol. 1994;8: 1-3.
59. Shah KM, Ohri AJ, Ali US. A randomized controlled trial of intravenous versus oral cyclophosphamide in steroid-resistant nephrotic syndrome in children. Indian J Nephrol. 2017;27:430-4.
60. International Study of Kidney Disease in children. Prospective, controlled trial of cyclophosphamide therapy in children with nephrotic syndrome. Report of the International study of Kidney Disease in children. Lancet. 1974;2:423-7.
61. Tarshish P, Tobin JN, Bernstein J, Edelmann CM. Cyclophosphamide does not benefit patients with focal segmental glomerulosclerosis. A report of the International Study of Kidney Disease in Children. Pediatr Nephrol. 1996;10:590-3.
62. Jellouli M, Charfi R, Maalej B, Mahfoud A, Trabelsi S, Gargah T. Rituximab in the management of pediatric steroid-resistant nephrotic syndrome: A systematic review. J Pediatr. 2018;197:191-7.e1.
63. Kamei K, Ishikura K, Sako M, Ito S, Nozu K, Iijima K. Rituximab therapy for refractory steroid-resistant nephrotic syndrome in children. Pediatr Nephrol. 2020;35:17–24.
64. Sinha A, Bhatia D, Gulati A, et al. Efficacy and safety of rituximab in children with difficult-to-treat nephrotic syndrome. Nephrol Dial Transplant. 2015;30:96-106.
65. Sinha A, Bagga A. Rituximab therapy in nephrotic syndrome: Implications for patients' management. Nat Rev Nephrol. 2013;9:154-69.
66. Wu B, Mao J, Shen H, et al. Triple immunosuppressive therapy in steroid-resistant nephrotic syndrome children with tacrolimus resistance or tacrolimus sensitivity but frequently relapsing. Nephrol (Carlton). 2015;20:18-24.
67. Okada M, Sugimoto K, Yagi K, Yanagida H, Tabata N, Takemura T. Mycophenolate mofetil therapy for children with intractable nephrotic syndrome. Pediatr Int. 2007;49:933-7.

68. Nikibakhsh AA, Mahmoodzadeh H, Karamyyar M, Hejazi S, Noroozi M, Macooie AA. Treatment of steroid and cyclosporine-resistant idiopathic nephrotic syndrome in children. Int J Nephrol. 2011;2011:930965.
69. Lee JM, Kronbichler A, Shin JI, Oh J. Current understandings in treating children with steroid-resistant nephrotic syndrome. Pediatr Nephrol. 2021;36:747-61.
70. Muso E, Mune M, Hirano T, et al. A prospective observational survey on the long-term effect of LDL apheresis on drug-resistant nephrotic syndrome. Nephron Extra. 2015;5:58-66.
71. Yu C-C, Fornoni A, Weins A, et al. Abatacept in B7-1-positive proteinuric kidney disease. N Engl J Med. 2014;370:1263-6.
72. van den Belt SM, Heerspink HJL, Gracchi V, de Zeeuw D, Wühl E, Schaefer F. Early proteinuria lowering by angiotensin-converting enzyme inhibition predicts renal survival in children with CKD. J Am Soc Nephrol. 2018;29:2225-33.
73. Webb NJA, Shahinfar S, Wells TG, et al. Losartan and enalapril are comparable in reducing proteinuria in children. Kidney Int. 2012;82:819-26.
74. Stotter BR, Ferguson MA. Should ACE inhibitors and ARBs be used in combination in children? Pediatr Nephrol. 2019;34: 1521-32.
75. Trachtman H, Nelson P, Adler S, et al. DUET: A phase 2 study evaluating the efficacy and safety of sparsentan in patients with FSGS. J Am Soc Nephrol. 2018;29:2745-54.
76. Sinha A, Bagga A, Banerjee S, et al; Expert group of Indian Society of Pediatric Nephrology. Steroid Sensitive Nephrotic Syndrome: Revised Guidelines. Indian Pediatr. 2021;58:461-81.
77. Kerlin BA, Ayoob R, Smoyer WE. Epidemiology and pathophysiology of nephrotic syndrome-associated thromboembolic disease. Clin J Am Soc Nephrol. 2012;7:513-20.
78. Suri D, Ahluwalia J, Saxena AK, et al. Thromboembolic complications in childhood nephrotic syndrome: A clinical profile. Clin Exp Nephrol. 2014;18:803-13.
79. Kerlin BA, Haworth K, Smoyer WE. Venous thromboembolism in pediatric nephrotic syndrome. Pediatr Nephrol. 2014;29:989-97.
80. Monagle P, Chan AKC, Goldenberg NA, et al. Antithrombotic Therapy in Neonates and Children: Antithrombotic Therapy and Prevention of Thrombosis, 9th edn. American College of Chest Physicians Evidence - Based Clinical Practice Guidelines. Chest. 2012;141:e737S-801S.
81. Dabbous MK, Sakr FR, Malaeb DN. Anticoagulant therapy in pediatrics. J Basic Clin Pharm. 2014;5:27-33.
82. Hari P, Khandelwal P, Smoyer WE. Dyslipidemia and cardiovascular health in childhood nephrotic syndrome. Pediatr Nephrol. 2020;35:1601-19
83. Sarkar S, Sinha A, Lakshmy R, et al. Ambulatory blood pressure monitoring in frequently relapsing nephrotic syndrome. Indian J Pediatr. 2017;84:31-5.
84. Lurbe E, Agabiti-Rosei E, Cruickshank JK, et al. 2016 European Society of Hypertension Guidelines for the Management of High Blood Pressure in Children and Adolescents. J Hypertens. 2016;34:1887-920.
85. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: Summary report. Pediatrics. 2011;128:S213-56.
86. Aljebab F, Choonara I, Conroy S. Systematic review of the toxicity of short-course oral corticosteroids in children. Arch Dis Child. 2016;101:365-70.
87. Ahmet A, Mokashi A, Goldbloom EB, et al. Adrenal suppression from glucocorticoids: Preventing an iatrogenic cause of morbidity and mortality in children. BMJ Paediatr Open. 2019; 3:e000569.
88. Liu D, Ahmet A, Ward L, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. Allergy Asthma ClinImmunol. 2013;9:30.
89. Kaku Y, Ohtsuka Y, Komatsu Y, et al. Clinical practice guideline for pediatric idiopathic nephrotic syndrome 2013: General therapy. Clin Exp Nephrol. 2015;19:34-53.
90. Foster BJ, Shults J, Zemel BS, Leonard MB. Risk factors for glucocorticoid-induced obesity in children with steroid-sensitive nephrotic syndrome. Pediatr Nephrol.2006;21:973-80.
91. Simmonds J, Grundy N, Trompeter R, Tullus K. Long-term steroid treatment and growth: A study in steroid-dependent nephrotic syndrome. Arch Dis Child. 2010;95:146-9.
92. Bierzynska A, Saleem MA. Deriving and understanding the risk of post-transplant recurrence of nephrotic syndrome in the light of current molecular and genetic advances. Pediatr Nephrol. 2018;33: 2027-35.
93. Gross O, Weber M, Fries JWU, Müller G-A. Living donor kidney transplantation from relatives with mild urinary abnormalities in Alport syndrome: Long-term risk, benefit and outcome. Nephrol Dial Transplant. 2009;24:1626-30.
94. Francis A, Didsbury M, McCarthy H, Kara T. Treatment of recurrent focal segmental glomerulosclerosis post-kidney transplantation in Australian and New Zealand children: A retrospective cohort study. Pediatr Transplant. 2018;22: e13185.
95. Kienzl-Wagner K, Waldegger S, Schneeberger S. Disease recurrence: The sword of Damocles in kidney transplantation for primary focal segmental glomerulosclerosis. Front Immunol. 2019;10:1669.
96. Vinai M, Waber P, Seikaly MG. Recurrence of focal segmental glomerulosclerosis in renal allograft: An in-depth review. Pediatr Transplant. 2010;14:314-25.
97. Dall'Amico R, Ghiggeri G, Carraro M, et al. Prediction and treatment of recurrent focal segmental glomerulosclerosis after renal transplantation in children. Am J Kidney Dis. 1999;34:1048-55.
98. Uffing A, Pérez-Sáez MJ, Mazzali M, et al. Recurrence of FSGS after kidney transplantation in adults. Clin J Am Soc Nephrol. 2020; 15:247-56.
99. Ding WY, Koziell A, McCarthy HJ, et al. Initial steroid sensitivity in children with steroid-resistant nephrotic syndrome predicts post-transplant recurrence. J Am SocNephrol. 2014;25:1342-8.
100. Koh LJ, Martz K, Blydt-Hansen TD; NAPRTCS Registry Investigators. Risk factors associated with allograft failure in pediatric kidney transplant recipients with focal segmental glomerulosclerosis. Pediatr Transplant. 2019;23:e13469.
101. Nehus EJ, Goebel JW, Succop PS, Abraham EC. Focal segmental glomerulosclerosis in children: Multivariate analysis indicates that donor type does not alter recurrence risk. Transplantation. 2013;96: 550-4.
102. Verghese PS, Rheault MN, Jackson S, Matas AJ, Chinnakotla S, Chavers B. The effect of peri-transplant plasmapheresis in the prevention of recurrent FSGS. Pediatr Transplant. 2018;22: e13154.
103. Shenoy M, Lennon R, Plant N, Wallace D, Kaur A. Pre-emptive rituximab and plasma exchange does not prevent disease recurrence following living donor renal transplantation in high-risk idiopathic SRNS. Pediatr Nephrol. 2020;35:1081-4.
104. Hansrivijit P, Ghahramani N. Combined rituximab and plasmapheresis or plasma exchange for focal segmental glomerulosclerosis in adult kidney transplant recipients: A meta-analysis. Int Urol Nephrol.2020;52:1377-87.
105. Kashgary A, Sontrop JM, Li L, et al. The role of plasma exchange in treating post-transplant focal segmental glomerulosclerosis: A systematic review and meta-analysis of 77 case-reports and case-series. BMC Nephrol. 2016;17:104.
106. Allard L, Kwon T, Krid S, et al. Treatment by immunoadsorption for recurrent focal segmental glomerulosclerosis after pediatric kidney transplantation: A multicentre French cohort. Nephrol Dial Transplant. 2018;33:954-63.

107. Cormican S, Kennedy C, O'Kelly P, et al. Renal transplant outcomes in primary FSGS compared with other recipients and risk factors for recurrence: A national review of the Irish Transplant Registry. Clin Transplant. 2018;32:e13152.
108. John TJ. IAP policy on age of children for pediatric care. Indian Pediatr.1999;36:461-3.
109. Watson AR, Harden P, Ferris M, Kerr PG, Mahan J, Ramzy MF. Transition from pediatric to adult renal services: A consensus statement by the International Society of Nephrology and the International Pediatric Nephrology Association. Pediatr Nephrol. 2011;26:1753-7.
110. Lipska-Ziêtkiewicz BS, Ozaltin F, Hölttä T, et al. Genetic aspects of congenital nephrotic syndrome: A consensus statement from the ERKNet–ESPN inherited glomerulopathy working group. Eur J Hum Genet. 2020;28:1368-78
111. Boyer, O, Schaefer, F, Haffner D, et al. Management of congenital nephrotic syndrome: Consensus recommendations by the ERKNet-ESPN Working Group. Nat Rev Nephrol.2021;17:277-89.
112. Joshi A, Sinha A, Sharma A, et al; NephQuest Consortium. Next-generation sequencing for congenital nephrotic syndrome: A multi-center cross-sectional study from India. Indian Pediatr. 2021;58: 445-51.

ANNEXURE I

***List of Participants**

Kamran Afzal, *Aligarh*; Indira Agarwal, *Vellore*; Vinay Agarwal, *New Delhi*; Kanav Anand, *New Delhi*; M Ashraf, *Srinagar*; Arvind Bagga, *New Delhi*; Sushmita Banerjee, *Kolkata*; Girish C Bhatt, *Bhopal*; Sudha Ekambaram, *Chennai*; Arpita Gogoi, *Dibrugarh*; Sanjeev Gulati, *New Delhi*; Pankaj Hari, *New Delhi*; Suprita Kalra, *New Delhi*; Kanika Kapoor, *New Delhi*; Priyanka Khandelwal, *New Delhi*; Sriram Krishnamurthy, *Puducherry*; Manish Kumar, *New Delhi*; Mukta Mantan, *New Delhi*; Jitendra K Meena, *New Delhi*; Kirtisudha Mishra, *New Delhi*; Amarjeet Mehta, *Jaipur*; OP Mishra, *Varanasi*; Aliza Mittal, *Jodhpur*; Saroj K Patnaik, *New Delhi*; Subal Pradhan, *Cuttack*; PK Pruthi, *New Delhi*; Sumantra Raut, *Kolkata*; Abhijeet Saha, *New Delhi*; Manisha Sahay, *Hyderabad*; Jyoti Sharma, *Pune*; Shobha Sharma; *New Delhi*; Jyoti Singhal, *Pune*; Aditi Sinha, *New Delhi*; Rajiv Sinha, *Kolkata*; Ranjeet Thergaonkar, *Mumbai*; Karalanglin Tiewsoh, *Chandigarh*; Susan Uthup, *Thiruvananthapuram*; Anand S Vasudev, *New Delhi*; Anil Vasudevan, *Bengaluru.*

Experts: Uma Ali, *Mumbai*; Amit K Dinda, *New Delhi*; Mohammed Faruq, *New Delhi*; Madhuri Kanitkar, *New Delhi*; Kumud Mehta, *Mumbai*; BR Nammalwar, *Chennai*; Kishore D Phadke, *Bengaluru*; Geetika Singh, *New Delhi*; RN Srivastava, *New Delhi.*

Web Table I Grading of Evidence [7]

Grade	*Quality of evidence*
A	Well designed and controlled studies; meta-analysis on applicable population; true effect lies close to the estimate of the effect
B	Studies with minor limitations; consistent findings from multiple observational studies; true effect is likely to be close to estimate of the effect, but there is a possibility that it is substantially different
C	Single, few or multiple studies with inconsistent findings or major limitations; confidence in the effect estimate is limited, the true effect may be substantially different from estimate of the effect
D	Expert opinion, case reports; very little confidence in effect estimate, true effect likely to be substantially different from estimate of effect
X	Situations where validating studies cannot be performed, and benefit or harm clearly predominates
Level	*Strength of recommendation*
1	"We recommend": Most patients should receive the recommended course of action
2	"We suggest": Different choices will be appropriate for different patients

Web Table II Gene List for Targeted Panel with Features of Steroid Resistant Nephrotic Syndrome (SRNS)

Gene	*Protein*	*Inherit-ance*	*Accession no; OMIM*	*OMIM phenotype*	*Key clinical features*
ACTN4	Actinin, alpha 4	AD	NM_004924; 603278	Focal segmental glomerulosclerosis (FSGS), type 1	Familial and sporadic SRNS (usually adolescent and adult)
ADCK4/ COQ8B	Coenzyme Q8B	AR	NM_024876; 615573	Nephrotic syndrome, type 9	FSGS or collapsing FSGS; one patient responded to coenzyme Q10
ALG1	Asparagine-linked glycosylation 1	AR	NM_019109; 605907	Congenital disorder of glycosylation, type Ik	Neurologic impairment and dysmorphic features
ANKFY1	Rabankyrin-5	AR	NM_001330063.2; 607927		Early onset illness
ANLN	Actin binding protein anillin	AD	NM_018685; 616032	FSGS, type 8	FSGS (onset between 9-70 years)
ARHGAP24	Rho GTPase-activating protein 24	AD	NM_001025616; 610586		FSGS
ARHGDIA	Rho GDP-dissociation inhibitor alpha	AR	NM_001185078; 615244	Nephrotic syndrome, type 8	Congenital nephrotic syndrome; SRNS early onset; diffuse mesangial sclerosis on biopsy
AVIL	Advillin	AR	NM_006576.3; 618594	Nephrotic syndrome, type 21	SRNS; diffuse mesangial sclerosis on biopsy
CD151	Tetraspanin (TM4)	AR	NM_004357; 609057	Nephropathy; deafness; SRNS; epidermolysis bullosa	Pretibial skin lesions, sensorineural deafness, lacrimal duct stenosis, nail dystrophy, thalassemia minor
CD2AP	CD2-associated protein	AD/AR	NM_012120; 607832	FSGS, type 3	FSGS
CLCN5	H^+/Cl^- exchange transporter 5	XR	NM_001127898.4; 300009	Dent disease; low molecular weight proteinuria, hypercalciuria	Failure to thrive; hypercalciuria, nephrolithiasis; low molecular weight proteinuria, albuminuria; FSGS
COL4A3	Type IV collagen α3	AR, AD	NM_000091; 120070	Alport syndrome 2, AR; Alport syndrome 3, AD	Alport syndrome; FSGS
COL4A4	Type IV collagen α4	AR	NM_000092; 120131	Alport syndrome 2, AR	Alport syndrome; FSGS
COL4A5	Type IV collagen α5	XLD	NM_000495; 301050	Alport syndrome 1, XL	Alport syndrome; FSGS

COQ2	Coenzyme Q2	AR	NM_015697; 609825	Coenzyme Q10 deficiency, primary, 1	Mitochondrial disease; isolated SRNS
COQ6	Coenzyme Q6	AR	NM_182476; 614647	Coenzyme Q10 deficiency, primary, 6	Early SRNS; sensorineural deafness; ataxia, facial dysmorphism; FSGS, diffuse mesangial sclerosis
CRB2	Crumbs cell polarity complex component 2	AR	NM_173689; 616220	FSGS, type 9	SRNS
CUBN	Cubilin	AR	NM_001081; 261100	Megaloblastic anemia	Megaloblastic anemia; proteinuria
DGKE	Diacylglycerol kinase, epsilon	AR	NM_003647; 615008	Nephrotic syndrome, type 7	
DLC1	DLC1 Rho GTPase activating protein		NM_182643.3; 604258		Child and adult steroid sensitive illness and SRNS; partial CNI response
E2F3	E2F transcription factor 3		NM_001949.4; 600427		FSGS, mental retardation; also with partial deletion of chromosome 6
EMP2	Epithelial membrane protein 2	AR	NM_001424; 615861	Nephrotic syndrome, type 10	Childhood SRNS; steroid sensitive illness also reported
FAT1	FAT tumor suppressor homolog 1	AR	NM_005245.4; 600976		SRNS, tubular ectasia, hematuria
FN1	Fibronectin	AD	NM_212482.3; 601894	Glomerulopathy with fibronectin deposits 2	Proteinuria, hematuria; glomerulomegaly, fibronectin positive subendothelial, mesangial deposits
GAPVD1	GTPase-activating protein, VPS9-domain protein 1		NM_001282680.3; 611714		Early-onset SRNS
INF2	Inverted formin 2	AD	NM_022489; 613237	FSGS, type 5	Isolated SRNS; Charcot-Marie-Tooth neuropathy with FSGS
ITGA3	Integrin α3	AR	NM_002204; 605025	Interstitial lung disease; epidermolysis bullosa	Congenital, SRNS; interstitial lung disease; epidermolysis bullosa (congenital)
ITGB4	Integrin β4	AR	NM_000213; 147557	Epidermolysis bullosa; pyloric atresia	Epidermolysis bullosa (junctional); pyloric atresia; FSGS
ITSN1	Intersectin-1	AR	NM_003024.3; 602442		Congenital, SRNS; steroid sensitive illness reported
ITSN2	Intersectin-2	AR	NM_019595.4;		Steroid sensitive illness

			604464		(minimal change) or membranoproliferative glomerulonephritis
KANK1	KN motif ankyrin repeat domain-containing protein 1	AR	NM_015158.3; 607704		Steroid sensitive illness
KANK2	KN motif ankyrin repeat domain-containing protein 2	AR	NM_015493; 617783		Steroid sensitive illness; steroid dependence; hematuria
KANK4	KN motif ankyrin repeat domain-containing protein 4	AR	NM_0181712.4; 614612		SRNS; hematuria
KIRREL1	Kin of IRRE-like protein 1	AR	NM_018240.7; 607428		SRNS
LAGE3	EKC/KEOPS complex subunit LAGE3	XR	NM_006014.4; 301006	Galloway-Mowat syndrome 2	Early-onset SRNS; FSGS; microcephaly, gyral abnormalities; delayed development
LAMB2	Laminin, beta-2	AR	NM_002292; 614199	Nephrotic syndrome, type 5; ocular anomalies	Pierson syndrome; SRNS, microcoria, neurodevelopmental delay
LCAT	Phosphatidylcholine-sterol acyltransferase	AR	NM_000229.2; 245900	Norum disease	Proteinuria, renal failure, anemia, corneal lipid deposits
LMNA	Prelamin-A/C	AD	NM_170707; 151660	Lipodystrophy type 2, partial	Familial partial lipodystrophy; FSGS
LMX1B	LIM homeobox transcription factor 1β	AD	NM_002316; 602575	Nail-patella syndrome	FSGS; SRNS, mild ridging to hypoplasia of nails, absent, hypoplastic patella; glaucoma
MEFV	Pyrin	AD/AR	NM_000243.2; 608107	Familial Mediterranean fever	Fever, pericarditis, pleuritis, arthralgia; nephrotic syndrome
MAFB	Transcription factor MafB	AD	NM_005461.5; 166300	Multicentric carpotarsal osteolysis syndrome	Proteinuria, end stage kidney disease; skeletal disorders; mental retardation; minor facial anomalies
MAGI2	Membrane-associated guanylate kinase inverted 2	AR	NM_012301.4; 617609	Nephrotic syndrome, type 15	SRNS; FSGS
MYO1E	Myosin IE	AR	NM_004998; 614131	FSGS, type 6	FSGS; collapsing FSGS
MYH9	Myosin-9	AD	NM_002473; 155100	Macrothrombocytes, granulocyte	MYH9-related disease; Epstein, Fechtner

				inclusions; nephritis, deafness	syndromes: nephritis, deafness, thrombocytopenia, giant platelets
NEU1	Sialidase-1	AR	NM_000434.4; 256550	Sialidosis, type I/II	SRNS; FSGS; hepatomegaly, corneal clouding, cherry red spots (nephrosialidosis)
NPHS1	Nephrin	AR	NM_004646; 256300	Nephrotic syndrome, type 1	Congenital, SRNS
NPHS2	Podocin	AR	NM_014625; 600995	Nephrotic syndrome, type 2	Congenital, SRNS
NUP85	Nucleoporin, 85-kDa	AR	NM_024844.5; 618176	Nephrotic syndrome, type 17	SRNS; FSGS
NUP93	Nucleoporin, 93-kDa	AR	NM_014669; 616892	Nephrotic syndrome, type 12	SRNS; FSGS
NUP107	Nucleoporin, 107-kDa	AR	NM_020401; 616730	Nephrotic syndrome, type 11 Galloway-Mowat syndrome-7	SRNS
NUP133	Nucleoporin, 133-kDa	AR	NM_018230.3; 618177; 618349	Nephrotic syndrome, type 18 Galloway-Mowat syndrome-8	Isolated FSGS
NUP160	Nucleoporin, 160-kDa	AR	NM_015231.2; 618178	Nephrotic syndrome, type 19	SRNS
NUP205	Nucleoporin, 205-kDa	AR	NM_015135; 616893	Nephrotic syndrome, type 13	Early onset SRNS
NXF5	Nuclear RNA export factor 5	XR	NM_032946; 300319		FSGS co-segregating with heart block
OCRL	Inositol polyphosphate 5-phosphatase	XR	NM_000276; 309000	Lowe syndrome	FSGS; absence of proximal tubular dysfunction reported
OSGEP	Probable tRNA N6-adenosine threonylcarbamoyltransferase	AR	NM_017807.4; 617729	Galloway-Mowat syndrome 3	SRNS
PAX2	Paired box protein 2	AD	NM_003987; 616002	FSGS, type 7	FSGS without extrarenal manifestations
PDSS2	Decaprenyl diphosphate synthase subunit 2	AR	NM_020381; 610564	Leigh syndrome	Mitochondrial disorder; proteinuria
PLCe1	Phospholipase C, epsilon-1	AR	NM_016341; 610725	Nephrotic syndrome, type 3	Congenital, SRNS

PMM2	Phosphomannomutase 2	AR	NM_000303; 212065	Disorder of glycosylation, type Ia	Psychomotor retardation, peripheral neuropathy with SRNS
PODXL	Podocalyxin	AD	NM_005397; 602632		FSGS
PTPRO	Protein-tyrosine phosphatase, receptor-type O	AR	NM_030667; 614196	Nephrotic syndrome, type 6	SRNS
SCARB2	Lysosome membrane protein 2	AR	NM_005506; 254900	Myoclonic epilepsy, 4; renal failure	Progressive myoclonic epilepsy; SRNS; FSGS
SGPL1	Sphingosine-1-phosphate lyase 1	AR	NM_003901.4; 617575	Nephrotic syndrome, type 14	Primary adrenal insufficiency, neurologic abnormalities; SRNS
SMARCAL1	SMARCAL1	AR	NM_014140; 242900	Schimke immunoosseous dysplasia	Spondyloepiphyseal dysplasia; immune deficiency, neurological features; FSGS
SYNPO	Synaptopodin	AD	NM_007286; 608155		Sporadic FSGS (promoter mutations)
SYNPO2	Synaptopodin-2	AR	Not available		Congenital childhood onset, SRNS
TBC1D8B	TBC1 domain family, 8B	XR	NM_017752.3; 301028	Nephrotic syndrome, type 20	Early-onset SRNS with FSGS
TNS2	Tensin 2	AR	NM_170754.3; 607717		Steroid dependence (minimal change, FSGS, diffuse mesangial sclerosis)
TP53RK	EKC/KEOPS complex subunit TP53RK	AR	NM_033550.4; 617730	Galloway-Mowat syndrome 4	Early onset SRNS
TPRKB	EKC/KEOPS complex subunit TPRKB	AR	NM_001330389.1; 617731	Galloway-Mowat syndrome 5	Early-onset SRNS
TRPC6	Transient receptor potential channel, subfamily C member 6	AD	NM_004621; 603965	FSGS, type 2	Familial and sporadic SRNS (chiefly adult)
TTC21B	Tetratricopeptide repeat protein 21B	AR	NM_024753; 613820	Nephronophthisis 12	Late onset FSGS; tubulointerstitial fibrosis and tubular atrophy; Joubert syndrome
WDR4	tRNA (guanine-N7-) methyltransferase subunit WDR4	AR	NM_001260475.1; 618347	Galloway-Mowat syndrome 6	Early-onset SRNS

WDR73	WD repeat domain 73	AR	NM_032856; 616144	Galloway-Mowat syndrome 1	SRNS
WT1	WT1 transcription factor	AD	NM_024426; 256370	Nephrotic syndrome, type 4	Isolated SRNS; Frasier & Denys-Drash syndromes
XPO5	Exportin 5	AR	NM_020750; 607845		Childhood SRNS
ZMPSTE24	CAAX prenyl protease 1 homolog	AR	NM_005857; 608612	Mandibuloacral dysplasia, type B lipodystrophy	FSGS; skeletal anomalies, dysplastic nails; skin pigmentation; calcified skin nodules
APOL1	Apolipoprotei n L-I		NM_003661; 612551	FSGS, type 4	G1, G2 risk alleles: Susceptibility to FSGS; end stage kidney disease in African, Hispanic Americans

OMIM Online Mendelian Inheritance in Man; AR autosomal recessive; AD autosomal dominant; CNI calcineurin inhibitors; XR X-linked recessive, XL X linked
Phenocopy genes (OMIM no.; phenotype): NPHP4 (606966; nephronophthisis 4); CLCN5 (300009; Dent disease 1); CTNS (219800; cystinosis); DGKE (615008; hemolytic uremic syndrome); NPHP13 (614377; nephronophthisis 13); GLA (301500; Fabry disease); FN1 (601894; glomerulopathy with fibronectin deposits 2); PAX2 (120330; papillorenal syndrome); COL4A3 (104200; Alport syndrome); COL4A4 (203780; Alport syndrome); COL4A5 (301050; Alport syndrome); AGXT (259900; primary hyperoxaluria type 1); FAT4 (612411; Van Maldergem syndrome 2); WDR19 (614377; nephronophthisis 13).

Web Table III Corticosteroid Response and Kidney Failure in Children with Genetic and Non-Genetic Forms of Steroid-Resistant Nephrotic Syndrome

Author, yr [Ref]	*Genetic cause, %**	*Complete, partial remission*		*Kidney Failure*^	
		Non-genetic, N	*Genetic, N*	*Non-genetic, N*	*Genetic, N*
Trautmann, 2018 [28]	373/1554 (24%)	159/387	10/74	113/501^1	116/241^1
Landini, 2020 [29]	37/64 (57.8%)$1	13/17	1/19$2	3/6^2	11/25^2
Nagano, 2020 [30]	69/230 (30%)	41/158	2/37	79/158^3	52/69^3
Mason, 2020 [18]	81/271 (29.9%)	69/149	9/26	41/149^4	16/26^4
Total#	1086/3902 (27.8%)#	282/711 (39.7%)	22/156 (14.1%)	236/814 (29.0%)	195/361 (61.5%)
Genetic versus non-genetic disease		*Odds ratio*	*95% confidence interval*		*P*
Non-response		4.00	2.52, 6.51		<0.0001
Kidney failure		2.87	2.22, 3.72		<0.0001

Only includes reports based on next-generation sequencing; latest or largest report for units with multiple papers

**Congenital nephrotic syndrome not excluded, except by Trautmann et al*

 # Includes 526 of 1783 families tested by Sadowski et al [26]

^ Numbers at [1]last follow up; [2]at 10-yr; or extrapolated from Kaplan Meier analysis, at [3]last follow up or at [4]10-yr

$1 Includes and $2 excludes 18 patients with phenocopies

Web Table IV Important Drug Interactions of Cyclosporine and Tacrolimus

Medication	*Effect*	*Management*
Drugs that decrease levels		
Anticonvulsants: Phenytoin, carbamazepine, phenobarbitone	Enzyme induction leads to lower levels; risk of non-response or relapse	Increase medication by 30%; monitor trough levels following change of dose or discontinuation of anticonvulsant
Antibiotics: Rifampin; caspofungin (only with tacrolimus)		Monitor trough levels following addition, change of dose or discontinuation of medication
Drugs that increase levels		
Erythromycin, clarithromycin Fluconazole, ketoconazole, voricanazole	Enzyme inhibition results in high levels and risk of nephrotoxicity	Monitor trough levels following addition, change of dose or discontinuation of medication Monitor serum creatinine, electrolytes, liver function tests
Diltiazem, verapamil		
Pharmacodynamic interactions		
Aminoglycosides, amphotericin B, nonsteroidal anti-inflammatory drugs	Risk of nephrotoxicity	Avoid if alternative options are available Monitor creatinine and electrolytes frequently
HMG-CoA reductase inhibitors	Myalgia, rhabdomyolysis	Start with low dose of statins; monitor for toxicity
Nifedipine, amlodipine, phenytoin (only with cyclosporine)	Higher incidence and severity of gingival hyperplasia	Avoid long-term combined use; change to alternative agent Dental and oral hygiene; regular dentist visits

Web Box I Management of Allograft Recurrence of Nephrotic Syndrome

Monitor proteinuria by urine protein to creatinine (Up/Uc) ratio

Daily for 1 week; weekly for 4-weeks; monthly for 1-yr; then every 3-6 months

Renal biopsy, especially if low grade proteinuria or graft dysfunction

Treatment of Recurrence

Plasma exchange

Membrane filtration or centrifugation based; heparin or citrate anticoagulation

Replacement fluid: 5% albumin; fresh frozen plasma

Schedule: Plasma exchange 1.5 times plasma volume (60-75 mL/kg) per session on alternate days for 2-weeks; single volume (40 mL/kg) once per week for 4-6 weeks

Medications

IV methylprednisolone 250 mg/m^2/day for 3 days; taper to previous dose of oral prednisolone

Increase dose of calcineurin inhibitors: Tacrolimus trough 8-12 ng/mL; cyclosporine trough 150-200 ng/mL

Rituximab 375 mg/m^2 two doses, one-week apart

Add angiotensin converting enzyme inhibitor once allograft function established with stable estimated GFR

Consider therapy with oral cyclophosphamide for 3 months in place of mycophenolate mofetil

Recurrence: Urine protein to creatinine ratio (Up/Uc) ≥1 mg/mg if anuric before transplant; or increase in Up/Uc by ≥1 mg/mg if proteinuria at time of transplant

Web Box II Evaluation of Patients with Congenital Nephrotic Syndrome

Extra-renal features: Dysmorphic features, eye, urogenital abnormalities; large placenta

Urinalysis; urine protein to creatinine ratio

Complete blood counts

Blood creatinine, protein, albumin, electrolytes, calcium, phosphate

Transaminases, alkaline phosphatase, 25-hydroxyvitamin D

Lipid profile, free thyroxine, thyroid stimulating hormone

Renal ultrasonography

Kidney biopsy: Not necessary, except if a genetic diagnosis is not established

Identifying the cause

Exome sequencing (*Web Table* II)

Serology for intrauterine infections (TORCH), syphilis, hepatitis B and C, HIV

Karyotyping (infants with ambiguous genitalia, extra-renal features)