Steroid Resistant Nephrotic Syndrome

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Introduction

Idiopathic nephrotic syndrome is characterized by severe proteinuria, hypoalbuminemia, and/or presence of edema. Whereas approximately 85% of affected children achieve complete remission of proteinuria upon corticosteroid treatment, those who do not achieve remission are labeled as having "steroid resistant nephrotic syndrome" (SRNS). While details related to steroid sensitive forms of nephrotic syndrome are discussed in Chap. 14 of this book, our chapter will focus on the epidemiology, diagnosis, treatment and clinical outcomes of those children who fail to enter clinical remission after treatment with glucocorticoids.

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Definitions

The most important implication for a child given the label of SRNS is that he or she is at increased risk for both the development of disease complications as well as progression to chronic kidney disease (CKD) and eventually end stage kidney disease (ESKD). A major challenge of discussing the multiple issues related to children with SRNS is that its very definition has been standardized within the pediatric nephrology community only recently. In 2020, an IPNA expert committee launched a set of clinical practice recommendations for SRNS in children and in 2021, KDIGO published a clinical practice guideline for the management of glomerular diseases including a pediatric section [1, 2]. The two guidance documents provide the same uniform definitions of SRNS and its subsets:

Steroid Resistant Nephrotic Syndrome (SRNS): Children who fail to enter complete clinical remission within 4 weeks of treatment with prednisone or prednisolone at standard dose [3, 4].

It should be noted that several alternative definitions of SRNS have been used in the past, such as failure to enter remission after 6 weeks of daily oral prednisone, 4 weeks of daily followed by 4 weeks of alternate day oral prednisone, or 4 weeks of daily oral prednisone followed by three intravenous pulses of methylprednisolone [5, 6]. It is hoped that the new definition will be

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followed both in research settings and in routine clinical practice. This will be a prerequisite to compare the efficacy of established and novel treatments for nephrotic syndrome.

Calcineurin inhibitor responsive SRNS: Partial remission after 6 months of treatment and/or complete remission after 12 months of treatment with a CNI at adequate doses and/or levels.

Calcineurin inhibitor resistant SRNS: Absence of at least partial remission after 6 months of treatment with a CNI at adequate doses and/or levels.

Multidrug resistant SRNS: Absence of complete remission after 12 months of treatment with two mechanistically distinct steroid-sparing agents at standard doses.

Secondary SRNS: A steroid sensitive nephrotic syndrome patient at disease onset who at subsequent relapse fails to achieve remission after 4 weeks of therapy with daily prednisone or prednisolone at standard dose. Emerging data in the literature has drawn attention to this subgroup of patients with NS [7]. A unique characteristic of this group is that up to 80% of patients in this subgroup who progress to ESKD will develop recurrence of disease following kidney transplantation [8, 9].

Epidemiology

The annual incidence of nephrotic syndrome in most countries studied to date is ~1.2–17.0 new cases per 100,000 children [4, 10–14], and the prevalence is ~16 cases per 100,000 children [4]. The incidence varies widely between countries and different ethnicities [14]. In young children there is a male preponderance, with a male to female ratio of 2:1, although this gender disparity completely disappears by adolescence [11, 15–18]. Steroid resistant nephrotic syndrome (SRNS) is seen in about 15–20% of all cases of childhood nephrotic syndrome. Monogenic SRNS is responsible for 10–30% of all SRNS. The higher percentage is seen in the regions of the World here in breeding is very high and also in population where there are founder mutations. The most common causes of monogenic autosomal SRNS are mutations in nephrin (*NPHS1*), podocin (*NPHS2*), phospholipase c epsilon 1 (*PLCE1*) and *nucleoporin* genes. Majority of all cases of autosomal dominant monogenic SRNS are due to mutations in inverted formin2 (*INF2*), transient receptor potential cation channel, subfamily C, member 6 (*TRPC6*) actinin4 alpha (*ACTN4*), and wilms tumor type 1 (*WT1*) genes.

The incidence of nephrotic syndrome has been largely unchanged over the last 35 years, but the histopathologic lesions associated with nephrotic syndrome appear to be evolving. Some reports from various countries suggest that the incidence of focal segmental glomerulosclerosis (FSGS) is increasing, even after correction for variations in renal biopsy practices, and also assuming that children who did not undergo a renal biopsy had minimal change nephrotic syndrome (MCNS) [9, 15–18].

The histologic patterns and incidence of nephrotic syndrome are also affected by **ethnicity and geographic location**. For instance, idiopathic nephrotic syndrome in the United Kingdom was found to be more common among Asian children living in the UK and Canada compared to European children [19, 20]. In contrast, in Sub-Saharan Africa, idiopathic nephrotic syndrome occurs less commonly and disease is more commonly due to infection-associated glomerular lesions [21–23]. In the US, nephrotic syndrome has a relatively higher incidence among children of various ethnic backgrounds. A review of children with nephrotic syndrome in Texas reported that the distribution of children closely resembled the ethnic composition of the surrounding community [15]. These data in conjunction with the data from African countries suggests that the interaction of environmental and genetic factors plays an important role in the pathogenesis of nephrotic syndrome. Despite this, race alone seems to have a clear correlation with the histologic lesion associated with nephrotic syndrome. Indeed, 47% of African American children with nephrotic syndrome in the above study were found to have FSGS, while only 11% of Hispanic and 18% of Caucasian children had this unfavorable pattern of injury [15]. The genetic basis for the high prevalence of

FSGS in people of African ancestry was established in 2010 when homozygous or compound heterozygous G1 and G2 genotype in the gene encoding apolipoprotein 1 (*APOL1*) were shown to confer ten times the odds of developing FSGS in African Americans [24].

The age at presentation with nephrotic syndrome also has strong correlations with the frequency of presentation, as well as the associated renal histology. The most common age for presentation with nephrotic syndrome is 2 years, and 70–80% of all cases of nephrotic syndrome develop in children <6 years of age [4, 10]. In addition, children diagnosed prior to 6 years of age comprised 80% of those with MCNS, compared to 50% of those with FSGS, and only 2.6% of those with MPGN [25]. When analyzed based on renal histology, the median age at presentation was 3 years for MCNS, 6 years for FSGS, and 10 years for MPGN [25]. Therefore, excluding presentation in the first 12 months of life, these data suggest that the likelihood of having MCNS as a cause for nephrotic syndrome decreases with increasing age, while the likelihood for having the less favorable diagnoses of FSGS or MPGN increases [25, 26].

The most common renal histologies seen in children with SRNS are FSGS, MCNS, MPGN and membranous nephropathy.

Additional variables associated with clinical steroid responsiveness include ethnicity and geographic location. While 20% of children in Western countries have steroid resistant nephrotic syndrome, studies from Africa reported steroid resistance in 50–90% of children with nephrotic syndrome, with higher proportions of children with steroid responsive disease in more affluent and diverse urban centers [23, 27–29].

Histopathological Findings

SRNS is a heterogeneous clinical condition with multiple etiologies. The histopathologic entities that may cause SRNS vary in different series depending on the age group and the population being studied. However, in different series focusing on children presenting after the first year of life, the common pathologic variants associated with SRNS include focal segmental glomerulosclerosis (FSGS), membranous glomerulopathy, membranoproliferative glomerulopathy (MPGN), and minimal change disease (MCD) [11, 15, 31–34]. The majority of cases are due to disease on the continuum between MCD and FSGS (Table 14.1). Since the MCD/FSGS spectrum represents the most common pathologic variants of SRNS, and since other chapters are devoted to each of the other histologic variants, the rest of this chapter will focus mainly on FSGS.

Table 14.1 Pathologic findings in steroid resistant nephrotic syndrome

Histology	South-Asia[a] [25, 26] n = 326	South-Africa [28] n = 183	Poland [27] n = 34	USA[b] [9, 12] n = 253
MCD	38.4	36.1	5.9	45.4
FSGS	41.5	36.1	32.4	26.5
MESGN	14.1	8.1	55.8	10.3
MEMB	4.0	–	–	1.2
MPGN	1.0	–	5.9	7.5
Others	1.0	19.7	–	9.1

[a] Two studies one each from Pakistan and India [25, 26]
[b] Summary of two studies, some of the patients were diagnosed with frequent relapsing and steroid dependent NS [9, 12]

Focal Segmental Glomerulosclerosis (FSGS)

FSGS is a pathologic finding that is characterized by focal glomerulosclerosis or tuft collapse, segmental hyalinosis, IgM deposits on immunofluorescence staining, and podocyte foot process effacement on electron microscopy [35]. In the majority of children, it is characterized by SRNS and progression to end-stage kidney disease (ESKD) within 5–10 years of diagnosis [30]. It was first described in kidney biopsies of adults with nephrotic syndrome by Fahr in 1925, although it was Rich who later made the observation that the lesion of FSGS in children with nephrotic syndrome classically starts from the corticomedullary junction before involving other parts of the renal cortex [36, 37]. The observation of Rich is probably the explanation for why many cases of FSGS

are initially misdiagnosed as MCD since early disease may be confined to the corticomedullary junction. The incidence of FSGS is estimated at seven per million people, and the incidence is higher in blacks than whites and the rate of decline in kidney function is also worse in blacks [38]. The incidence of FSGS is increasing in all populations. In a predominantly adult cohort, Kitiyakara et al. reported an 11-fold increase among dialysis patients over a 21 year period, and a similar pattern was reported in a population-based study in the USA [39, 40]. The most compelling pediatric data to date is a metanalysis that examined over 1100 nephrotic patients over two time points. This study demonstrated a twofold increase in the incidence of FSGS in children [41]. The reason for the increasing incidence is unknown, but possible explanations include changing criteria in the selection of patients for kidney biopsy, better diagnostic instruments, or changing environmental factors such as infection-driven disease. For example, patients with severe acute respiratory syndrome due to coronavirus 2 (SARS-CoV-2) can develop nephrotic syndrome with renal histology findings of FSGS due to direct podocyte infection and or cytokine production [42].

Table 14.2 Etiology of FSGS

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

Clinical and Pathologic Classification of FSGS

Until recently, FSGS was classified based on presumed causes. The etiology was unknown in more than 80% of cases (primary or idiopathic FSGS) and the remainder secondary to other disease processes such as infectious agents like hepatitis, HIV, toxic agents, ischemia, obesity and other glomerulonephritides. A list of causes of FSGS is shown in Table 14.2.

With the recent advances in genomic science, hereditary causes of FSGS are increasingly being recognized. Although this group is estimated to be responsible for not more than 30% of all cases, detailed studies of hereditary FSGS have shed more light on the molecular pathogenesis of the disease [43].

The morphological changes in kidney biopsies of patients with FSGS are heterogeneous. In order to standardize the pathological diagnosis of FSGS and relate histologic findings to clinical course, the Columbia classification of FSGS was proposed [44]. In this classification schema, five patterns of FSGS have been proposed including: (1) FSGS not otherwise specified (NOS), (2) Perihilar variant, (3) Cellular variant, (4) Tip variant, and (5) Collapsing variant (Table 14.3 and Fig. 14.1). The clinical significance of the

Table 14.3 Outcome of FSGS histologic subtypes in the NIH-sponsored FSGS trial [21]

FSGS subtypes	Frequency (%) n = 138	% with ESKD at 3 years
NOS	68	20
Collapsing	12	47
Tip	10	7
Perihilar	7	Number too small
Cellular	3	Number too small

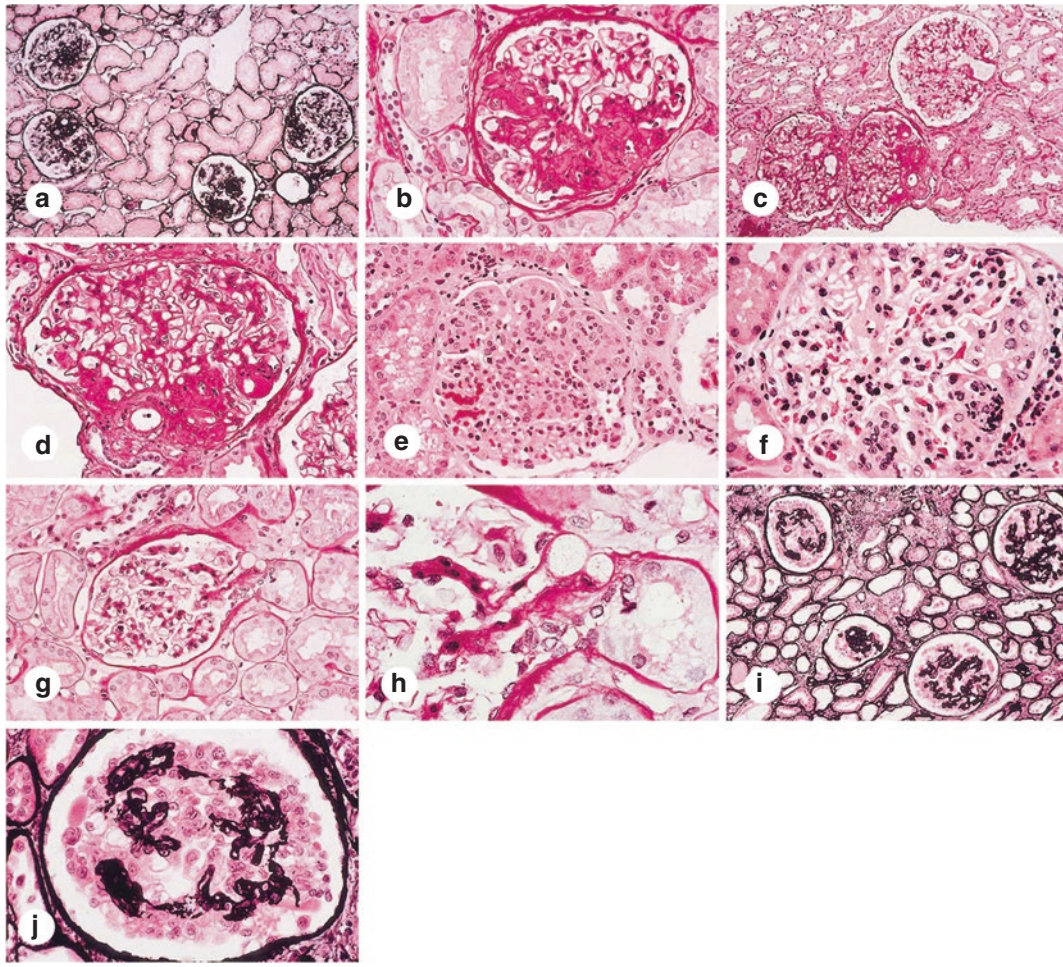

Fig. 14.1 Columbia classification of FSGS: *FSGS NOS:* (**a**) Low power magnification showing segmental sclerosis in two glomeruli. Lesions are characterized by increased matrix and obliteration of the capillary lumen. Distribution of lesions within the tuft is variable. (**b**) PAS staining at higher magnification showing obliteration of glomerular tuft by increased matrix and hyaline deposit. Sclerosed segments form adhesions to Bowman's capsule, note that there is no podocyte hypertrophy or hyperplasia. *FSGS perihilar variant:* (**c**) Low power examination showing segmental sclerosis affecting the vascular pole in one of three glomeruli. The lesion shows increased sclerosis and hyalinosis and there is adhesion of the sclerotic segment to the Bowman's capsule in the vascular pole region. (**d**) Higher magnification of C showing increased sclerosis and glassy hyalinosis deposited in the vascular pole segment of the tuft. *FSGS cellular variant:* (**e**) The glomerulus in this image shows endocapillary hypercellularity. The involved segments are engorged with endocapillary cells including mononuclear leukocytes. (**f**) Further demonstration of numerous endocapillary leukocytes mimicking endocapillary glomerulonephritis. In addition there is hypertrophy and hyperplasia of overlying podocytes. *FSGS tip variant:* (**g**) Low power view shows a segmental lesion involving the tip domain at the origin of the tubular pole. (**h**) Higher magnification of the lesion in G showing endocapillary foam cells and adhesion of the sclerotic segment to Bowman's capsule at the mouth of the proximal tubule. *FSGS collapsing variant*: (**i**) Low power magnification shows four glomeruli with global collapse of the tuft and podocyte hypertrophy and hyperplasia with tubular degenerative changes. (**j**) High power magnification shows global occlusion of capillary lumina by implosive collapse of the glomerular basement membranes. There is no significant increase in intracapillary cells or matrix. Overlying podocytes form a cellular corona over the collapsed tuft. Some of the enlarged podocytes appear binucleated and have lost their cohesion to the tuft. (Adapted with permission from reference [44])

variants is still being studied. In a cohort of adults with FSGS, it was reported that collapsing FSGS had the highest rate of renal insufficiency at presentation and worst long term outcome [45]. The most comprehensive prospective report of the clinical significance of the classification in children comes from the analysis of the kidney biopsies from the patient cohort in the NIH sponsored FSGS trial [46]. In this study FSGS NOS was the most common variant, being responsible for 68% of all cases, with collapsing, tip, perihilar and cellular variants responsible for 12%, 10%, 7% and 3%, respectively. Patients with collapsing FSGS were more likely to be black and to have nephrotic syndrome with renal impairment at presentation, compared to patients with NOS and tip variants [46]. Furthermore, globally sclerotic changes were found more commonly in the NOS variant while segmental sclerosis, tubular atrophy and interstitial fibrosis were found more commonly in collapsing FSGS [46]. At the end of 3 years follow up, 47% of patients with collapsing FSGS were in ESKD compared with 20% and 7% for the NOS and tip variants, respectively [46] (Table 14.3). These findings were confirmed in a study of 201 Japanese FSGS patients [47].

Integrated molecular and morphologic classification: Emerging data is recognizing the fact that FSGS and related morphologic descriptions such as diffuse mesangial sclerosis and minimal change disease are non-specific diagnoses but morphologic changes resulting from multiple injuries to the podocyte [48]. It is now proposed that these morphologic entities should be called **podocytopathies** [49]. The advantages of looking at FSGS and the other morphologic patterns as podocytopathies are (1) focusing on a cell that is central to pathogenesis and therefore a target for biochemical analysis and cellular therapy, (2) facilitating identification of other cellular lineage that may be working in concert with the podocyte to preserve the function and the integrity of the GFB, and (3) enabling clinical work-up focusing on identifying causes or risk factors for podocyte injury and therefore more informed prognosis and personalized therapy [48].

Pathogenesis

The hallmark of nephrotic syndrome is glomerular proteinuria [48]. While there are other causes of proteinuria, proteinuria in nephrotic syndrome results from leakage of protein through the glomerular filtration barrier (GFB). The GFB is composed of three layers: podocyte (glomerular epithelial cell), glomerular basement membrane, and fenestrated endothelium (Fig. 14.2) [24, 48–108]. Defects in any of the three layers can result in proteinuria [107, 108].

Hereditary and Monogenic Forms of SRNS

Over the past 20 years, investigations of inherited forms of nephrotic syndrome led to recognition of the importance of the podocyte in the pathogenesis of SRNS [24, 48–110]. The majority of

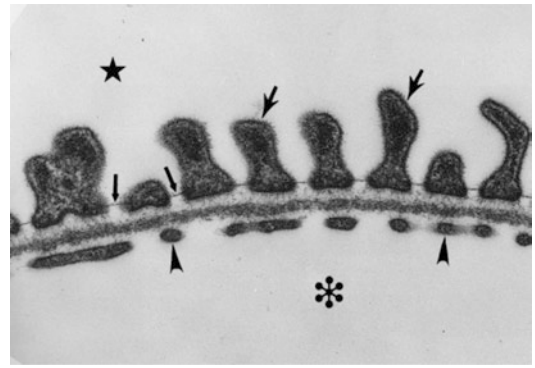

Fig. 14.2 Electron micrograph of the components of the glomerular filtration barrier. During normal glomerular filtration, plasma water is filtered from the glomerular capillary lumen (asterisk) through the fenestrated endothelial cell layer (arrowheads), then across the glomerular basement membrane (GBM) and through the slit diaphragms (small arrows) which bridge the filtration slits between adjacent podocyte foot processes (large arrows) and finally into the urinary space (star) where it enters the lumen of the proximal tubule. These podocyte foot processes are normally tall and evenly-spaced along the GBM, but during nephrotic syndrome they become spread out along the GBM, with apical displacement of the slit diaphragms. The layer of negatively-charged glycocalyx can be seen in this image as a blurry coating on the apical surfaces of the podocyte foot processes. (Adapted with permission from reference [50])

monogenic causes of SRNS affect the structure and function of the podocyte [24, 48–110]. The podocyte is a terminally differentiated epithelial cell with limited ability to regenerate [111]. The prominence of the podocyte in the pathophysiology of SRNS is highlighted by the fact that most common causes of monogenic NS are genes with preferential or selective expression in the podocyte.

In a large cohort of patients with SRNS, the top six monogenic causes of SRNS were *NPHS2* (encodes podocin), *NPHS1* (encodes nephrin), *PLCE1* (encodes phospholipase C epsilon 1), *WT-1* (encodes Wilms tumor 1), *LAMB2* (encodes laminin beta 2) and *SMARCAL* (encodes SW/SNF2 related, matrix associated, actin dependent regulator of chromatin, subfamily a-like 1) (Fig. 14.4 and Table 14.4) [112, 113]. Beyond

Table 14.4 Genetic causes of FSGS and SRNS

Gene	Protein	Mode of Inheritance
Slit diaphragm genes		
NPHS1	Nephrin	AR
NPHS2	Podocin	AR
PLCE1	Phospholipase C epsilon 1	AR
CD2AP	CD2-associated protein	AD, AR
TRPC6	Transient receptor potential channel C6	AD
CRB2	Crumbs family member 2	AR
FAT1	FAT atypical cadherin	AR
KIRREL1	kirre like nephrin family adhesion molecule 1	AR
Transcription factors and nuclear genes		
WT1	Wilm's tumor protein 1	AD
LMX1B	LIM homeobox transcription factor 1-beta	AD
SMARCL1	SMARCA-like protein	AR
NUP93	Nuclear pore complex protein 93	AR
NUP107	Nuclear pore complex protein 107	AR
NUP205	Nuclear pore complex protein 205	AR
NUP160	Nuclear pore complex protein 160	AR
NUP85	Nuclear pore complex protein 85	AR
NUP133	Nuclear pore complex protein 133	AR
XPO5	Exportin 5	AR
E2F3	E2F transcription factor	AD
NXF5	Nuclear RNA export Factor 5	X-linked recessive
PAX2	Paired box protein 2	AD
LMNA	Lamin A and C	AD
WDR73	WD repeat domain 73	AR
Cytoskeletal and membrane genes		
ACTN4	Alpha-actinin 4	AD
INF2	Inverted formin 2	AD
MYO1E	Myosin 1E	AR
MAGI2	Membrane Associated Guanylate kinase, inverted 2	AR
ANLN	Anillin actin binding protein	AD
PTPRO	Protein-tyrosine phosphatase-R O	AR
EMP2	Epithelial membrane protein 2	AR
CUBN	Cubilin	AR
PODXL	Podocalyxin	AR, AD
ARHGAP24	Rho GTPase-activating protein 24	AD
ARHGDIA	Rho GDP dissociation inhibitor alpha	AR

(continued)

Table 14.4 (continued)

Gene	Protein	Mode of Inheritance
DAAM2	Dishevelled associated activator of morphogenesis 2	AR
SYNPO	Synaptopodin	AD
SYNPO2 (Also localized to mesangial cells)	Synaptopodin 2	AR
DLC1	Deleted in liver cancer 1	AR
KANK 1/2/4	Kidney ankyrin repeat-containing protein	AR
ITSN1/2	Intersectin protein	AR
CDK20	Cyclin-dependent kinase 20	AR
NOS1AP	Nitric oxide synthase 1 adaptor protein	AR
Mitochondrial, lysosomal, metabolic, and cytosolic genes		
COQ2	Coenzyme Q2 4-hyroxybenzoate polyprenyl transferase	AR
COQ6	Coenzyme Q6 monooxygenase	AR
PDSS2	Prenyl-diphosphate synthase subunit 2	AR
ADCK4	AarF domain containing kinase 4	AR
SCARB2	Scavenger receptor class B, member 2	AR
PMM2	Phosphomannomutase 2	AR
ALG1	Asparagine-linked glycosylation 1	AR
TTC21B	Tetratricopeptide repeat protein 21B	AR
CDK20	Cyclin-dependent kinase 20	AR
CFH	Complement factor H	AR
DGKE	Diacylglycerol kinase epsilon	AR
Glomerular basement membrane genes		
LAMB2	Laminin subunit beta-2	AR
ITGB4	Integrin beta 4	AR
ITGA3	Integrin alpha 3	AR
COL4A 3/4/5	Type IV collagen alpha 3,4,5	AR, AD, X-linked
Endosomal regulator genes		
GAPVD1	GTPase Activating Protein And VPS9 Domains 1	AR
ANKFY1	Ankyrin Repeat And FYVE Domain Containing 1	AR

these top six monogenic causes of SRNS, pathogenic variants have been identified in over 60 genes in patients with SRNS (Table 14.4). Recent large cohort studies revealed that altogether 20–30% of sporadic childhood onset SRNS may be due to single gene defects [112–115]. In animal models, including transgenic mice and zebrafish, most identified single gene causes of SRNS result in podocyte dysfunction. Mechanisms of podocyte dysfunction include: (1) slit diaphragm abnormalities (*CD2AP, NPHS1, NPHS2*, and *FAT1*) (2) impaired podocyte actin cytoskeleton regulation and/or adhesion to the glomerular basement membrane (*ACTN4, ANLN, ARHGAP24, INF2, SMARCAL and TRPC6*); (3) defective podocyte differentiation (*PLCE1* and *WT1*), (4) mitochondrial dysfunction (*ADCK4*, *COQ2*, *COQ6, COQ8B* and *tRNA (Leu))* and (5) nuclear pore dysfunction (*NUP94, NUP107, NUP160*), Table 14.4 [48, 116–118].

Beyond the podocyte, pathogenic variants in genes encoding for key molecular components of the glomerular basement membrane are increasingly being recognized as monogenic causes of SRNS. These include *COL4A3* and *COL4A4*, which encode for type 4 collagen of the GBM, and *LAMA5* and *LAMB2*, forming laminin LM-521; α5β2γ1 that is a key component of the glomerular basement membrane. While *COL4A3* and *COL4A4* mutations typically present with the more classic phenotype of Alport syndrome (see Chap. 16), they may also phenocopy FSGS and present with SRNS [119, 120]. Further discussion of monogenic SRNS can be found in Chap. 15.

Common Gene Variants Associated with SRNS/FSGS

In addition to monogenic causes of SRNS, common variants in the gene encoding for apolipoprotein L1 (*APOL1*) are associated with FSGS [24, 122]. *APOL1* contributes to innate immunity and protection against *Trypanosoma*, the cause of African sleeping sickness. The APOL1 protein forms a channel that contributes to *Trypansomal* lysis. Two common variants (known as G1 [2 single nucleotide polymorphisms S342G and I384M] and G2 [a 6 base pair deletion (p.NYK388K] are common in people of West African descent and are associated with protection against resistant *Trypanosoma brucei rhodesiense* and *gambiense*. However, carriage of any combination of *APOL1* high risk genotype defined as homozygous or compound heterozygous G1/G2 genotypes: (G1/G1; G1/G2; or G2/G2) are associated with increased risk for kidney disease [123]. In children of African descent with SRNS, prevalence of *APOL1* high risk genotype may be as high as 40% [124, 125]. The mechanisms of *APOL1* related kidney disease continue to be a focus of ongoing investigations. The prevalence of high risk genotype is about 14% in African Americans, however less than 25% of individuals with these high risk genotypes will develop kidney disease suggesting that genetic and environmental second hits may be needed for phenotypic manifestations. Increased podocyte APOL1 expression with enhanced inflammatory signaling may be one such second hit [126, 127]. Other pathways implicated in APOL1 related kidney disease include podocyte lipid and mitochondrial dysfunction and alterations in ion channel functions [126, 128, 129]. Interestingly *APOL1* high risk genotype is also associated with increased susceptibility to infection related nephropathy, including HIV and COVID-19 nephropathy [130, 131].

Circulating Factors

Beyond genetic factors, a major mechanism of idiopathic SRNS is the presence of a circulating pathogenic factor or absence of factors that prevent proteinuria [132]. Evidence supporting the role of circulating factors includes the recurrence of FSGS post-transplant that is amenable to treatment with plasmapheresis and immunosuppression in some patients [133]. In addition, administration of plasma from FSGS patients alters glomerular and podocyte morphology *in vitro* [134]. Despite extensive efforts, a single circulating factor has not been identified to date. Several candidate factors have been proposed; one of these is sUPAR, the soluble urokinase receptor, which was shown to be elevated post FSGS recurrence and induced proteinuria in a mouse model of FSGS [135]. However, additional studies failed to confirm sUPAR as the circulating factor, although its role in disease progression remains the subject of ongoing investigations [133]. Other circulating factors that have been implicated include cardiotrophin-like cytokine factor-1 (CLCF-1), CD40 antibodies, and apolipoprotein A-Ib (ApoA-Ib) [133]. CLCF-1 is a cytokine that functions in B-cell stimulation. CD40 is a costimulatory protein expressed on immune cells. Elevated CLCF1 levels and anti-CD40 antibodies were identified in sera from patients with recurrent FSGS [136]. Application of CLCF1 or anti-CD40 antibodies to cultured podocytes induced actin cytoskeleton alterations [136]. ApoA-1 is a circulating component of the HDL complex; The ApolA-1b variant was identified by urine proteomics studies as increased in patients with recurrent FSGS [137].

Podocyte Endowment, Loss, Regeneration and Glomerulosclerosis

Glomerulosclerosis is the most common pathologic finding underlying SRNS. Regardless of the initial factor, podocyte damage and loss is key to development of the lesions of glomerulosclerosis [138]. The mechanisms by which podocyte damage evolves into the pathological appearance seen in FSGS have been studied extensively in murine models of FSGS [73]. The initial defect appears to be a reduction in podocyte number and the inability of podocytes to completely cover the glomerular tufts. The reduction in podocyte density causes the loss of separation between the glomerular tuft and Bowman's capsule, leading to the formation

of synechiae or adhesions between the tuft and the Bowman's capsule [73]. The perfused capillaries lacking podocytes at the site of tuft adhesion then deliver their filtrate into the interstitium instead of Bowman's space (Fig. 14.3) [73]. This misdirected filtration through capillaries lacking podocytes leads to progression of segmental injury, tubular degeneration and interstitial fibrosis [73]. Further evidence for the role of podocytopenia in the pathogenesis of FSGS was shown using a rat model of diphtheria toxin-induced podocyte depletion in which the extent of podocyte loss is regulated [74]. In this model, mild podocyte loss resulted in hypertrophy of the remaining podocytes to cover the glomerular basement membrane. However, with moderate to severe depletion FSGS and global sclerosis developed; 30–40% of podocyte loss appear to be sufficient to drive progressive glomerulosclerosis [74].

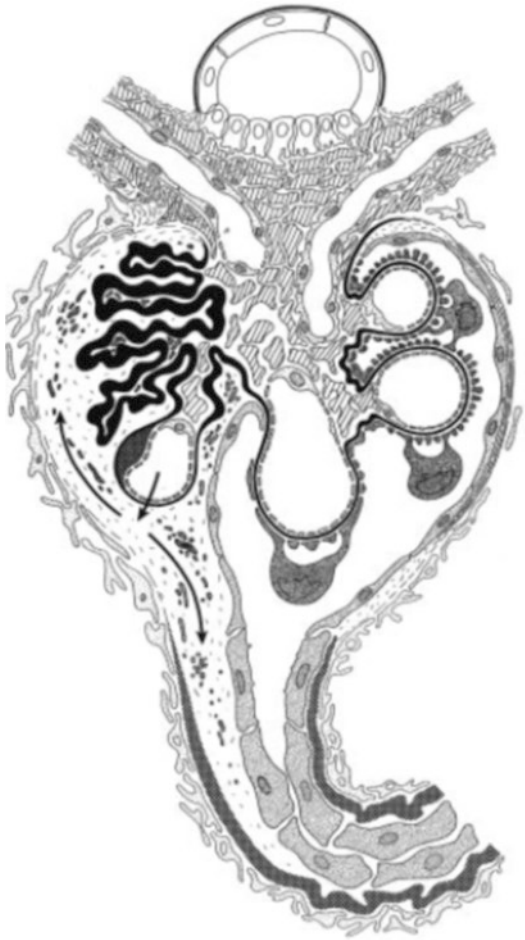

Fig. 14.3 Kriz's misdirected filtration hypothesis of evolving FSGS lesion: The glomerular basement membrane (GBM) is shown in black, podocytes are densely stippled, parietal epithelial cells are less densely stippled and interstitial as well as endothelial cells are loosely stippled, mesangial cells are hatched. The tuft adhesion contains several collapsed capillary loops. It also contains a perfused loop, which is partially hyalinized. The filtrate of this loop is delivered into a paraglomerular space that is separated from the interstitium by a layer of fibroblasts. This newly created space extends onto the outer aspect of the tubule by expanding and/or separating the tubular basement membrane from its epithelium. (Reproduced with permission from reference [73])

Diagnostic Evaluation

Patient and Family History

In patients diagnosed with SRNS, the medical history should be explored for potential secondary causes of the disease such as sickle cell disease, HIV, SLE, as well as recent hepatitis B, malaria or parvovirus B19 infections. Family history should be assessed for other family members affected by nephrotic syndrome and/or chronic kidney disease, and parental consanguinity should be checked.

Clinical Assessment

The clinical evaluation of children with SRNS should include an assessment of fluid status, as well as careful exploration of extrarenal disease features such as dysmorphic features, ambiguous genitalia, skeletal, skin, ocular, hearing and neurological abnormalities. Any abnormalities should prompt further diagnostic evaluation.

Laboratory Workup

Proteinuria should be quantitated by measuring the urinary protein:creatinine ratio (uPCR) in spot urine or 24-h protein excretion. Urine dipstick is not considered sufficient to make the diagnosis or monitor treatment responsiveness in

SRNS. Basic chemistries including serum creatinine, serum albumin, a complete blood count, a lipid profile and coagulation testing are important for estimating renal function, confirming the presence or absence of overt nephrosis, and evaluating the risk for disease complications.

SRNS patients require a diligent effort to rule out secondary disease processes. Tests for systemic autoimmune disorders, including antinuclear antibody (ANA), anti–double stranded DNA (anti-dsDNA) antibodies, ANCA, and complement C3 levels should be performed and testing for hepatitis B and C, HIV, malaria, parvovirus B19 and depending on geographic area and ethnicity, sickle cell disease, tuberculosis, and even syphilis may be indicated.

Genetic Testing

Genetic screening is emerging as a critically important clinical tool in the management of children with SRNS. Identification or exclusion of pathogenic gene variants potentially allows for (1) a rational approach to the use of immunosuppressive agents and avoidance of side effects; (2) selection of targeted therapies that may induce remission and/or delay progression to ESKD (e.g., COQ10 supplementation in patients with hereditary COQ10 deficiency; (3) prediction of clinical course and risk of post-transplant disease recurrence; (4) avoidance of kidney biopsy; and (5) genetic counseling and possible prenatal screening [139]. In view of these considerations, the IPNA SRNS guideline recommends genetic testing for all children as soon as the diagnosis of primary SRNS is established [1]. When considered later in the course of the disease, genetic screening is not indicated in patients who have responded to intensified immunosuppressive therapy and in patients with secondary SRNS.

Kidney Biopsy

Kidney biopsy allows the confirmation of a primary podocytopathy (MCD, FSGS, or DMS) and the exclusion of other differential diagnoses such as membranous nephropathy or MPGN. Biopsy is therefore indicated in all children with SRNS except in those with an established monogenic cause of SRNS, potentially in familial and/or syndromic cases, and in patients with known secondary SRNS due to infection or malignancy. Even in suspected or confirmed hereditary forms of SRNS, kidney biopsy may sometimes be indicated, particularly in patients with CKD stage 2 and higher, to grade the amount of tubular atrophy, interstitial fibrosis and glomerulosclerosis as prognostic markers [32, 33].

Management

The IPNA SRNS Clinical Practice Recommendation contains a refined algorithm for the management of SRNS in children (Fig. 14.4). We will describe and explain the rationale for the preferred therapeutic approaches along the lines of this recommendation.

Confirmation Period

When the diagnosis of SRNS is established after 4 weeks of standardized oral corticosteroid therapy, it is suggested to utilize a 2- to 3-week period to further confirm and elaborate the diagnosis before starting new immunosuppressive therapies other than steroids. During this period, genetic testing should be initiated and a kidney biopsy performed, oral prednisone therapy continued and/or three intravenous steroid pulses may be optionally performed. Importantly, renin-angiotensin system (RAS) blockade should be implemented by up-titrating an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) to full antiproteinuric efficacy. It is essential to measure proteinuria at the end of this period to avoid confounding the antiproteinuric effect of RAS blockade with that of any subsequent immunomodulatory therapies. If genetic screening reveals a monogenic form of SRNS, RAS blockade should be continued at the maximally effective dose, steroid therapy discontinued and no alternative immunosuppressive

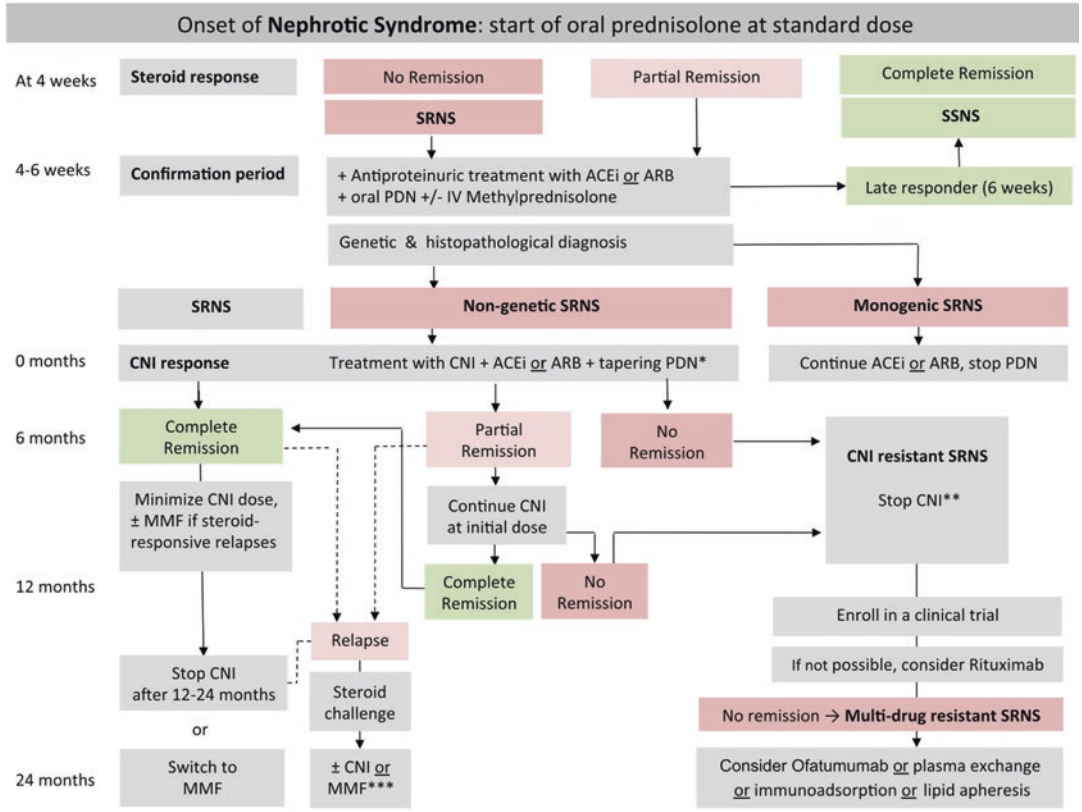

Fig. 14.4 IPNA clinical practice recommendation for management of SRNS in children (Reproduced from [1] with permission)

therapies should be started (or stopped if already started) in order to avoid a futile, potentially toxic treatment.

Therapeutic Pathway

If no genetic disorder is identified, a calcineurin inhibitor (CNI, tacrolimus or cyclosporin A) should be started, the RAS blocker continued at unchanged dose, and oral prednisone weaned over 4–5 months. The response to calcineurin inhibition should be evaluated after 6 months of treatment. If complete remission has been achieved, the patient can be classified as **CNI-responsive SRNS**. In this case, the CNI dose should be minimized and optionally supplemented by MMF. In case of persistent remission, the CNI should be stopped after 12–24 months, optionally continuing or switching to MMF monotherapy. If partial remission is achieved at 6 months, treatment should be continued for a total of 12 months. If complete remission does not occur, the CNI should be discontinued and the patient should receive the diagnosis **CNI-resistant SRNS**. In these patients, a B-cell depleting monoclonal antibody (e.g. Rituximab) can be tried. If this treatment does not yield full remission, the patient should receive the diagnosis **multidrug-resistant SRNS**. Children with CNI-resistant or multidrug-resistant SRNS are candidates for clinical trials and experimental extracorporeal rescue therapies, such as plasma exchange, immunoadsorption and lipid apheresis.

Pharmacotherapies

In the following, we describe the evidence base supporting the use of antiproteinuric and immunosuppressive pharmacotherapies in the therapeutic pathway above. It should be emphasized that due to the rarity of the disease, randomized trial evidence for any of the drugs is scarce or absent. Generally, the apparent efficacy of all of the immunosuppressive agents is lower in SRNS compared to those with frequently relapsing or steroid sensitive nephrotic syndrome [140, 141]. However, most previous treatment studies did not identify and exclude patients with genetic forms of SRNS who are highly unlikely to respond to immunosuppressive treatment. Since these cases comprise up to 30% of SRNS cases, most trial results must be considered substantially confounded. Finally, spontaneous remission of SRNS can occur and may explain some occasional responses of largely ineffective therapies.

RAS Blockade

Several controlled and non-controlled clinical studies have demonstrated the antiproteinuric efficacy of ACE inhibitors and angiotensin-receptor blockers (ARBs) in adults and children with glomerular diseases [142–148]. The antiproteinuric effects of ACEIs and ARBs are due to their ability to reduce glomerular capillary plasma flow rate, decrease transcapillary hydraulic pressure, and alter the permselectivity of the glomerular filtration barrier. On average, RAS blockers reduce proteinuria by approximately 30% in children with SRNS [149], although even complete remissions have been reported [150]. ACEIs and ARBS should be administered at the maximum approved and tolerated dosages since proteinuria reduction is dose dependent. However, the use of RAS blockers may increase the risk for AKI in patients with intravascular volume depletion [151]. Combined treatment with ACEi and ARBs is not recommended as it increases the risk for adverse events [152]. ACE inhibitor therapy may lead to a phenomenon known as 'aldosterone escape' with a long-term increase in plasma aldosterone levels. The addition of aldosterone blockade with ACE inhibition reduces urine protein excretion by 30–58% in patients with both diabetic and non-diabetic proteinuria [153]. The long-term safety of this form of combined RAS blockade remains to be elucidated.

Calcineurin Inhibition

Several randomized trials have suggested improved complete or partial remission rates in patients with SRNS when treated with cyclosporine compared with placebo, no treatment, or intravenous methylprednisolone pulses (~75% vs. 22%) [154–158].

Out of 433 children with primary SRNS in the PodoNet registry treated with CsA or Tacrolimus in the year following diagnosis, 30% achieved complete and 19% partial remission [159]. CsA and tacrolimus show similar efficacy in inducing remission [160].

In addition to immunomodulation, antiproteinuric effects of the calcineurin inhibitors may in part be mediated by hemodynamic effects that reduce renal blood flow [161]. In addition, calcineurin inhibitors may reduce proteinuria by inhibition of calcineurin-mediated degradation of synaptopodin and stabilization of the podocyte actin cytoskeleton [162, 163].

While CNIs are generally not recommended in patients with reduced eGFR due to their nephrotoxic effects, their use may be justified in SRNS patients with CKD and no other option for disease control [162]. CsA and tacrolimus have similar nephrotoxicity, but gingival hyperplasia and hypertrichosis are more prevalent with CSA and glucose intolerance occurs more frequently with tacrolimus (Table 14.5).

Mycophenolate-Mofetil (MMF)

The efficacy of MMF in inducing or maintaining remission in children with SRNS has not been demonstrated against placebo or no treatment in randomized clinical trials.

Table 14.5 Treatment options for steroid resistant nephrotic syndrome

Drug	Efficacy Evidence	Toxicity	Benefit
ACE Inhibitors/ ARBs	Good	May lower eGFR Teratogenicity	Slowed progression of CKD
IV Corticosteroids	Good	Weight gain Hypertension Glucose intolerance Hyperlipidemia Striae	May ensure achieving therapeutic drug levels.
Cyclosporine	Good	Nephrotoxicity Hypertension Gingival hyperplasia	May only require low dose
Tacrolimus	Good	Nephrotoxicity Hypertension Glucose Intolerance	May only require low dose
Mycophenolate Mofetil	Mixed	GI intolerance Teratogenicity	No nephrotoxicity
Rituximab	Mixed	Infections Hypogammaglobulinemia Long-term effects unknown	May enable discontinuation of daily immunosuppressive medications

In a multicenter randomized trial of 192 children and young adults with steroid resistant FSGS, MMF in combination with dexamethasone was similarly effective as CsA (33% vs. 46%] and the rates of adverse events were similar [163]. MMF was less effective than tacrolimus in maintaining remission (45% vs. 90%) [164]. In the PodoNet registry, MMF therapy was associated with complete or partial remission in only 4 of 24 cases (17%) [159]. CNI/MMF co-treatment yielded full remission in four and partial remission in 10 of 34 patients, i.e. not different from CNI monotherapy [159].

B-Cell Depleting Agents

Rituximab is a chimeric monoclonal antibody directed against CD20. Rituximab-induced B-lymphocyte depletion may act on proteinuria in nephrotic syndrome by inducing regulatory T lymphocytes, as has been observed in patients with lupus nephritis [164]. Experimental findings suggest that Rituximab may also directly protect podocytes by stabilizing the podocyte cytoskeleton and preventing apoptosis through an interaction with the sphingomyelin phosphodiesterase acid-like 3b protein that is expressed in podocytes [165].

In a retrospective review of 33 patients with SRNS treated with two to four doses of intravenous rituximab, and followed for ≥12 months, 9 (27%) patients with SRNS showed complete remission, 7 (21%) had partial remission, and 17 (52%) had no response after 6 months of observation [166]. A similar response pattern was reported from a randomized trial in Korean children and in 66 children followed in the PodoNet registry [159, 167]. However, in an open-label, controlled trial that randomized 31 children with SRNS to either receive rituximab or continue prednisone and calcineurin inhibitors, no subjects in either arm achieved significant reduction of proteinuria. Hence, the efficacy of rituximab in the treatment of SRNS is unclear and there is a need for a randomized control trial [168].

More recently, case reports suggested that Ofatumumab (OFA), a fully humanized anti-CD20 monoclonal antibody, may be useful in inducing remission in patients with hypersensitivity reaction to rituximab or in children who are resistant to multiple immunomodulators including rituximab [169, 170]. However, a recent low-dose ofatumumab randomized placebo-controlled trial was prematurely terminated because the first 13 patients (25% of targeted

enrollment) did not respond to the treatment [171]. Meanwhile, Ofatumumab has been withdrawn from the market.

Newer Therapies and Ongoing Clinical Trials

For children with CNI-resistant SRNS, consideration for entry into clinical trials evaluating novel therapies on the horizon should be strongly considered.

The FONT2 study (Novel Therapies in the Treatment of Resistant FSGS) aimed to compare novel therapies in patients with FSGS that have failed standard immunosuppressive therapies with conservative management [172]. In vitro studies have documented decreases in glomerular permeability when isolated glomeruli were incubated with galactose-containing sera [173]. The proposed mechanism suggests galactose may bind a glomerular permeability factor thus rendering it ineffective. Another proposed mechanism for proteinuria in patients with SRNS implicate Tumor Necrosis Factor-alpha (TNF-α), a pro-inflammatory cytokine that is important in the recruitment of leukocytes to the site of glomerular injury, induction of cytokines and growth factors, generation of oxygen radicals with increased glomerular endothelial cell permeability, cytotoxicity, and induction of apoptosis. In the FONT2 trial, 21 patients were randomized to one of the three study arms to receive the TNF-α antibody **adalimumab, galactose,** or standard medical therapy for 26 weeks. None of the adalimumab-treated subjects achieved the primary outcome of ≥50% reduction in proteinuria, whereas two subjects in the galactose and two in the standard medical therapy arm had a 50% reduction in proteinuria without a decline in eGFR, suggesting that some patients may benefit from treatment with oral galactose [173].

ACTH (Adrenocorticotropic Hormone) was the therapy of choice for children with nephrotic syndrome in the 1950s before corticosteroids became widely available [174, 175]. The development of an ACTH analog has made this therapy available once again as a second line agent in the treatment of SRNS. The largest published series to date by Hogan et.al reports a cumulative remission rate of 29% in 24 patients with SRNS and SDNS treated with subcutaneous ACTH [176]. In a recent systematic review that included 98 patients with FSGS, 42% achieved remission following treatment with ACTH. However, it should be noted that the population comprised frequently relapsing, steroid dependent, and steroid resistant patients [177].

Sparsentan, a dual endothelin and ARB was found to decrease proteinuria by 45% vs. 19% in a phase 2 randomized double-blind trial of those treated only with irbesartan with no differences in serious adverse events between the groups [178]. A phase-3 multicenter trial is in progress.

A small post-approval study for **low-density lipoprotein (LDL) apheresis** for children with CNI-resistant SRNS has shown increased treatment responsiveness and improved or stable eGFR over the follow-up period, it should be noted that this was not a randomized control trial [179].

Common variants in APOL1 gene termed G1 and G2 account for a significant proportion of the excess risk of progressive kidney disease in individuals of recent African ancestry with an estimated lifetime risk of kidney disease in 15% in those with a high-risk genotype [180, 181]. Novel **APOL1 inhibitors** are currently in clinical development. A Phase II trial investigating the APOL1 inhibitor VX-147 has started recruitment [182]. Antisense oligonucleotides are short, synthetic, modified chains of nucleotides that bind to the target mRNA, inducing its degradation and preventing the mRNA from being translated into a detrimental protein product. Preclinical studies with antisense oligonucleotides are showing promise as a novel therapeutic approach for APOL1 associated nephropathy [183, 184].

Treatment of Monogenic SRNS

Increased availability of genetic testing for children with SRNS has enabled the development of more personalized treatment decisions. The clinical value of genetic testing in SRNS is illustrated by our ability to make decisions on the intensity and duration of immunosuppression, as well as pre- and post-transplant management based on genomic findings [8, 9, 185, 186]. Generally, >95% of patients with monogenic SRNS will not respond to treatment with immunomodulatory agents [121, 159], and hence it is recommended to withdraw immunosuppressive therapy. RAS inhibitors should be administered at maximally effective and tolerated doses. There are anecdotal reports of individuals with mutations in *WT1, PLCE1, and MYO1E* who achieved partial or complete remission when exposed to immunosuppressive treatments, in particular calcineurin inhibitors [64, 69, 121, 187]. It is unclear if these responses, which are usually transient, are due to immunomodulatory effects or rather to their effects on stabilizing the podocyte cytoskeleton.

One of the promises of the genomic revolution is that identification of genetic causes of SRNS will lead to identification of specific and non-toxic therapeutic agents. Along this line, some monogenic causes of SRNS have given clue to novel therapeutic agents. An intriguing example is Coenzyme Q10 (CoQ10) supplementation in patients with mutations in genes encoding for components of the CoQ10 synthase complex (COQ6, COQ2, COQ8B) [67, 139, 188]. Other examples are Vitamin B12 supplementation in patients with mutations in the cubilin (CUBN) gene, and targeting of *TRPC6*, *TRPC5*, and RhoGTPases for potential treatment of some form of monogenic SRNS [62, 189, 190].

Long-Term Prognosis of SRNS

Most studies examining the long-term prognostic factors for kidney survival in patients with SRNS were from small cohorts, frequently single-center studies, with short term follow up, and often incomplete datasets [191, 192]. A multi-center study of 75 children with FSGS reported that within 5 years from the diagnosis of FSGS, 21% of children had developed ESKD, 23% had developed CKD, and 37% had developed persistent proteinuria, while only 11% remained in remission [30]. The most comprehensive study to date has been performed by the PodoNet consortium [159]. In this study, clinical, treatment-related, genetic, and laboratory data including kidney biopsy findings were collected from >1300 patients with SRNS with an average follow up time of about 4 years but extending up to 15 years. The overall proportion of SRNS patients with preserved kidney function was 74%, 58%, and 48% at 5, 10, and 15 years respectively. Risk factors for disease progression included lacking responsiveness to intensified immunosuppression (IIS) protocols, genetic disease, and FSGS on biopsy. Ten-year ESKD-free survival rates were 94%, 72%, and 43% in patients with complete remission, partial remission, and IIS resistance respectively (Fig. 14.5). After 15 years, kidney function was preserved in 96% of IIS-responsive, 53% of multidrug resistant and 17% of genetic SRNS patients. The histopathological findings at time of diagnosis were also predictive of outcome but less so than IIS responsiveness and genetic disease status, with 37% 15-year ESKD-free survival in patients with FSGS as compared to 79% in those with minimal change disease. The predictive value of IIS responsiveness and genetic status was independent of the histopathological diagnosis.

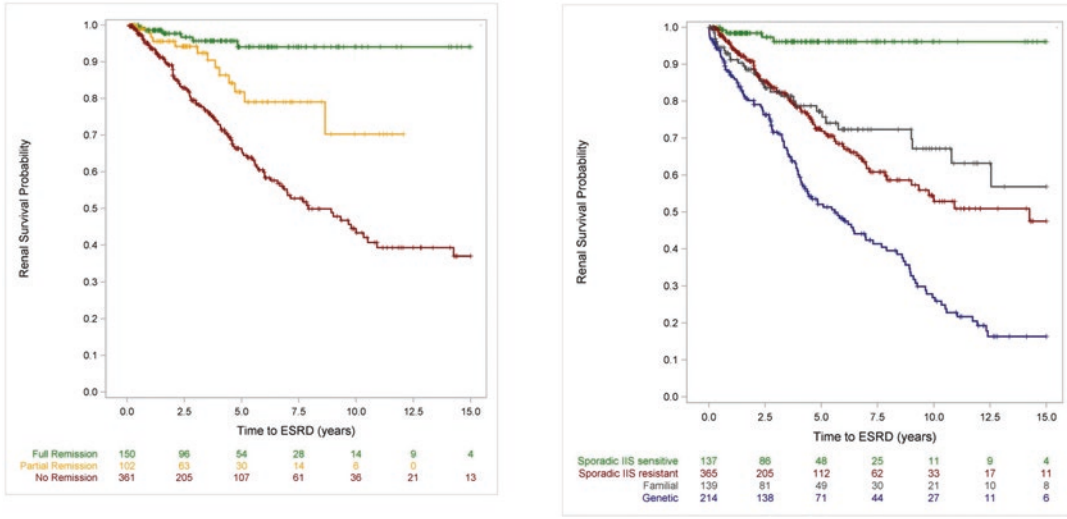

Fig. 14.5 ESKD-free survival in children with SRNS followed in PodoNet Registry. *Left panel:* Survival according to responsiveness to calcineurin inhibitor therapy (green; full remission, yellow; partial remission, red; no remission). *Right panel***:** ESKD-free survival according to responsiveness to intensified immunosuppression (IIS) and genetic familial disease status (green: IIS responsive sporadic SRNS, red: multidrug resistant SRNS; grey: familial SRNS without identified genetic cause; blue: genetic SRNS). Reproduced from [159] with permission

Complications of Nephrotic Syndrome

Hyperlipidemia

Hyperlipidemia is a common clinical finding in children with nephrotic syndrome. The characteristic lipid profile includes elevations in total plasma cholesterol, very low-density lipoprotein (VLDL), and low-density lipoprotein (LDL) cholesterol, triglyceride, lipoprotein A, as well as variable alterations (more typically decreased) in high-density lipoprotein (HDL) cholesterol [193, 194]. While the hyperlipidemia in children with SSNS is often transient and usually returns to normal after remission, children with SRNS refractory to therapy often have sustained hyperlipidemia. Such chronic hyperlipidemia has been associated with an increased risk for cardiovascular complications and progressive glomerular damage in adults [195–199]. Based on this, pharmacologic treatment of hyperlipidemia in children with refractory nephrotic syndrome may both reduce the risk for cardiovascular complications later in life and reduce the risk of disease progression.

The potential usefulness of hydroxymethylglutaryl CoA (HMG CoA) reductase inhibitors (statins) in children with SRNS has been reported in a few uncontrolled trials. One study reported a 41% reduction in cholesterol and 44% reduction in triglyceride levels within 6 months of treatment [200]. A second study found significant reductions within 2–4 months in total cholesterol (40%), LDL cholesterol (44%), and triglyceride (33%) levels, but no significant changes in HDL cholesterol levels [201]. Treatment was found to be very safe in these studies, with no associated adverse clinical or laboratory events. Although the long-term safety of statins in children has not yet been established, these medications appear to be generally well tolerated in adults with nephrotic syndrome, with only minor side effects such as asymptomatic increases in liver enzymes, creatine kinase, and rarely diarrhea [202].

Thrombosis

The risk of thromboembolic events in children with nephrotic syndrome is estimated to be 1.8–5% with a higher risk reported in children with SRNS compared with those with SSNS [203, 204]. Factors contributing to an increased risk of thrombosis during nephrotic syndrome include abnormalities of the coagulation cascade, such as increased clotting factor synthesis in the liver (factors I, II, V, VII, VIII, X, and XIII) and loss of coagulation inhibitors such as anti-thrombin III in the urine. Other prothrombotic risks present in these children include increased platelet aggregability (and sometimes thrombocytosis), hyperviscosity resulting from increased fibrinogen levels, hyperlipidemia, prolonged immobilization, and the use of diuretics. In one series, the use of diuretics was the major iatrogenic risk factor for thrombosis [204].

The majority of episodes of thrombosis are venous in origin. The most common sites for thrombosis are the deep leg veins, ileofemoral veins, and the inferior vena cava. In addition, use of central venous catheters can further increase the risk of thrombosis. Renal vein thrombosis (RVT) can also occur and may manifest as gross hematuria with or without acute renal failure. Development of these features should prompt either renal Doppler ultrasonography or magnetic resonance angiography to rule out RVT. Pulmonary embolism is another important complication that may be fatal if not recognized early. Rarely, cerebral venous thrombosis, most commonly in the sagittal sinus, has also been reported [205]. In addition to imaging studies, development of thrombosis should prompt an evaluation for possible inherited hypercoagulable states.

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

Nutrition

Several recommendations supported by observational data exist regarding nutrition in pediatric patients with nephrotic syndrome. Specifically, children with nephrotic syndrome and edema should be evaluated for malabsorption and subsequent malnutrition due to bowel wall edema. In edematous patients, long-term sodium restriction is appropriate with a maximum goal of approximately 2500 mg/day. In patients with persistent hyperlipidemia due to inability to control nephrosis, a low saturated fat diet should be instituted with their HMG CoA-reductase inhibitor. Protein intake should only be supplemented at the Recommended Daily Allowance (RDA) [206]. Although it would appear intuitive that states of excess urinary protein loss should warrant increase dietary protein intake, several studies have successfully challenged this notion. In nephrotic rats, augmentation of dietary protein was found to stimulate albumin synthesis by increasing albumin mRNA content in the liver, but there was also a notable increase in glomerular permeability and subsequently increased albuminuria [207]. No change in albumin synthesis was noted with dietary protein restriction in this model or in nephrotic patients.

Immunization

Children with nephrotic syndrome are at increased risk for infections, including but not limited to streptococcus and staphylococcal species due to urinary losses of IgG, loss of factors crucial for regulation of the alternative complement pathway, and large fluid collections prone to breeding bacteria. Live-viral vaccines (rotavirus vaccine, varicella vaccine, measles, mumps, and rubella vaccine, and the live-attenuated influenza vaccine) are generally recommended to be avoided in CKD patients who are immunosuppressed and therefore should be avoided in patients that are frankly nephrotic and/or currently receiving immunosuppressive therapy. Anti-pneumococcal vacci-

nation using the 23-valent polysaccharide vaccine (PPSV23) is recommended for children with nephrotic syndrome [208]. Due to the low immunogenicity of this vaccine in children less than 2 years of age, the 13-valent polysaccharide pneumococcal vaccine (PCV13) is recommended in this age group, followed by supplemental immunization with PPSV23 over the age of 2 years at least 8 weeks after the final dose of PCV13. A second dose of PPSV23 should be repeated in 5 years.

Kidney Transplantation

Recurrence of nephrotic syndrome may occur in up to 30% in the first kidney allograft of patients with ESKD due to FSGS and approach 100% in those who have a history of prior allograft loss due to FSGS. The risk post-transplant recurrence appears to be mainly determined by the underlying disease etiology, i.e. immune-mediated vs. genetic. Whereas patients with secondary steroid resistance have about 80% risk of recurrence, the risk appears to be close to zero in patients with genetic forms of SRNS [7–9, 139]. Hence, genetic testing should be considered mandatory in all children with SRNS considered for kidney transplantation.

In addition, young age, mesangial proliferation in the native kidneys, rapid progression to ESKD, pre-transplant bilateral nephrectomy, and white ethnicity have been associated with increased risk of recurrence post-transplant [209, 210]. The histologic variant type of FSGS does not appear to be predictive of disease recurrence. There is a higher risk of recurrence in living donor transplant pediatric recipients; however, the reduced risk of rejection and a lower immunosuppression in living-related transplants may overcome the deleterious effect of recurrent glomerulonephritis [211].

The management of recurrent FSGS disease remains controversial and results from observational reports vary. The implementation of plasma exchange is supported in part by the idea of a circulating permeability factor. Up to 70% of children with recurrent FSGS treated with repeated plasma exchanges and/or rituximab may achieve at least a partial remission.

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