IPNA Clinical Practice Recommendations for the diagnosis and Management of children with SSNS

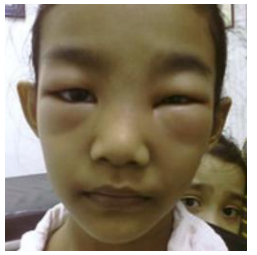
slideset for teaching purposes

Prepared by the IPNA Best Practice and Standard Committee

IPNA Webinar
December 1, 2022

Second IPNA-CPR Project

coordinated by the IPNA Best Practices & Standards Committee



Pediatric Nephrology
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GUIDELINES

Check for updates

IPNA clinical practice recommendations for the diagnosis and management of children with steroid-sensitive nephrotic syndrome

Agnes Trautmann[1] · Olivia Boyer[2] · Elisabeth Hodson[3] · Arvind Bagga[4] · Debbie S. Gipson[5] · Susan Samuel[6] · Jack Wetzels[7] · Khalid Alhasan[8] · Sushmita Banerjee[9] · Rajendra Bhimma[10] · Melvin Bonilla-Felix[11] · Francisco Cano[12] · Martin Christian[13] · Deirdre Hahn[14] · Hee Gyung Kang[15] · Koichi Nakanishi[16] · Hesham Safouh[17] · Howard Trachtman[18] · Hong Xu[19] · Wendy Cook[20] · Marina Vivarelli[21] · Dieter Haffner[22] · on behalf of the International Pediatric Nephrology Association

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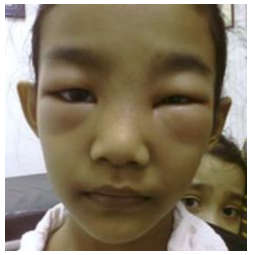
Rationale for this guideline



- Idiopathic nephrotic syndrome is the most frequent pediatric glomerular disease affecting from 1.15 to 16.9 per 100,000 children per year globally
- 85-90% are steroid-sensitive => SSNS
- 70-80% show at least one relapse during follow-up
- 50% of these will experience frequent relapses (FRNS) or become steroid dependent (SDNS)
- 10-30% of patients continue to show relapses as young adults
- There are no international, evidenced-based, systematically developed recommendations on the diagnosis and management of children with SSNS,
  except of a focused document from KDIGO

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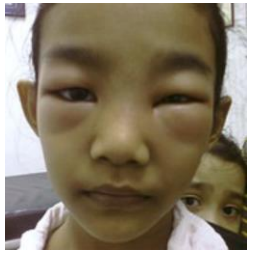
Agree on the aims of the management of the particular disease: SSNS



Treat-to-target:

- ✓ achieve freedom from recurrence
- ✓ minimize side effects („nihil nocere“)
- ✓ improve qualitiy of life

Methodology

The project used the GRADE method (9 PICO questions) and followed the RIGHT Statement for Practice Guidelines

Core group: Recommendations developed based on evidence from the literature

Strength of recommendations and evidence quality were graded by using the **AAP grading system**

Expert Voting Panel (N=32)

23 pediatric nephrologists including 3–5 representatives of each IPNA Regional Society with expertise in the management of SSNS in children.

Voting group members were asked by e-questionnaire to provide a level of agreement on a 5-point scale (strongly disagree -> strongly agree) **(Delphi method)**.

<70% consensus: Recommendations discussed and modified by the core group

≥70% consensus
Recommendation accepted

PICO: Patient (or Population), Intervention, Comparison, Outcome; **AAP**: American Academy of Pediatrics; **RIGHT**, Reporting Items for practice Guidelines in HealThcare.

Methodology: **AAP Grading System**

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 recommend **A strong**	Weak recommendation (based on balance of benefit and harm)
Level B Trials or diagnostic studies with minor limitations; consistent findings from multiple observational studies	**B moderate** erate endation **B strong**	**B weak**
Level C Single or few observational studies or multiple studies with inconsistent findings or major limitations	**C weak** **C moderate**	**C weak**
Level D Expert opinion, case reports, reasoning from first principles	Weak recommend (based on low-quality e **D weak**	No recommendation may be made
Level X Exceptional situations where validating studies cannot be performed and benefit or harm clearly predominates	**X moderate** ate dation S recom **X strong**	

AAP: American Academy of Pediatrics

Definitions

Definition: **Nephrotic Syndrome**

Nephrotic-range proteinuria

UPCR ≥200 mg/mmol (2 mg/mg) in first morning void
or 24hr urine sample ≥1000 mg/m^2/day
corresponding to 3+ or 4+ by urine dipstick

+

Hypoalbuminemia
serum albumin <30 g/l

or

Edema when
serum albumin level is not available

Nephrotic syndrome

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Definition: SSNS versus SRNS

Onset of **Nephrotic Syndrome**: start of oral prednisolone at standard dose (60 mg/m^2/day or 2 mg/kg/day), max. 60 mg/day

B moderate

We recommend confirming nephrotic range proteinuria at least once by quantification of proteinuria by UPCR (based on first morning void or 24 hr urine sample) before initiating treatment for the first episode.

Steroid response	Complete Remission	Partial Remission	No Remission
At 4 weeks	**≤ 20 mg/mmol (≤ 0.2 mg/mg)** or negative/ trace dipstick on ≥ 3 consecutive occasions	**> 20 but < 200 mg/mmol (> 0.2 but < 2.0 mg/mg) and,** if available, **serum albumin ≥ 30 g/l**	**≥ 200 mg/mmol (≥ 2.0 mg/mg)** or corresponding to 3+ or 4+ by urine dipstick
	SSNS		**SRNS**
	Complete remission within 4 weeks of PDN		**Lack of complete remission** within 4 weeks of PDN
At 6 weeks	**SSNS Late Responder**		

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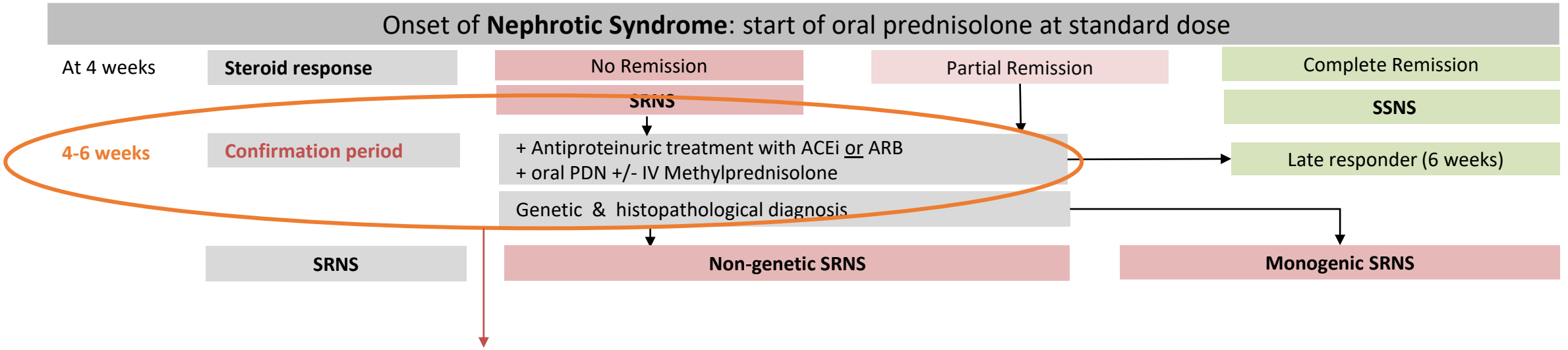
Definition: Confirmation Period for the Diagnosis of SRNS



We suggest using the confirmation period

C weak

B moderate

B moderate

- To assess the response to further treatment with corticosteroids (daily oral prednisolone with/without 3 pulses of methylprednisolone)
- To initiate RAAS inhibitors (ACEi or ARB) as 1st line NON-immunosuppressive treatr
- To perform genetic testing and/or renal biopsy

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Definitions: **Forms of SSNS**

Infrequently relapsing nephrotic syndrome (modified definition)

< 2 relapses in the 6 months following remission of the initial episode;

or fewer than 3 relapses in any subsequent 12 month period

Frequently relapsing nephrotic syndrome (FRNS) (modified definition)

≥ 2 relapses in the first 6-months following remission of the initial episode

or ≥ 3 relapses in any 12 months

Steroid-dependent nephrotic syndrome (SDNS)

A patient with SSNS who experiences 2 consecutive relapses during recommended PDN therapy for first presentation or relapse or within 14 days of its discontinuation

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Definitions: **Relapse**

Relapse

Urine dipstick ≥ 3+ (≥300 mg/dl) or UPCR ≥ 200 mg/mmol (≥ 2 mg/mg)
on a spot urine sample on 3 consecutive days,
with or without reappearance of edema in a child who had previously achieved complete remission

Complicated relapse (new definition)

A relapse requiring hospitalization due to one or more of the following: severe edema, symptomatic hypovolemia or AKI requiring IV albumin infusions, thrombosis, or severe infections (e.g. sepsis, peritonitis, pneumonia, cellulitis)

Introduction of a steroid-sparing agent?

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Treatment-Related Definitions: **SSNS**

Sustained remission (new definition)

No relapses over 12 months with or without therapy

SSNS controlled on therapy (new definition)

Infrequently relapsing NS or sustained remission while on immunosuppression in the absence of significant drug-related toxicity

Introduction of a steroid-sparing agent?

SSNS not controlled on therapy (new definition)

Either frequently relapsing NS despite immunosuppression or significant drug-related toxicity while on immunosuppression

Steroid toxicity (new definition)

New or worsening obesity/overweight, sustained hypertension, hyperglycemia, behavioral/psychiatric disorders, sleep disruption,
impaired statural growth (height velocity <25th percentile and/or height <3rd percentile) in a child with normal growth before start of steroid treatment,
Cushingoid features, striae rubrae/distensae, glaucoma, ocular cataract, bone pain, avascular necrosis

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Diagnostic Work-Up

Initial diagnostic work-up

- We recommend that children presenting with NS undergo a diagnostic work-up as outlined in **Fig. 2** and **Table 2** (grades are given in the table) *-> details on following slides*

B
moderate

- We do not recommend routine kidney biopsy and genetic testing in the initial diagnostic work-up of children with NS who present with typical features and age >1 year.

B
weak

- We recommend considering genetic testing and/or kidney biopsy in infantile onset NS (age 3-12 months).

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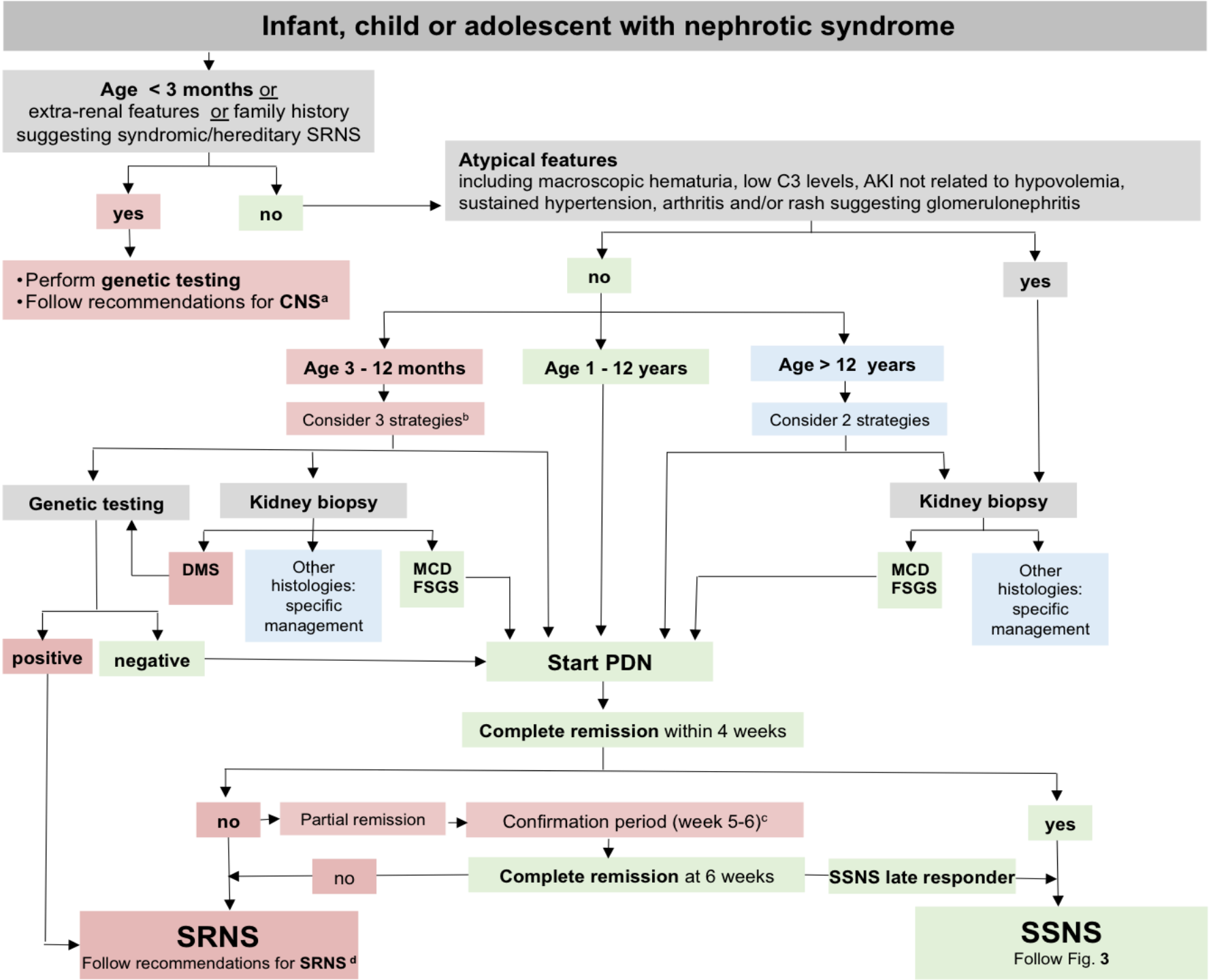
Management and initial diagnostic work-up



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Clinical evaluation

A
strong

Relevant patient history

- Presence of gravity dependent edema
- Fever episodes, pain, abdominal discomfort, fatigue

C
weak

- Consider especially in patients from endemic areas before starting immunosuppressant medications

  - Search for risk factors for secondary causes (e.g. sickle cell disease, HIV, systemic lupus erythematosus, hepatitis B, malaria, parvovirus B19, medications)

  - Screen for tuberculosis

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Clinical evaluation

Physical examination

A strong

- Blood pressure, assess volume status and extent of edema (ascites, pericardial & pleural effusions);
- Lymphadenopathy
- Signs of infection (respiratory tract, skin, peritonitis, urinary tract)

Further work-up is recommended in case of:

A strong

- **Extrarenal features**, e.g. dysmorphic features or ambiguous genitalia or eye abnormalities (microcoria, aniridia), rash, arthritis

Family history

A strong

Consanguinity, kidney disease in family members, extrarenal manifestations, HIV or tuberculosis in endemic regions

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Biochemistry

B
moderate

SPOT URINE

- Protein/creatinine ratio (in first morning void)
- Urinalysis: including hematuria
- Recommended at least once before starting treatment of the first episode.

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Biochemistry

BLOOD

A strong
- Complete blood count, creatinine, eGFR, urea, electrolytes, albumin

A strong
- Recommended in patients with <u>macroscopic hematuria</u>
  Complement C3, C4, antinuclear and anti-streptococcal antibodies, and ANCA

D weak
- Consider before start of PDN treatment
  Varicella and MMR specific IgG, in non-immunized children

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Imaging

D
weak

- **Kidney ultrasound**

  Consider a kidney ultrasound in all children with INS to exclude kidney malformations and venous thrombosis and in patients with reduced eGFR, hematuria or abdominal pain and always before kidney biopsy.

D
weak

- **Chest X-ray**

  Recommended in case of suspected lymphoma.

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Age at presentation as an indicator for kidney biopsy?

KDIGO 2021

- Perform kidney biopsy
  in children with NS aged ≥ 12 years.

  Why 12 years? Why not 15 years?
  There is no clear age limit

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C
weak

Consider kidney biopsy in patients >12 years of age on a case-by-case basis.

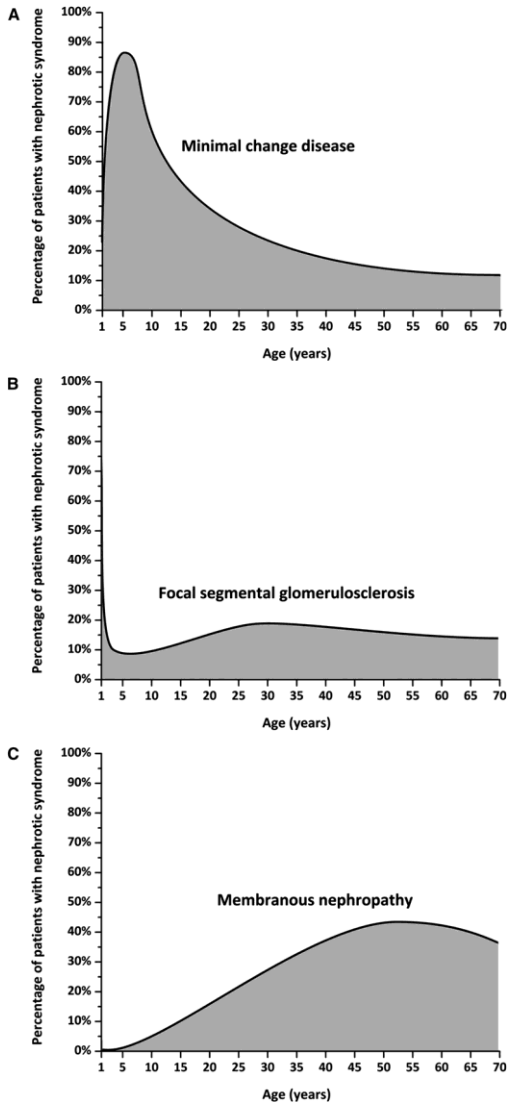

Figure 1. | Etiology of nephrotic syndrome according to age from 1 year onwards. (A) Minimal change disease. (B) Focal segmental glomerulosclerosis. (C) Membranous nephropathy. Data are approximated from Nachman *et al.* (1) and Cameron (2).

Histopathology – Kidney Biopsy

A strong	• Recommended in patients with atypical features including macroscopic hematuria, low C3 levels, AKI not related to hypovolemia, sustained hypertension, arthritis and/or rash
B weak	• Consider in patients with infantile onset NS if genetic screening is not available (age 3-12 months).
C weak	• Consider in patients >12 years of age on a case-by-case basis.
C weak	• Consider in patients with persistent microscopic hematuria in specific populations with a high incidence of glomerular diseases such as IgA nephropathy in East Asia.
A strong	• Recommended in patients diagnosed with SRNS.

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Genetic Testing

A strong

- Recommended in patients
  - with congenital NS
  - extrarenal features and/or family history suggesting syndromic/hereditary SRNS.

C weak

- Consider in patients with infantile onset NS (age 3-12 months) (Fig. 2).

A strong

- Recommended in patients diagnosed with SRNS.

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Primary immunosuppressive treatment

Dose, duration and dosing strategy of PDN in the initial episode of NS

- After completing the initial diagnostic workup of a child presenting with nephrotic syndrome as outlined above, and a decision is made to start PDN,

  we recommend that **infants > 3 months and children or adolescents (1-18 years)** with their **first episode** of idiopathic NS should receive **daily PDN** for either

  4 weeks at 60 mg/m^2 or 2 mg/kg (maximum dose 60 mg/day), followed by **alternate day PDN** at 40 mg/m^2 or 1.5 mg/kg (maximum dose of 40 mg on alternate days) for **4 weeks**,

  A strong

  or

  6 weeks at 60 mg/m^2 or 2 mg/kg (maximum dose 60 mg/day), followed by **alternate day PDN** at 40 mg/m^2 or 1.5 mg/kg (maximum dose of 40 mg on alternate days) for **6 weeks**.

  A strong

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Dose, duration and dosing strategy of PDN in the initial episode of NS

B
moderate

- We recommend administering oral PDN as a **single morning dose** for the treatment of the initial episode and subsequent relapses.

A
strong

- We do **not** recommend a tapering schedule during alternate day dosing.

B
weak

- We suggest that **PDN dose** should be **calculated by either weight or body surface area** based on the estimated dry weight.

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Monitoring during the acute phase and follow-up

Proteinuria – Home Monitoring

X
moderate

- We recommend educating families to monitor urine protein at home to enable early identification of response to PDN and of relapses.

C
weak

- We suggest using the heat coagulation or sulfosalicylic acid test as alternative methods for home monitoring if dipstick testing for proteinuria is not available.

The heat coagulation test is outlined in the suppl material

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Monitoring

- We recommend **regular monitoring** for patients with NS during the acute phase and during follow up as outlined in **Table 4** (grades are given in the table). *-> details on following slides*

X
moderate

- We recommend **considering a kidney biopsy** in patients with SSNS during follow-up if the findings may influence therapy or clarify prognosis.

  This includes patients on prolonged CNI exposure (> 2 years) especially with high doses, and/or with signs of CNI toxicity such as unexplained decrease in eGFR.

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Home Monitoring – Dipstick Assessment

X
moderate

- We recommend daily home urine dipstick testing until remission.

D
weak

- We suggest home urine dipstick testing, at least twice weekly in the first 1-year, individualize thereafter.

X
moderate

- We recommend daily testing if
  1+ or more
  Or
  during episodes of fever, infections and/or suspected relapse (edema)

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First line therapy of relapsing SSNS

Treatment of Relapse

B
moderate

We recommend that **SSNS relapse** be treated

- with single daily dose of PDN (2 mg/kg per day or 60 mg/m^2 per day, maximum 60 mg) until complete remission (UPCr ≤ 20 mg/mmol (0.2 mg/mg) or negative or trace dipstick on 3 or more consecutive days)
- and then decreased to alternate day PDN (1.5 mg/kg per dose or 40 mg/m^2 per dose, maximum 40 mg) for 4 weeks.

A
strong

We do not recommend a tapering schedule during alternate day dosing.

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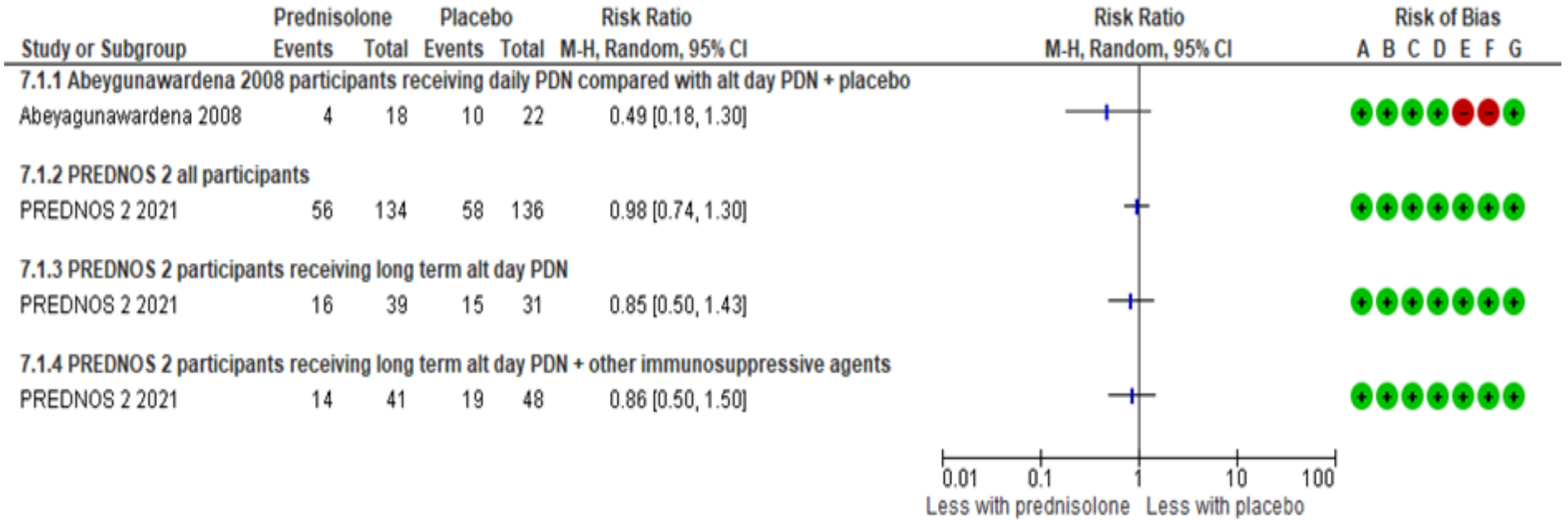
RELAPSE prevention



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure S1 shows a forest plot of the number of children with SSNS and with URTI-related relapses in those receiving low-dose daily PDN for 5-7 days compared with those receiving placebo using data from two RCTs (15 mg per m^2 BSA which is equivalent to 0.5 mg/kg in PREDNOS 2, and 0.36 mg/kg for Abeyagunawardena 2008)

The data indicate that daily low-dose PDN **did not reduce the risk of relapse with URTI** in children with SSNS since the 95% confidence for each point estimate cross 1.

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Prevention of Relapse at Onset of Infections

B
moderate

We do not recommend the routine use of a short course of low-dose daily PDN at the onset of an upper respiratory tract infection (URTI) for prevention of relapses

D
weak

We suggest considering a short course of low dose daily PDN at the onset of an URTI in children who are already taking low dose alternate day PDN and have a history of repeated infection-associated relapses.

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Second line therapy of relapsing SSNS

Optimal approach to children with FRNS and SDNS

B
moderate

- We recommend the **use of maintenance treatment** (see Table 5) in all patients with **FRNS** or **SDNS**.

A
strong

- In patients with **FRNS** we recommend either the **introduction of a steroid-sparing agent** as detailed below or **low-dose maintenance PDN** given as an alternate-day or a daily dose.

B
strong

- We recommend **introduction of a steroid-sparing agent** in children:
  - who are **not controlled on therapy**, or
  - who suffer a **complicated relapse**, or
  - with **SDNS**

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Selection of steroid-sparing agent I

X
strong

- We recommend that the selection of the steroid-sparing agent be made in **conjunction with patients or guardians** in order **to choose the most appropriate medication for each individual** according to their values and preferences.
  This requires not only information on the **efficacy of these medications**, but also **disclosure of possible side effects** as listed in **Table 5.**

A
strong

- We recommend the introduction of one of the **following-steroid sparing agents** (alphabetical order):
  - calcineurin inhibitors (CNIs)
  - cyclophosphamide (CYC)
  - levamisole (LEV)
  - mycophenolate mofetil (MMF)/ mycophenolic sodium (MPS)

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Table 5 Dose, monitoring, adverse effects, and cost of all agents used as maintenance in FRNS and SDNS patients

Therapeutic agent Dose	Monitoring	Adverse Effects	Cost
Low Dose Alternate-Day PDN ≤0.5 mg/kg/alt day, max 20 mg alt day **Low Dose Daily PDN** ≤0.25 mg/kg/day, max 10 mg/day	Quarterly: blood pressure, height, weight Yearly: ophthalmological examination	Obesity/weight gain, hypertension, diabetes mellitus, behavioral/psychiatric disorders, sleep disruption, growth failure, cushingoid features, striae rubrae/distensae, glaucoma, cataract, bone pain, avascular necrosis	Low
Calcineurin inhibitors **Cyclosporin A** Start: 3–5 mg/kg per day (maximum dose 250 mg) in 2 divided doses, Target: C_0 60–100 ng/mL or C_2 300–550 ng/mL (aiming for the lowest possible dose to maintain remission) **Tacrolimus** Start: 0.1–0.2 mg/kg per day (maximum dose 10 mg) in 2 divided doses Target: C_0 level between 3 and 7 ng/mL (aiming for the lowest possible dose to maintain remission)	Quarterly: Blood pressure CBC, creatinine, eGFR, K^+ LFTs, lipids Uric acid (CsA) Mg^+ (TAC) Fasting glucose (TAC) Drug levels Consider discontinuation or a kidney biopsy after 2–3 years to avoid/detect toxicity	Acute and chronic nephrotoxicity, hypertension, seizures, tremor, posterior reversible encephalopathy syndrome (PRES) Hirsutism (CsA), gum hyperplasia (CsA), diabetes mellitus (TAC) TAC drug levels can increase in case of intense diarrhea Consider risk of toxicity due to drug interactions (e.g., macrolide antibiotics, certain anti-epileptic agents, and grapefruit juice increase drug levels)	Intermediate price, CsA less than TAC
Cyclophosphamide 2 mg/kg per day (maximum dose 150 mg) over 12 weeks (oral) or 3 mg/kg per day (maximum dose 150 mg) over 8 weeks Single morning dose preferable No more than a single course (max TCD 168 mg/kg) Give in conjunction with alternate day oral PDN starting with a dose of 40 mg/m^2 (1.5 mg/kg) and reducing to 10 mg/m^2 (0.3 mg/kg) over the duration of treatment	CBC every 14 days during therapy	Leukopenia, severe infections, alopecia, nail discoloration, seizure, infertility, GI upset (abdominal pain, diarrhea), hemorrhagic cystitis, jaundice Fertile individuals must be warned of the need to avoid unplanned pregnancy (CYC can cause fetal malformation)	Low
Levamisole 2–2.5 mg/kg/alternate day (maximum dose 150 mg) In some cases, LEV is initially alternated with oral PDN on non-LEV days	Quarterly: CBC, LFTs Twice-yearly: ANCA titers (also at baseline)	Arthritis, vasculitic rash, neutropenia, abnormal LFTs	Low
Mycophenolate mofetil (MMF)/mycophenolic sodium (MPS) **MMF**: Start: 1200 mg/m^2 per day in two divided doses every 12 hours[a] (maximum dose 3000 mg) **MPS:** 360 mg corresponds to 500 mg of MMF Therapeutic drug monitoring using a limited sampling strategy: The most effective MPA $AUC_{0–12}$ is above 50 mg×h/L[b]	Quarterly: CBC LFTs	Abdominal pain, diarrhea, weight loss (may be improved by the use of MPS). Leukopenia, anemia and abnormal LFTs Verrucae Fertile females must be warned of the need to avoid unplanned pregnancy (MMF/MPS can cause fetal malformations)	High; MPS more expensive than MMF

Selection of steroid-sparing agent II

B
moderate

- We recommend using **RTX** as a steroid-sparing agent in children with FRNS or SDNS who are not controlled on therapy **after a course of treatment with at least one other steroid-sparing agent** at adequate dose especially in case of **non-adherence**.

X
strong

- We recommend **switching to a different steroid-sparing** agent when a patient is **not controlled on therapy** with the initial agent.

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Discontinuation of maintenance treatment

X
strong

- We recommend considering
  - **tapering and discontinuation of maintenance treatment** with PDN, LEV, MMF/MPS or a CNI
  - in all children in **sustained remission for at least 12 months**

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When using Calcineurin inhibitors (CNI)....

B moderate

- We recommend **therapeutic drug monitoring** to ensure optimal dosing

B moderate

- When using **cyclosporin A (CsA)**
  - we recommend a starting dose of 3-5 mg/kg/day (maximum dose 250 mg) divided into 2 doses (every 12 hours) to achieve trough blood levels of 60-100 ng/ml or 2 hour post-dose levels of 300-550 ng/ml

C moderate

- When using **tacrolimus (TAC)**,
  - we recommend a starting dose of 0.1-0.2 mg/kg/day (maximum dose 10 mg) in 2 doses (every 12 hours) to achieve trough blood levels of 3-7 ng/ml.

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When using Calcineurin inhibitors (CNI)....

X strong	• We recommend that the lowest effective CNI dose should be given to maintain patients controlled on therapy
B moderate	• We recommend avoiding prolonged use of CNIs for more than a total of 2-3 years
B moderate	• If CNIs have to be continued, we recommend that a kidney biopsy be considered after 2-3 years to exclude toxicity

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When using Cyclophosphamide (CYC)….

- We recommend **starting** when the patient is **in steroid-induced remission** and **using**
  either a single course of 2 mg/kg per day (maximum dose 150 mg) given orally for 12 weeks
  or a single course of 3 mg/kg per day (maximum dose 150 mg) for 8 weeks given orally

B moderate

B moderate

- We recommend that the maximal cumulative dose of CYC not exceed 168 mg/kg.

C moderate

- We recommend that, if adherence is uncertain, a single course of monthly intravenous CYC (500 mg/m^2 per dose (max single dose 1 g) x 6 months) can be given.

B moderate

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When using Cyclophosphamide (CYC)….

D
weak

- We suggest administering CYC in combination with alternate day oral PDN starting with a dose of 40 mg/m^2 (1.5 mg/kg) and reducing to 10 mg/m^2 (0.3 mg/kg) over the course of treatment.

D
weak

- We recommend monitoring for neutropenia (absolute neutrophil count <1,500/µL) with complete blood counts every 2 weeks
  and
  ceasing CYC if the child develops leukopenia (<4,000/µL) or neutropenia (< 1,500/µL) or significant thrombocytopenia (< 50,000/µL)
  and
  restarting after recovery of blood cell counts using a lower dose.

X
strong

X
strong

C
moderate

- We recommend maintaining a high fluid intake to ensure a high urine output during treatment.

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When using Levamisol (LEV)....

B
moderate

- We recommend levamisole at a dose of 2-2.5 mg/kg given on alternate days (with maximum dose of 150 mg) after remission was achieved by PDN at recommended dose.

X
moderate

- We recommend ANCA measurement at baseline, if available and every 6-12 months during therapy.

X
moderate

- We recommend monitoring clinically for rash and measuring complete blood count and hepatic transaminases every 3-4 months.

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When using Mycophenolate mofetil (MMF)/ mycophenolic sodium (MPS)...

B
moderate

- When using MMF, we recommend a starting dose of 1200 mg/m^2 BSA (maximum dose 3000 mg) divided into two oral doses every 12 hours.

B
moderate

- Alternatively, we recommend using the corresponding MPS dose, i.e. 360 mg of MPS corresponds to 500 mg MMF.

C
weak

- We suggest starting MMF/MPS therapy while the child is still receiving alternate day steroid therapy since the immunosuppressive effect of MMF/MPS is delayed.
  In most children, alternate day steroids can then be tapered and discontinued within 6-12 weeks.

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When using Mycophenolate mofetil (MMF)/ mycophenolic sodium (MPS)…

B
moderate

- We recommend using therapeutic drug monitoring, aiming for a 12-h mycophenolic acid (MPA) area under the curve above 50 mg·h/L in patients not controlled on MMF therapy despite using recommended dosing.

X
strong

- We recommend that sexually active adolescent females only receive MMF/MPS if they are using adequate contraception.

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When using Rituximab (RTX)...

B
moderate

- We recommend using RTX as a steroid-sparing agent in children with FRNS or SDNS who are not controlled on therapy after a course of treatment with at least one other steroid-sparing agent at adequate dose, especially in case of non-adherence.
  This is especially preferable, both in terms of safety and of effectiveness, above the age of 7-9 years.

C
weak

C
moderate

- When using RTX we recommend a dosage of 375 mg/m^2 for each infusion, ranging from 1-4 infusions (maximum single dose 1000 mg) preferably when the patient is in remission.

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When using Rituximab (RTX)...

B strong

- We recommend monitoring CD19(+) total B cell counts at baseline and following RTX treatment at 7 days post infusion to ensure adequate B cell depletion indicated by an absolute CD19 cell count < 5 cells/mm3 or < 1% of total lymphocytes.

B strong

- We recommend monitoring IgG levels at baseline and periodically following RTX treatment to detect hypogammaglobulinemia (IgG below age-related normal range).

B moderate

- We recommend premedication with paracetamol/acetaminophen, antihistamines and/or steroids.

B strong

Following RTX infusion/s, we recommend tapering off oral PDN and other steroid-sparing agents within 2-3 months.

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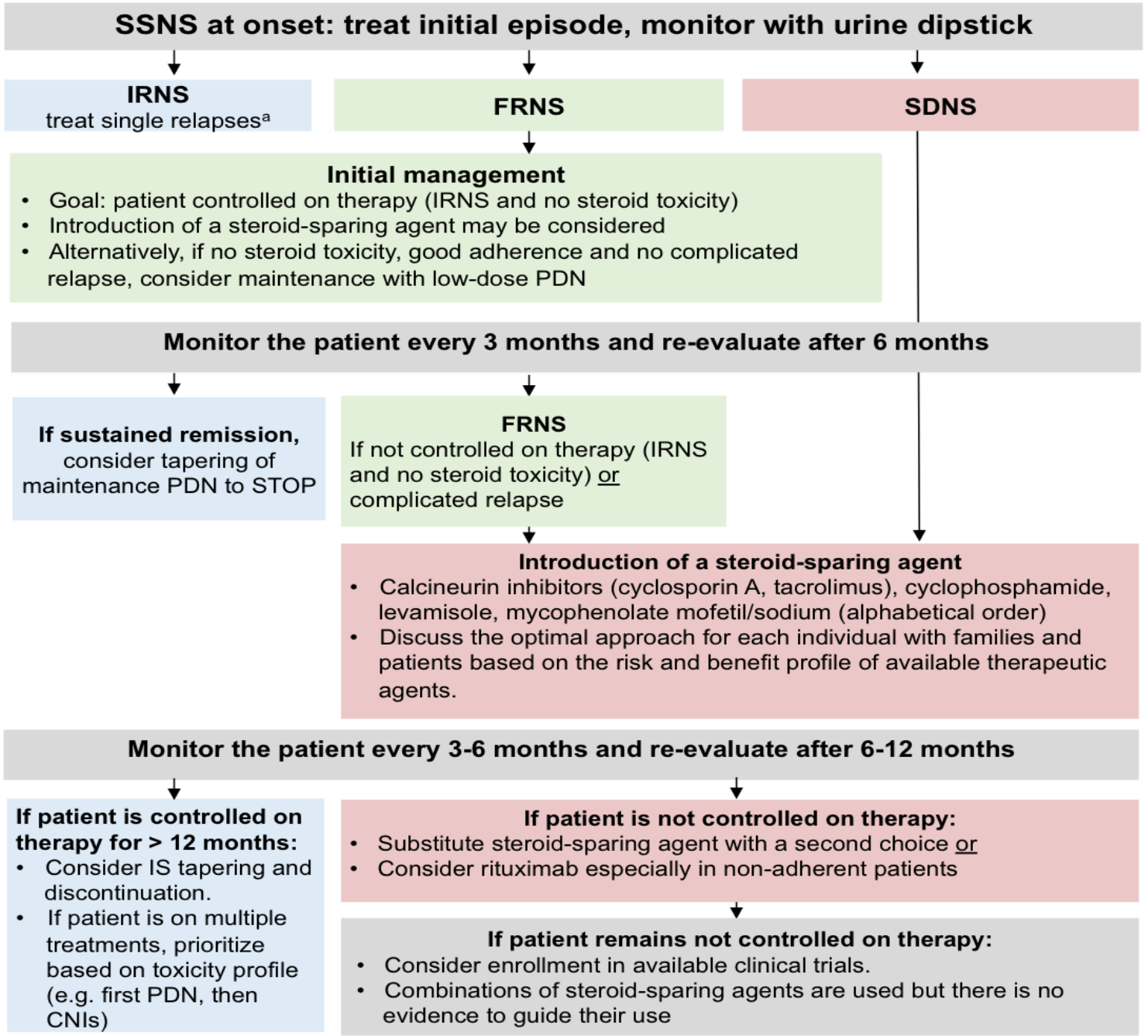
Management of children with SSNS



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Adjunctive measures: Edema control

Management of volume status, edema and blood pressure

General measures

A strong	• We recommend evaluating the **volume status** of a child in the acute nephrotic state.
C moderate	• We do **not** recommend **routine fluid restriction** in SSNS patients
C weak	• We suggest **fluid restriction in case of hyponatremia** (< 130 meq/L) **and/or severe edema** in a hospital setting.
C moderate	• We recommend a **low-salt diet** (suggested maximum dose of 2-3 meq/kg/day) **during relapses** with moderate or severe edema, and **normal salt intake while in remission**.

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Management of volume status, edema and blood pressure

General measures II

A
strong

- We recommend **monitoring for hypertension** in all children with SSNS and following current hypertension guidelines in children with confirmed, persistent hypertension

X
strong

- We recommend against ACEi or ARBs administration in SSNS to control edema or high blood pressure in relapse.

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Management of volume status, edema and blood pressure

In case of hypovolemia or AKI

X
strong

- In patients with **signs of hypovolemia**, we recommend **withholding diuretics** due to the risk of thrombosis, hypovolemic shock and AKI, and **discontinuing ACEi or ARBs**.

C
moderate

- We recommend using 20% or 25% **albumin infusions** in patients with **signs of hypovolemia** (including oliguria, AKI, prolonged capillary refill time, tachycardia, and abdominal discomfort) and **adding furosemide** (1–2mg/kg given i.v.) in the middle and/or at the end of the infusion if volume has been restored and urine output is insufficient.

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Management of volume status, edema and blood pressure

In case of hypovolemia or AKI II

C
weak

- In cases of **hypovolemic shock and/or hypotension**, we suggest using 4% or 5% albumin without furosemide.

X
strong

- In cases of **AKI without hypovolemia**, we recommend general management of AKI including
  - fluid management,
  - avoidance of nephrotoxic agents and
  - modification of medication dosage when appropriate.

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Management of volume status, edema and blood pressure

Management of severe edema

C
moderate

- In patients with severe edema, we recommend **albumin infusions of 0.5-1 g/kg** of 20% or 25% albumin given over a **period of 4-6h and adding furosemide** (1-2 mg/kg given i.v. over 5-30 min) in the middle and/or at the end of the infusion in the absence of marked intravascular volume contraction and/or hyponatremia.

X
strong

- We recommend **careful use of albumin infusions** especially in hypertensive patients or those with decreased urine output to prevent hypervolemia and pulmonary edema.

C
weak

- In a fluid-overloaded, edematous, hypertensive child, we suggest considering antihypertensive treatment with diuretics combined with fluid and salt restriction.

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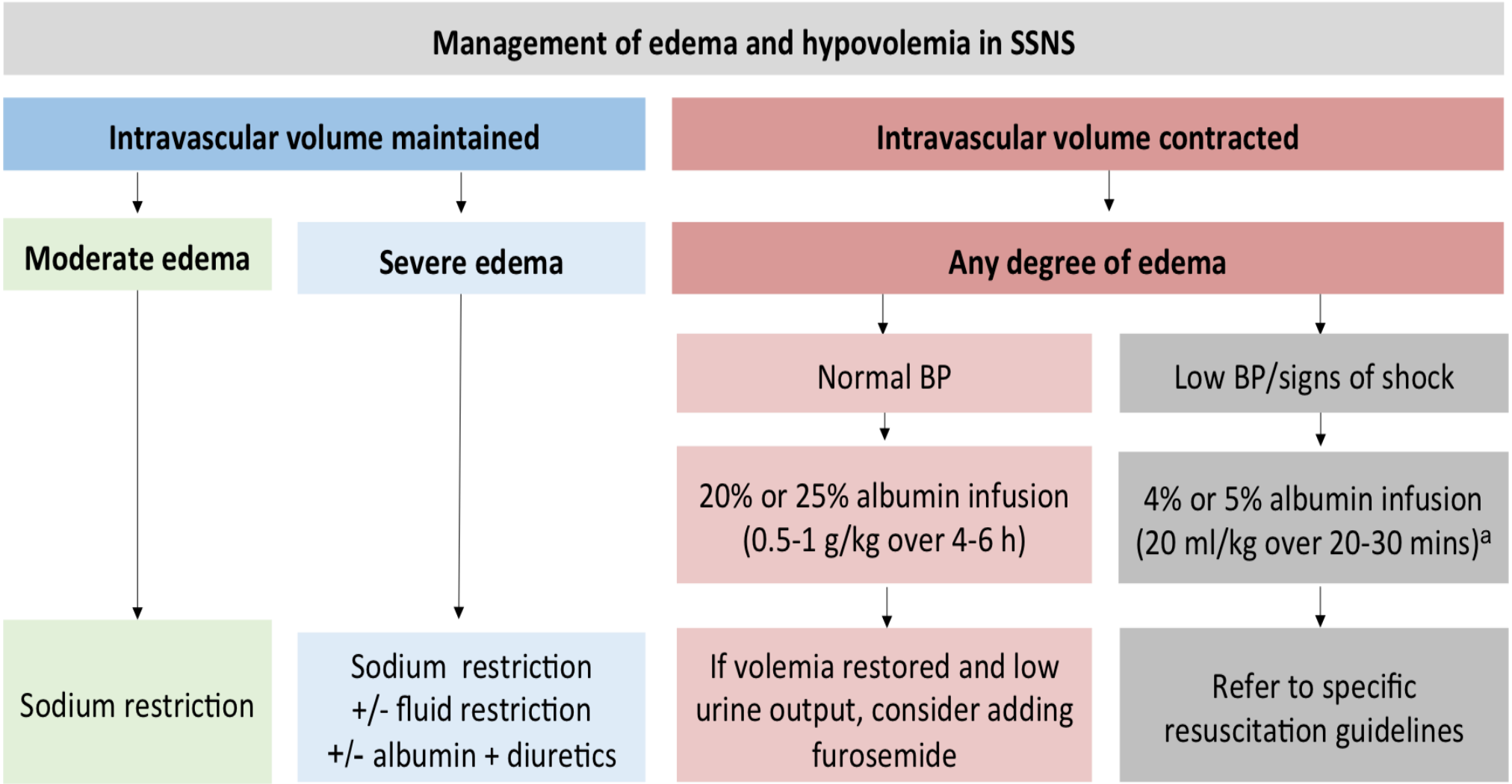
Management of Edema



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Prevention and treatment of viral and bacterial infections:
Antibiotics

C
weak

- We suggest that **antibiotic prophylaxis** should **not** be given **routinely** to children with SSNS.

A
strong

- We recommend **prompt antibiotic treatment** in the case of a **suspected bacterial infection**.

A
strong

- We recommend **treating peritonitis** with IV antibiotics targeting S. pneumoniae.

D
weak

- We suggest giving **cotrimoxazole prophylaxis** to patients **on RTX** therapy during CD19+ B cell depletion, if receiving additional immunosuppressive co-medications.

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Immunoglobulin infusions

D
weak

- We suggest **considering preventive IVIG infusions** in the case of persistent **low plasma total IgG levels** (eg. related to RTX infusion) **and recurrent and/or severe infections**

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Vaccinations I

A
strong

- We recommend **reviewing the child's vaccination status at disease onset** and completing all inactivated **vaccinations** following the vaccination schedule that is recommended for healthy children without delay, especially for encapsulated bacteria (*pneumococcus, meningococcus, haemophilus influenzae*).

A
strong

- We recommend **administering inactivated influenza vaccine annually**.

X
strong

- We recommend anti-COVID-19 vaccination in children with SSNS following the national recommendations.

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Vaccinations II

A
strong

- We recommend **following national vaccination guidelines** for the administration of live attenuated vaccines in immunocompromised patients.

X
strong

- We do **not** recommend live vaccinations in patients on high-dose immunosuppression and in the first 6 months after RTX treatment.

A
strong

- We recommend **vaccinating the household** against influenza annually, against COVID-19 and with live vaccines if live vaccines are contraindicated in the child with SSNS.

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Varicella – Exposure and Infection

A strong

- In case of **exposure to chickenpox** in children **with immunosuppressive treatment** who have **not been immunized against VZV**, we recommend prophylactic treatment with specific VZV IVIGs or oral acyclovir or valacyclovir for 5-7 days starting within 7-10 days of the exposure.

C weak

- We suggest **treatment of VZV infection** with intravenous high-dose acyclovir for 7-10 days.

D weak

- In the **case of chickenpox**, we suggest reducing doses of immunosuppressive drugs.

A strong

- We recommend vaccinating non-immunized patients while in remission and not on high-dose immunosuppressive medications, as well as vaccinating non-immunized siblings and parents against VZV.

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COVID-19

X
strong

- We recommend treating COVID-19 in children with SSNS as in the general pediatric population.

C
weak

- We suggest not reducing the immunosuppressive therapy in case of mild symptoms.

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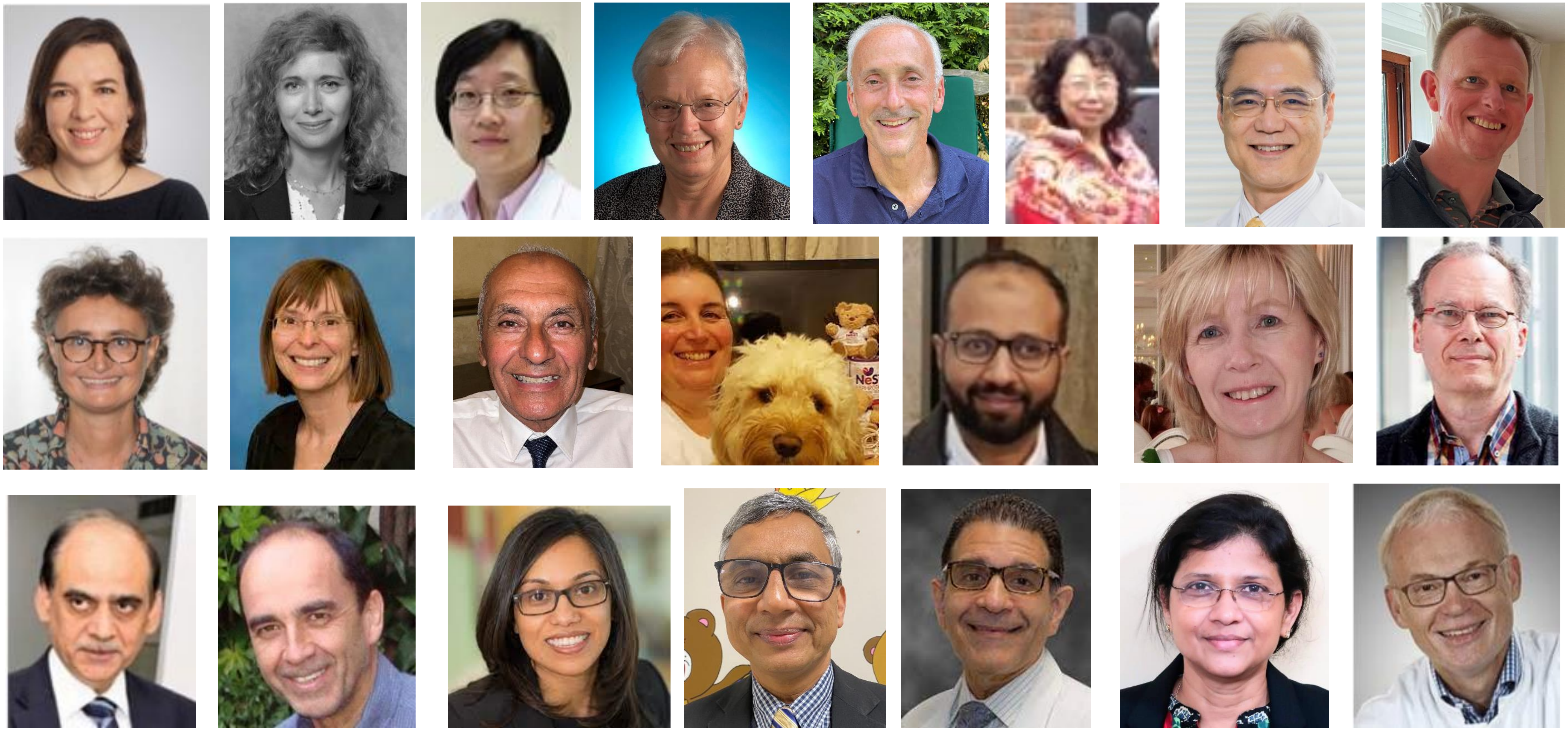
Acknowledgements

Core group members: SSNS guideline



Acknowledgements: IPNA SSNS guideline

Core group (n=22)

20 Pediatric Nephrologists from IPNA regional societies
Dieter Haffner, ESPN, Hannover, Germany (coordinator)
Olivia Boyer, ESPN, Paris, France
Agnes Trautmann, ESPN, Heidelberg, Germany
Marina Vivarelli, ESPN, Rome, Italy
Elisabeth Hodson, ANZPNA Sydney, Australia
Martin Christian, ESPN, Nottingham, UK
Francisco Cano, ALANEPE, Santiago, Chile
Melvin Bonilla-Felix, ALANEPE, San Juan, Puerto Rico
Debbie Gipson, ASPN, Ann Arbor, USA
Howard Trachtman, ASPN, Ann Arbor, USA
Susan Samuel, ASPN, Edmonton, Canada
Deirdre Hahn, ANZPNA Sydney, Australia
Hong Xu AsPNA, Shanghai, China
Hee Gyung Kang, AsPNA, Seoul, Korea
Arvind Bagga, AsPNA, New Delhi, India
Sushmita Banerjee, AsPNA Kolkata, India
Khalid Alhasan, AsPNA, Riadh, Saudi Arabia
Hesham Safouh, AFPNA, Cairo, Egypt
Rajendra Bhimma, AFPNA, Durban, South Africa
Koichi Nakanishi, JSPN, Okinawa, Japan

Core group continued

Adult Nephrology & Transition
Jack Wetzels, Utrecht, The Netherlands
Patient representative
Wendy Cook, London, UK

External expert group (n=12)

Pediatric endocrinologists: Agnes Linglart (Paris, France), Dirk Schnabel (Berlin, Germany);
General pediatrician: Adamu Sambo (Gloucestereshire, UK)
Transition: Marjo van Helden (Nijmegen, Netherlands), Ben Sprangers (Leuven, Belgium);
Dieticians: Stefanie Steinmann (Hannover, Germany), Sheridan Collins (Sydney, Australia), Katie Byrne (Michigan, United states)

Patient representatives: Clemens and Juliane Brauner (Hannover, Germany), Chandana Guha (Sydney, Australia), Stephane Serre (Toulouse, France).

Voting Panel (n=32)

Experts from IPNA regional societies:
ESPN, ANZPNA, JSPN, ASPN, ALANEPE, AsPNA, AFPNA

IPNA

Additional recommendations are given in the published guideline on the following topics:

- Thrombosis, viral & bacterial infections, vaccination
- Preservation of bone health
- Intermittent endocrine and metabolic changes during the acute nephrotic state
- Lifestyle and nutrition
- Sun protection
- Childhood-adult transition

✓ **Supplementary material** showing, e.g. evidence tables for the given recommendations, demonstration of heat coagulation test can be downloaded from the journal website

✓ **Translations** and **educational material for patients and families** will be provided soon in **20 languages** on the IPNA website

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