ERKNet
The European Rare Kidney Disease Reference Network

ESPN/ERKNet
Educational Webinars on Pediatric Nephrology
& Rare Kidney Diseases : November 3, 2020

european society for paediatric nephrology

Steroid Resistant Nephrotic Syndrome

Update from the IPNA Guidelines

Part 1: Diagnosis and initial evaluation

IPNA International Pediatric Nephrology Association
GREAT CARE FOR LITTLE KIDNEYS. EVERYWHERE

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Bambino Gesù
OSPEDALE PEDIATRICO

De Ægritudinibus Infantium

Cornelius Roelans de Mechlinia (1450-1525)

zuccaro et succo cirulli cū pauco capillorē et zuccaro t
ptatur zirupo acetoso ossacara sirupo violarū sirupo
nenufarino sirupo iulep cum aqua ordei ¶ In quo/
dam libello contra idem ficinuens puero febricitanti fi/
at tale emplastrū ¶ Rx ordeum excoriatum ai viola ali
quantulum coctinā et ipsam farinam distempera cum
lucco absinthi malue et plantaginis et umbilici vene/
rio et fac emplastrū et sup furculā pectoris pone.

¶ Quinagesimaprima egritudo purroni est inflatio
todus corporis purroni ¶ Auicenna quarti tercia trac
tatu primo capitulo xi.

Inflationes accidunt secundum duos modos
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cirurgie tractatu primo capitulo undecimo ait ¶ In
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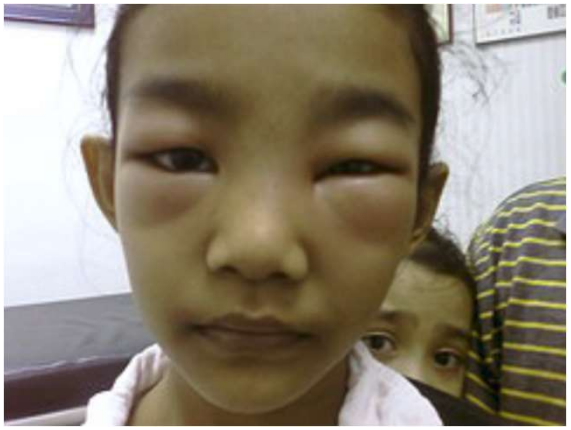
ri et carnē quā nō est vera cutis Inflatiōes aut fiūt ex huiusmodi
magis grossis nō prohibentibus veram cutem penetrare Aggregā/
tor consilio opinionis inflationes ego in pleuritidem est semo
ni que fit ex aquositate grossa vel ventositate ad cutis

"La quinquesimaprima egritudo purroni est inflatio todus corporis purroni"

"The fifty-first disease of children is the swelling of their entire body"

Idiopathic nephrotic syndrome in children



Steroid-sensitive NS
75-90%

Steroid-resistant NS
10-25%

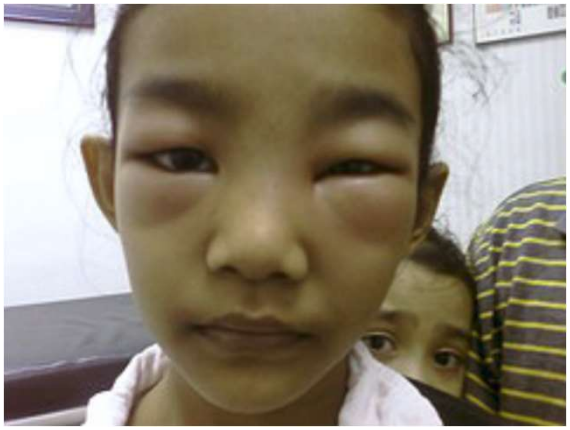
Multiple Relapses
60-80%

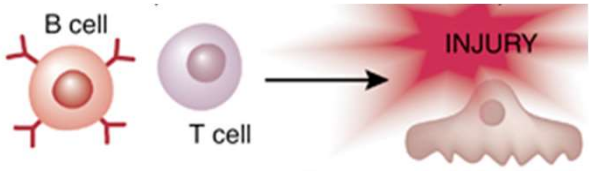
ESKD and Renal Tx **30-70%**

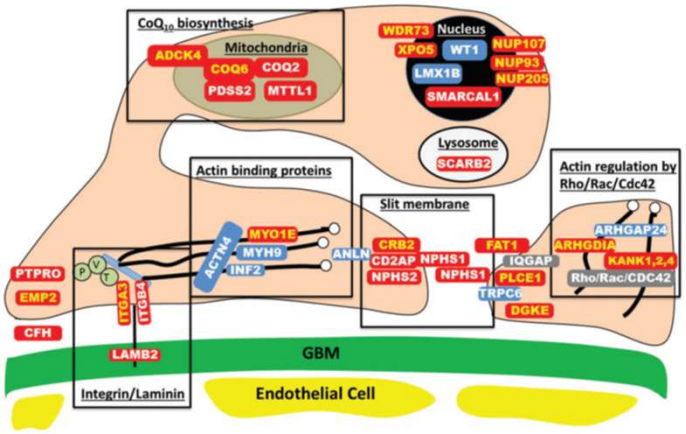
Steroid resistant nephrotic syndrome in children

Monogenic/familial

Immune-mediated







Lovric et al, Nephrol Dial Transpl 2016

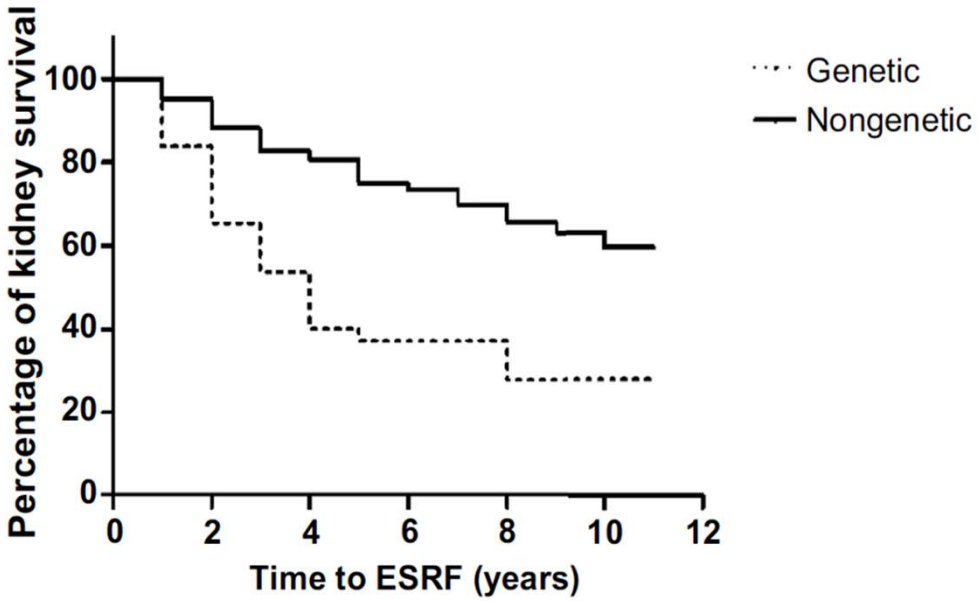
Table 1. Partial List of Proposed Humoral Mediators of Glomerular Permeability in Idiopathic Nephrotic Syndromes

Candidate Factor	Major Findings	Example References
Permeability factors from T cells	Stimulation of T cells from nephrotic individuals releases substance(s) that induce vascular permeability in guinea pigs; secreted products of a T-cell hybridoma from MCD individual induces proteinuria when injected into rats	11, 22
Hemopexin	Present in normal and MCD plasma; proteinuria after injection into rats with decreased nephron expression in rat glomeruli	23-25
IL-13	Overexpression in rats produces features of nephrotic syndrome without histologic changes	26
CLC-1	Present in FSGS plasma; induces permeability in isolated glomeruli; decreases nephron expression ex vivo and in vitro	27
Angptl4	Induced in multiple rodent proteinuric models; podocyte transgenic rats develop proteinuria	27
suPAR	Induced in FSGS, but not MCD, patient sera; transgenic mice develop FSGS and proteinuria	6

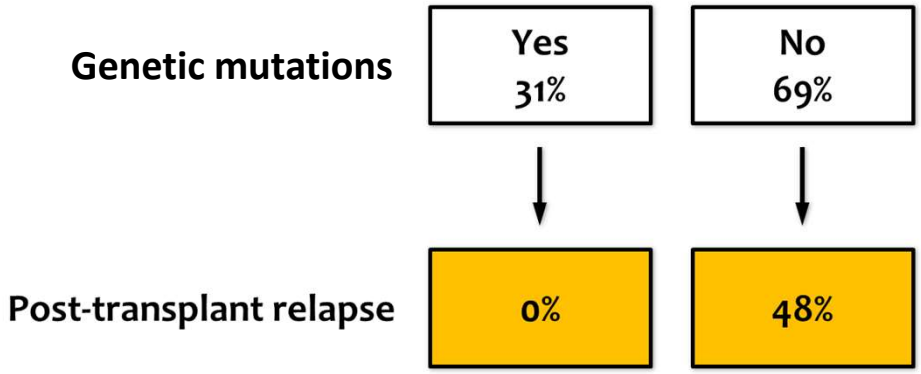
Note: Other proposed mediators include vascular endothelial growth factor, heparinase, sialidase, and C-mip (intracellular protein).

Parikh et al, AJKD 2011

Genetic vs. Immune-mediated forms of primary SRNS



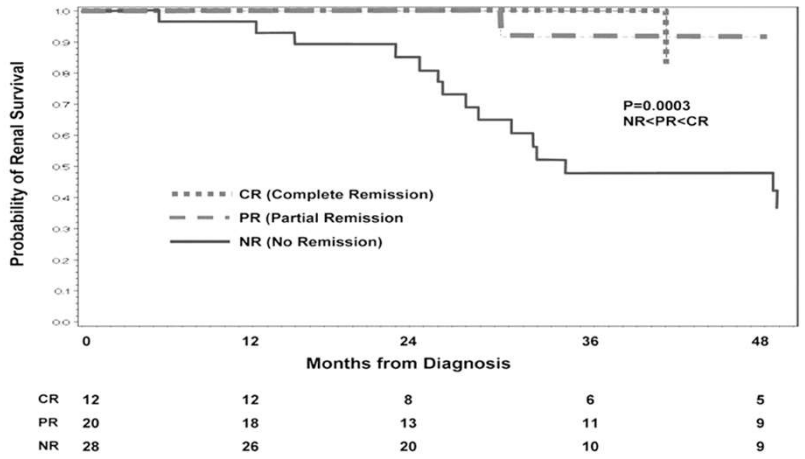
Bierzynska et al, Kidney Int 2017



Adapted from Puckelwartz and Schnaper, Kidney Int 2017

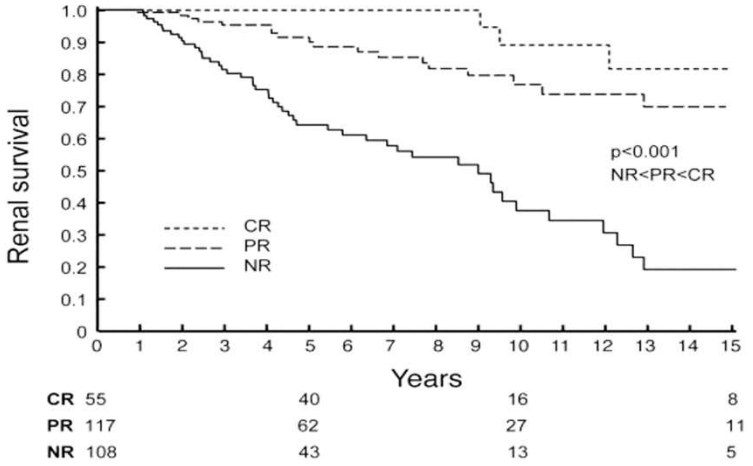
Why is it so important to achieve remission in SRNS???

CHILDREN (N=60)



Gipson 2006

ADULTS (N=280)



Troyanov 2005

Courtesy EM Hodson

CHALLENGES OF PROVIDING GUIDELINES FOR SRNS MANAGEMENT:

- Rarity
- Severity
- Heterogeneity
- Lack of high quality data (few RCTs)

Dieter Haffner ESPN Hannover, Germany

Core group of 18 Pediatric Nephrologists:

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Janina Müller-Seile - Erlangen, Germany Adult Nephrology & Transition
Jan Ulrich Becker - Cologne, Germany Nephropathology

External expert group:
3 patients representatives
1 dietitian

External voting panel:
23 pediatric nephrologists including 3–5 representatives of each IPNA Regional Society with expertise in the management of SRNS in children. Voting group members were asked by electronic questionnaire to provide a level of agreement on a 5-point scale (strongly disagree, disagree, neither agree/disagree, agree, strongly agree) (Delphi method).

IPNA

Aggregate evidence quality	Benefit or harm predominates	Benefit and harm balanced
Level A • Intervention: well-designed and conducted trials, meta-analyses on applicable populations • Diagnosis: independent gold-standard studies of applicable populations	Strong recommendation	Weak recommendation (based on balance of benefit and harm)
Level B Trials or diagnostic studies with minor limitations; consistent findings from multiple observational studies	Moderate recommendation	
Level C Single or few observational studies or multiple studies with inconsistent findings or major limitations		
Level D Expert opinion, case reports, reasoning from first principles	Weak recommendation (based on low-quality evidence)	No recommendation may be made
Level X Exceptional situations where validating studies cannot be performed and benefit or harm clearly predominates	Strong recommendation Moderate recommendation	

TABLES OF EVIDENCE (ERKNet team, Dr Agnes Trautmann):

- 60 observational studies
- 26 completed RCTs
- 4 ongoing RCTs

Evidence is listed in the supplementary tables

https://link.springer.com/article/10.1007/s00467-020-04519-1

PRIORITIES OF THE GUIDELINES:

- To provide state-of-the art guidance
- To be mindful of different resources and situations
- To be a starting point of a work-in-progress
- To provide common ground for collaborations and studies
- To suggest future lines of research

DEFINITIONS

Nephrotic-range proteinuria

- 40 mg/m2/hr or 1000 mg/m2/day
- Urinary protein/creatinine ratio 200mg/mmol or 2 mg/mg
- Urinary dipstick 3+ or 4+

DEFINITIONS

Nephrotic-range proteinuria

- 40 mg/m2/hr or 1000 mg/m2/day
- Urinary protein/creatinine ratio 200mg/mmol or 2 mg/mg
- Urinary dipstick 3+ or 4+

Is a 24 hr urine collection necessary to monitor proteinuria?

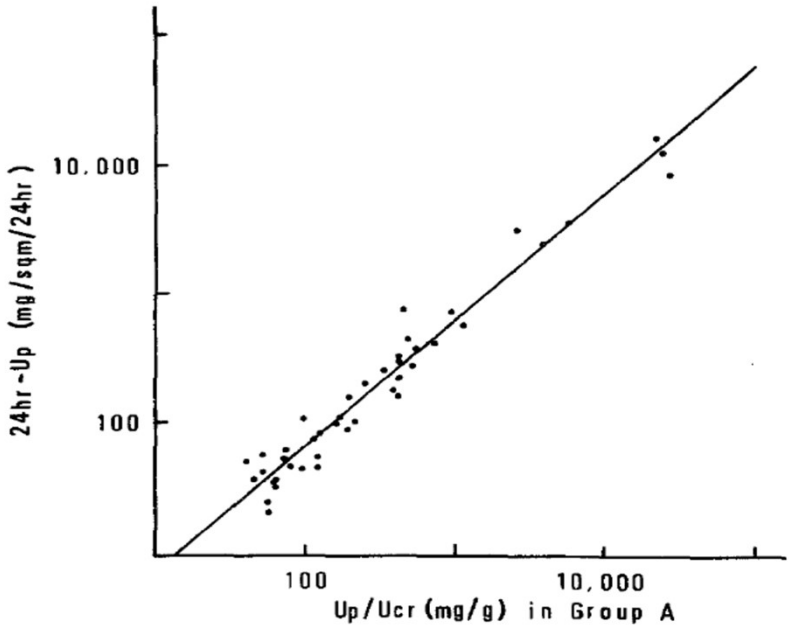


Fig. 1. Relationship between ratio of urinary protein to creatinine (*Up/Ucr*) in group A and 24-h urinary excretion of protein (*24 h-Up*) corrected for body surface area. Linear regression describing relationship is calculated on log transformed data ($y = 1.04x + 1.47$, $r = 0.984$).

Untimed (spot) urine samples, preferably the first morning specimen, can be used (UPCR).

Huang Y et al, Ped Neph 2020

- Hogg RJ, Furth S, Lemley KV, Portman R, Schwartz GJ, Coresh J, Balk E, Lau J, Levin A, Kausz AT, Eknoyan G, Levey AS: National Kidney Foundation's Kidney Disease Outcomes Quality Initiative clinical practice guidelines for chronic kidney disease in children and adolescents: evaluation, classification, and stratification. Pediatrics. 2003; 111: 1416–21;
- Houser M: Assessment of proteinuria using random urine samples. J Pediatr. 1984; 104: 845–848.
- Houser MT, Jahn MF, Kobayashi A, Walburn J: Assessment of urinary protein excretion in the adolescent: effect of body position and exercise. J Pediatr. 1986; 109: 556–561.
- Yoshimoto M, Tsukahara H, Saito M, Hayashi S, Haruki S, Fujiswana S, Sudo M: Evaluation of variability of proteinuria indices. Pediatr Nephrol. 1990; 4: 136–139.

Normal values of proteinuria expressed as UPCR for **age range**

Age	g/g creatinine	g/mol creatinine
0–6 months	0.70	80
6–12 months	0.55	60
1–2 years	0.40	45
2–3 years	0.30	30
3–5 years	0.20	20
5–7 years	0.15	19
7–17 years	0.15	18

Typical **dipstick results** are expressed semiquantitatively:

- Negative: 0 mg/dl,
- Trace: 15 to 30 mg/dl,
- 1+ : 30 to 100 mg/dl,
- 2+: 100 to 300 mg/dl,
- 3+: 300 to 1000 mg/dl,
- 4+>: 1000mg/dl

van der Watt, Ped Neph 7th ed. 2016

Nephrotic-range proteinuria: UPCR ≥200 mg/mmol (2 mg/mg) in first morning void or 24hr urine sample ≥1000 mg/m2/day corresponding to 3+ or 4+ by urine dipstick

Nephrotic syndrome: Nephrotic-range proteinuria and either hypoalbuminemia (serum albumin <30 g/l) or edema when serum albumin level is not available

Complete remission: UPCR (based on first morning void or 24 hr urine sample) ≤20 mg/mmol (0.2 mg/mg) or negative or trace dipstick on ≥ 3 consecutive occasions

Partial remission: UPCR (based on first morning void or 24 hr urine sample) > 20 but < 200 mg/mmol and, if available, serum albumin ≥ 30 g/l

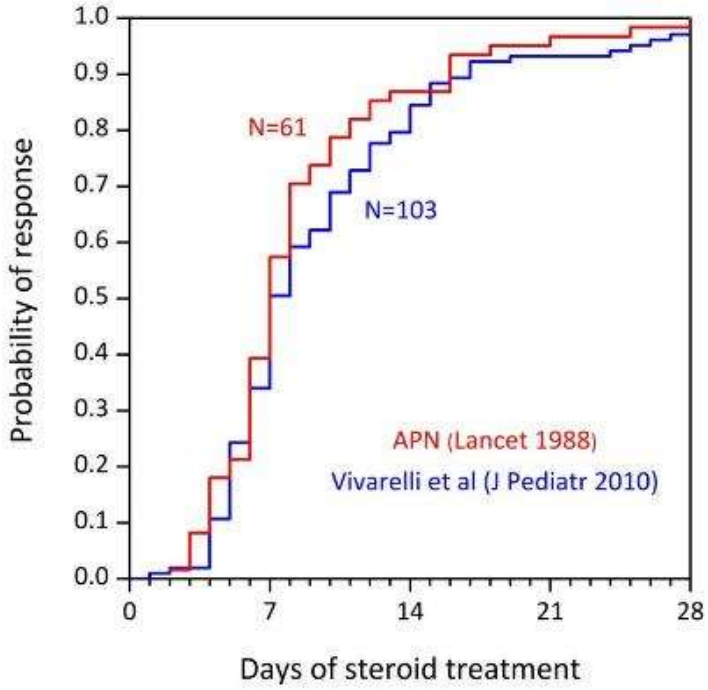
Relapse: Recurrence of nephrotic-range proteinuria in a child who had previously achieved partial or complete remission. In children, relapse is commonly assessed by urine dipstick and is thus defined as dipstick ≥ 3+ on 3 consecutive days.

DEFINITIONS

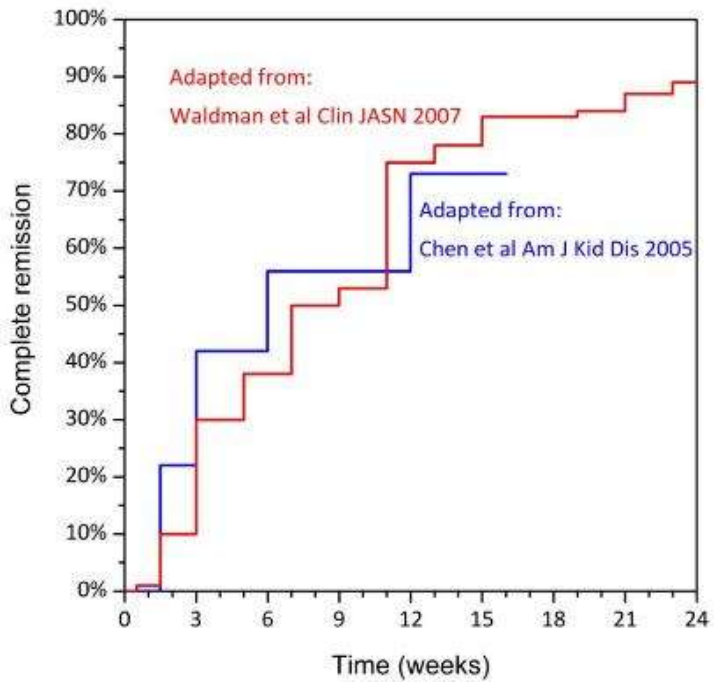
SRNS

Most children who will respond to PDN do so within 4 weeks

Children



Adults



Courtesy of Francesco Emma

When should a child be labelled as having SRNS?

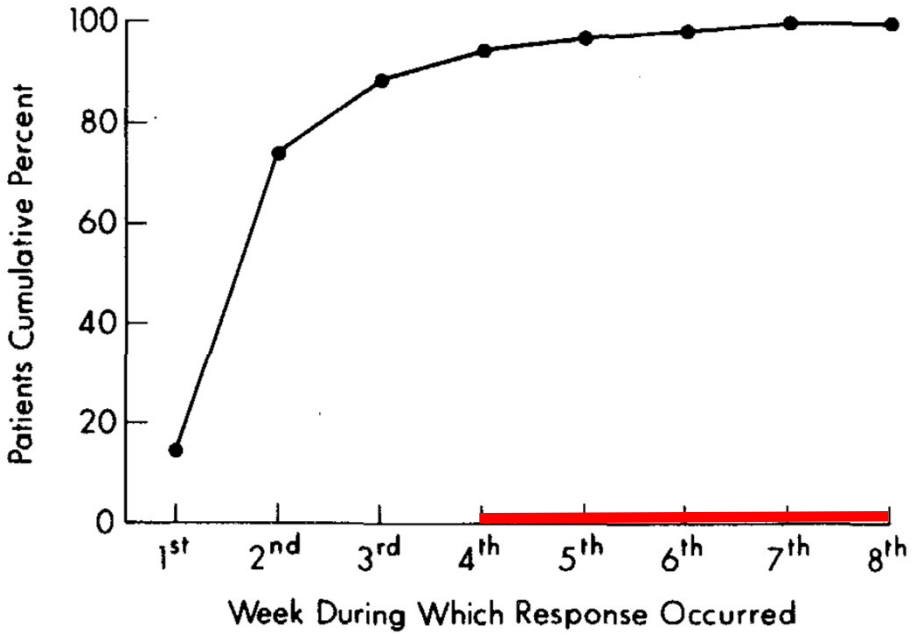


Figure. Cumulative distribution of time to response for initial responders.

International Study of Kidney Disease in Children. J Paediatr 1981

Onset of NS: start of oral PDN at standard dose 60 mg/m2/day

At **4 weeks** evaluate response to steroid therapy:

Complete remission → SSNS

No remission → SRNS

Partial remission → wait and see for a 2 week «confirmation period»

At **6 weeks re-**evaluate response to steroid therapy:

Complete remission → SSNS late responder

Partial or no remission → SRNS

INITIAL WORK-UP

All forms of NS

In all patients:

- Assess fluid status
- Anthropometry: Height/weight/BMI in all, head circumference < 2 yrs age
- Assess pubertal stage

- Vaccination status

- Check for HBV, HCV, syphilis, varicella, HIV, TB in endemic areas before start of PDN

- Blood and urine work-up: CBC, renal function, transaminases, urinalysis, thyroid, fasting glucose, blood lipids, baseline coagulation, C3 and C4, total IgGs

- Renal US

- Dietary assessment

SUBSEQUENT WORK-UP

SRNS

CONFIRMATION PERIOD: between 4-6 weeks from PDN start, in a SRNS or strong suspect SRNS patient

Look for clues of cause

Secondary causes of SRNS: Parvovirus B19, CMV, Hepatitis B, HIV, malaria, sickle-cell disease, lymphoma, SLE

Genetic forms of SRNS:

- Family history: ask for consanguinity and for family cases of renal (hematuria, proteinuria, CKD of unknown origin) and extra-renal disease (deafness, nail/knee)
- Physical examination: search for extra-renal features (ambiguous genitalia, dysmorphic features, neurological examination, sight, hearing)

If a genetic form of SRNS is suspected, performing urinalysis of siblings is suggested

GENETIC SCREENING

Why to perform genetic screening in SRNS?

- To provide specific treatment, when available
- To withdraw useless or harmful therapy
- To avoid a renal biopsy
- To provide an estimate of the risk of ESKD (high) and of the risk of post-transplant recurrence (low)
- To allow screening for dangerous co-morbidities
- To provide family counselling

When to perform genetic screening in SRNS?

In all patients with a diagnosis of primary SRNS,

EXCEPT in pts with secondary cause, in pts with initial steroid-sensitivity («secondary» SRNS)

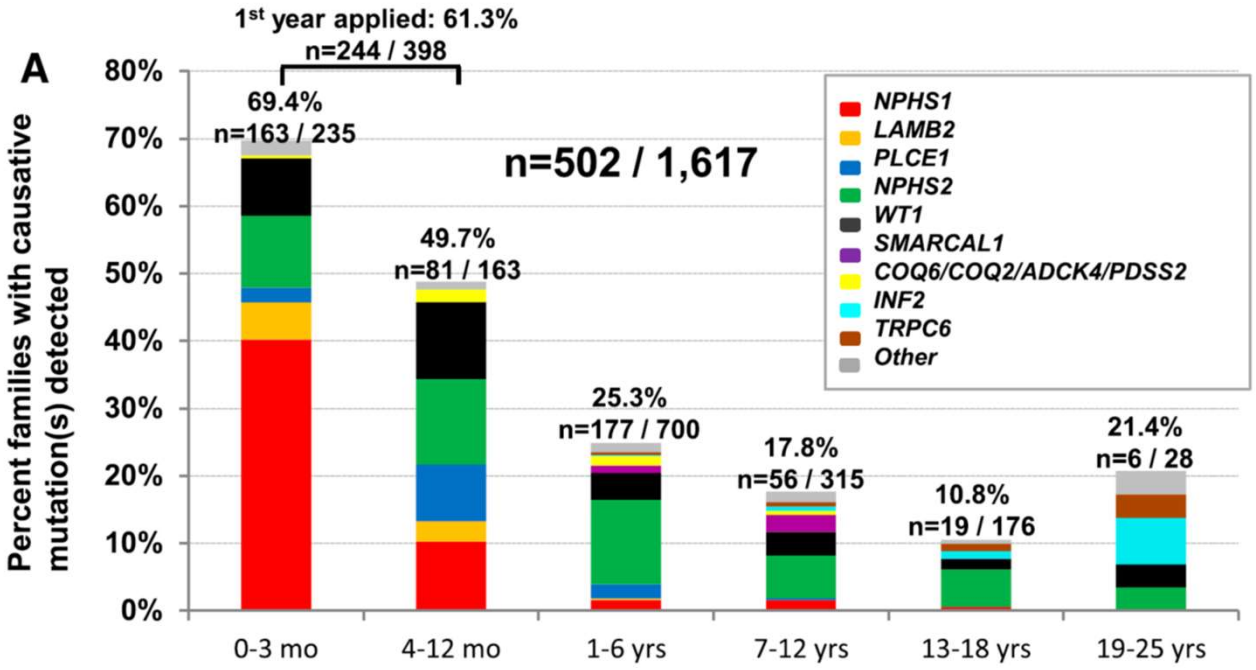
In low-resource settings, priority should be given to:

-familial forms

-children with extra-renal features, especially if very young

-pre-renal transplant

Frequency of genetic SRNS per age group



Sadowski et al, J Am Soc Nephrol 2015

How to perform genetic screening in SRNS?

Gene causing SRNS	Mode of inheritance	Total SRNS families with molecular diagnosis
NPHS2	AR	177 (9.93)
NPHS1	AR	131 (7.34)
WT1	AD	85 (4.77)
PLCE1	AR	37 (2.17)
LAMB2	AR	20 (1.12)
SMARCAL1	AR	16 (0.89)
INF2	AD	9 (0.5)
TRPC6	AD	9 (0.53)
COQ6	AR	8 (0.45)
ITGA3	AR	5 (0.28)
MYO1E	AR	5 (0.28)
CUBN	AR	5 (0.28)
COQ2	AR	4 (0.22)
LMX1B	AD	4 (0.22)
ADCK4	AR	3 (0.17)
DGKE	AR	2 (0.11)
PDSS2	AR	2 (0.11)
ARHGAP24	AD	1 (0.06)
ARHGDIA	AR	1 (0.06)
CFH	AR	1 (0.06)
ITGB4	AR	1 (0.06)
Total		526 (29.5)

21%

25%

30%

- NGS panel
- Genetic counseling

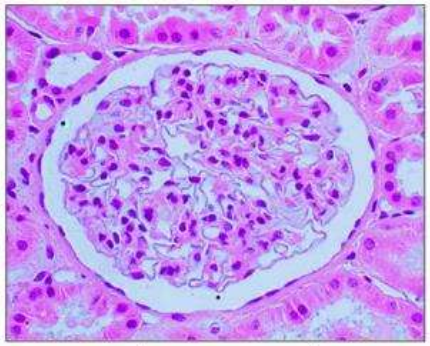
Lovric et al, Nephrol Dial Transpl 2016

RENAL BIOPSY

Frequency of renal histology pictures in children with SRNS

25-40%

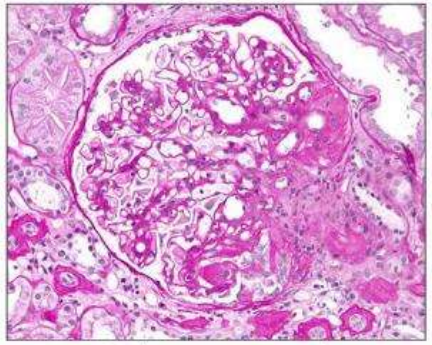
Minimal change disease
MCD



5 days post-transplant

35-55%

Focal segmental glomerulosclerosis
FSGS

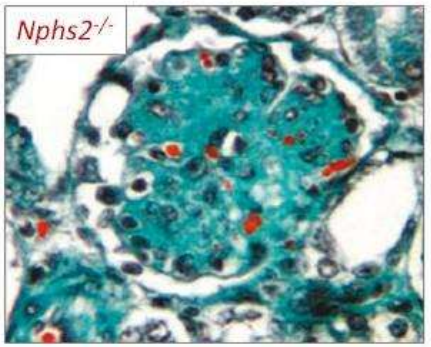


37 days post-transplant

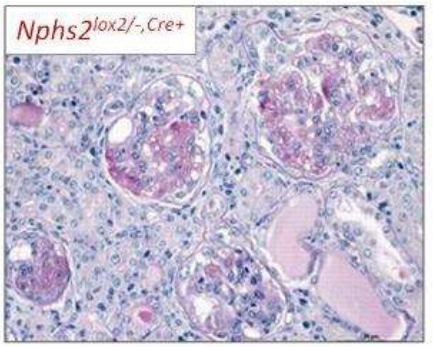
Acute → *Chronic*

10-15%

Diffuse mesangial sclerosis
DMS



Focal segmental glomerulosclerosis
FSGS



Early onset → *Late onset*

Roselli et al, Mol Cell Biol 2004 - Mollet et al, JASN 2009

20% other glomerular diseases: IgAN, IMN, C3G, SLE, Alport, TMA

modified from Tullus, Lancet Child Adolescent Health 2018

Why to perform a renal biopsy in SRNS?

- To exclude rare cases of other glomerular disorders presenting as SRNS (IgAN, IMN, C3G, SLE, Alport, TMA)
- To diagnose DMS
- To evaluate TI fibrosis and general status of kidney sclerosis
- Following CNIs, to assess for CNI-induced renal damage

When to perform a renal biopsy in SRNS?

In all patients with a diagnosis of primary SRNS,

EXCEPT in pts with secondary cause (infection/malignancy).

In pts with a strong clinical suspicion of a genetic cause:
-familial forms
-children with extra-renal features, particularly of young age
PROVIDED genetic results are readily available, genetic testing is suggested before/in lieu of a renal biopsy

INITIAL MANAGEMENT

SRNS

SUPPORTIVE MEASURES

- Balanced fluid intake
- Moderate sodium intake with a dietitian

- Diuretics
- Albumin infusion (in case of refractory edema and/or symptomatic hypovolemia or oliguria)

PREVENTION OF THROMBOSIS

TREATMENT

- Glucocorticoid
- RAAS inhibition
- CNI

PREVENTION OF THROMBOSIS IN SRNS

Recommended: mobilizing patients, avoiding central venous lines

Not recommended: routine prophylactic anticoagulation

LMW heparin or oral anticoagulation prophylaxis and thrombophilic screening suggested if positive family/personal history for thrombotic events or additional risk factors:

- central venous lines
- severe protracted hypoalbuminemia
- illness/infection with dehydration, immobilization

TREATMENT AT 4-6 WEEKS FROM ONSET IN SRNS

Glucocorticoids: i.v. methylprednisolone boli can be used, oral PDN is gradually tapered on alternate days and stopped in 6 months

RAAS inhibition: should be started of possible in all patients with EITHER an ACE-inhibitor OR an ARB.

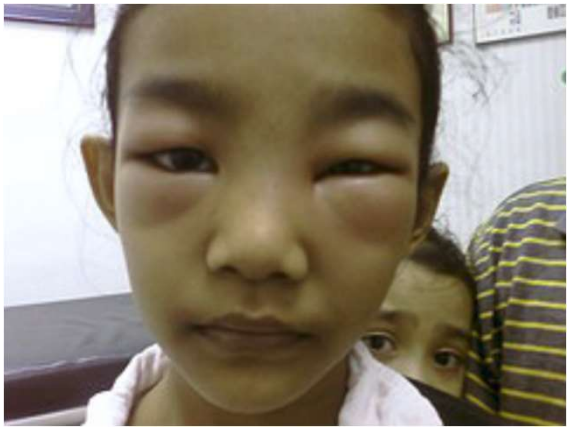
- Aim for maximum tolerated dose
- Caution if hyperkalemia, initial CKD, intravascular volume depletion
- Contraception necessary in fertile females

CNI

DEFINITIONS

SRNS subcategories

Idiopathic nephrotic syndrome in children



Steroid-sensitive NS
75-90%

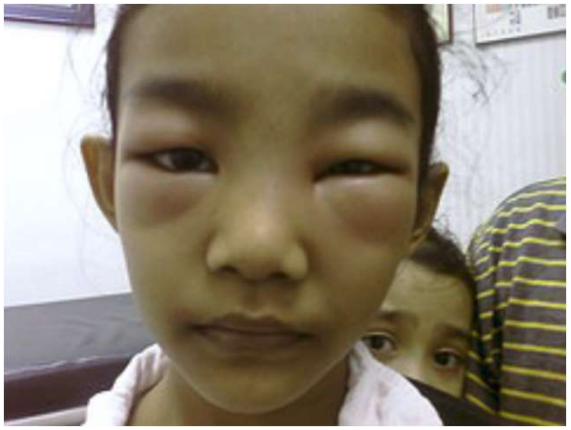
Steroid-resistant NS
10-25%

SRNS responsive to second-line agents
15-20%

Multidrug-resistant NS
5-15%

ESKD

Idiopathic nephrotic syndrome in children



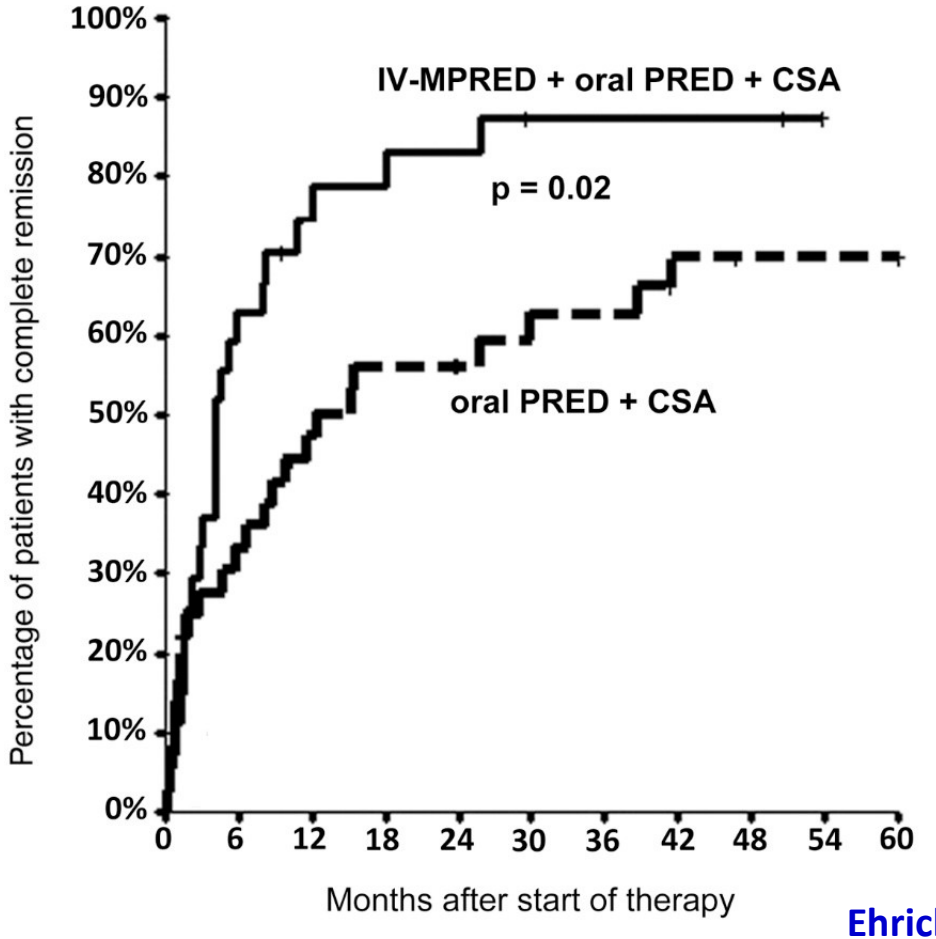
Steroid-sensitive NS
75-90%

Steroid-resistant NS
10-25%

CNI responsive NS
15-20%

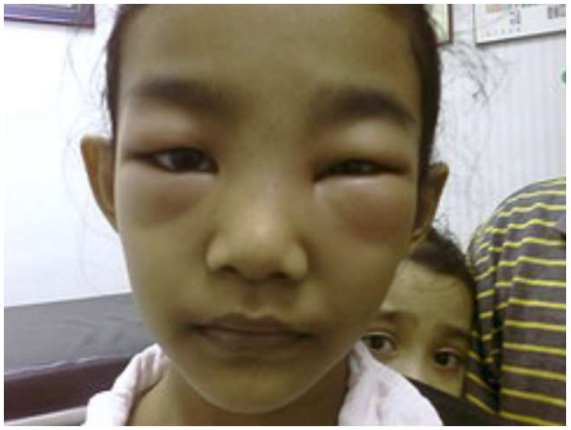
CNI-resistant NS
5-10%

Well over 50% of children with SRNS will respond to a CNI



Ehrich et al, Nephrol Dial Transpl 2007

Idiopathic nephrotic syndrome in children



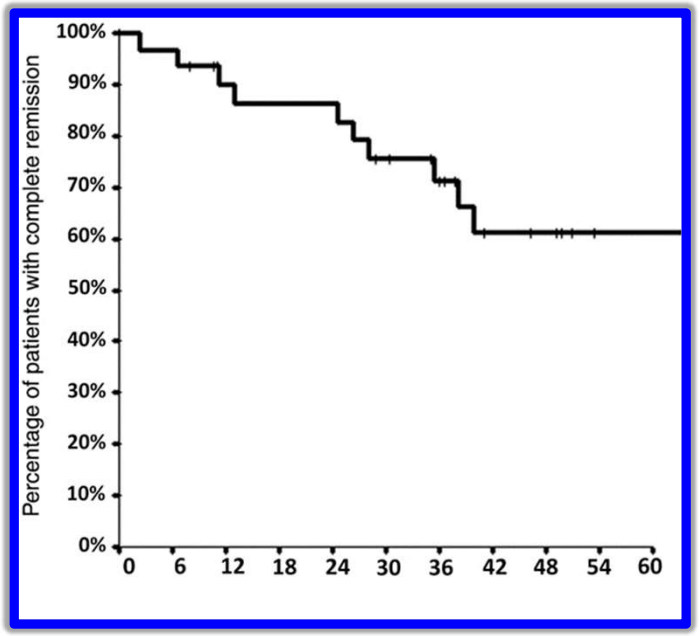
Steroid-sensitive NS
75-90%

Steroid-resistant NS
10-25%

CNI responsive NS
15-20%

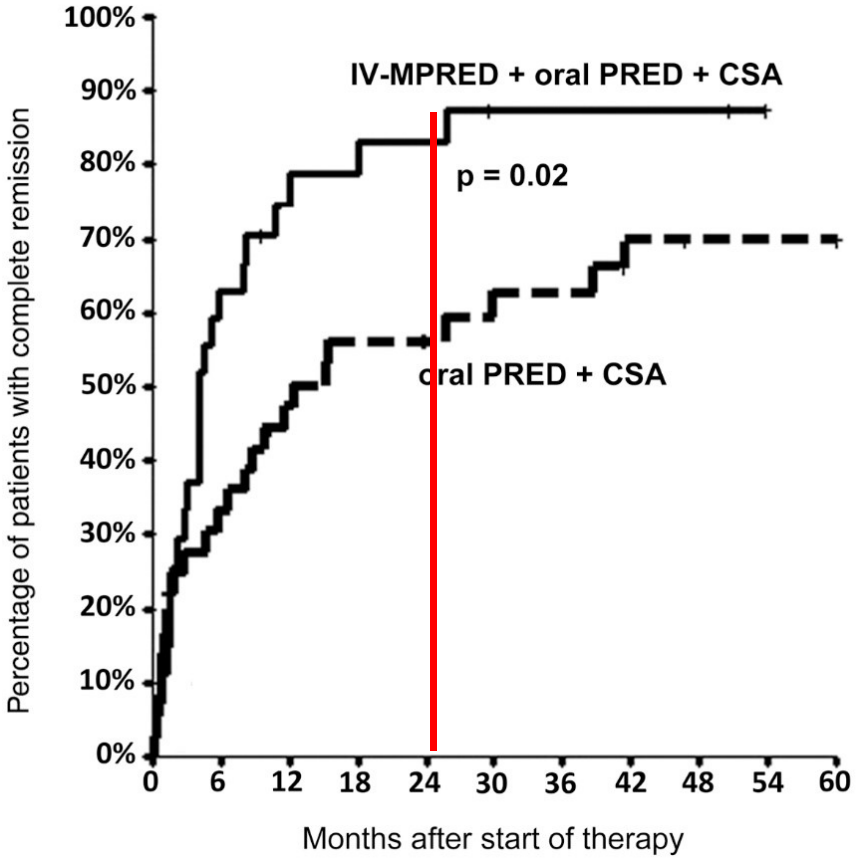
Multiple relapses
SDNS

Infrequent relapses
on steroid-sparing drug



Ehrich et al, Nephrol Dial Transpl 2007

How long before you give up on a CNI in a child with SRNS?



Ehrich et al, Nephrol Dial Transpl 2007

It can take a looong time.

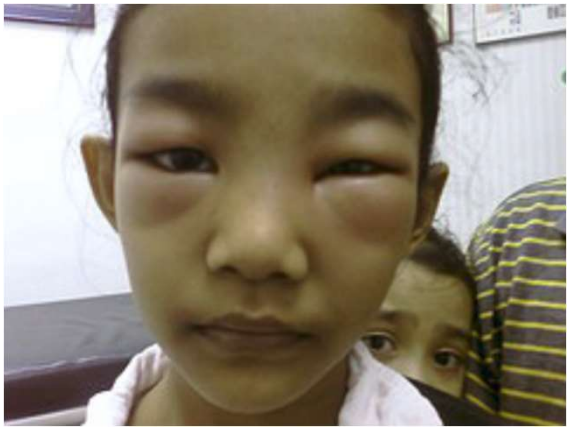
However:

- Need to avoid unnecessary toxicity in non-responders
- Opportunity to try other therapeutic options

SRNS subcategories

CNI-resistant SRNS: Absence of at least partial response to a CNI after 6 months of treatment at adequate doses and/or levels

Idiopathic nephrotic syndrome in children



Steroid-sensitive NS
75-90%

Steroid-resistant NS
10-25%

CNI responsive SRNS
15-20%

CNI-resistant SRNS
5-10%

Multi-drug responsive SRNS

Multi-drug resistant SRNS

SRNS subcategories

CNI-resistant SRNS: Absence of at least partial response to a CNI after 6 months of treatment at adequate doses and/or levels

Multi-drug resistant SRNS: Absence of complete remission after 12 months of treatment with 2 mechanistically distinct steroid-sparing agents at standard doses

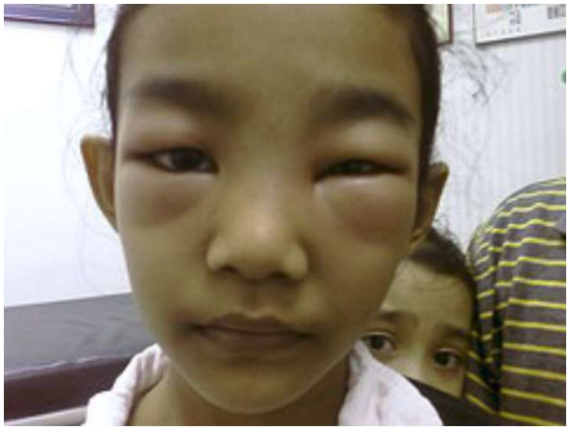
Idiopathic NS in children

Steroid-sensitive NS
75-90%

Multiple Relapses
60-80%

Secondary SRNS
14%

High risk of ESKD and
80% recurrence
after transplantation



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Secondary steroid-resistance: Children with initial steroid-sensitivity who in subsequent relapses develop SRNS

Recurrent nephrotic syndrome post-renal transplantation: A child with SRNS presenting post-renal transplantation with nephrotic-range proteinuria in the absence of other apparent causes and/or with podocyte foot process effacement on kidney biopsy.

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Next Webinars

IPNA Clinical Practice Webinars

Date: **12 Nov 2020**

Speaker: **Agnes Trautmannn**

Topic**: Steroid Resistant Nephrotic Syndrome: update from the IPNA Guideline Part 2: Therapeutic managment**

ERKNet/ERA-EDTA Advanced Webinars on Rare Kidney Disorders

Date: **24 Nov 2020**

Speaker: **Roman Ulrich Müller**

Topic**: Management of autosomal dominant polycystic kidney diseases – state of the art**

ESPN/ERKNet Educational Webinars on Pediatric Nephrology & Rare Kidney Diseases

Date: **01 Dec 2020**

Speaker: **Olivia Boyer**

Topic**: Congenital Nephrotic Syndrome**

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