Nephrotic syndrome: What should a pediatrician know?

Moderator:

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JIPMER

Panelists:

Dr Saravanan M

Dr Narmadha S

Dr Manasi Garg

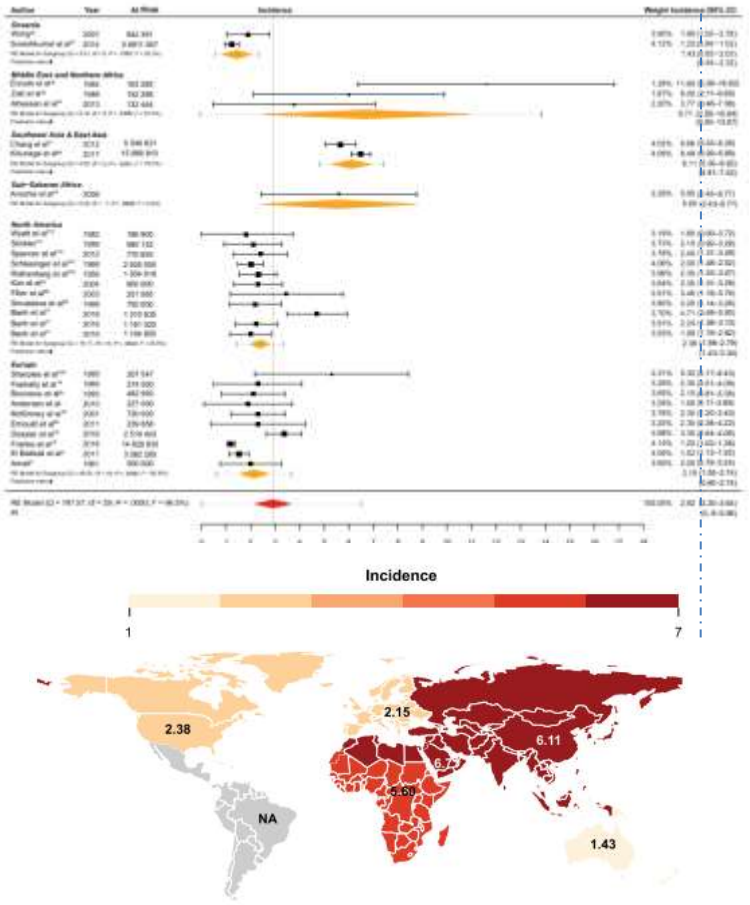
Dr Arpitha KR

Nephrotic syndrome is a rare disease

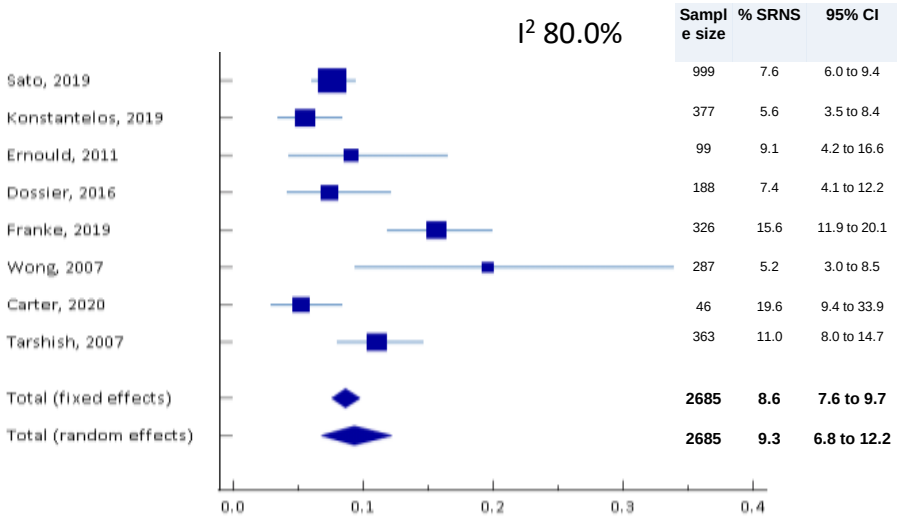
Steroid sensitive nephrotic syndrome

Incidence 2.9 (0-15) per 100000 children/yr

Prevalence 12-16 per 100000 children



Steroid resistant NS
2–4 per million/yr



Sample size	% SRNS	95% CI
999	7.6	6.0 to 9.4
377	5.6	3.5 to 8.4
99	9.1	4.2 to 16.6
188	7.4	4.1 to 12.2
326	15.6	11.9 to 20.1
287	5.2	3.0 to 8.5
46	19.6	9.4 to 33.9
363	11.0	8.0 to 14.7
2685	**8.6**	**7.6 to 9.7**
2685	**9.3**	**6.8 to 12.2**

Pediatric Nephrotic syndrome: Guidelines for management

	ISPN	Other societies	KDIGO	IPNA
Steroid sensitive NS	2000 2008 **2021**	*ISKDC, 1971* British, 2001 French, 2005 German, 2006, 2021 Dutch, 2010, 2016 Japanese, 2013, 15 Canadian*, 2014 Italian, 2017 Ibadan, 2020	2012 **2021**	**2022**
Steroid resistant NS	2009 **2021**		2012 **2021**	**2020**

RECOMMENDATIONS

Steroid Sensitive Nephrotic Syndrome: Revised Guidelines

Aditi Sinha,[1] Arvind Bagga,[1] Sushmita Banerjee,[2] Kirtisudha Mishra,[3] Amarjeet Mehta,[4] Indira Agarwal,[5] Susan Uthup,[6] Abhijeet Saha,[7] Om Prakash Mishra[8] and Expert Group of Indian Society of Pediatric Nephrology*

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RECOMMENDATIONS

Consensus Guidelines on Management of Steroid-Resistant Nephrotic Syndrome

Anil Vasudevan,[1] Ranjeet Thergaonkar,[2] Mukta Mantan,[3] Jyoti Sharma,[4] Priyanka Khandelwal,[5] Pankaj Hari,[5] Aditi Sinha,[5] Arvind Bagga,[5] Expert Group of Indian Society of Pediatric Nephrology*

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Idiopathic Steroid sensitive nephrotic syndrome of children

Case 1

- A 6-year-old girl develops periorbital edema for 3 days with mild oliguria
- BP- 98/60 mm Hg
- Urinalysis- **Urine albumin 4+**
- **Up: Uc 8.4**
- **Serum albumin 2.3 g/dL**
- **Serum cholesterol 473 mg/dL**

- Is this nephrotic syndrome?

Dr Saravanan

Steroid sensitive nephrotic syndrome Revised Consensus guidelines: ISPN 2021

Guideline 1: Evaluation

- **1.1** In a patient presenting with recent onset of edema, we recommend the following investigations to confirm the diagnosis of nephrotic syndrome: *(i)* urinalysis; *(ii)* blood levels of urea, creatinine, albumin and total cholesterol **Not graded**

- **1.2** We suggest additional evaluation in selected patients **Not graded**

- **1.3** We recommend that parents be taught to maintain a record of proteinuria (by dipstick or boiling), infections and medications received **Not graded**

- Nephrotic syndrome, characterized by edema, heavy proteinuria (>1 g/m^2 daily) and hypoalbuminemia (serum albumin <3 g/dl) is among the most common chronic kidney diseases in childhood.

KDIGO Clinical Practice Guideline on Glomerular Diseases: Public Review draft. Available at https://kdigo.org/guidelines/gn/; last accessed 15 June 2020

- What are the definitions of disease course for nephrotic syndrome as per ISPN guidelines?

Dr Narmadha

Definitions of Disease Course

Nephrotic range proteinuria	Urine protein 3+ or 4+; spot urine protein to creatinine ratio (Up/Uc) >2 mg/mg in first morning urine; proteinuria >1 g/m^2/day
Remission	Urine protein nil or trace (Up/Uc <0.2 mg/mg) for 3 consecutive early morning specimens
Relapse	Urine protein ≥3+ (Up/Uc >2 mg/mg) for 3 consecutive early morning specimens, having been in remission previously
Frequent relapses	Two or more relapses in the first 6-months after stopping initial therapy; ≥3 relapses in any 6-months; or ≥4 relapses in a yr
Steroid dependence	Two consecutive relapses when on alternate day steroids, or within 14 days of its discontinuation
Steroid resistance	Lack of complete remission despite therapy with daily prednisolone at a dose of 2 mg/kg (or 60 mg/m^2) daily for 6 weeks

Urine albumin dipstick testing after Furosemide is not reliable

Case 2

- 8-year-old girl presents with periorbital puffiness
- Urine albumin 3+, serum albumin 1.5 g/dL, serum cholesterol 380 mg/dL, Up: Uc 12.1
- Develops gross hematuria during hospital stay
- No flank pain
- BP- 98/70, serum creatinine 0.45 mg/dL
- **Would kidney biopsy be useful?** **Dr Manasi**

Guideline 2: Kidney biopsy

- **2.1** We recommend kidney biopsy in nephrotic syndrome in presence of:
- *(i)* **gross hematuria** or persistent microscopic hematuria, sustained hypertension, or acute kidney injury not attributed to hypovolemia;
- *(ii)* systemic features: fever, rash, arthralgia, low complement C3;
- *(ii)* initial or late corticosteroid resistance; and
- *(iii)* prolonged (>30-36 months) therapy with calcineurin inhibitors (CNI), or reduced kidney function during their use.

- **2.2** We suggest performing kidney biopsy prior to initiating therapy with CNI

Indication for biopsy in Case 2: Gross hematuria

Case 3

- A 5-year old girl with idiopathic nephrotic syndrome
- Treatment received at another hospital:
- 1 mg/kg/day prednisolone x 4 weeks followed by:
- 0.75 mg/kg followed by tapering over 3 months

- Is this the recommended regimen?
- **How do we treat 1st episode and relapses in nephrotic syndrome?** Dr Arpitha

Guideline 3: Therapy for the first episode of nephrotic syndrome

- We recommend that therapy for the initial episode of nephrotic syndrome should comprise of prednisolone at a dose of 60 mg/m^2/day (2 mg/kg/day, maximum 60 mg) **for 6 weeks**, followed by 40 mg/m^2 (1.5 mg/kg, maximum 40 mg as single morning dose) on alternate days **for the next 6 weeks**, and then discontinued. **1A**

ISKDC. J Pediatr 1981

Arbeitsgmeinschaft fur Padiatrische Nephrolgie Eur J Pediatr 1993

Guideline 4: Therapy of relapses

- We recommend that relapses be treated with prednisolone at 60 mg/m^2/day (2 mg/kg/day; maximum 60 mg) in single or divided doses **until remission** (protein trace/nil for 3 consecutive days), followed by 40 mg/m^2 (1.5 mg/kg, maximum 40 mg) on alternate days for **4-weeks**. **1C**

- Prednisolone dosing: Body weight vs body surface area. Which is better?
- Single or divided doses?

Dr Manasi

Prednisolone Dosing : Weight vs BSA

	Type of study	Time to remission	Time to relapse	No. of relapses 12-24 months	Relapse rate	Adverse effects
Basu et al 2020	Randomized clinical trial				6-month relapse-free survival rates were similar	
Raman et al 2016	Open-labelled randomised trial	No difference	Shorter for BW based regimen	No difference	No difference	incidence of hypertension was higher (p = 0.048) in the BSA group
Feber et al 2009	Retrospective	Not reported	Not reported	Not reported	Not reported	Not reported
Hirano et al 2013	Retrospective review of medical records	No difference	Shorter time to relapse with BW regimen	No difference	Higher rates of SD NS in BW grp	No difference in AE in both groups
Saadeha et al 2011	Non- randomised prospective study	No difference	No difference	No difference	Increase in FR in BW grp	No difference

IPNA

Younger children in particular will receive higher mg of PDN (up to 15%) using a BSA compared to weight

To avoid PDN overdosing in fluid-overloaded children, we *suggest* calculating the PDN dose based on the **estimated dry weight**

ISPN

"Recent reports suggest that it *may be prudent* to dose by BSA to avoid underdosing, **particularly in younger children**"

Single vs. Divided doses

- No difference in time to remission, duration of remission or rates of relapses *(Ekka 1997, Warshaw 1989)*
- Lower toxicity profile with single morning dose *(Li 1994)*

IPNA: Consider potential benefits of each to decide

- **Once-daily dose**: better adherence to therapy, lesser risk of HPA axis suppression and sleep disturbances.
- **Divided doses**: Minimizes pill burden or volume of liquid formulation per dose

NO role for antacids; prescribed only if symptomatic

Ekka BK, Bagga A, Srivastava RN. Single- versus divided-dose prednisolone therapy for relapses of nephrotic syndrome. Pediatric Nephrology 1997;11(5):597-9.
Warshaw BL, Hymes LC. Daily single-dose and daily reduced-dose prednisone therapy for children with the nephrotic syndrome. *Pediatrics*. 1989;83(5):694-699.
Li X, Li Z, Cheng Z. Treatment of children with simple nephrotic syndrom using prednison once per day. Acta Academiae Medicinae Hubei 1994;15(4):386-8.

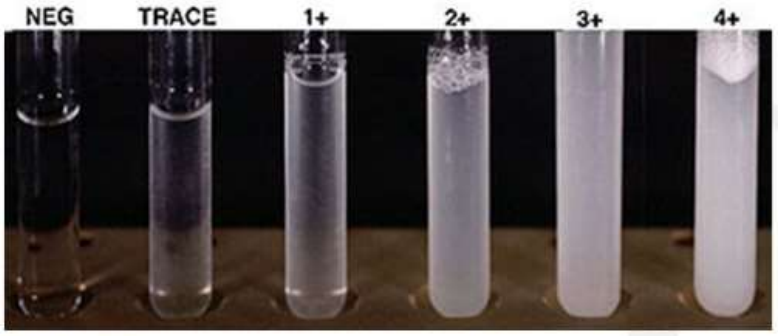
- **How do we educate parents regarding monitoring of children with nephrotic syndrome?** Dr Saravanan

Regular Monitoring

Parents taught to maintain a record:

- Proteinuria (dipstick preferred)
- Infections
- Medications received
- Any concerns

Clinic: Edema, perfusion, infection, BP, drug toxicities, anthropometry, vaccinations

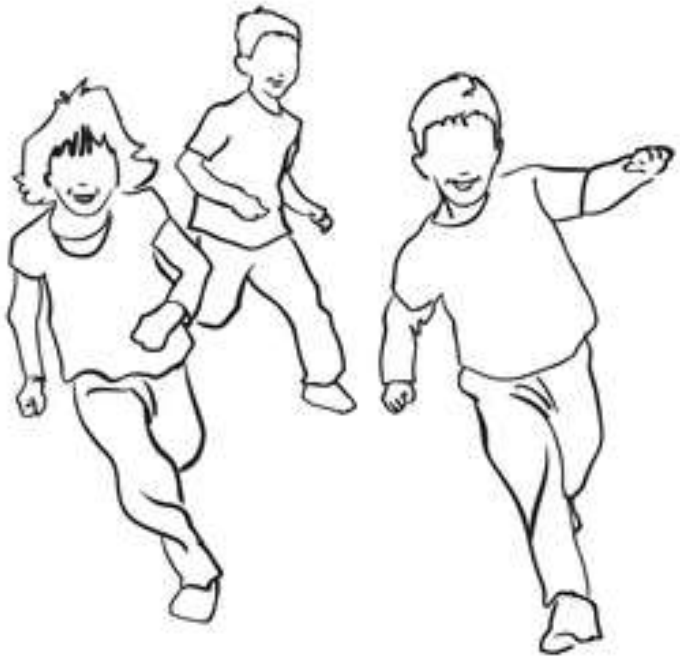


Parental education

Maintain a diary

Ensure normal childhood

Date	Urine test	Prednisolone	Other drugs	Remarks
1.9.19	3+	30 mg	Lasix 1 tablet	Cough & cold
2.9.19	3+	30 mg		Cough better
3.9.19	3+	30 mg		Well
4.9.19	3+	30 mg		Well
5.9.19	3+	30 mg		Well

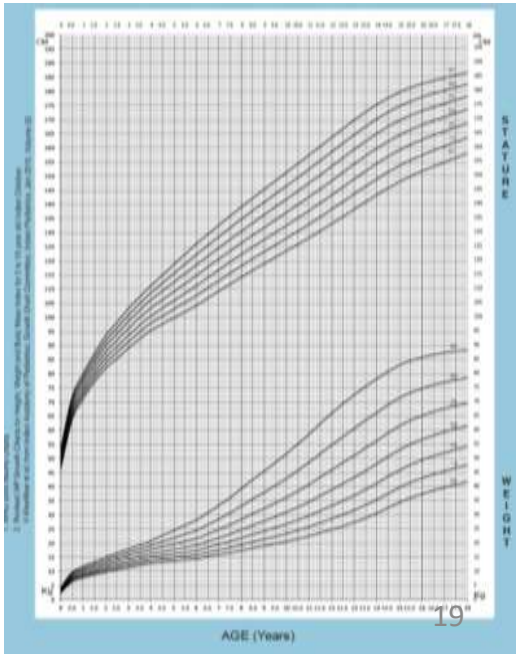


Diet

Schooling

Activities

Vaccination

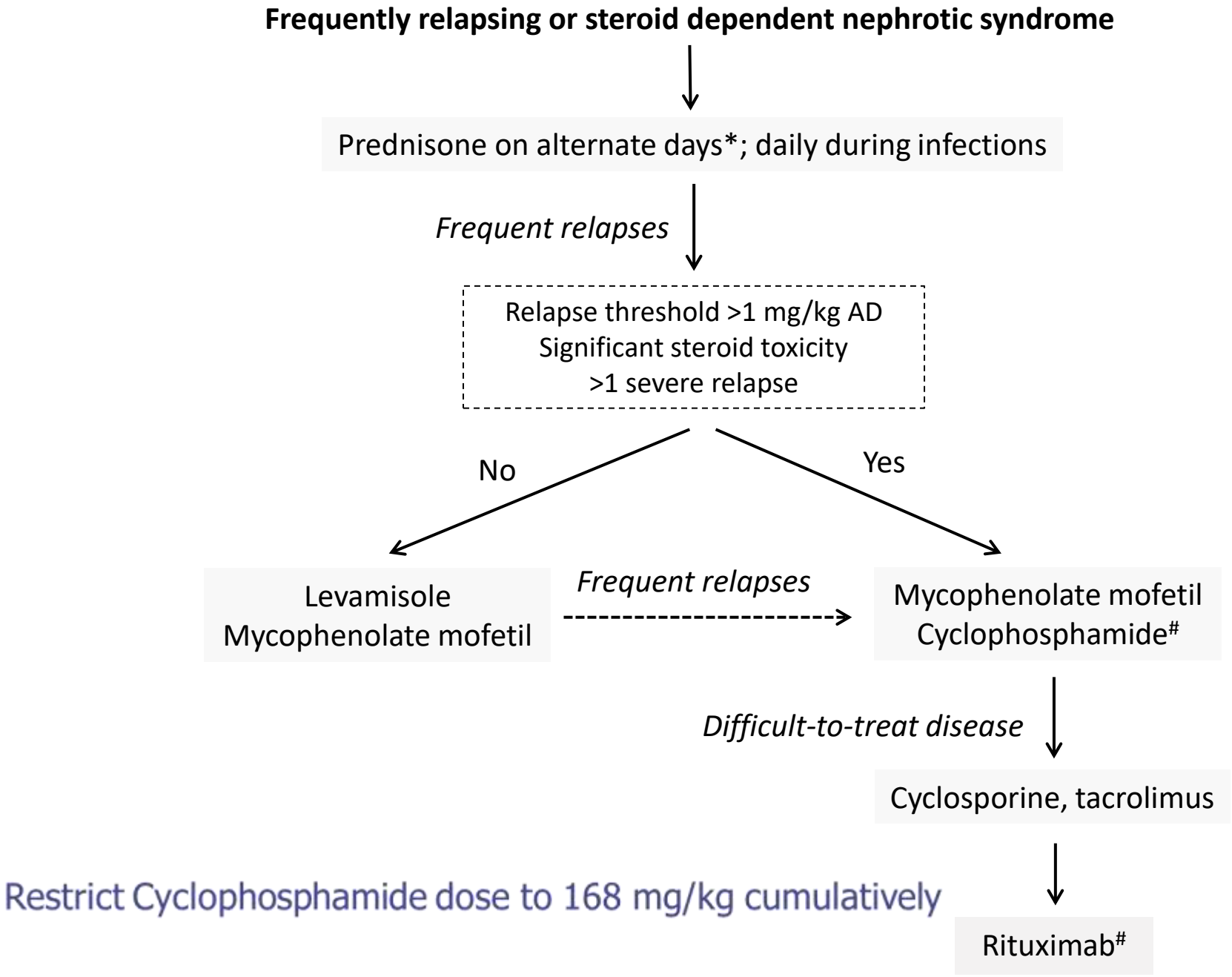


Case 4

- 4-year-old girl, case of nephrotic syndrome
- Age of onset 2 years
- Repeated relapses
- Managed with prednisolone courses during 1st year
- Steroid threshold to maintain remission: 0.9 mg/kg on LTAD prednisolone
- Levamisole with alternate day prednisolone started in the 3rd year; given for 6 months
- Failed on levamisole….(3 relapses in 6 months)
- **Next line of management?** Dr Narmadha

Guideline 5: Management of frequent relapses and steroid dependence

- In patients with frequent relapses, we suggest tapering prednisolone to a dose of 0.5-0.7 mg/kg on alternate-days, for 6-12 months. 2B

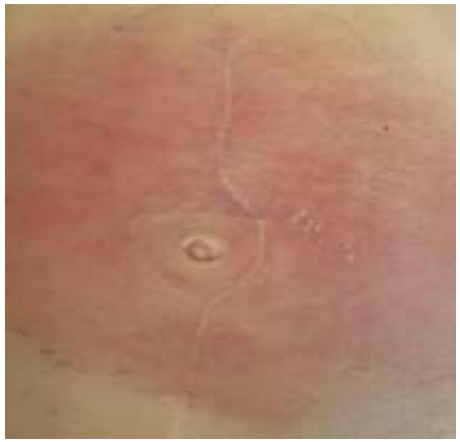


Restrict Cyclophosphamide dose to 168 mg/kg cumulatively

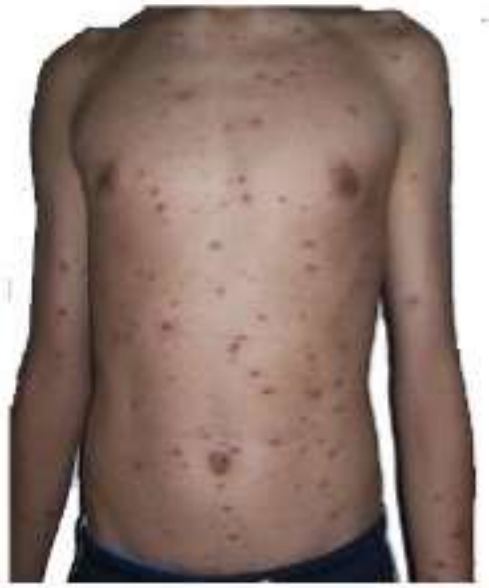
- **What complications can occur in nephrotic syndrome?** **Dr Arpitha**

Complications during relapse

Generalised edema and severe ascites, genital edema



Cellulitis



Disseminated varicella

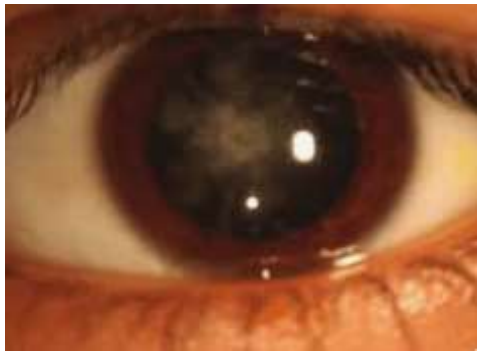
Peritonitis, pneumonia
Acute kidney injury
Thrombotic complications
Hypovolemia

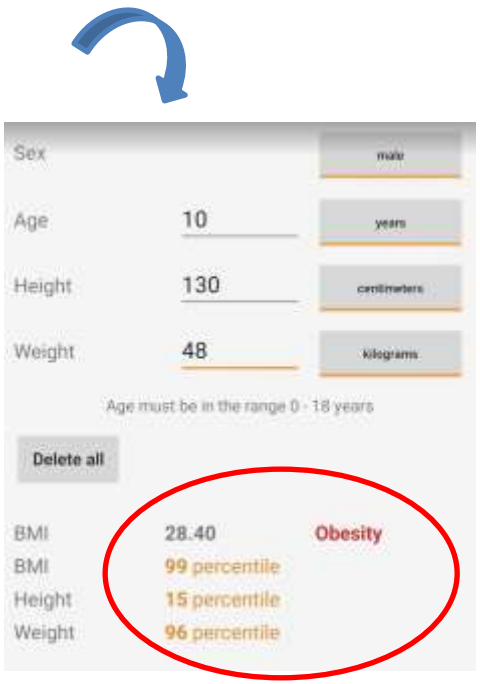
- **How do we monitor for steroid toxicity?**

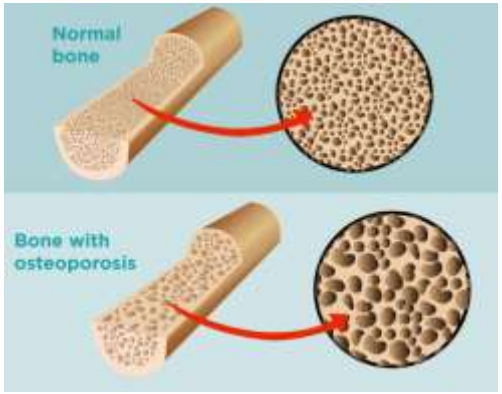
- **How do we monitor for adverse effects of steroid sparing agents?**

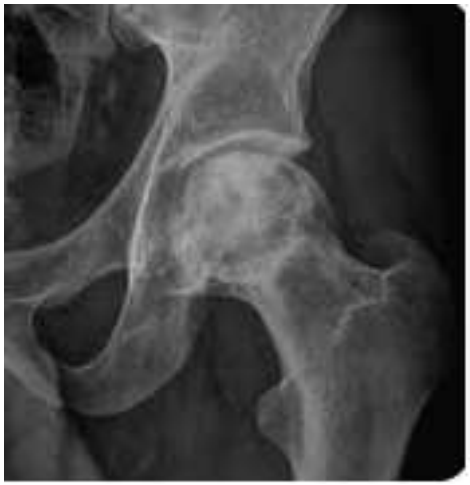
Dr Saravanan

Steroid Toxicities









- Impaired glucose tolerance
- Obesity, short stature, infections

Immunosuppression for FRNS/SDNS: monitor for toxicity

Name	Dose	Duration	Adverse effects
Prednisolone	0.5-0.7 mg/kg on alternate days*#	1-2 years	Cushingoid features; short stature; hypertension; raised intraocular pressure; glucose intolerance; cataract; elevated transaminases
Levamisole	2-2.5 mg/kg on alternate days	2-3 years	Leukopenia, ANCA positive vasculitic rash, high transaminases, seizures
Cyclophosphamide	2-2.5 mg/kg/d orally	8-12 weeks	Leukopenia, alopecia, infections; discolored nails; hemorrhagic cystitis; small risk of gonadal toxicity and malignancies
Mycophenolate mofetil	600-1200 mg/m^2/d in divided doses; AUC >45 mg·h/l	2-3 years	Abdominal pain, diarrhea, nausea, weight loss; viral warts; leukopenia; elevated transaminases
Cyclosporine	3-5-5 mg/kg/d in divided doses; trough 80-120 ng/ml*****	2-3 years	*Both:* Acute kidney injury, nephrotoxicity, hyperkalemia, hepatotoxicity
Tacrolimus	0.1-0.2 mg/kg/d in divided doses; trough 4-8 ng/ml*****	2-3 years	*Cyclosporine:* Gingival hyperplasia, hypertrichosis; hypertension; dyslipidemia *Tacrolimus*: tremors, seizures, headache; diarrhea; glucose intolerance; hypomagnesemia
Rituximab	375 mg/m^2 as slow IV infusion	2 doses one week apart$	Chills, fever; serum sickness, bronchospasm Neutropenia; *P. jirovecii* pneumonia; reactivation of hepatitis B, JC virus; acute lung injury; hypogammaglobulinemia

- What is difficult-to-treat nephrotic syndrome?
- What are the treatment options for this entity?

Dr Arpitha

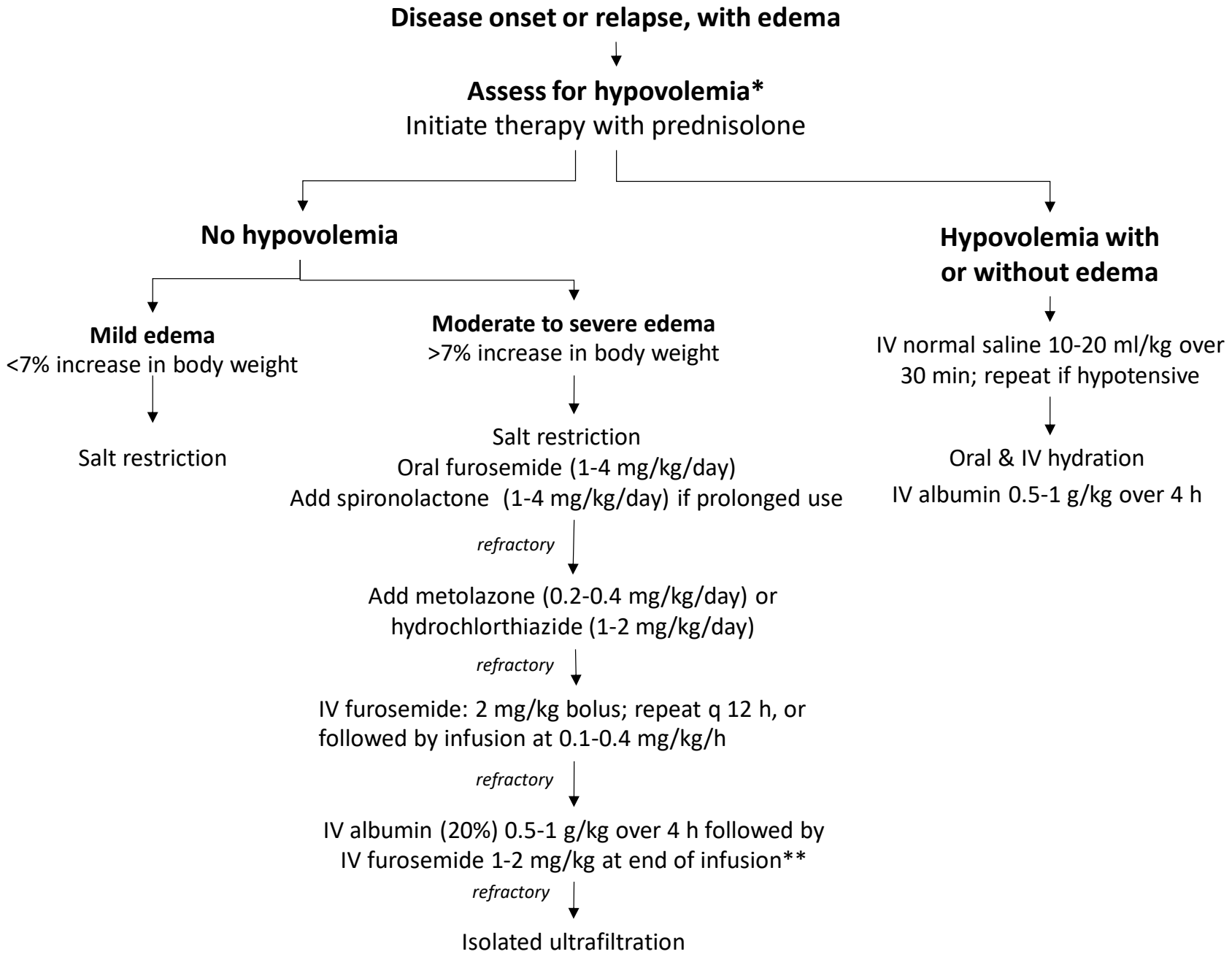
Difficult to treat steroid sensitive nephrotic syndrome

- Both of the following: (i) Relapsing disease, with either frequent relapses or infrequent relapses and significant steroid toxicity; and (ii) Failure of ≥2 steroid sparing agents (including levamisole, cyclophosphamide, MMF)
- **We recommend therapy with either cyclosporine or tacrolimus in patients with difficult-to-treat SSNS.**
- We recommend therapy with rituximab in patients who have either failed CNI or have received these agents for a prolonged duration.
- We suggest that therapy with rituximab be administered during disease remission after ruling out infections, and should target B cell depletion.

Case 5

- A 10 year old boy with FRNS on levamisole with prednisolone develops relapse
- Hemoglobin is 15 g/dL, BP 104/70 mm Hg
- He is severely edematous with scrotal edema and massive ascites
- He is prescribed furosemide for edema control elsewhere
- **Your comments? What are the treatment options for moderate to severe edema in nephrotic syndrome?**

Dr Narmadha


Disease onset or relapse, with edema
Assess for hypovolemia*
Initiate therapy with prednisolone
No hypovolemia
Hypovolemia with or without edema
Mild edema
<7% increase in body weight
Salt restriction
Moderate to severe edema
>7% increase in body weight
Salt restriction
Oral furosemide (1-4 mg/kg/day)
Add spironolactone (1-4 mg/kg/day) if prolonged use
refractory
Add metolazone (0.2-0.4 mg/kg/day) or hydrochlorthiazide (1-2 mg/kg/day)
refractory
IV furosemide: 2 mg/kg bolus; repeat q 12 h, or followed by infusion at 0.1-0.4 mg/kg/h
refractory
IV albumin (20%) 0.5-1 g/kg over 4 h followed by IV furosemide 1-2 mg/kg at end of infusion**
refractory
Isolated ultrafiltration
IV normal saline 10-20 ml/kg over 30 min; repeat if hypotensive
Oral & IV hydration
IV albumin 0.5-1 g/kg over 4 h

Guideline 6: Management of Hypovolemia and Edema

- **6.1 Hypovolemia**
- We recommend that patients with moderate to severe edema should be assessed for intravascular volume status (clinically/ labs) before initiating therapy with diuretics.
- We recommend the use of normal saline and IV albumin in patients with disease relapse and hypovolemia.
- **We suggest that patients with furosemide-refractory edema be managed (i) combination of loop diuretics with thiazide; (ii) co-administration of human albumin with IV furosemide**

Case 6

- A 2 year old child, follow up case of IFRNS presents with fever and diarrhea
- On examination, sick and toxic looking
- Abdominal examination- no tenderness
- Still, ascitic tap was done and revealed 250 neutrophils/cu.mm

- **Diagnosis?**
- **How could this complication have been prevented to a large extent?** **Dr Manasi**

Guideline 7: Infections and Immunization

- **7.1** We suggest that serious bacterial infections (peritonitis, pneumonia, cellulitis, etc) be managed appropriately as per guidelines

- 7.2 Immunization
- (i) age-appropriate killed, subunit and inactivated vaccines (including **Pneumococcal, varicella, influenza**);
- (ii) live vaccines following standard principles

- Killed, inactivated or subunit vaccines are not contraindicated, but may have reduced efficacy during immunosuppression.

- The risk of relapse following vaccination is negligible.

Vaccination schedule for Pneumococcal vaccine (previously unimmunised)

- **< 2 year old:**

2 doses of PCV-13 ≥8 weeks apart

0r

3 doses if first 2 doses were given at < 1 yr

- **2-6 years old**:

2 doses of PCV-13 ≥8 weeks apart

Then, 1 dose of PPSV-23 8 weeks later

- **≥ 6 years old:**

1 dose of PCV-13 followed by one dose of PPSV-23 8 weeks later

Principles of immunisation with live vaccines in nephrotic syndrome (ISPN 2021): avoid while on steroids in general

Immunosuppression	***Advice***
Receiving high dose prednisolone (≥2 mg/kg/d; ≥20 mg/day if >10 kg) for <14 d	Vaccinate immediately after discontinuing treatment
Receiving high dose prednisolone (≥2 mg/kg/d; ≥20 mg/day if >10 kg) for ≥14 d	Vaccinate 1-month after discontinuing corticosteroids
Receiving low-moderate dose prednisolone (<2 mg/kg/d or equivalent; <20 mg/d)	No live vaccines, until discontinuation of steroid therapy
Low-dose alternate day prednisolone and pressing need for vaccine	Live vaccine may be administered
Patients receiving cyclophosphamide	Avoid live vaccines until off therapy for 3 months
Patients receiving calcineurin inhibitors, levamisole or mycophenolate mofetil	Avoid live vaccines until off therapy for 1 month
Therapy with rituximab	Avoid live vaccines until after B-cell recovery (~6-9 months)
Immunocompetent siblings and household contacts	Do not administer oral polio vaccine; may receive measles-mumps-rubella, rotavirus and varicella vaccines
Household contacts older than one year	Administer influenza vaccine annually

What are the Long-term patient & kidney outcomes in SSNS? Dr Saravanan

- 2/3 may not have relapses beyond adolescence
- Risk factors for illness persisting beyond 18-yr of age include early age at onset, and FRNS and SDNS course
- Relapse during adulthood is usually not as frequent as during childhood, and the relapse rate decreases with age
- Kidney failure is uncommon (<1%) in patients with SSNS

Pediatr Nephrol. 2023;38:877-919.

Idiopathic Steroid resistant Nephrotic Syndrome of Childhood

Case 7

- 3-year-old child presents with clinical and biochemical features of nephrotic syndrome
- 6 weeks of daily prednisolone given @ 2 mg/kg/day
- Urine albumin 2+, edema present, serum albumin 2.5 g/dL
- **Diagnosis?**
- **Is renal biopsy essential?**
- **Should we do NGS?**

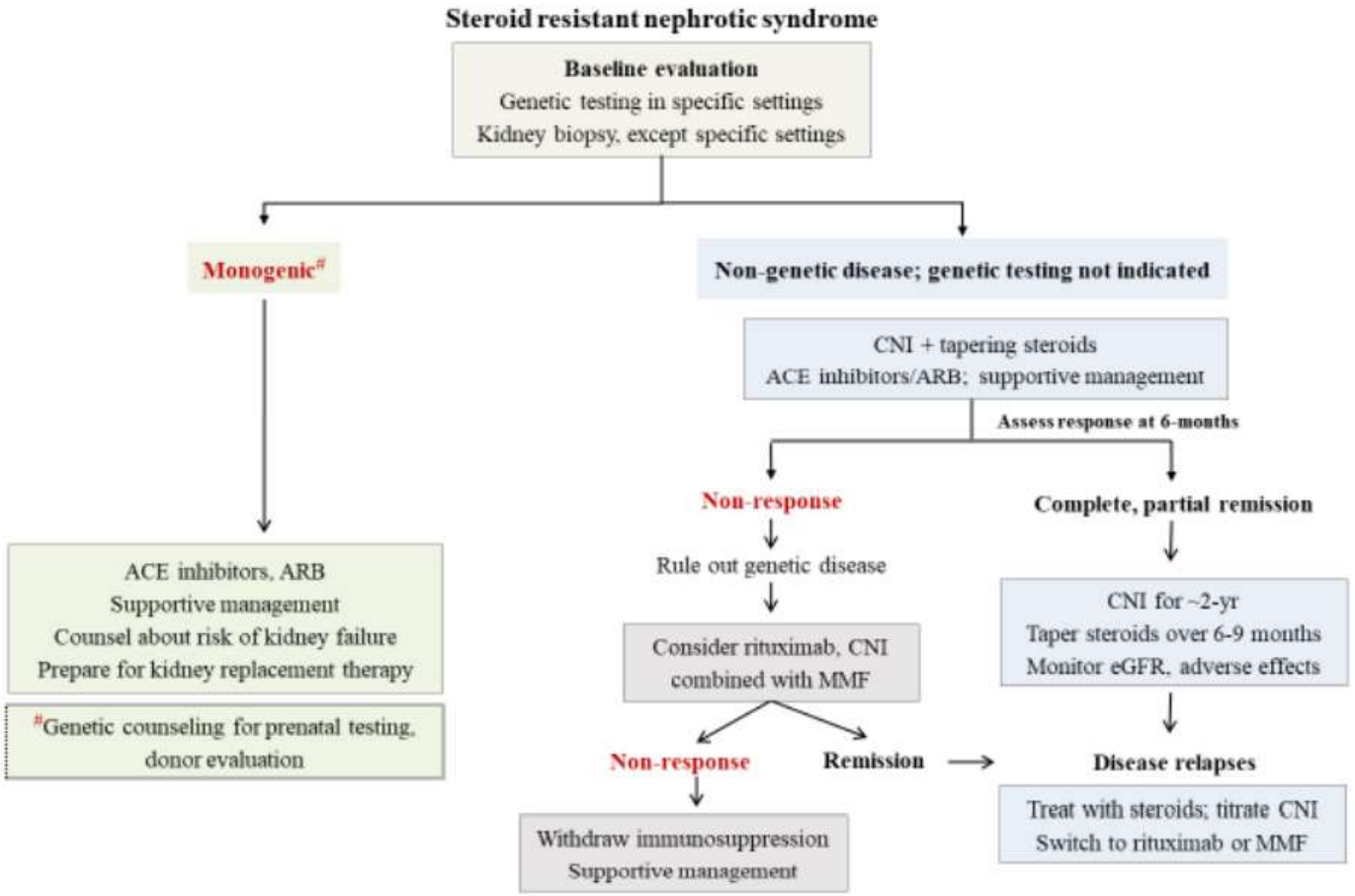
Dr Manasi

Guideline 1: Diagnosis of SRNS

- 1.1 We recommend that steroid-resistance be defined in patients not showing complete remission, despite 6-weeks treatment with prednisolone. 1B
- 1.2 We suggest similar definitions for initial and late (secondary) steroid-resistance. X (ungraded)

Guideline 2: Evaluation of patients

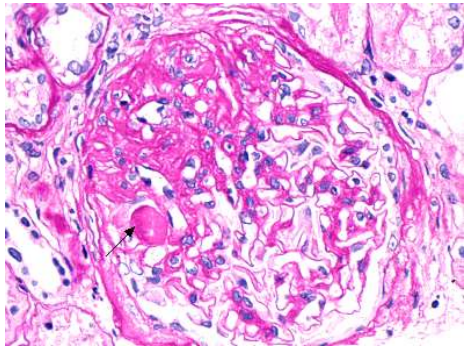
- We recommend the following in all patients with SRNS: Quantitation of proteinuria; serum creatinine; estimated glomerular filtration rate (eGFR); and kidney biopsy. 1A

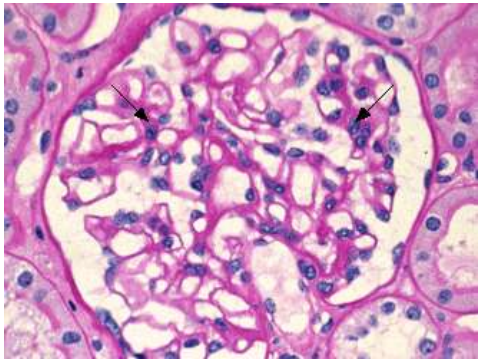


Kidney biopsy

Children with steroid resistance

FSGS 45-55%; MCD 30-35%





PodoNet; N=1655; **CJASN** 2015

Adults

Focal segmental glomerulosclerosis	22%
Membranous nephropathy	22%
IgA nephropathy	6%
MPGN	6%

Nephrology 2020; 25: 55–62

Guideline 3: Indications for genetic studies

- We recommend genetic studies in the following patients:

- Congenital nephrotic syndrome;
- initial resistance during infancy;
- nephrotic syndrome with extrarenal features;
- familial steroid-resistance;
- non-response to calcineurin inhibitors;
- prior to transplantation.

1B

Case 8

- A 10 year old boy with SRNS- initial resistance (FSGS on biopsy)
- **Which is the first line for immunosuppression in this child as per current guidelines?**

Dr Narmadha

Guideline 4: Therapy of patients with SRNS

- **We recommend calcineurin inhibitors (CNI) as first-line therapy for patients with initial or late steroid-resistance.** 1A
- We suggest continuing therapy with CNI for at least 24-months if partial or complete remission is achieved. 2C
- We suggest that CNI therapy should be withheld or discontinued for patients with AKI stage 2-3 or eGFR <60 ml/min/1.73 m^2. 2C

Efficacy of Treatment Regimes for SRNS

Drug	Dosage*	Remission
Calcineurin inhibitors		
Cyclosporine and prednisolone**	4-6 mg/kg/day in two divided doses for 2-3 years	50-80%
Tacrolimus and prednisolone**	0.12-0.15 mg/kg/day in two divided doses for 2-3 years	70-85%
Cyclophosphamide		
Oral cyclophosphamide and prednisolone**	2-3 mg/kg/day for 12 weeks	25-30%
IV cyclophosphamide and prednisolone**	500-750 mg /m^2 once every month for 6 months	40-65%
Pulse corticosteroids		
IV methylprednisolone, oral cyclophosphamide and prednisolone#	20-30 mg/kg for 6 alternate day pulses; then once a week for 8 doses, fortnightly for 4 doses, once a month for 8 doses; finally bimonthly for 4 doses	40-70%
IV dexamethasone, oral cyclophosphamide and prednisolone#	4-5 mg/kg for 6 alternate day pulses; then every fortnight for 4 doses; finally once a month for 8 doses	30-50%

** Dosage refers to that of the italicized agent; ** Prednisolone dose: 1.5 mg/kg on alternate days for 4 weeks; 1.25 mg/kg next 4 weeks; 1 mg/kg for 4 months; 0.5-0.75 mg/kg for 12-18 months; # Oral cyclophosphamide for 12 weeks (weeks 3-15); tapering doses of prednisolone over 12 months*

- **Are there alternative immunosuppressive therapies for SRNS?** **Dr Arpitha**

Guideline 5: Alternate immunosuppressive therapy

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

  2B

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

- **How do we treat CNI- resistant steroid resistant nephrotic syndrome?** **Dr Saravanan**

Guideline 6: Treatment of CNI-resistant nephrotic syndrome

- In patients with non-genetic forms of SRNS and non-response to therapy with CNI, we suggest additional treatment with:
- **either IV rituximab or oral mycophenolate mofetil.**

Cochrane 2019

Interventions for idiopathic steroid-resistant nephrotic syndrome in children

CSA vs placebo /no treatment	↑ CR or PR at 6 m 4 studies, n=74: RR 3.15, 95% CI 1.04 to 9.5 (LC)
CNI vs IV CP	↑ CR or PR at 3-6 m 2 studies, n=156: RR 1.98, 95% CI 1.25 to 3.13 (LC)
Tac vs CSA	no difference in CR/PR 2 studies, n=58: RR 1.05, 95% CI 0.87 to 1.25 (LC)
CSA vs MMF + Dexa	No difference in CR/PR 1 study, n=138: RR 2.14, 95% CI 0.87 to 5.24 (MC)
Oral CP + Pred vs Pred alone	No difference in CR 2 studies, n=84: RR 1.06, 95% CI 0.61 to 1.87) (LC)
IV CP vs. oral CP	No difference in CR 2 studies, n=61: RR 1.58, 95% CI 0.65 to 3.85 (LC)
IV CP vs. oral CP +IV Dexa	No difference in CR 1 study, n=49: RR 1.13, 95% CI 0.65 to 1.96 (LC)
RTX + CSA/Pred vs. CSA / Pred	No difference in % proteinuria reduction 31 children: -12; 95% CI -73 to 110 (vLC)
ACEi for proteinuria	Two studies reported significantly reduced proteinuria

TAC vs MMF (after 6 mo on TAC) (AIIMS) Kidney Int. 2017	Sustained remission, infrequent relapses at one year - MMF (44.8%) < TAC group (90.3%)

Case 9

- A 2 year old girl with CNI- resistant SRNS undergoes NGS
- Homozygous NPHS2 pathogenic mutation is identified.
- **Which immunosuppressive agent should be given further?** **Dr Narmadha**

Guideline 7: Immunosuppressive therapy with pathogenic or likely pathogenic variants

- We **do not recommend** that patients with confirmed mutation in podocyte genes receive therapy with calcineurin inhibitors or other immunosuppressive agents.

  1B

Genetic testing

Positive in 20-30%

80% are in *NPHS1, NPHS2, WT1, COQ2, PLCE1, LAMB2*

Table 3 Genes to be included in Next Generation Sequencing (from [8]) in a child with SRNS

Gene	Inheritance	Accession no.	Disease
*ACTN4**	AD	NM_004924	Familial and sporadic SRNS (usually adult)
*ADCK4**	AR	NM_024876	SRNS
ALG1	AR	NM_019109	Congenital disorder of glycosylation
ANKFY1	AR	NM_001330063.2	Pediatric SRNS
ANLN	AD	NM_018685	FSGS (mainly adult)
ARHGAP24	AD	NM_001025616	FSGS
ARHGDIA	AR	NM_001185078	CNS
AVIL	AR	NM_006576.3	SRNS
CD151	AR	NM_004357	NS, pretibial bullous skin lesions, neurosensory deafness, bilateral lacrimal duct stenosis, nail dystrophy, and thalassemia minor
CD2AP	AD/AR	NM_012120	FSGS/SRNS
CFH	AR	NM_000186	MPGN type II + NS
CLCN5	XR	NM_001127898.4	Dent's disease ± FSGS ± hypercalcuria and nepthrolithiasis
*COL4A3**	AR	NM_000091	Alport's disease/FSGS
COL4A4	AR	NM_000092	Alport's disease/FSGS
*COL4A5**	XR	NM_000495	Alport's disease/FSGS
COQ2	AR	NM_015697	Mitochondrial disease/isolated nephropathy
COQ6	AR	NM_182476	NS ± sensorineural deafness; DMS
*CRB2**	AR	NM_173689	SRNS
CUBN	AR	NM_001081	Intermittent nephrotic range proteinuria ± with epilepsy
*DGKE**	AR	NM_003647	Hemolytic-uremic syndrome, SRNS
DLC1	AR	NM_182643.3	Childhood and adult SSNS and SRNS
E2F3	AD	NM_001949	FSGS + mental retardation (whole gene deletion)
EMP2	AR	NM_001424	Childhood-onset SRNS and SSNS
FAT1	AR	NM_005245.4	Combination of SRNS, tubular ectasia, hematuria, and facultative
FN1	AD?	NM_212482.3	Fibronectin glomerulopathy
GAPVD1	AR	NM_001282680.3	Early-onset NS
INF2	AD	NM_022489	Familial and sporadic SRNS, FSGS-associated Charcot-Marie-Tooth neuropathy
ITGA3	AR	NM_002204	Congenital interstitial lung disease, nephrotic syndrome, and mild epidermolysis bullosa
ITGB4	AR	NM_000213	Epidermolysis bullosa and pyloric atresia + FSGS
ITSN1	AR	NM_003024.3	CNS/SRNS/SSNS (with MCD/FSGS on biopsy)
ITSN2	AR	NM_019595.4	SSNS/SDNS (with MCD/MPGN on biopsy)
KANK1	AR	NM_015158	SSNS
KANK2	AR	NM_015493	SSNS/SDNS ± hematuria
KANK4	AR	NM_181712	SRNS + hematuria
KIRREL1	AR	NM_018240.7	SRNS
LAGE3	AR	NM_006014.4	NS with primary microcephaly
LAMA5	AR	NM_005560.6	Childhood NS
*LAMB2**	AR	NM_002292	Pierson syndrome
LCAT	AR	NM_000229.2	Norum disease
LMNA	AD	NM_170707	Familial partial lipodystrophy + FSGS
*LMX1B**	AD	NM_002316	Nail patella syndrome; also FSGS without extrarenal involvement
MAFB	AD	NM_005461.5	FSGS with Duane retraction syndrome
MAGI2	AR	NM_012301.4	NS ± neurological impairment

Table 3 (continued)

Gene	Inheritance	Accession no.	Disease
MMACHC	AR	NM_015506.3	Cobalamin C deficiency, TMA, and nephrotic syndrome
*MYO1E**	AR	NM_004998	Familial SRNS
NEU1	AR	NM_000434.4	Nephrosialidosis (sialidosis type II + childhood NS)
NPHP4	AR	NM_015102.5	Nephronophthisis with FSGS and nephrotic range proteinuria
*NPHS1**	AR	NM_004646	CNS/SRNS
*NPHS2**	AR	NM_014625	CNS, SRNS
NUP85	AR	NM_024844.5	SRNS
*NUP93**	AR	NM_014669	Childhood SRNS
*NUP107**	AR	NM_020401	Childhood SRNS
NUP160	AR	NM_015231.2	SRNS
NUP205	AR	NM_015135	Childhood SRNS
NXF5	XR	NM_032946	FSGS with co-segregating heart block disorder
*OCRL**	XR	NM_000276	Dent's disease-2, Lowe syndrome, ± FSGS, ± nephrotic range proteinuria
OSGEP	AR	NM_017807.4	NS with primary microcephaly
PAX2	AD	NM_003987	Adult-onset FSGS without extrarenal manifestations
PDSS2	AR	NM_020381	Leigh syndrome
PLCe1	AR	NM_016341	CNS/SRNS
PMM2	AR	NM_000303	Congenital disorder of glycosylation
*PODXL**	AD	NM_005397	FSGS
PTPRO	AR	NM_030667	NS
SCARB2	AR	NM_005506	Action myoclonus renal failure syndrome ± hearing loss
SGPL1	AR	NM_003901.4	Primary adrenal insufficiency and SRNS
SMARCAL1	AR	NM_014140	Schimke immuno-osseous dysplasia
SYNPO	AD	NM_007286	Sporadic FSGS (promoter mutations)
TBC1D8B	XR	NM_017752.3	Early-onset SRNS with FSGS
TNS2	AR	NM_170754.3	SSNS/SDNS (with MCD/FSGS/DMS on biopsy)
TP53RK	AR	NM_033550.4	NS with primary microcephaly
TPRKB	AR	NM_001330389.1	NS with primary microcephaly
*TRPC6**	AD	NM_004621	Familial and sporadic SRNS (mainly adult)
TTC21B	AR	NM_024753	FSGS with tubulointerstitial involvement
WDR73	AR	NM_032856	Galloway-Mowat syndrome (microcephaly and SRNS)
*WT1**	AD	NM_024426	Sporadic SRNS (children may be associated with abnormal genitalia); Denys-Drash and Frasier syndrome
XPO5	AR	NM_020750	Childhood SRNS
ZMPSTE24	AR	NM_005857	Mandibuloacral dysplasia with FSGS
MYH9	AD/assoc.	NM_002473	MYH9-related disease; Epstein and Fechtner syndromes
*APOL1**	G1, G2 risk alleles	NM_003661	Increased susceptibility to FSGS and ESRD in African Americans, Hispanic Americans and in individuals of African descent

- What is the role of ACEI/ARB in SRNS patients? Dr Manasi

Guideline 8: Angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB)

- We recommend that all patients with SRNS should receive therapy with ACE inhibitors or ARB. 1B

Case 10

- A 16 year old girl SRNS-LR (age of onset being 2 years) presents with relapse after 1 year relapse free duration
- The eGFR is 120 mL/min/1.73 sq m
- The parents are anxious that she is still relapsing
- They were counselled elsewhere for renal transplant
- **Your comments?** **Dr Saravanan**

Guideline 13: Transplantation

- We recommend that kidney transplant be considered in all patients with **SRNS and chronic kidney disease stage-5.** 1B

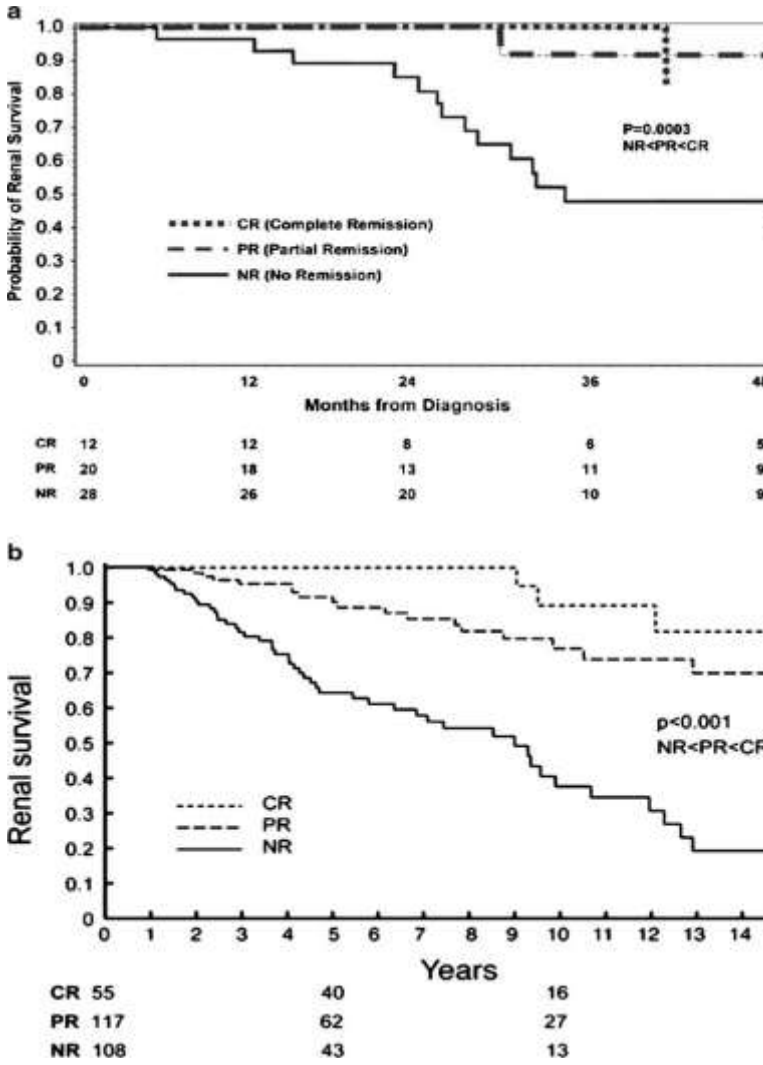
- We recommend that genetic testing be performed before transplant to assist in donor selection and predict the risk of recurrence in allograft. 1B

- What are the long-term outcomes of SRNS? Dr Arpitha

SRNS (FSGS) and probability of ESKD

- **In mutation negative SRNS (FSGS), at 5 years**
- If CR- 90 % have preserved eGFR
- If PR- 75 % have preserved eGFR
- If NR- Only 45 % have preserved eGFR

- **In mutation positive SRNS (FSGS), at 5 years**
- 75 % will progress to ESKD



Steroid resistant nephrotic syndrome: Summary

	ISPN guidelines 2021
Definition	6 weeks daily prednisone
Kidney biopsy	All; except if monogenic SRNS identified
Genetic testing	Specific subsets of initial SRNS, congenital NS; not in late SRNS
Monogenic SRNS	Therapy not advised; may continue after counseling if partial remission
eGFR	Avoid immunosuppression if eGFR<60
CsA, tacrolimus	Duration of therapy at least 2-yr
Cyclophosphamide	IV may be used; oral not advised
Indications for MMF	(i) Prolonged CNI use & relapses; (ii) CNI-resistant SRNS
Rituximab	(i) Prolonged CNI use & relapses; (ii) CNI-resistant; (iii) allograft recurrence

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Key messages

- Rational treatment of SSNS and SRNS (ISPN 2021 guidelines); use steroids and alternate immunosuppressive agents according to these guidelines
- Immunise all nephrotic syndrome children against pneumococcus, varicella and influenza
- Use diuretics judiciously: Avoid diuretics if hemoconcentration or hypovolemia
- Kidney biopsy/ NGS in nephrotic syndrome is indicated in specific situations
- Monitor for steroid toxicity as well as adverse effects of alternate agents
- Growth monitoring, BP monitoring, ophthalmological screening essential in these children
- Watch for infections, thrombotic complications and AKI in these children

Thank You