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Originals

Nephrotic syndrome: From theory to treatment

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A B S T R A C T

Objective: to broaden knowledge of the disease as well as of the genetic advances which have marked its prognosis, and unify the new therapeutic options in the treatment of difficult patients. Approaching the nephrotic child with an updated perspective will decrease acute mortality, complications, and the progression to chronic kidney disease and renal replacement therapy.

Methods: This is a narrative review using systematic review tools. The Pubmed, Embase, Proquest, Cochrane Library and LILACS databases were searched using the following MeSH terms in English: ***edema, glomerulopathy, glucocorticoids, hyperlipidemia, hypoalbuminemia, podocytes and proteinuria***; and, based on DeCS, in Spanish: ***edema, glomerulopatía, glucocorticoide, hiperlipidemia, hipoalbuminemia, podocitos and proteinuria***, with no limit on publication dates. The search was performed from 2016 to 2018 and included clinical practice guidelines, systematic reviews, metanalyses and topical reviews which evaluated the definition, causes, clinical signs and symptoms, diagnosis, and treatment of nephrotic syndrome (NS) in children. The Delphi method was used to evaluate quality, supported by the authors' experience, to unify the treatment and implementation of initial management of NS in Colombia by pediatricians and pediatric nephrologists.

Results: Nephrotic syndrome is the most common manifestation of noninflammatory primary glomerulopathies in children, and is characterized by massive proteinuria with secondary profound hypoalbuminemia, hyperlipidemia and edema. Primary NS constituted 15 to 30% of the causes of end stage renal disease (ESRD) between 1960 and 2010 in Colombia. Its peak onset is during school age, with a 2:1 male:female ratio. There are new biological treatment alternatives, and comprehensive, interdisciplinary treatment is key in improving the final outcome in children.

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Introduction

Nephrotic syndrome (NS), characterized by massive proteinuria, hypoalbuminemia, generalized edema and hypercholesterolemia, is the most common clinical manifestation of noninflammatory primary glomerulopathies. This group of diseases also includes minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS) and membranous glomerulopathy (MG) (1-7), which supplied 15 to 30% of the pediatric end stage renal disease (ESRD) etiology in Colombia between 1960 and 2010 (8,9).

The incidence of NS is variable in Holland, Libya, France, England, New Zealand, Australia, United States and Japan (10,11) and has increased in England (12). In 2015, there were an estimated two to seven cases per 100,000 children, with a prevalence of 16 per 100,000 children. It was more common in African Americans, Arabs and Asians, with a 2:1 preponderance of males (10, 13). Its peak onset is during the preschool years, followed by school age (10, 12), similar to what was seen in Medellín, Colombia at four years between 1960 and 2010 (14). Given the differences in the treatment instated by pediatricians and pediatric nephrologists with regard to doses and the length of the first treatment, the presence of adverse effects associated with immunosuppression (15), as well as the final outcome (which varies by medical center and according to the available human resources) (16), this review was carried out in an effort to broaden knowledge of the disease, unifying the genetic advances which have defined its prognosis, as well as new therapeutic options in the management of difficult patients.

Etiology and classification

Nephrotic syndrome is classified by age of onset as congenital (under three months), infantile (four to twelve months) and childhood (> 12 months). According to etiology, it is classified as primary or genetic, idiopathic vs. secondary, and according to its response to treatment as sensitive or resistant to steroids (17). Patients who do not improve despite treatment with steroids, immunosuppressants and biological agents, or who are difficult to treat, require genetic assessment. These include congenital NS; age of onset less than 12 months of age; family history of NS; prenatal diagnosis; decreased kidney function/kidney failure due to NS; kidney biopsy results showing diffuse mesangial sclerosis or FSGS; association with other syndromes such as Denys-Drash, Frasier, Pierson, nail-patella and Alport; association with systemic diseases such as thrombotic microangiopathy, Fabry and von Gierke disease, fish-eye disease, Norum-Gjone disease, mitochondrial diseases, and Schimke immunoosseus dysplasia; as well as to predict the risk of post-transplant proteinuria (18-22). The genes which should be included in the genetic panel are: ACTN4, ARHGDIA, CD2AP, COQ8B, DGKE, EMP2, INF2, LAMB2, NPHS1, NPHS2, NUP93, NUP107, NUP205, PLCE1, PTPRO, TRPC6 and WT1. The available genetic tests can be found online (23).

Table 1 describes the genes implicated thus far in the etiology of primary NS through structural protein disruption (taken from OMIN).

Pathophysiology

The glomerular filtration barrier is composed of the fenestrated endothelium, glomerular basement membrane (GBM), and the filtration diaphragm between the podocyte foot processes and the visceral epithelial cells which cover the outer surface of the glomerular capillary loops´ basement membranes. Molecules in this filtration barrier connect the cytoskeleton with the extracellular matrix, and their alteration causes proteinuria (30-33).

Histopathology

The four types of non-inflammatory primary glomerulopathies manifesting with NS are:

Minimal change disease: this is the main cause of NS in 70-90% of children over one year old, with no glomerular histological changes on light microscopy and generally negative immunofluorescence (34, 35).

Focal segmental glomerulosclerosis: segmental or global sclerosis with cortical, tubular, interstitial and vascular involvement and podocyte necrosis (36, 37).

Membranous glomerulopathy: less frequent in children (38), described as thickening of the GBM due to subepithelial IgG deposition, usually IgG4 and C3 (39, 40).

Membranoproliferative glomerulonephritis: this type is uncommon, presenting mesangial proliferation, glomerular vessel changes, hypocomplementemia and subendothelial or intramembranous immune complex or C3 deposition (41).

There are two theories regarding the pathophysiology of NS: 1. Underfill and Overfill

Table 1. Genes implicated in the etiology of NS

Genetic causes of nephrotic syndrome						
Gene	**Location**	**Protein**	**Inheritance**	**Disease**	**Clinical expression**	**Phenotype**
NPHS1	19q13.12	Nephrin	AR	MCD, FSGS, DMP.	Massive prenatal proteinuria	NS Finnish
NPHS2	1q25-q31	Podocin	AR	MCD, FSGS, DMP.	Infantile proteinuria, hyperlipidemia, edema and hypoproteinemia which progresses to ESRD in the first to second decade of life	SRNS
PLCE1	10q23.33	Phospholipase C	AR	DMS, FSGS	Rapid progression to ESRD	NS, type 3
WT1	11p13	DNA-zinc finger binding protein	AD	DMS, FSGS	Early ESRD some pubertal/ sexual differention disorders	NS, type 4
			AD, SM	DMS	Sexual differentiation disorder, Wilms tumor and ESRD in early childhood	Denys Drash
			AD, SM	FSGS	Sexual differentiation disorder and ESRD in early childhood	Frasier
LAMB2	3p21.31	Laminin	AR	FSGS	Very early onset ESRD, onset of edema in utero, and myopia, nystagmus and strabismus	NS, type 5
				DMS	CNS, microcoria, ciliary and pupillary muscle hypoplasia	Pierson syndrome
PTPRO	12p12.3	Glomerular epithelial protein 1	AR	Pedicel fusion	Massive proteinuria; require kidney transplantation	NS, type 6
DGKE	17q22	Diacylglycerol kinase epsilon	AR	MPGN	Proteinuria in the first decade and ESRD	NS, type 7
ARHGDIA	17q25.3	Rho-GDP dissociation inhibitor	AR	Pedicel fusion	Massive proteinuria with progressive kidney failure	NS, type 8
COQ8B	19q13.2	Ubiquinone	AR	FSGS, collapsing FSGS	Proteinuria between 10-20 years of age, pericardial effusion	NS, type 9
EMP2	16p13.13	Epithelial membrane protein 2	AR	Pedicel fusion	Proteinuria	NS, type 10
NUP107	12q15	Nucleoporin	AR	FSGS MCD	ESRD in the first decade of life, kidney transplant	NS, type 11
NUP93	16q13	Nucleoporin	AR	FSGS	ESRD in the first years of life	NS, type 12
NUP205	7q33	Nucleoporin	AR	FSGS	ESRD	NS, type 13
CD2AP	6p12.3	Intercellular junction, actin regulator		FSGS	Proteinuria	FSGS
ACTN4	19q13.2	Cytoskeleton	AD	FSGS	Proteinuria and decreased renal function	FSGS
INF2	14q32.33	Actin polymerization protein		FSGS	Moderate proteinuria progressing to ESRD in adolescents, microsopic hematuria and HTN	FSGS
TRPC6	11q22.1	Calcium ion channel	AD	FSGS	Proteinuria	FSGS

Acronyms: AD: autosomal dominant; AR: autosomal recessive; MCD: minimal change disease; DMS: diffuse mesangial sclerosis; FSGS: focal segmental glomerulosclerosis; MPGN: membranoproliferative glomerulonephritis; HTN: arterial hypertension; SM: somatic mutation; DMP: diffuse mesangial proliferation; NS: nephrotic syndrome; CNS: congenital nephrotic syndrome; SRNS: steroid resistant nephrotic syndrome.

Table 2. Causes of secondary NS (4, 17, 24-29)

Secondary causes of NS in pediatrics

A.	Systemic diseases
I.	Cyanotic congenital heart disease
II.	Renal artery stenosis
III.	Hypertensive kidney disease
IV.	Vasculitis: SLE, Henoch Schönlein purpura, polyarteritis nodosa, RA, HUS, Granulomatosis with polyangiitis
V.	Amyloidosis
VI.	Diabetes Mellitus
VII.	Cholesterol embolism
B.	Infectious diseases
I.	Ventriculoatrial or ventriculoperitoneal shunt infection
II.	Viral: HIV, HBV, HCV, parvovirus B19,
III.	Tuberculosis
IV.	Parasitosis: Malaria, ehrlichiosis, schistosomiasis
V.	Episodes of respiratory infections, infectious diarrhea and/or urinary infections.
C.	NS secondary to neoplasms
I.	Lymphoblastic leukemia
II.	Acute myeloid leukemia
III.	Wilms tumor
IV.	Hodgkin´s lymphoma
V.	Thymoma
D.	Transplants
I.	Graft vs. host disease
II.	Bone marrow transplant
E.	Allergies
I.	Atopy
II.	Bee or wasp stings
F.	NS secondary to medications
I.	Antibiotics
II.	Antinflamatorios no esteroideos
III.	Immunouppressants: gold salts, D- penicillamine, methotrexate, ifosfamide, sulfasalazine, interferon α, β, γ, calcineu-rin inhibitors
IV.	Lithium
V.	Captopril
VI.	Immunizations
VII.	Bisphosphanates
VIII.	Antineoplastics: arabinosides, anthracyclines, alkylating agents, antiangiogenesis agents, tyrosine kinase inhibitors.
IX.	GM-CSF
X.	Iodinated contrast media
G.	NS secondary to toxin exposure
I.	Mercury
II.	Lead
III.	Cadmium
IV.	Arsenic
V.	Heroin
VI.	Cocaine

Acronyms: RA: rheumatoid arthritis; GM-CSF: granulocyte-monocyte colony-stimulating factor; SLE: systemic lupus erythematosus; NS: nephrotic syndrome; HUS: hemolytic uremic syndrome; STORCH: syphilis, toxoplasmosis, rubeola, cytomegalovirus, herpes I and II; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus.

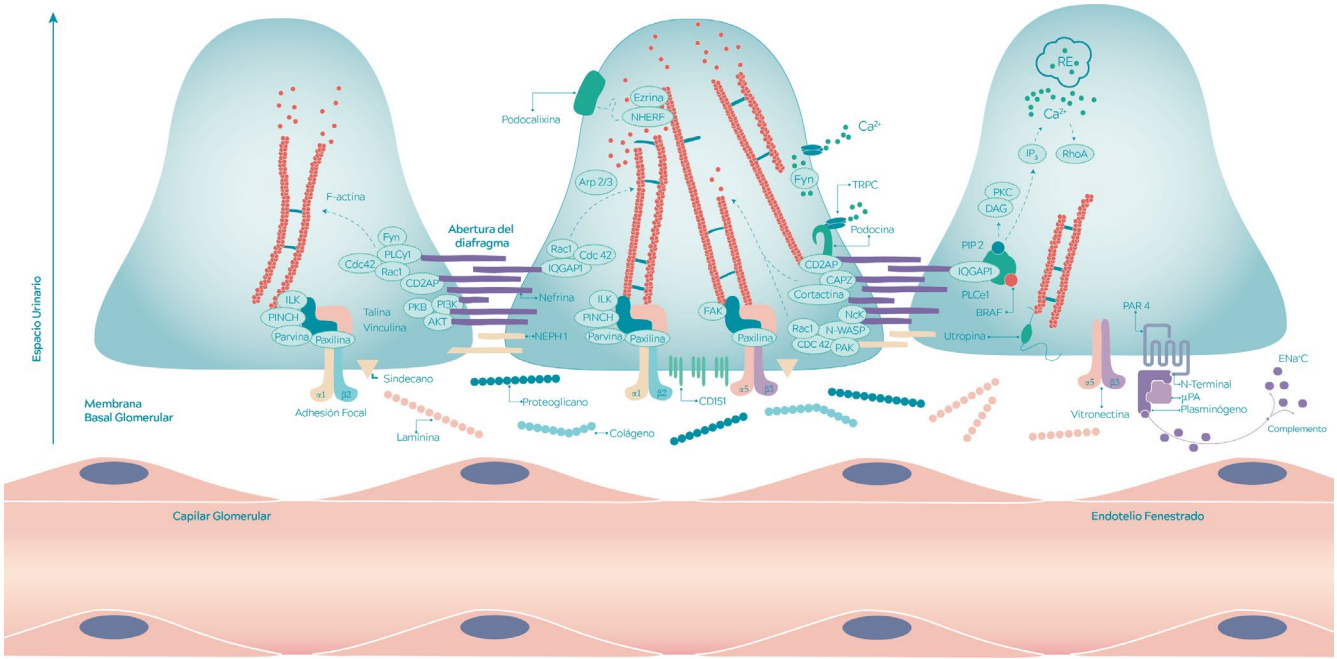


Figure 1. Structure of the glomerular basement membrane and the integrative signaling pathways and interactions between the podocytes, diaphragm and cytoskeleton. Source: taken and adapted from (33)

Acronyms: integrin-linked kinase (ILK); focal adhesion kinase (FAK); α-actinin-4; nephrin protein type 1 (NEPH1); transient receptor potential channel 6 (TRPC6); CD2-associated protein (CD2AP); transforming protein RhoA (RhoA); Ras-related C3 botulinum toxin substrate 1 (Rac1); cell division control protein 42 homolog (Cdc42); integrin α3 (α3); actin-related protein 2/3 (Arp2/3); integrin α1 (α1); serine/threonine-protein kinase B-raf (BRAF); calcium (Ca2+); F – actin capping protein (CAPZ); diacylglycerol (DAG); endoplasmic reticulum (ER); actin filaments (F-actin); tyrosine-protein kinase Fyn (Fyn); inositol 1,4,5-triphosphate (IP3); IQ motif containing GTPase activating protein 1 (IQGAP1); Na + / H + exchanger regulatory factor (NHERF); neural Wiskott-Aldrich syndrome protein (N-WASP); p21-activated kinases (PAK); particularly interesting new Cys-His protein 1 (PINCH); phosphatidylinositol biphosphate (PIP2); phosphoinositide 3-kinase (PI3K); protein kinase C (PKC); phospholipase Cα1 (PLCα1); phospholipase Cα1 (PLCα1); plasminogen activator receptor (PAR-4); urokinase plasminogen activator receptor (uPAR); collecting duct epithelial sodium channel (ENa+C).

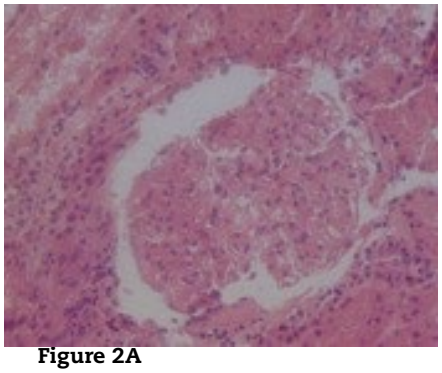


Figure 2A

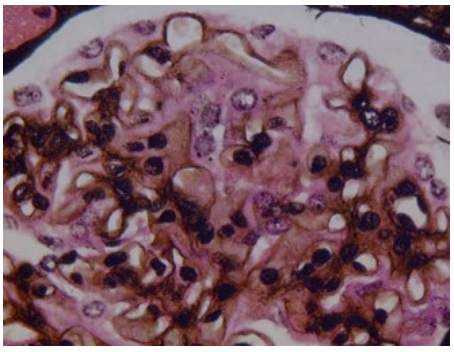
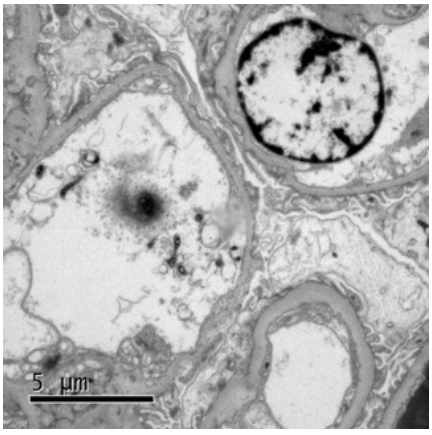


Figure 2B



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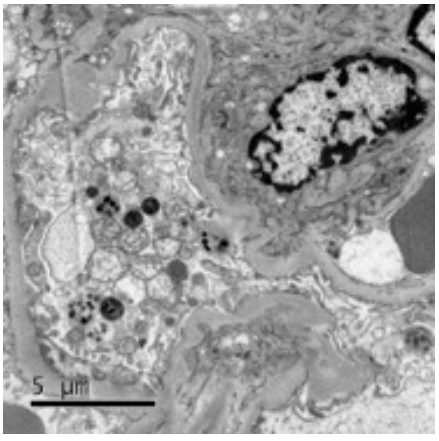

Figure 2D

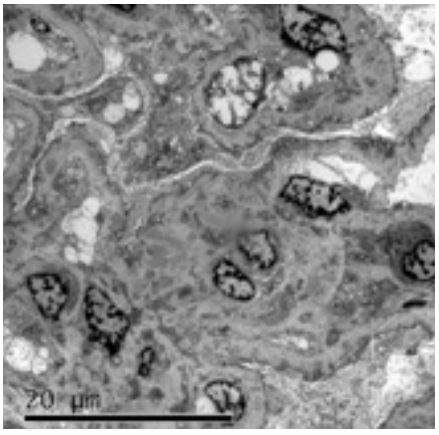

Figure 2E

Figure 2A. Hematoxylin and eosin 40 x. Uniform thickening of the glomerular capillary basement membrane and mesangial expansion; 2B. Methenamine silver stain 100x. Note the irregularity of the membranes, mostly in the form of "craters", which indicates the presence of subepithelial and intramembranous depositions (yellow arrow). These are characteristic defects of membranous glomerulopathies; 2C. Transmission electron microscopy: the observed changes show pedicel irregularity and segmental fusion (blue arrows). In this case, it is accompanied by irregularity in the thickness of the membranes, in which the yellow lines (somewhat thin) may be compared with the green ones. The podocyte damage may be chronic and podocyte failure may conclude in the thinning of some segments and not of others; 2D. Transmission electron microscopy: fused podocytes in most of the pictured loops, expanded mesangial matrix and electron-dense deposits corresponding to IgA (blue arrows); 2E. Transmission electron microscopy: the blue arrows indicate the mesangial areas in which electron-dense deposits corresponding to immune complexes are seen. Mesangial expansion can also be seen. The yellow arrows show the subepithelial and intramembranous deposits which correspond to the crater images seen with methenamine silver staining. Source: Department of pathological anatomy, Fundación Santa Fe de Bogotá. Original images taken by and property of Dr. Adriana Flórez, FSFB institutional pathologist.

Underfill is the onset of nephrotic edema with sodium retention due to proteinuria and hypoproteinemia, decreased intravascular oncotic pressure, water passage from the plasma to the interstitium and sodium retention commensurate to the intravascular volume depletion, with increased renin and aldosterone.

Overfill is a primary sodium excretion defect, possibly in the distal convoluted tubules, due to atrial natriuretic peptide resistance, interstitial inflammation, vasoconstriction, increased sodium reabsorption and edema.

These two mechanisms are not mutually exclusive; they depend on the NS stage, degree of hypoproteinemia and oncotic pressure (42). Another related mechanism is sodium retention by epithelial sodium channels (ENaC) in the collecting duct increased by plasminogen, tubular plasmin and urokinase plasminogen activator receptors (the latter responsible, together with integrin αvα3, for podocyte anchoring), evidenced by podocyturia (43, 44).

Clinical signs

Ascites, hepatomegaly, abdominal pain and diarrhea appear in the acute or relapse phases of the disease, caused by intestinal edema. The physical exam should consider the pathophysiology and individual clinical signs of each child, with a special emphasis in the initial exam on vital signs, degree of edema, volemic state and a search for infection (2, 45). Primary peritonitis, subcutaneous cellulitis, pneumonia, meningitis and sepsis should be ruled out, given the urinary loss of properdin which increases encapsulated bacterial infections (especially Streptococcus pneumoniae) (46), not forgetting complications due to hypercoagulability secondary to decreased antithrombin III and proteins C and S, as well as thrombocytosis and platelet hyperactivity (47).

The initial study should include a complete blood count; BUN; creatinine; electrolytes; lipid profile; total and differential protein levels; urinalysis; C3; C4; ANA; anti-DNA; hepatitis B surface antigen; hepatitis C and HIV IgM antibodies; syphilis serology; proteins C, S and antithrombin III; immunoglobulins; and 24-hour proteinuria or urine protein/creatinine ratio in an isolated sample; along with autoimmune and infectious markers, as applicable (44). Prior to beginning steroids, a tuberculin test must be performed (due to the risk of disseminated tuberculosis in patients positive for this mycobacterium), and albendazole must be administered for three days to eliminate parasites and avoid infestation.

Diagnostic criteria (2)

1. Edema.
2. Nephrotic proteinuria: >40 mg/m2/hour; >300 mg/dl, 3+ on a test strip. In children without bladder control: urine protein/creatinine ratio >2 mg/mg [>200 mg/mmol] in an isolated sample. A 24-hour estimate could also be made using the following formula: UP/UCr (isolated) * 0.63 = gr/m2/day.
3. Hypoalbuminemia: ≤ 2.5 gr/dl.
4. Hyperlipidemia: Total cholesterol > 200 mg/dl and triglycerides > 200 mg/dl.

Indications for kidney biopsy (2, 48)

The kidney biopsy should be of a sufficient size and quantity to allow all the components of the uriniferous tubule to be seen. At a minimum, it should contain 20 glomeruli to assess the activity or chronicity of the renal impairment.

- **In SSNS:**

– Late failure to respond to steroids.
– High index of suspicion of an underlying disease.
– Decreased kidney function in patients receiving calcineurin inhibitors.
– Kidney injury, macroscopic hematuria and/or arterial hypertension.
– Age under one year (or greater than 10).
– Familial nephrotic syndrome.
– Steroid resistant NS.
– C3 hypocomplementemia.

- **Throughout its progression:**

– Unfavorable response to treatment, late steroid resistance.
– Prior to prescribing ant-calcineurins or extended treatment (>24 months) with anticalcineurins which requires ruling out natural progression of the renal disease vs. drug toxicity.
– In NS with frequent relapses or steroid dependency, the need for kidney biopsy must be individually assessed.
– Following six weeks of treatment for SRNS or at the onset of nephritis, since it is a predictor of FSGS NS and maximizes the diagnosis of this etiology, with limited use in MCD.

Specific treatment

Corticosteroids are indicated in all patients at the first sign of disease. Between 80 and 90% of children with NS are steroid sensitive (SSNS), and there is also some evidence of the usefulness of short-burst steroids in preventing relapses during upper respiratory infections (1, 2, 3, 49). The Kidney Disease Improving Global Outcomes (KDIGO) recommendation for SSNS is oral prednisolone or prednisone for at least 12 weeks. The recommendation is to give oral prednisolone in a single daily dose, beginning at 60 mg/m2/day or 2 mg/kg/day, with a maximum of 60 mg/day. It is recommended that the daily dose be administered for at least four to six weeks, followed by alternate-day doses of 40 mg/m^2 or 1.5 mg/kg (maximum 40 mg every other day) for two to five months with steroid tapering (2,3).

In infrequently relapsing SSNS, oral prednisolone is recommended in a single daily dose of 60 mg/m2/day or 2 mg/kg/day, maximum 60 mg/day, until complete remission has been achieved for at least three days. Once remission is achieved, single daily or alternate-day doses of 40 mg/m2/dose or 1.5 mg/kg/dose, with a maximum of 40 mg daily or on alternate days, are recommended for at least four weeks (3). Meanwhile, the recommended treatment for frequently relapsing nephrotic syndrome (FRNS) and steroid dependent nephrotic syndrome (SDNS) after achieving remission for three days is to continue alternate-day steroids for at least three months. If alternate-day steroids do not achieve remission, daily dosing is recommended, monitoring the adverse effects of steroid therapy, such as decreased vertebral bone mineralization (50, 51, 52). Dual-energy x-ray absorptiometry is recommended. Vitamin D and its serum transport proteins are lost in the urine, especially if steroids are also being used, since these drugs damage bone structure and cause osteopenia, osteoporosis and the risk of fractures, among other things. Personalized vitamin D and calcium supplementation is recommended while monitoring blood levels, given the risk of hypercalciuria and urolithiasis (53).

Daily or alternate-day steroids are recommended in children with SDNS or FRNS during respiratory tract infections or other infectious episodes, to decrease the risk of relapse (3, 49). In the event of adverse effects from the steroids, steroid sparing agents are recommended, such as those described in Table 3.

Symptomatic treatment

Diet: The current recommendations for sodium and protein intake according to the scientific committee of the Japanese Society of Pediatric Nephrology are:

- Diuretics:

The administration of loop diuretics is indicated when there is an increased volume of distribution and oliguria related to capillary leakage due to hypoalbuminemia (73). Their use is only indicated in debilitating edema and with prior correction of hypovolemia, since they foster acute kidney injury and thromboembolic complications, as shown in Table 5.

Albumin infusion is not indicated in nephrotic syndrome except in severe nephrotic syndrome with severe underfilling (some Minimal Change or primary FSGS cases), in which a very low oncotic pressure leads to hypoperfusion-induced acute renal failure. In this scenario, albumin infusion with furosemide is temporarily indicated to decrease edemas and improve tissue oxygenation, along with concomitant immunosuppression. Some of the indications available in the literature are: (74-77):

- Decreased effective intravascular volume
- Pleural effusion
- Genital edema
- Ascites
- Anasarca
- Hepatorenal syndrome
- Spontaneous bacterial peritonitis
- Hypovolemic hyponatremia
- Hepatic cirrhosis
- Diuretic-refractory edema

Albumin is available in 5% and 25% solutions, both containing 130-160 mEq/L; the dosing in children is 0.5-1 gr/kg/dose IV, infused over 24 hours for patient stability and repeated every 24 to 48 hrs., or as needed. It is contraindicated in heart failure or severe anemia; its rapid infusion may cause fluid overload; hypersensitivity reactions may occur; it may cause a rapid rise in plasma sodium. The 25% solution is contraindicated in premature infants due to the risk of intraventricular hemorrhage. If dilution is required, 5% dextrose in distilled water or saline solution is used; dilution with sterile water should be avoided (78).

Anticoagulants

To prevent thromboembolic complications, it is advisable to avoid bedrest, correct hypovolemia, and eliminate unnecessary arterial or deep vein sticks, central catheters or IV infusions. The therapeutic objectives are: to improve symptoms; stop the progression and stabilize the clot to avoid longitudinal spread involving additional venous segments or expansion of the circumference; prevent PTE; reopen the occluded vessel; decrease post-thrombotic sequelae and avoid cardiac arrest (79, 80) in patients with a high thrombotic risk (anasarca, previous thromboembolism, steroid resistance, prolonged steroid treatment and membranous GN), especially if there is concurrent hypovolemia or prolonged immobility. The presence of any of the following abnormalities justifies anticoagulant treatment: hypoalbuminemia <2 g/dl, fibrinogen >6 g/l, antithrombin III <70 %, or D-dimers >1,000 ng/ml. Objective: INR between 2 and 3 until an albumin >2 g/dl is reached (2, 34).

Low molecular weight heparin is the treatment of choice for deep vein thrombosis (DVT) and PTE due to its direct targeting of activated factor X with less action on factor II (thrombin) compared to unfractionated heparin. The other advantages of low molecular weight heparin over unfractionated heparin are: more predictable bioavailability due to dose-independent excretion; a longer-lasting effect allowing a lower administration frequency with less need for monitoring (which is important in children with poor venous access); and a lower rate of heparin-induced thrombocytopenia and osteoporosis (79, 80). There are two: enoxaparin and dalteparin. Most pediatric studies have been done on enoxaparin,

Table 3. Advantages and disadvantages of immunosuppressant medications

Agent	Dose	Mechanism of action	Monitoring and indication
Cyclophosphamide	ID 2.0-2.5 mg/kg (max 100 mg/kg/dose), every day for 8-12 weeks. Max cumulative dose according to KDIGO: 168 mg/kg, and according to Japan: 300 mg/m2.	Alkylating agent	Hematological, gonad dysfunction. SDNS (54)
Chlorambucil	0.1-0.2 mg/kg/D for eight weeks. Maximum dose: 11.2 mg/kg.	Alkylating agent	Hematological SDNS
Levamisole	2-2.5 mg, for 6 to 12 months, maximum 24 months (55).	Stimulates Th1 with decreased Th2, induced transcription of Il-18 (56).	Infections and hematological SDNS
Cyclosporine	2.5-5 mg/kg/day, divided in two doses adjusted by serum levels according to KDIGO.	Inhibits Il-2, Th1 and Th2, APC and B lymphocyte Ab production (57).	Nephrotoxic: serum levels two hours after administration (C2 levels) (57). Cosmetic side effects; Risk of arteriolar hyalinosis (58). SRNS
Tacrolimus	0.1 – 0.25 mg/kg/day divided in two doses, according to serum levels.	Inhibits calcineurin (11, 59)	Nephrotoxic Risk of diabetes mellitus SRNS
Mycophenolate mofetil	600 -1,200 mg/m2/day or 24-36 mg/kg/day (maximum dose 2 gr/day).	Inhibits inosine monophosphate dehydrogenase (60).	Hematological; Gout SRNS
Rituximab	ID SDNS and FRNS: 375 mg/m2 (11).	Anti CD20 and reduces CD80 expression (61, 62, 63).	Cytopenias, pulmonary fibrosis, hypoproteinemia, multifocal leukoencephalopathy, pneumocystis pneumonia, ulcerative colitis, allergic reactions, fulminant hepatitis and myocarditis (61, 62, 63). Refractory NS especially SDNS, less in SRNS.
Abatacept	10 mg/kg.	Inhibits B7-1 (CD80) and CD86 (64, 65, 66).	Infections. Refractory NS.
Adalimumab	24 mg/m2 subcutaneously every 14 days. (Maximum dose: 40 mg).	Human anti-TNF alpha IgG monoclonal antibody.	Edema, fatigue, infection, headache, cough, digestive symptoms (67). Refractory NS.
Ofatumumab	300 mg/1.73 m2. Maximum dose 2,000 mg/1.73 m2, diluted in 1 bag of normal saline.	Human anti-CD20 monoclonal antibody (68).	Hypersensitivity, sore throat, cough, bronchospasm and dyspnea (69, 70, 71). Refractory NS.

Abbreviations: CS: corticosteroids; ID: initial dose; MCD: minimal change disease; FSGS: focal segmental glomerulosclerosis; NS: nephrotic syndrome; SDNS: steroid-dependent nephrotic syndrome; SSNS: steroid-sensitive nephrotic syndrome; SD SSNS: steroid-dependent steroid-sensitive nephrotic syndrome; FRSSNS: frequently relapsing steroid-sensitive nephrotic syndrome; FRNS: frequently relapsing nephrotic syndrome.

Table 4. Diet recommendations in nephrotic syndrome

Age (years)	Boys		Girls	
	Sodium gr/day	Protein gr/day	Sodium gr/day	Protein gr/day
1-2	<4.0	15	<4.0	15
3-5	<5.0	20	<5.0	20
6-7	<6.0	25	<6.0	25
8-9	<7.0	30	<7.0	30
10-11	<8.0	35	<7.5	35
12-14	<9.0	40	<7.5	40
15-17	<9.0	45	<7.5	45

Source: adapted and translated from (72).

Table 5. Available diuretics

Diuretic agent	Dose	Interval(hours)	Route
Furosemide	Neonates: 1 mg/kg/day	12-24	IV/PO
	Infants: 1-4 mg/kg/day	6-12	PO
	Children: 1-2 mg/kg/day	6-12	IV
	Following the IV admin. of a 1-2 mg/kg dose Maximum 0.1-0.4 mg/kg/hour		IV
Hydrochlorothiazide	Infants: 1-2 mg/kg/day	12-24	PO
Spironolactone	Premature (<32 weeks): 1mg/kg/day	24	PO
	Term: 1-2 mg/kg/day	12	PO
	Infants/children: 1-3 mg/kg/day	6-12	PO

Source: adapted and translated from (73). Acronyms: IV: Intravenous; PO: Oral.

whose only disadvantage is subcutaneous (SC) administration, which could be problematic in some children (79, 80). In addition, there is insufficient pediatric evidence assessing the use of alternative anticoagulants such as direct thrombin inhibitors (lepirudin, argatroban and bivalirudin) and selective factor Xa inhibitors (fondaparinux and idraparinux) (79). The initial enoxaparin dose is: for children < 3 months 1.7 mg/kg SC every 12 hours; from 3 months to 2 years 1.2 mg/kg SC every 12 hrs., for children > 2 years 1 mg/kg SC every 12 hrs., and, in obese children, 0.8 mg/kg SC every 12 hrs.. The maximum dose is 170 mg, the therapeutic objective is an anti-Xa between 0.5-1U/ml 4-6 hours post administration (81, 82) and its anticoagulant effect is reversed with protamine (79, 80, 81). Subsequent treatment involves vitamin K antagonists for three months or until the underlying cause of secondary PTE has resolved, while treatment for idiopathic PTE is for six to 12 months (81, 82). The warfarin dose is 0.2 mg/kg/day (maximum 10 mg). When an international normalized ratio (INR) of two is achieved on two consecutive days, heparin is discontinued, as long as heparin and warfarin have maintained a therapeutic INR for five days, given the pharmacological overlapping between the two medications (79, 80, 81, 82), keeping in mind that children with mechanical valves require an INR of 2.5-3.5 (79).

The indications for thrombolysis are: obstructive arterial thrombosis, risk of organ or limb loss, superior vena cava syndrome due to thrombosis, bilateral renal vein thrombosis, massive or heparin resistant PTE and instability of the child, venous sinus thrombosis with progressive neurological deterioration, a large atrial thrombus, and congenital heart disease with an obstructed shunt. Meanwhile, relative indications include inferior vena cava thrombosis or acute obstructive ileofemoral thrombosis, as well as compression syndromes: May-Thurner syndrome and Paget-Schroetter syndrome (79, 83). Its contraindications are: active bleeding, general surgery in the previous 10 days, invasive procedures in the previous three days, convulsions in the last 48 hours, hypertension, risk of bleeding in critical zones and neurosurgery, ischemia, bleeding or neurotrauma in the last 30 days, inability to achieve a platelet count >75,000 and inability to maintain fibrinogen >100 mg/dl. The dose of tissue plasminogen activator (rt-PA) is 0.1-0.5 mg/kg/hour for 6 to 48 hours, monitoring D-dimer and fibrinogen. In case of bleeding, cryoprecipitate is administered at 1 U/5 kg (79, 80, 82, 84, 85). The indications for thrombectomy or embolectomy are PTE, when thrombolysis is contraindicated and there is insufficient time for effective anticoagulation. Its risks are blood vessel puncture, thromboembolic migration or thromboembolic pulmonary hypertension (84). The dose of antiagreggants such as acetylsalicylic acid is between 1 and 5 mg/kg/day to prevent thrombosis.

Hypolipidemic agents

Children and adolescents with NS, proteinuria and chronic kidney disease on dialysis or post-kidney transplant have accelerated atherosclerosis due to abnormal lipid metabolism and atherogenic risk factors (86). There are two types of vascular disease: the usual atherosclerotic disease which develops in the intima, and atherosclerotic disease with calcification of the media, generally known as Mönckeberg´s disease (87). This accelerated atherosclerosis also affects the renal vascular system and may contribute to deteriorated renal function (88). In children with ESRD of any cause on dialysis, medial calcification of the coronary arteries has been noted at an early age, caused by calcium and phosphorus metabolism disorders, inflammation, uremic toxins and volume overload (87). Impaired kidney function is a cardiovascular risk factor; this cardiovascular risk and risk of premature death increases when the GFR drops below 60 ml/min/1.73. Individualized lifestyle changes, including a diet low in saturated fat and exercise, are recommended for these patients (87).

According to the National Blood, Heart and Lung Institute (NBHLI), certain conditions and risk factors are involved in considering hypolipidemic treatment: a family history of acute myocardial infarction; angina; coronary artery bypass; sudden death in a parent, grandparent, uncle or aunt (male <55 years and female <65 years); HTN treated with antihypertensives; obesity; type 1 and 2 diabetes mellitus; chronic kidney disease; end stage renal disease; post-kidney transplantation; orthotopic heart transplantation; Kawasaki disease with aneurysms; heterozygous familial hypercholesterolemia; chronic inflammatory diseases (SLE and juvenile rheumatoid arthritis); NS and HIV (89). To consider the need to begin medi-

cation, two fasting lipid profile measurements must be taken, with a two week but no greater than three-month interval between measurements (90). The pleiotropic effects of statins are highlighted: decreased inflammation; immunomodulation; decreased endothelial and smooth muscle proliferation, which reduces cardiovascular risk in children; and data from adult studies cannot be extrapolated to children (91, 92).

Hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor

Inhibits cholesterol synthesis in the liver and increases the expression of hepatic LDL receptors and serum high density lipoprotein (HDL) levels, while decreasing low density lipoprotein (LDL) and triglycerides. Its adverse effects include myopathy, hepatotoxicity and rhabdomyolysis. The pediatric doses are: simvastatin 10-40 mg/day; lovastatin 10-40 mg/day; atorvastatin 10-20 mg/day and pravastatin 20-40 mg/day.

Overweight during NS remission is related to steroid duration and dosage, with comorbidities like hyperlipidemia and arterial hypertension (93, 94). The higher the proteinuria, the more difficult it is to control arterial pressure (95). Arterial hypertension (HTN) due to hypervolemia, as well as hyperlipidemia, confer cardiovascular risk, added to premature endothelial dysfunction/atherogenesis (96), and thus antihypertensive control is required. The available antihypertensives are as follows (97):

Vaccination

A. Live vaccines should be administered at least four weeks prior to beginning immunosuppression and they should not be given within two weeks of beginning immunosuppression. Live attenuated vaccines should be given at least two weeks before beginning immunosuppressive treatment (98).

B. KDIGO considers live vaccines (measles, rubeola, mumps, varicella, rotavirus and oral polio) to be contraindicated in immunosuppressed children or those receiving cytotoxic treatment: defer live vaccines until prednisolone is < 1 mg/kg/day (< 20 mg/day) or < 2 mg/kg/dose on alternate days (< 40 mg/dose); > 3 months after the last dose of cyclophosphamide or chlorambucil and > 4 weeks after the last dose of calcineurin inhibitors or mycophenolate (2).

C. Immunosuppression reduces the response to vaccines (99, 100); however, this is not a contraindication for inactivated (dead) vaccines (100). It is recommended that immunosuppressed children have antibody titers measured 4-6 weeks after vaccination to assess the immune response and schedule new immunizations (100).

D. The hepatitis B vaccine should be administered to all those who have not been vaccinated or immunized.

E. Immunization against encapsulated bacteria, including Haemophilus influenzae, Streptococcus pneumoniae and Neisseria meningitidis, should be given, especially if it has not been previously given.

F. Pneumococcal vaccine:

- Unvaccinated up to two years old: 2-4 doses of the 13-valent conjugate (or at least the 7-valent).
- Unvaccinated between two and five years old: two doses of the available conjugate with a four to eight-week interval between doses, followed eight weeks later by a dose of 23-valent polysaccharide vaccine.
- Children over five years old receive a single 23-valent polysaccharide dose. Repeat vaccination every five years should be considered for children with active NS.

G. Seasonal influenza vaccines are administered to the patient and his/her family to reduce relapses and morbidity.

H. The varicella vaccine is administered in two doses, separated by a one to three-month interval.

I. The oral poliomyelitis (OPV) vaccine should be deferred in patients and their siblings unless they are in stable remission, without immunosuppressants, or they can be isolated from the vaccinated family members.

Conclusions

1. Children with NS need interdisciplinary care aimed at decreasing the progression of renal disease requiring renal replacement, acute complications and sequelae.
2. A genetic etiology should be ruled out in patients who do not respond to steroid, immunosuppressant or biological treatment.
3. The diagnosis and follow up of children with NS con tribute to the secondary prevention of disease and treatment complications such as osteoporosis, dys lipidemia, arterial hypertension, thromboembolism, progression to end-stage renal disease with dialysis, multiple organ dysfunction and death. Keeping in mind all the available treatment options including antihypertensives, hypolipidemics, antiaggregants, anticoagulation and thrombolysis.
4. Steroids are the first line treatment for NS. Children on this treatment should be followed and their side effects monitored, such as osteoporosis, with its respective calcium and vitamin D supplementation.
5. Vaccination of children with NS is essential for preventing infections due to the disease itself or secondary to the treatment´s immunosuppression.

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Table 6. Antihypertensive medications

Antihypertensive	Dose	Interval (hours)	Route of administration
Angiotensin converting enzyme inhibitors			
Captopril	Infants: 0.3 mg-2.5mg/kg/day	8-12	Oral
	Children and adolescents: 0.3-6 mg/kg/day	8-12	Oral
Enalapril	0.1-0.5 mg/kg/day	12	Oral
	5-10µg/kg/dose	8-24	Intravenous
Lisinopril	Children: ID: 0.07-0.1 mg/kg/day	24	Oral
	<0.5-0.6 mg/kg/day		
Angiotensin receptor blockers			
Losartan	ID: 0.5 mg/kg/day. Not to exceed 12.5-25 mg/day.	24	Oral
	Up to: 1.4 mg/kg/day not to exceed 150 mg/day.		
Valsartan	Children 1-5 years old: 0.4-3.4 mg kg/day	24	Oral
	6-16 years: ID: 1.3 mg/kg/day. ≤ 2.7 mg/kg/day		Oral
Beta blockers			
Metoprolol	Children: ID: 0.1-0.25 mg/kg/dose, every 12 hours. Not to exceed 12.5-25 mg, up to a maximum dose of 1-2 mg/kg/dose every 12 hours. Not to exceed 100 mg.		Oral
Carvedilol	Children: ID: 0.1 mg/kg/day every 12 hours, not to exceed 3.125 mg, up to a maximum daily dose of 0.8-1 mg/kg/day. Not to exceed 25 mg.		Oral

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