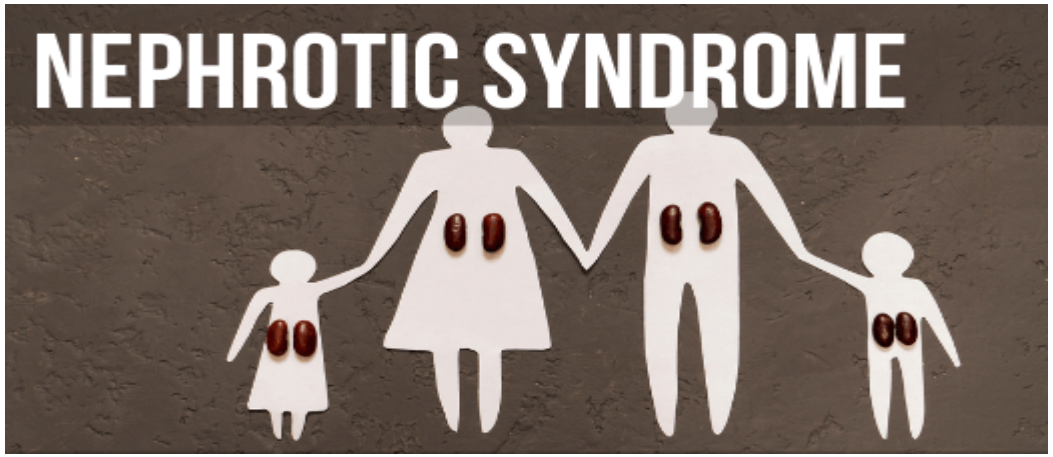
No conflict of interest

Updates on Steroid Sensitive Nephrotic Syndrome Management



Ajaya Kumar Dhakal, FISN

- A 5 year old child diagnosed with nephrotic syndrome. Before you started Prednisolone, the child went in to the spontaneous remission.

- Will you start Prednisolone?

- NS is common kidney diseases in children.
- Manifestations of systemic illness in 5-10% of patients.
- One third still have active disease when reaching adulthood.
- Relapses of SSNS - no detrimental effect on kidney function.

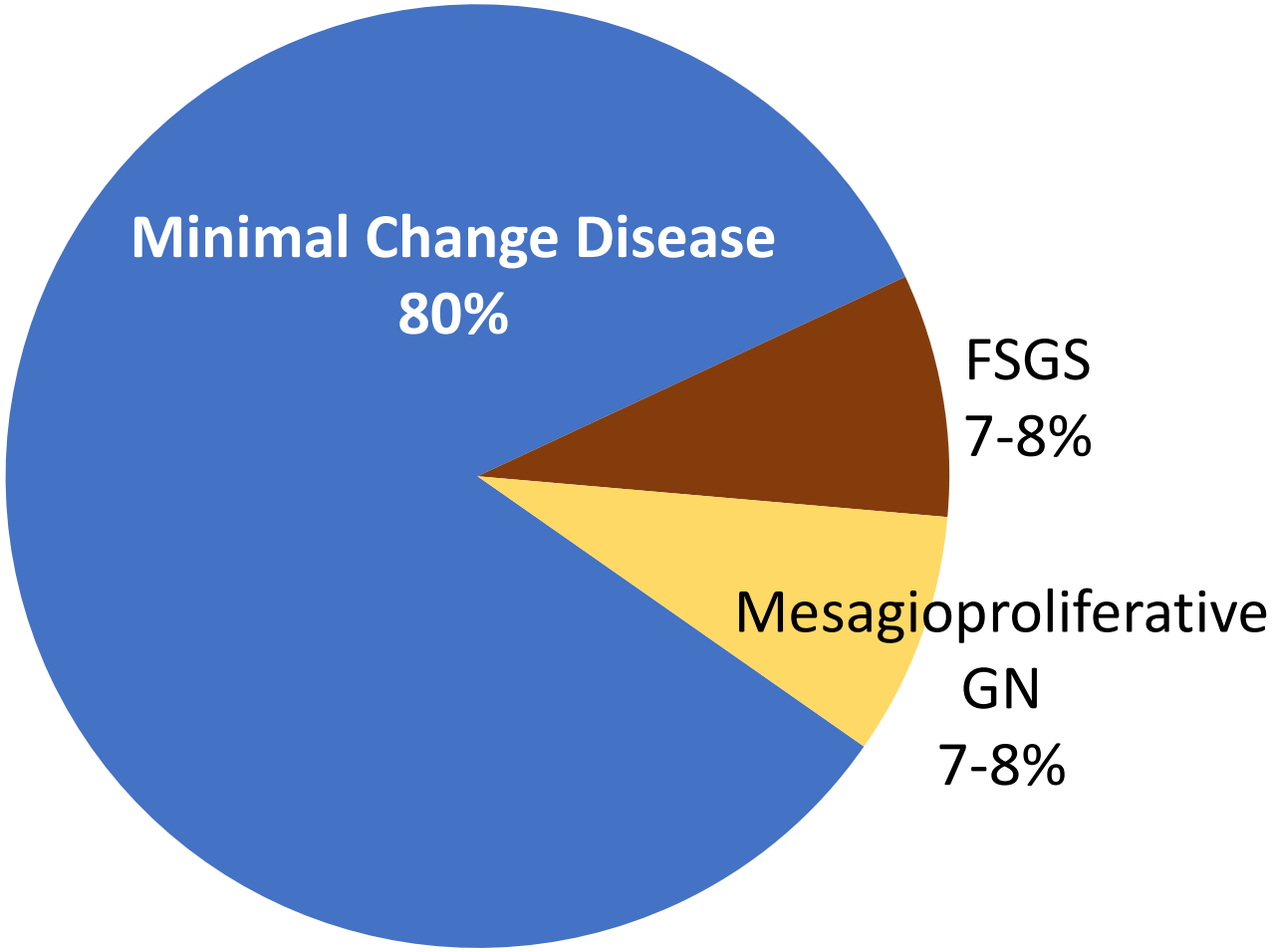
Different guidelines

- ISPN – Indian Society of Pediatric Nephrology
- IPNA- International Pediatric Nephrology Association
- KDIGO = Kidney Disease Improving Global Outcome

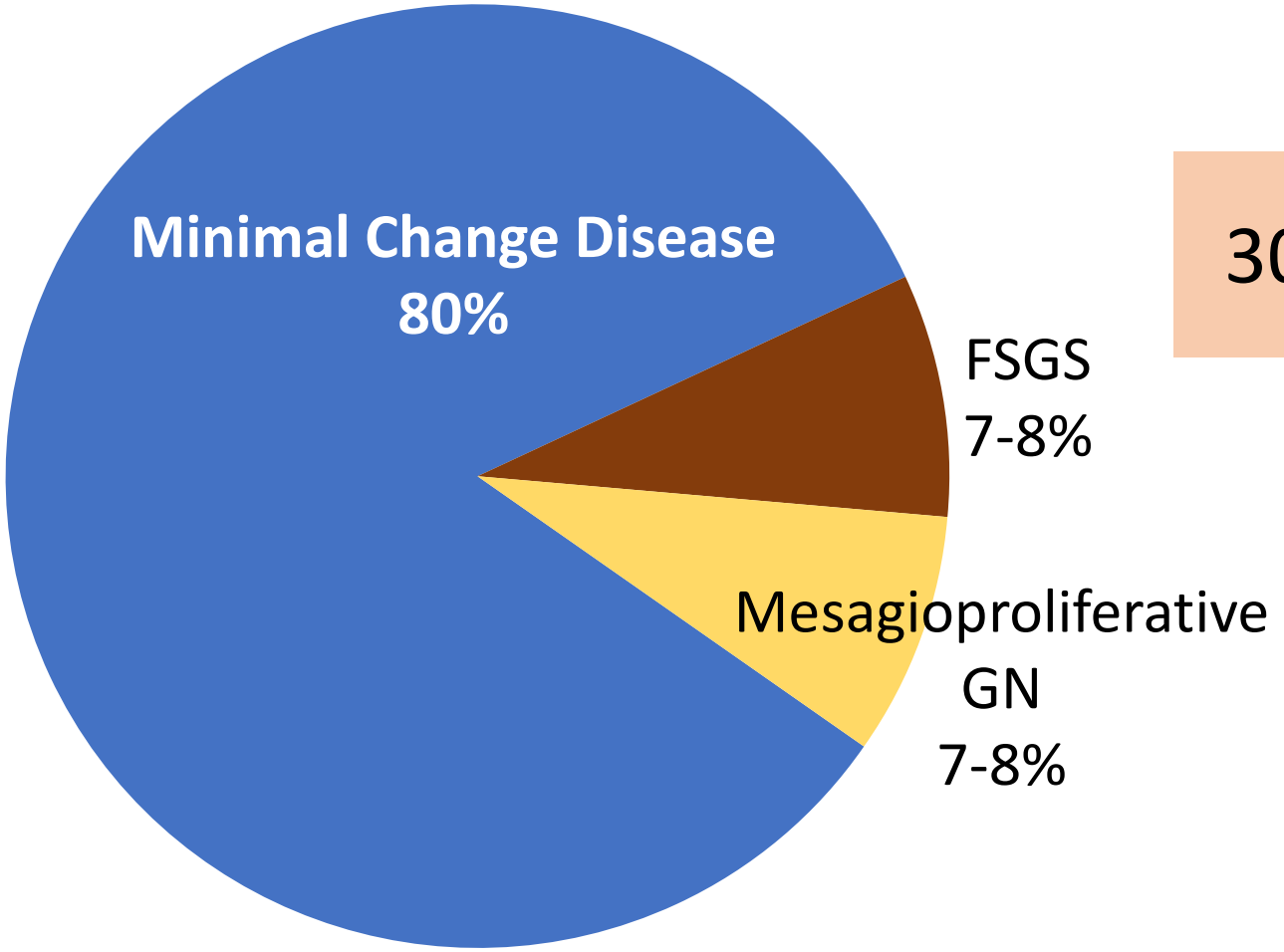
Nephrotic syndrome

Traditional	ISPN 2021	KDIGO 2021	IPNA 2023
Nephrotic range proteinuria Hypoalbuminemia (<2.5 g/dl) Cholesterol > 200mg/dl **and** Edema	Nephrotic range proteinuria Hypoalbuminemia (<3 g/dl) **and** Edema	Nephrotic range proteinuria **And** Either Hypoalbuminemia (<3 g/dl) or Edema when serum albumin not available	Nephrotic range proteinuria **and** Either Hypoalbuminemia (<3 g/dl) or Edema when serum albumin not available

Histopathology



Histopathology Vs Steroid sensitivity



90%

30%

50%

Course

85-90%
Steroid Sensitive

60-80%
Develop Relapse

30-50%
Infrequent relapse

30-50%
Frequent relapse or
Steroid dependence

3-10%
Late steroid
resistance

Investigations

Essential at onset

- Urinalysis
- 24 hour protein or UPCR – Nephrotic range uncertain
- Complete blood counts
- Blood urea nitrogen, creatinine, electrolytes, serum albumin, total protein, cholesterol
- Tuberculin test
- Ultrasound

IPNA –
Serum cholesterol not recommended

ISPN-
USG only if biopsy , RVT, gross hematuria

ISPN 2021

IPNA 2023

KDIGO 2021

Investigations

Additional evaluation at onset

- **Chest x- ray** – TB suspected or positive tuberculin test, lymphoma.
- **Complement C3, C4, ANA, ASOT** and **ANCA** – gross hematuria, HTN, IgA suspected.
- **Serum transaminases**- jaundice, liver disease, HBsAg, HCV infection

Periodic monitoring

Frequently relapsing or SDNS: Urea, creatinine, serum albumin, electrolytes

ISPN 2021

IPNA 2022

KDIGO 2021

Genetic testing at presentation

- Congenital NS, family history
- Consider Infantile onset NS (age 3–12 months)
- SRNS patients

Eg: NPHS 1 and NPHS 2
WT1

IPNA 2023

Table 1. Summary of genetic testing modalities

	Target and resolution	Detects	Advantages	Disadvantage
Karyotyping	Genome ≥10Mb	Aneuploidies, chromosomal abnormalities	Low cost Detects balanced translocations	Low resolution
Chromosomal microarray	Genome ≥200 kb–400 kb	Small chromosomal rearrangements/CNVs Detects regions of homozygosity in SNP based array	High resolution for CNVs	Limited ability to detect inversions and balanced translocations CNVs in repetitive regions and pseudogenes
Sanger sequencing	Specific gene Single base	SNVs/small INDELs (<1 kb)	Targeted, rapid and simple interpretation High accuracy (error rate 0.001–1%)	Low throughput Labor intensive
Massive parellel sequencing (Second generation sequencing, NGS)				
Targeted gene panel	Specific gene of interest for the clinical phenotype Single base	SNVs/small INDELs (<1 kb)	Targeted high throughput Reduced analysis time Minimize potential detection of secondary and incidental findings	Unable to identify genes not on panel Limited potential for reanalysis
Exome sequencing	Coding regions of the genome (exome) Single base	SNV/small INDELs (<1 kb)	Covers entire coding regions of genome Useful for reanalysis	Coverage per base is generally lower than with targeted panels Misses noncoding variants Low limited detection in CG-rich and repetitive regions Potential detection of undesired secondary and incidental findings
Genome sequencing	Coding and noncoding regions of the genome	SNV/small INDELs (<1 kb), CNV	Identification of deep splicing and intronic variants Identification of structural variants	High costs Generates large amount of data Potential detection of undesired

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Genetic testing in Nepal

- Available in Nepal recently - outsourcing
- FSGS panel – Rs 35000 - 36 genes
- WES costs – Rs 48000
- Done in few patients – Col A4 mutations
- Results expected – 6 to 12 weeks

Kidney Biopsy

- **SRNS**
- **Nephrotic syndrome with *secondary features / atypical features*** - macroscopic hematuria, low C3 levels, AKI not related to hypovolemia, sustained hypertension, arthritis and/or rash
- Infantile onset NS if genetic screening is not available (age 3–12 months).
- >12 years of age on a case-by-case basis.

Kidney Biopsy

- Kidney biopsy – Light microscopy , Immunofluorescence, electron microscopy.
- LM, IF – available in Nepal
- EM - India

Nepalese Scenario

Table 2. Histopathological appearance in nephrotic syndrome

	SRNS	SDNS	FRNS	Nephrotic syndrome with atypical features
Minimal change disease	2	6	1	2
Focal segmental glomerulosclerosis	3	2	0	3
Membranoproliferative glomerulonephritis	1	0	0	0
Mesangioproliferative glomerulonephritis	0	0	0	1
Membranous nephropathy	1	0	0	0
IgA nephropathy	1	0	0	1
IgG nephropathy	0	0	1	0
Total (n=25)	8	8	2	7

Shrestha D, Dhakal AK, Basnet NB, et al. Histopathological audit of renal biopsy in Nepalese children: two center experience. J Pathol Nep 2018;18:1244-50.

Nepalese Scenario

Table 3. Spectrum of glomerular diseases and their clinical presentation

INDICATIONS / FINAL DIAGNOSES	Nephrotic Syndrome
Lupus Nephritis	1(2.77%)
Minimal Change Disease	19(52.77%)
IgA Nephropathy	3(8.33%)
Focal Segmental Glomerulosclerosis	8(22.22%)
Crescentic GN	1(2.77%)
Membranoproliferative GN	2(5.55%)
Postinfectious GN	
Membranous Nephropathy	1(2.77%)
Thrombotic Microangiopathy	
Acute Kidney Injury	
Henoch-Schonlein Purpura Nephritis	
IgM Nephropathy	

Amatya M, Pant AD .Clinical and histopathological study of renal biopsy in Nepalese children: A single center experience. PLoS ONE 2022;17(10).

Table 4. Histological appearance in children in relation to indication for biopsy other than nephrotic syndrome

J Pathol Nep 2018

	Mixed nephritic-nephrotic features
IgA Nephropathy	6
Diffuse proliferative glomerulonephritis	8
Lupus nephritis	1
HSP nephritis	0
Mesangioproliferative glomerulonephritis	3
Crescentic glomerulonephritis	0
Membranoproliferative glomerulonephritis	1
Minimal change disease	1
Normal histology	0

PLoS One 2022

INDICATIONS / FINAL DIAGNOSES	Nephrotic proteinuria + hematuria
Lupus Nephritis	
Minimal Change Disease	
IgA Nephropathy	1(25%)
Focal Segmental Glomerulosclerosis	1(25%)
Crescentic GN	1(25%)
Membranoproliferative GN	1(25%)
Postinfectious GN	
Membranous Nephropathy	
Thrombotic Microangiopathy	
Acute Kidney Injury	
Henoch-Schonlein Purpura Nephritis	
IgM Nephropathy	

Table 1 Clinical characteristics and laboratory parameters at presentation

Clinical Features	N=77	Frequency (%)
Hypoalbuminemia (<2.5 gm/dl)		7 (9.1%)
Hyponatremia		7 (9.1%)
Hypoalbuminemia + Nephrotic range proteinuria		5 (6.5%)
Hypoalbuminemia + Nephrotic range Proteinuria + Hypercholesterolemia		1 (1.3%)
Quantitative proteinuria		
Nephrotic range	21 (27.3%)	
Subnephrotic range	16 (20.8%)	

PSGN may atypically presents as Nephrotic syndrome- treatment of PSGN resolves the symptoms without needing steroids

Dhakal AK, Shrestha D, Singh SK, Acharya S. Clinical profile of children with acute post-streptococcal glomerulonephritis. Pediatric Nephrology. 2023 May 2:1-0.

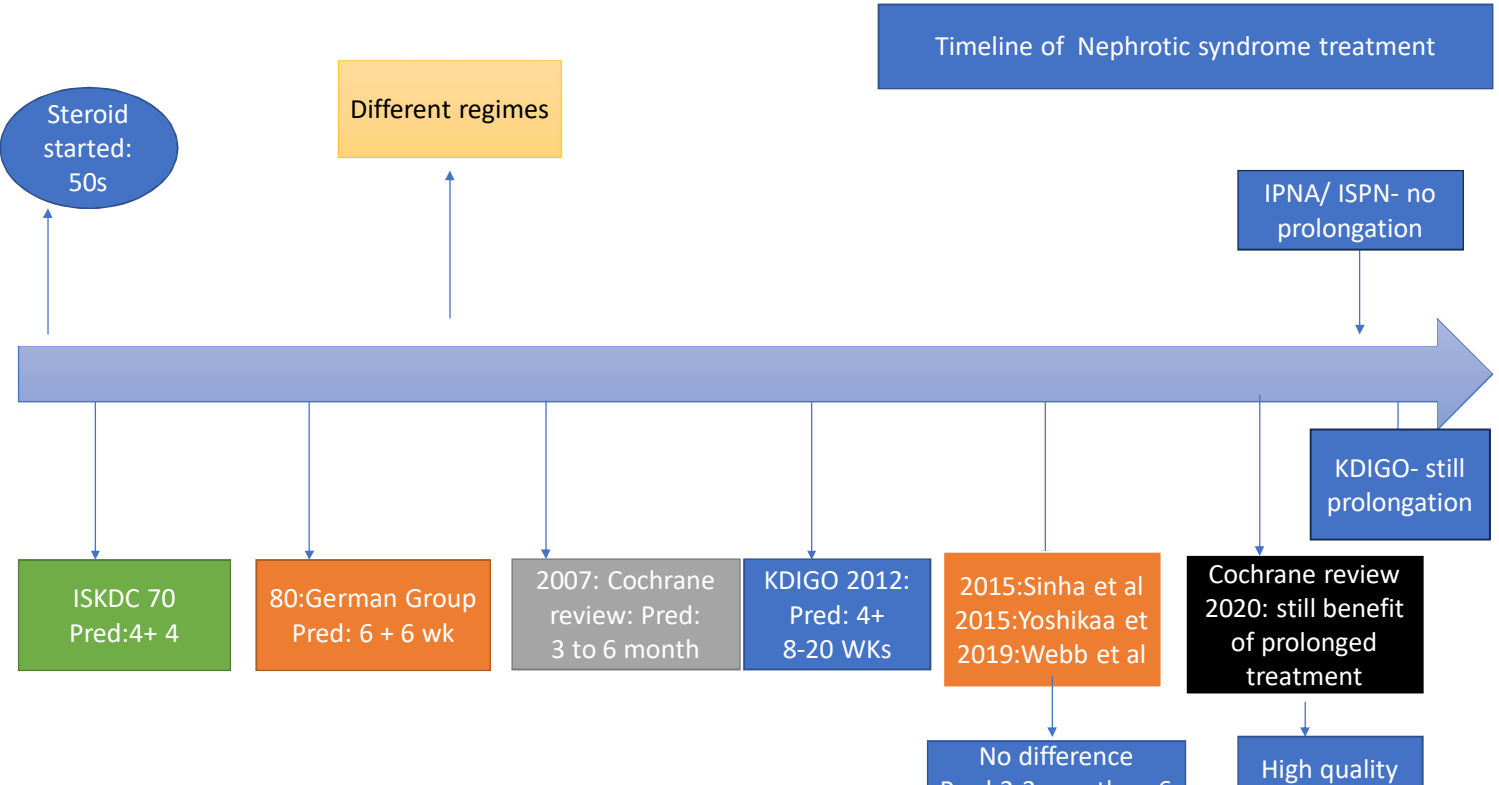
Beware

- PSGN
- IgA nephropathy
- HSP nephritis
- SLE

This disease presenting as nephrotic syndrome is common in Nepal.

Exact data – not available

Treatment aspects


Timeline of Nephrotic syndrome treatment
Steroid started: 50s
Different regimes
IPNA/ ISPN- no prolongation
KDIGO- still prolongation
ISKDC 70 Pred:4+ 4
80:German Group Pred: 6 + 6 wk
2007: Cochrane review: Pred: 3 to 6 month
KDIGO 2012: Pred: 4+ 8-20 WKs
2015:Sinha et al 2015:Yoshikaa et 2019:Webb et al
Cochrane review 2020: still benefit of prolonged treatment
No difference
High quality

Treatment: First episode

ISPN 2008	ISPN 2021	KDIGO 2021	IPNA 2023
6-wk daily and 6-wk alternate days Weight-based dosing. no prolonged therapy.	**6-wk daily** **and** **6-wk AD** Body surface area (BSA) or weight-based dosing. No prolonged therapy	**4-6 wk daily** **and** **4-6 wk AD** Body surface area (BSA) or weight-based dosing. Prolonged therapy (16-24 wk) if <4-6 year old or if delayed remission	**4-6 wk daily** **and** **4-6 wk AD** Body surface area (BSA) or weight-based dosing No prolongation of therapy

General consideration

- Daily : 60 mg/m^2 or 2 mg/kg (maximum dose 60 mg/day)
- Alternate day: 40 mg/m^2 or 1.5 mg/kg (maximum dose of 40 mg)
- Recent studies : Weight based dosing Vs Body surface area (better)

General consideration

- Prednisolone dosing-
  - Daily - Single or divided-doses (ISPN) / Single dose (IPNA , KDIGO)
  - Alternate- Single morning doses (ISN/IPNA/KDIGO)
- Use of deflazacort, betamethasone, dexamethasone or methylprednisolone is not advised
- Prednisolone is best given following food
- Antacids, ranitidine or proton pump inhibitors is not routinely required

Steroid resistance

Parameter	ISPN 2008	ISPN 2021	KDIGO 2021	IPNA 2023
Steroid resistance -Lack of complete remission despite daily therapy with prednisolone - Duration require	4 week	6 week	4 week	4 week

Treatment: First Relapses / Infrequent relapses

ISPN 2021	KDIGO 2021	IPNA 2023
Prednisolone- 60 mg/m^2/day or (2mg/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	**Same**	**Same**

Steroid during Intercurrent infections

ISPN 2021	KDIGO 2021	IPNA 2023
Daily for 5-7 days , if receiving AD prednisolone	Daily at 0.5 mg/kg for 5-7 days whether on /off steroids	No steroid during URTI if off steroid Short course daily if on steroid and history of infection associated relapse

Randomized Controlled Trial > JAMA Pediatr. 2022 Mar 1;176(3):236-243.
doi: 10.1001/jamapediatrics.2021.5189.

Evaluation of Daily Low-Dose Prednisolone During Upper Respiratory Tract Infection to Prevent Relapse in Children With Relapsing Steroid-Sensitive Nephrotic Syndrome: The PREDNOS 2 Randomized Clinical Trial

Martin T Christian [1], Nicholas J A Webb [2], Samir Mehta [3], Rebecca L Woolley [3], Nafsika Afentou [4], Emma Frew [4], Elizabeth A Brettell [3], Adam R Khan [3], David V Milford [5], Detlef Bockenhauer [6 7], Moin A Saleem [8 9], Angela S Hall [10], Ania Koziell [11 12], Heather Maxwell [13], Shivaram Hegde [14], Hitesh Prajapati [15], Rodney D Gilbert [16], Caroline Jones [17], Karl McKeever [18], Wendy Cook [19], Natalie Ives [3]

Frequently relapsing NS

ISPN 2021	KDIGO 2021	IPNA 2023
≥ 2 relapses in first 6 months after initial therapy ≥ 3 relapses in any 6 months ≥4 relapses in 1 year	≥ 2 relapses in first 6 months ≥4 relapses in 1 year	≥2 relapses in the first 6-months following remission of the initial therapy ≥3 relapses in any 12 months

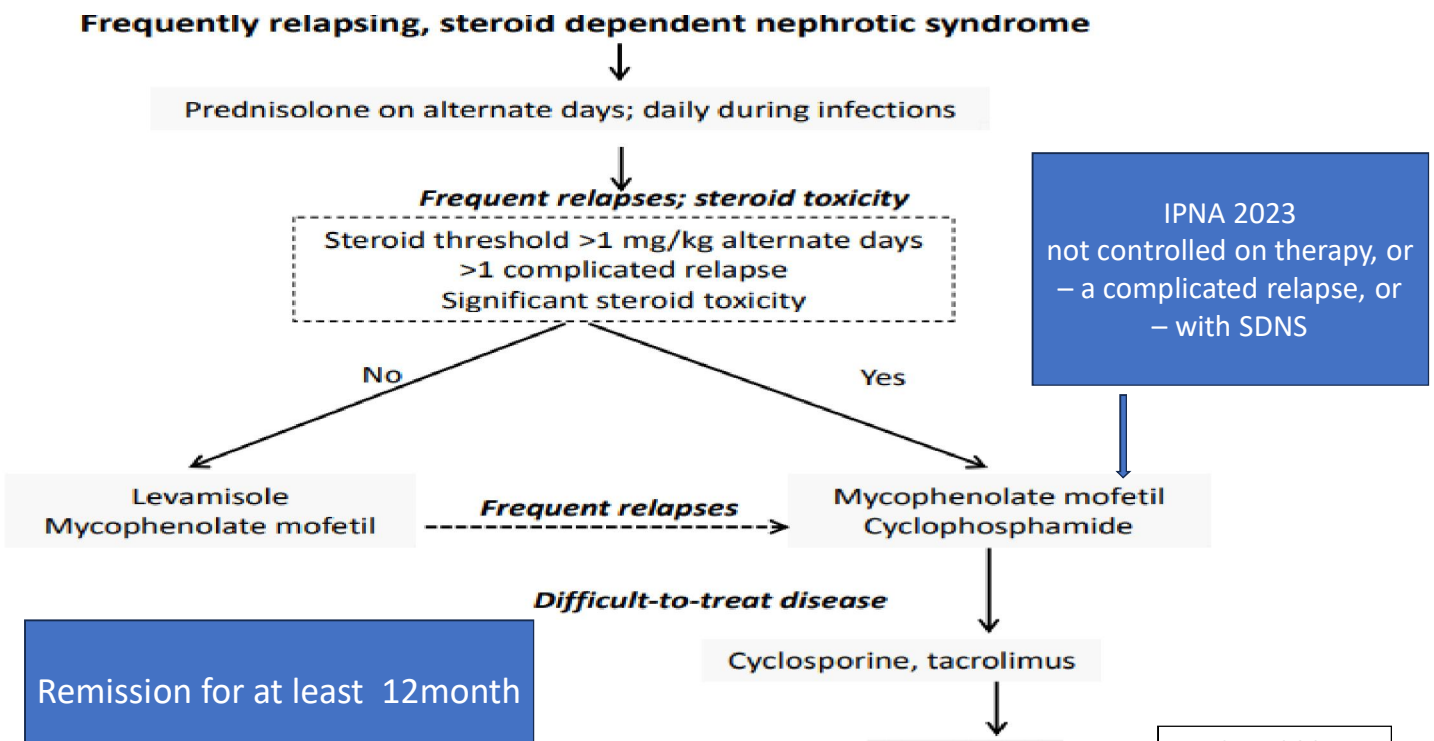
Steroid dependent NS

SSNS who experiences 2 consecutive relapses during recommended PDN therapy for first presentation

or relapse

or within 14 days of its discontinuation

ISPN 2021	Taper to 0.5-0.7 mg/kg AD for 6-12 months
KDIGO 2021	Limited role in view of risk of toxicity
IPNA 2023	Taper to 0.5 mg/kg AD for 6-12 months (Max 20 mg)


Frequently relapsing, steroid dependent nephrotic syndrome
Prednisolone on alternate days; daily during infections
Frequent relapses; steroid toxicity
Steroid threshold >1 mg/kg alternate days
>1 complicated relapse
Significant steroid toxicity
No
Yes
IPNA 2023
not controlled on therapy, or
– a complicated relapse, or
– with SDNS
Levamisole
Mycophenolate mofetil
Frequent relapses
Mycophenolate mofetil
Cyclophosphamide
Difficult-to-treat disease
Cyclosporine, tacrolimus
Remission for at least 12month

Constraints

- Levamisole is as effective as MMF in FRNS *(Sinha A et al. Kidney Int. 2019)*
  - not readily available

- Oral cyclophosphamide is not readily available

- We have been using MMF as steroid sparing agents. We have not encountered any major side effect.

- Cost is an issues.

- We have use rituximab in three kids with SDNS – good response

(cost: 45000 thousands)

- Kidney biopsy prior to initiating therapy with CNI. (**DISAGREEMENTS**)
  - ISPN – Biopsy needed
  - IPNA / KDIGO- No Biopsy

- CNI more than two years needs biopsy (IPNA / KDIGO /ISPN)

- Frequent Relapses / SDNS patients do not require a biopsy before
  - Levamisole,
  - Cyclophosphamide,
  - Mycophenolate mofetil (MMF)
  - Rituximab.

Is Age an indication for performing a kidney biopsy?

- 12-years or above
  - Adolescent onset nephrotic syndrome: persistent microscopic hematuria, low C3 and steroid resistance

- 1 year or below
  - Infant likely have other than minimal change disease history
  - Non availability of genetic tests

Patient education

- Counselling- disease, prognosis

- Teach parents
  - Dipsticks + Features of relapse

  - Home monitoring:
    - record relapse
    - medications and febrile illness

- Sun protection measures - on maintenance immunosuppression with steroid-sparing agents.

- Regular physical activity to prevent thromboembolic events, weight gain on steroid, and loss of muscle and bone mass.

- Healthy nutrition (avoiding high fat and/or high caloric food) while on steroids.
- A low salt diet during relapse with moderate or severe edema, and normal salt intake while in remission.
- Dietary protein intake = general pediatric population.
- Calcium- inadequate calcium intake and vitamin D – deficient - supplementation

Risk of relapse

- At 1 year : 70-90% relapses
- Younger than 6 year have more severe course: trial ongoing
- Relapses decreases with age

- Presence of IgM on surface T lymphocytes thought to predicter of relapse but needs large studies.

- Chances of SDNS /FRNS- SRNS

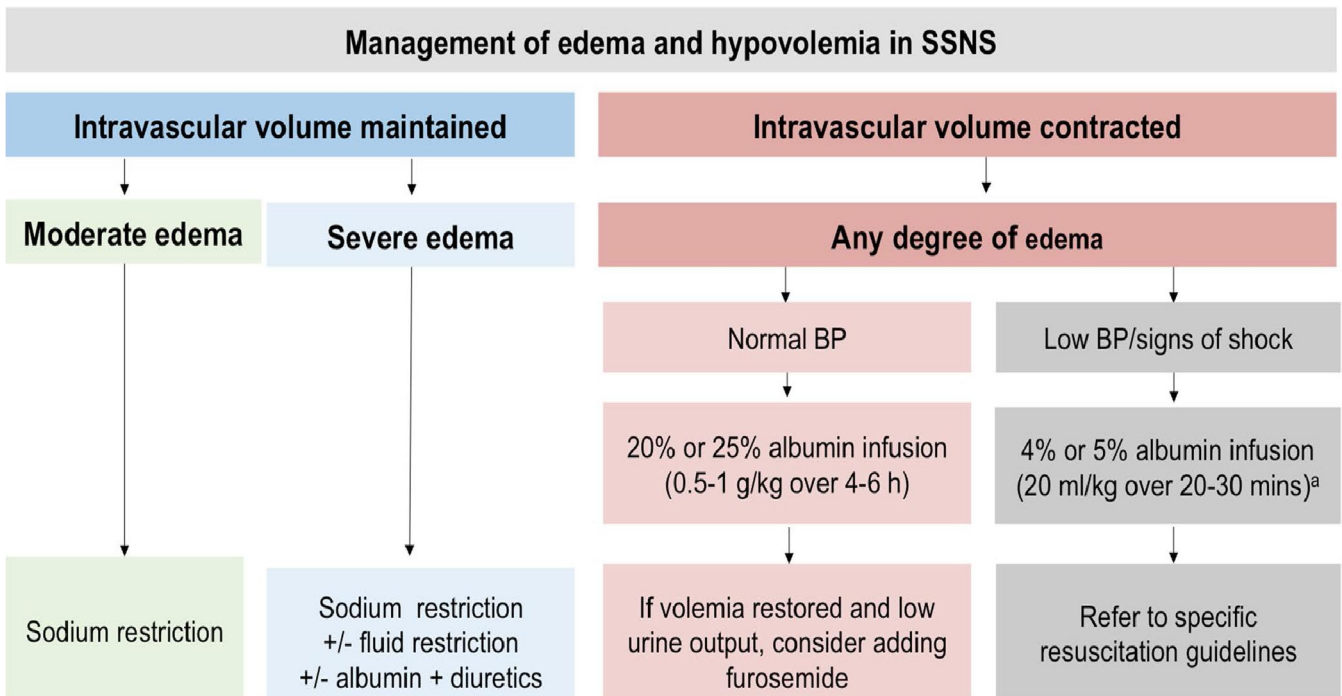
Complications of Nephrotic syndrome

Direct complications of Nephrotic

- Hypovolemia
- Anasarca
- Infections
- Renal insufficiency
- Thromboembolism

Medication related complications

- Steroids
- Immunosuppressives


Management of edema and hypovolemia in SSNS
Intravascular volume maintained
Intravascular volume contracted
Moderate edema
Severe edema
Any degree of edema
Normal BP
Low BP/signs of shock
20% or 25% albumin infusion (0.5-1 g/kg over 4-6 h)
4% or 5% albumin infusion (20 ml/kg over 20-30 mins)a
Sodium restriction
Sodium restriction +/- fluid restriction +/- albumin + diuretics
If volemia restored and low urine output, consider adding furosemide
Refer to specific resuscitation guidelines

Management of serious infections

ISPN 2021

Infections	*Organisms*	*Diagnosis*	*Treatment*
Peritonitis	*S. pneumoniae, S. pyogenes E. coli,* Gram negative bacteria	Ascitic fluid: >100 white cells/mm^3, >50% neutrophils Ascitic fluid: Culture, latex agglutination, PCR	Ceftriaxone or cefotaxime for 7-10 d Ampicillin and gentamicin/amikacin for 7-10 d[a]
Pneumonia	*S. pneumoniae, S. aureus, H. influenzae* Influenza H1N1 *M. tuberculosis*	Chest X ray; blood culture; sputum for Gram stain and culture Throat swab for H1N1 by PCR Tuberculin test; pleural tap, gastric aspirate, sputum: acid fast bacilli, CBNAAT	Oral: Amoxicillin, coamoxiclav, cefuroxime for 10-14 d[^] Parenteral: Ceftriaxone; or ampicillin and amikacin for 7-10 d[^] Oseltamivir for 5 d Therapy as per National Tuberculosis Elimination Program [16]
Cellulitis	*S. aureus, S. pyogenes H. influenzae* Gram negative bacteria	Pus for culture, sensitivity Blood culture	Parenteral: Coamoxiclav; cloxacillin with ceftriaxone for 7-10 d[^]
Sepsis	*S. pneumoniae,* Gram negative bacteria	Complete blood counts; C-reactive protein, procalcitonin; blood culture	Ceftriaxone and amikacin for 10-14 d
Varicella	Varicella zoster virus	Clinical	IV acyclovir (1500 mg/m^2/day in three doses) or oral acyclovir (80 mg/kg/day in four doses) for 7-10 d

Original Article | Published: 15 May 2019

Randomized controlled trial on immunomodulatory effects of azithromycin in children with steroid-dependent nephrotic syndrome

Happy Sawires, Hanan Abdelaziz, Heba Mostafa Ahmed, Osama Botrous & Michael Agban

Pediatric Nephrology **34**, 1591–1597 (2019) | Cite this article

effects of azithromycin in children with steroid-dependent nephrotic syndrome

- Nephrotic syndrome
    - Mumps
    - Varicella

Live vaccines immunization in Nephrotic Syndrome

ISPN 2021

Immunosuppression	Advice
Receiving high dose prednisolone (≥2 mg/kg/day; ≥20 mg /day if >10 kg) for <14 days	Vaccinate immediately after discontinuing treatment
Receiving high dose prednisolone (≥2 mg/kg/day; ≥20 mg /day if >10 kg) for ≥14 day	Vaccinate 1 –month after discontinuing corticosteroids
Receiving low – moderate dose of prednisolone (<2 mg/kg/day or equivalent ; <20 mg/day)	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 CNI, MMF, Levamisole	Avoid live vaccines until off therapy for 1 months
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 MMR, Rotavirus, Varicella vaccines
Household contacts older than one year	Administer influenzae vaccine annually

Vaccination

- Chickenpox
- Meningococcal
- Hemophilus influenzae
- Infleunza vaccine
- Pneumococcal vaccine

Case 1:

- A 5 year old child diagnosed with nephrotic syndrome. Before you started Prednisolone, the child went in to the remission.

- Will you start Prednisolone?

Case 2.

- A 5 year old child diagnosed with first episode of nephrotic syndrome. You started Prednisolone, the child went in to the remission (D14). However, the prednisolone was stopped D16 by parents.

- Now, came 4 months later with swelling for few days, found to have a relapse.

- How will you treat this child?
  - as a first relapse or treat again as a first episode

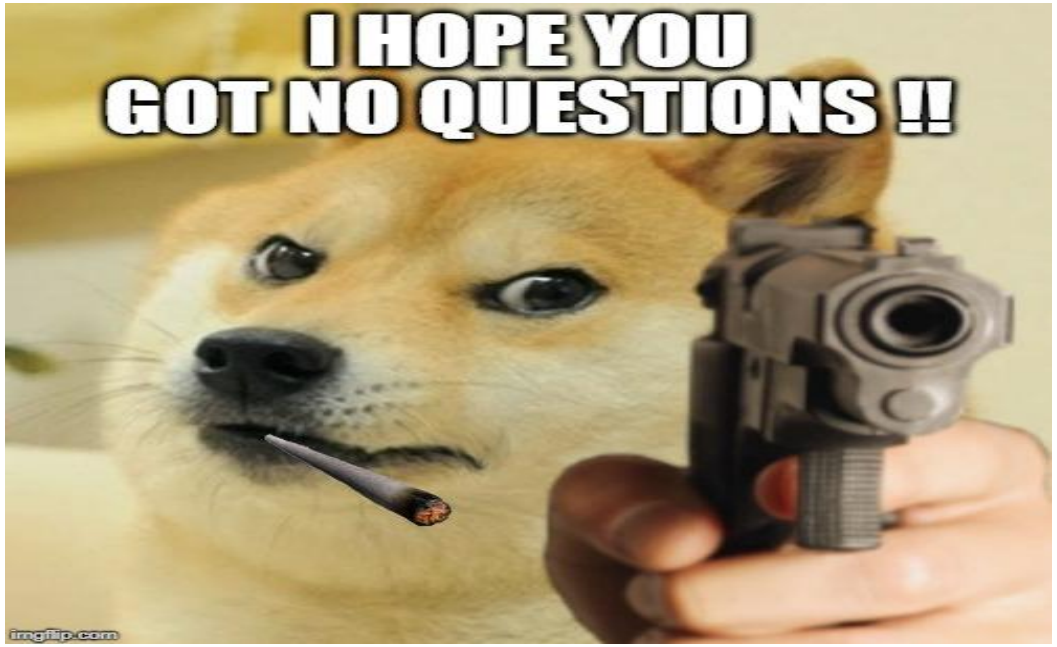
Case 3:

- A Nephrotic child, off steroid and recently diagnosed URTI. There is proteinuria 1+ but no edema at D10 of illness.

- How will you treat it?

Conclusion

- Nephrotic syndrome may be the manifestations of systemic disease.
- Prednisolone is the mainstay of the therapy
- Steroid resistant Nephrotic Syndrome is the absolute indication of renal biopsy.
- Nephrotic syndrome guidelines are changing rapidly.
- Genetic tests in Nephrotic Syndrome will be key in the future.


I HOPE YOU
GOT NO QUESTIONS !!
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