ESPN Working Group Glomerular Disease 2022

• Antonia Bouts	Introduction and upcoming elections
• Olivia Boyer	Update NS guideline projects
• Marina Vivarelli	ESPN-sponsored study on evaluation of immune and vaccine competence in pediatric SSNS
• Julien Hogen	Update membranous nephropathy (PEDMAN) project
• Rezan Topaloglu and Adriana Sulhrie	Lupus registry
• Claire Dossier	Nephrovir-3 results & joint project LEARNS-2
• Alexandra Zurowski	RTX and hypogammaglobulinemia
• Matko Malais	COVID, ANCA, Takayashu.
• Kjell Tulus	RTX in FRSDNS and SRNS, CNI in SRNS, Lupus cohort.

Election new Board member WG GD

Chair: Antonia Bouts (2021)

Members:

Olivia Boyer (2021)

Rezan Topaloglu (2019)

Aleksandra Zurowska (2021)

Chair for 3 years with option for second period.

During 3 years all board members will be replaced one by one

Completed Studies/ guideline Projects:

1. Survey in collaboration with ERKNet and IPNA: **Incidence and severity of COVID-19 infection in the population of children affected by kidney diseases on immunosuppression** (Matko Marlais, Kjell Tullus, Marina Vivarelli).
2. **Hypogammaglobulinemia in RTX treated children with SDNS or FRNS**: results of an ESPN survey (Alexandra Zurowska, Magdalena Rozynska-Duklas, Rezan Topaloglu, Olivia Boyer, Antonia Bouts, Marina Vivarelli).
3. **Clinical practice recommendations for recurrent FSGS/SRNS**. (Lutz Weber, Burkhard Tonshoff, Ryszard Grenda, Antonia Bouts, Rezan Topaloglu, ..., Lars Pape)
4. Guidelines for treatment of SRNS: **IPNA SRNS guidelines** (Haffner D)
5. Guidelines for treatment of SSNS: **IPNA SSNS guidelines** (Haffner D) (almost completed)

Completed Studies/ guideline Projects:

6. Management of congenital nephrotic syndrome: consensus recommendations ERKNet-ESPN Working Group. (Olivia Boyer, Franz Schaefer, …..Elena Levtchenko, Marina Vivarelli)
7. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. (Brad Rovin, Sharon Adler, ….Pierre Ronco, Marina Vivarelli, Jack Wetzels, Jurgn Floege)
8. Long-term Efficacy and Safety of Repeated Rituximab to Maintain Remission in Idiopathic Childhood Nephrotic Syndrome: An International Study. (E Chan, …Hogan J, ….Kemper M,..Vivarelli M, Tullus K)
9. A clinical approach to children with C3-glomerulopathy. (Vivarelli M, ..Thurman J)
10. Belimumab for the treatment of children with FRNS: the BELNEPH study. (Vivarelli M, Colucci M, Gargiulo A,…Emma F).
11. Update on the treatment of steroid-sensitive nephrotic syndrome. (Zotta F, Vivarelli M, Emma F)

Ongoing Studies:

1. Retrospective study employing the CERTAIN database, in collaboration with the Transplantion WG, on **Treatment of FSGS recurrence post-renal transplant** (Antonia Bouts, Burkhard Tonschoff, Marina Vivarelli)
2. Survey; collaboration with ERKNet & IPNA: **Pediatric cases of ANCA vasculitis**: prevalence,
   renal phenotype, management, outcome (Kjell Tullus, Matko Marlais, Nikoleta Printza, Marina Vivarelli).
3. **Pediatric cases on idiopathic membranous nephropathy** (Julien Hogan, Claire Dossier, Marina Vivarelli, Pierre Ronco)
4. Survey; collaboration with ERKNet and IPNA: **Incidence and severity of COVID-19 infection in the population of children affected by kidney diseases on immunosuppression** (Matko Marlais, Kjell Tullus, Marina Vivarelli).
5. **Pediatric SLE registry** in collaboration with ERKNet (Dieter Haffner, Rezan Topaloglu)
6. INTENT study (Heidelberg, Germany: L Weber): **Initial treatment of INS in children with MMF**
   vs prednisone (recruitment ongoing)
7. NEPHROVIR-3 (Paris, France: C Dossier): **Efficiency of Levamisole in association with prednisone in the treatment of the first flare** (Feb 2021 first year follow-up ended)
8. LEARNS (Amsterdam, The Netherlands: A Bouts): **Prevention of relapses with Levamisole as adjuvant therapy to corticosteroids in children with first episode of INS**.

Planned Studies:

1. Relapse NS after corona vaccination, an ERKNET survey. (ESPN?)
2. Pediatric INS evolution into adulthood. (Giulia Bassanese)
3. The incidence of HGG in SDNS and FRNS children and the risk factors for its development. (Alexandra Zurowska).
4. Prevalence of newly discovered antigens in children with Membranous Nephrothy and screening for new antigens. (Julian Hogan).

european society for paediatric nephrology

ESPN immune glomerulopathy WG

Update on Clinical Practice Recommendations 2022

IPNA

Olivia Boyer, MD, PhD

Pediatric Nephrology
Imagine Institute
Hôpital Necker Enfants Malades,
Université de Paris, France

Chair of the IPNA Best Practice and Guideline Committee

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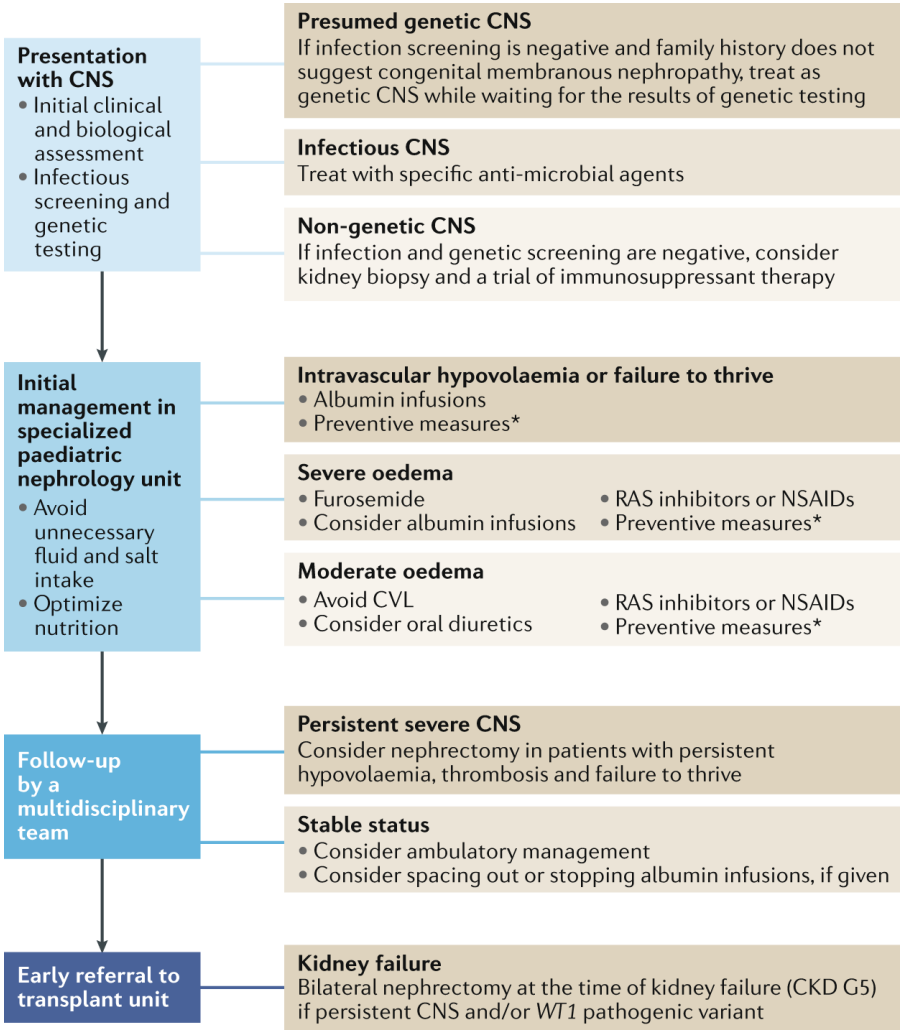
Société de Néphrologie Pédiatrique · ERKNet · ORKiD · Necker Enfants Malades Hôpital Universitaire · imagine Institut des Maladies Génétiques · Université de Paris

Consensus statement on congenital nephrotic syndrome



ERKNet The European Rare Kidney Disease Reference Network

european society for paediatric nephrology

CONSENSUS STATEMENT

OPEN

Check for updates

Management of congenital nephrotic syndrome: consensus recommendations of the ERKNet-ESPN Working Group

Olivia Boyer[1,2], Franz Schaefer[3], Dieter Haffner[4,5], Detlef Bockenhauer[6], Tuula Hölttä[7], Sandra Bérody[1], Hazel Webb[6], Marie Heselden[8], Beata S. Lipska-Ziętkiewicz[9,10], Fatih Ozaltin[11], Elena Levtchenko[12] and Marina Vivarelli[13]

https://pubmed.ncbi.nlm.nih.gov/33514942/

European Journal of Human Genetics (2020) 28:1368–1378
https://doi.org/10.1038/s41431-020-0642-8

ESHG

ARTICLE

Genetic aspects of congenital nephrotic syndrome: a consensus statement from the ERKNet–ESPN inherited glomerulopathy working group

Beata Stefania Lipska-Ziętkiewicz[1,2] · Fatih Ozaltin[3] · Tuula Hölttä[4] · Detlef Bockenhauer[5] · Sandra Bérody[6] · Elena Levtchenko[7] · Marina Vivarelli[8] · Hazel Webb[5] · Dieter Haffner[9,10] · Franz Schaefer[11] · Olivia Boyer[6,12]

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7608398/

https://www.erknet.org/fileadmin/files/user_upload/2020-12-02_Boyer_CNS.pdf

Clinical practice recommendation on SRNS in children

IPNA

Pediatric Nephrology
https://doi.org/10.1007/s00467-020-04519-1

GUIDELINES

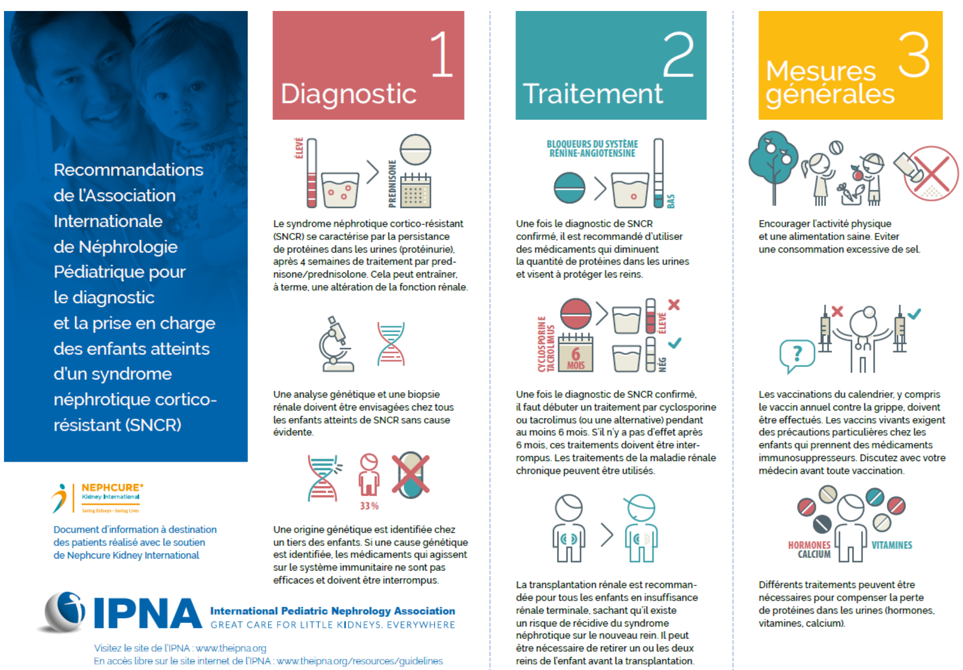
Check for updates

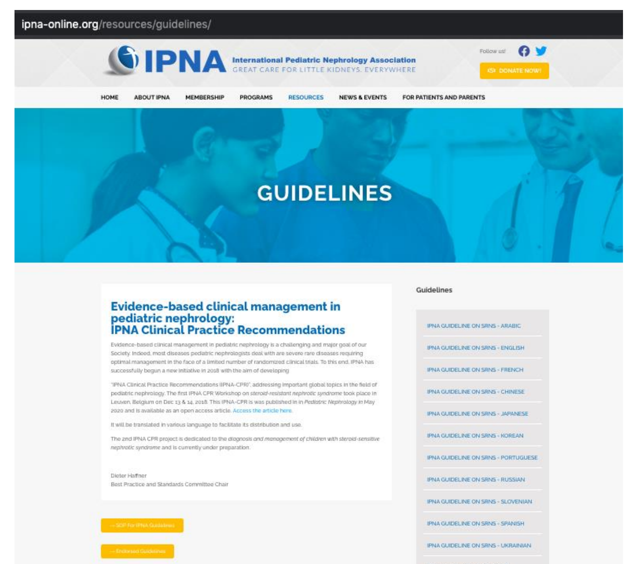
IPNA clinical practice recommendations for the diagnosis and management of children with steroid-resistant nephrotic syndrome

Agnes Trautmann[1] • Marina Vivarelli[2] • Susan Samuel[3] • Debbie Gipson[4] • Aditi Sinha[5] • Franz Schaefer[1] • Ng Kar Hui[6] • Olivia Boyer[7,8] • Moin A Saleem[9] • Luciana Feltran[10] • Janina Müller-Deile[11] • Jan Ulrich Becker[12] • Francisco Cano[13] • Hong Xu[14] • Yam Ngo Lim[15] • William Smoyer[16] • Ifeoma Anochie[17] • Koichi Nakanishi[18] • Elisabeth Hodson[19] • Dieter Haffner[20,21,22] • on behalf of the International Pediatric Nephrology Association

Received: 21 December 2019 / Revised: 7 February 2020 / Accepted: 21 February 2020

https://ipna-online.org/resources/guidelines/


Recommandations de l'Association Internationale de Néphrologie Pédiatrique pour le diagnostic et la prise en charge des enfants atteints d'un syndrome néphrotique cortico-résistant (SNCR)
NEPHCURE Kidney International
Document d'information à destination des patients réalisé avec le soutien de Nephcure Kidney International
IPNA International Pediatric Nephrology Association
GREAT CARE FOR LITTLE KIDNEYS. EVERYWHERE
Visitez le site de l'IPNA : www.theipna.org
En accès libre sur le site internet de l'IPNA : www.theipna.org/resources/guidelines
1 Diagnostic
ÉLEVÉ
PREDNISONE
Le syndrome néphrotique cortico-résistant (SNCR) se caractérise par la persistance de protéines dans les urines (protéinurie), après 4 semaines de traitement par prednisone/prednisolone. Cela peut entraîner, à terme, une altération de la fonction rénale.
Une analyse génétique et une biopsie rénale doivent être envisagées chez tous les enfants atteints de SNCR sans cause évidente.
33 %
Une origine génétique est identifiée chez un tiers des enfants. Si une cause génétique est identifiée, les médicaments qui agissent sur le système immunitaire ne sont pas efficaces et doivent être interrompus.
2 Traitement
BLOQUEURS DU SYSTÈME RÉNINE-ANGIOTENSINE
BAS
Une fois le diagnostic de SNCR confirmé, il est recommandé d'utiliser des médicaments qui diminuent la quantité de protéines dans les urines et visent à protéger les reins.
CYCLOSPORINE TACROLIMUS
6 MOIS
ÉLEVÉ
NÉG
Une fois le diagnostic de SNCR confirmé, il faut débuter un traitement par cyclosporine ou tacrolimus (ou une alternative) pendant au moins 6 mois. S'il n'y a pas d'effet après 6 mois, ces traitements doivent être interrompus. Les traitements de la maladie rénale chronique peuvent être utilisés.
La transplantation rénale est recommandée pour tous les enfants en insuffisance rénale terminale, sachant qu'il existe un risque de récidive du syndrome néphrotique sur le nouveau rein. Il peut être nécessaire de retirer un ou les deux reins de l'enfant avant la transplantation.
3 Mesures générales
Encourager l'activité physique et une alimentation saine. Eviter une consommation excessive de sel.
Les vaccinations du calendrier, y compris le vaccin annuel contre la grippe, doivent être effectués. Les vaccins vivants exigent des précautions particulières chez les enfants qui prennent des médicaments immunosuppresseurs. Discutez avec votre médecin avant toute vaccination.
HORMONES CALCIUM
VITAMINES
Différents traitements peuvent être nécessaires pour compenser la perte de protéines dans les urines (hormones, vitamines, calcium).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FOR PATIENTS AND PARENTS
GUIDELINES
Evidence-based clinical management in pediatric nephrology:
IPNA Clinical Practice Recommendations
Guidelines

IPNA guidelines on SSNS in children

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Wendy Cook, patient representative

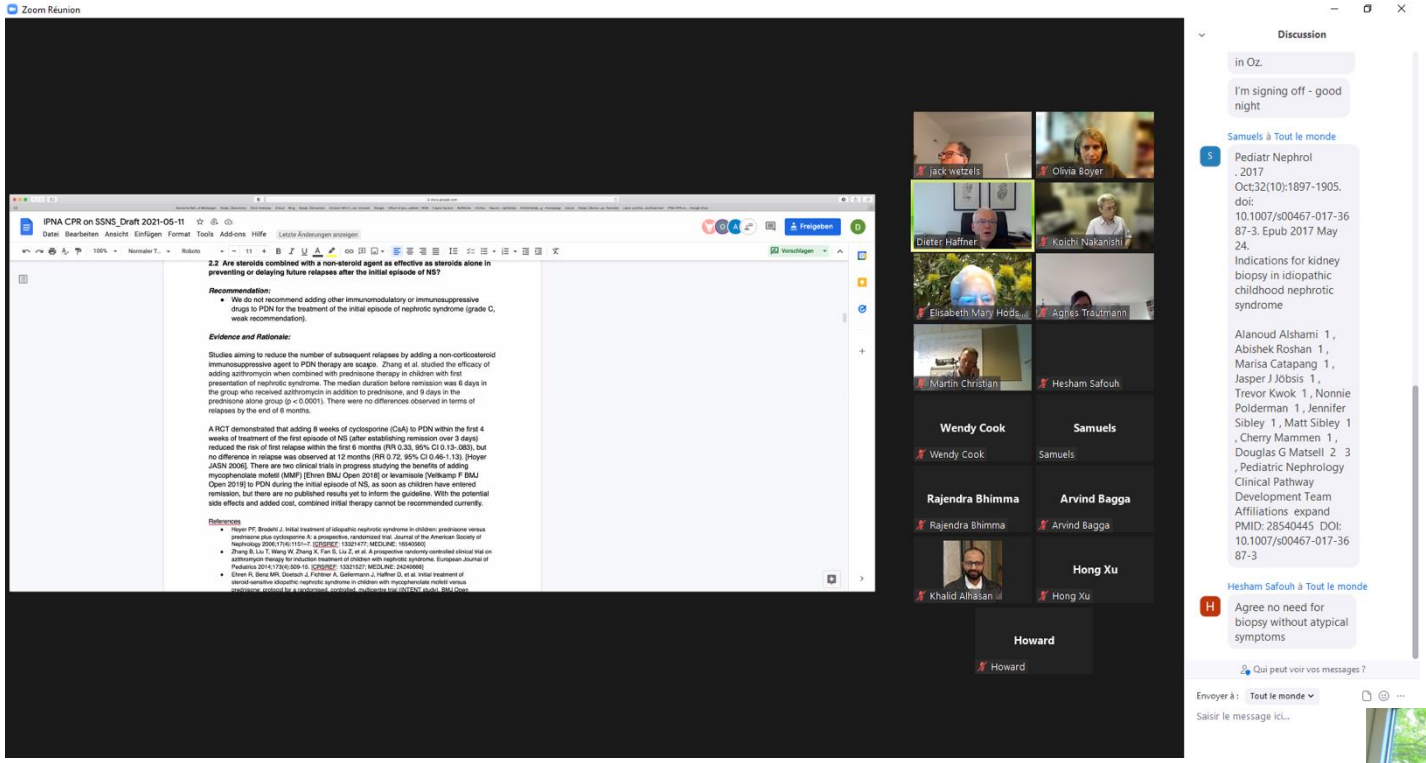
IPNA guidelines on SSNS in children

Evidence review (Dr Agnes Trautmann, ERKNet)

- 9 relevant PICO questions
- Delphi method for voting

Aggregate evidence quality	Benefit or harm predominates	Benefit and harm balanced
Level A • Intervention: well-designed and conducted trials, meta-analyses on applicable populations • Diagnosis: independent gold-standard studies of applicable populations	Strong recommendation 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	Moderate recommendation B Moderate	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 recommendation (based on low-quality evider 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 Moderate ommendation Strong recommendation X strong	

Working on the guidelines for the SSNS management



=> 128 page document to be edited and validated

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IPNA guidelines on SSNS in children: outline

IPNA

- Definitions
- Indications for biopsies
- 1st line steroid regimen, relapses
- Maintenance therapies
- Daily steroids for infections.

IPNA guidelines on SSNS in children: definitions

- **Infrequently relapsing nephrotic syndrome**

< 2 relapses in the 6 months following remission of the initial episode;
or fewer than 4 relapses in any subsequent 12 month period

- **Frequently relapsing nephrotic syndrome (FRNS)**

> 2 relapses in the first 6-months following remission; or > 3 relapses in any 12 months

- **Steroid-dependent nephrotic syndrome (SDNS)**

2 consecutive relapses during recommended PDN therapy for first presentation or relapse or within 14 days of PDN discontinuation.

- **Sustained remission**

No relapses over 12 months with or without therapy

- **SSNS controlled on therapy**

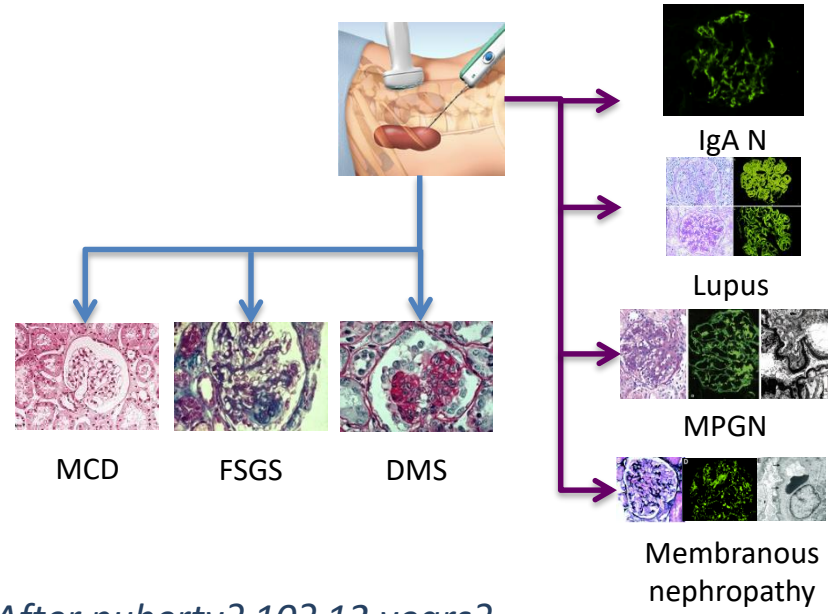
Infrequently relapsing NS while on IS in the absence of significant drug-related toxicity

- **SSNS not controlled on therapy**

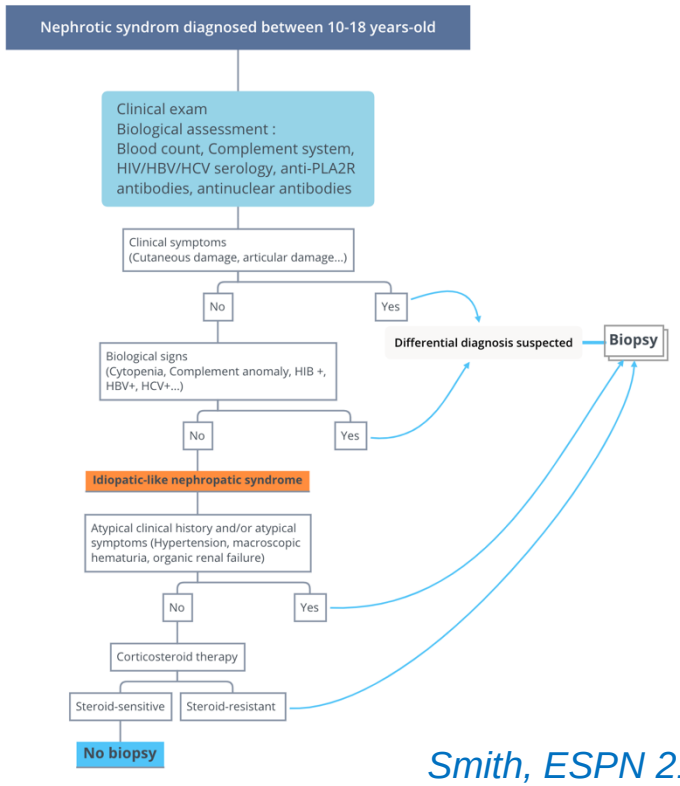
Either frequently relapsing NS despite immunosuppression or significant drug-related toxicity while on immunosuppression

- **Complicated relapse :** 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)

IPNA guidelines on SSNS in children: Biopsy



After puberty? 10? 12 years?



Smith, ESPN 21

A strong

No Kidney Bx at onset in children/adolescents, EXCEPT in

- pts with **atypical presentation**: macroscopic hematuria, low C3 levels, AKI not related to hypovolemia, sustained hypertension, arthritis and/or rash.
- pts with Hu (30–49/HPF) in populations with high prevalence of IgAN
- Infantile NS: **3-12 months + NGS**
- **SRNS**

B Moderate

A strong

No Kidney Bx before introduction of CNIs

Only if CNI exposure > 2 years, and/or with signs of CNI toxicity such as ↓ eGFR

No indication for genetic testing in SSNS (SDNS/FRNS) or secondary SRNS

IPNA guidelines on SSNS in children: 1st line steroid therapy

After completing the initial diagnostic workup, 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

A strong

- **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 40 mg per day) for 4 weeks**, OR

4 RCTs, 775 children, idem KDIGO 2021

- 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 40 mg per day) for 6 weeks.

B Moderate

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

no difference in efficacy with a lower toxicity profile

A strong

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

C Weak

We **do not recommend adding other immunomodulatory** or immunosuppressive drugs to PDN for the treatment of the initial episode of nephrotic syndrome

IPNA guidelines on SSNS in children: RELAPSE

B Moderate

We recommend that SSNS relapse be treated with single daily PDN (2 mg/kg per day or **60 mg/m² per day, maximum 60mg**) until complete remission on 3 days and then decreased to alternate day PDN (1.5 mg/kg per day or **40 mg/m² per day, maximum 40 mg) for 4 weeks**

A strong

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

Results of the PROPINE randomized controlled study suggest tapering of prednisone treatment for relapses of steroid sensitive nephrotic syndrome is not necessary in children.

AIM

Comparison of two prednisone regimens using the same cumulative dose:

- Short course without tapering (36 days)
- Long course with tapering (72 days)

PATIENT POPULATION

- Steroid Sensitive Nephrotic Syndrome
- Age 3-17 years
- ≥ 1 relapse in the past year
- normal renal function

RESULTS

Relapse after 6 months:

Short course 38 patients → 48%

Long course 40 patients → 58%

CONCLUSION:

A prolonged tapering schedule of prednisone offers no benefits against relapses over a shorter course without tapering

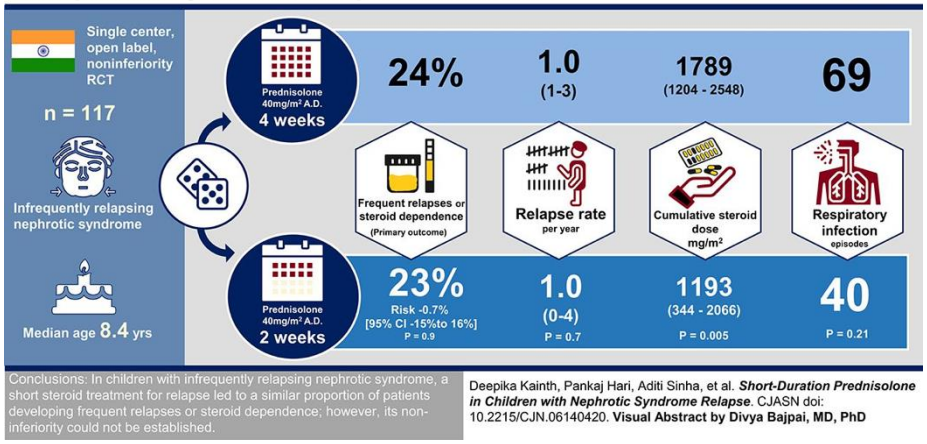
ISN kidney INTERNATIONAL

OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

Gargiulo et al

Is short-duration prednisolone effective in treatment of nephrotic syndrome relapse in children?

CJASN Clinical Journal of the American Society of Nephrology



Conclusions: In children with infrequently relapsing nephrotic syndrome, a short steroid treatment for relapse led to a similar proportion of patients developing frequent relapses or steroid dependence; however, its non-inferiority could not be established.

Deepika Kainth, Pankaj Hari, Aditi Sinha, et al. ***Short-Duration Prednisolone in Children with Nephrotic Syndrome Relapse***. CJASN doi: 10.2215/CJN.06140420. **Visual Abstract by Divya Bajpai, MD, PhD**

+ ongoing RCT in The Netherlands 2 vs. 6 weeks.

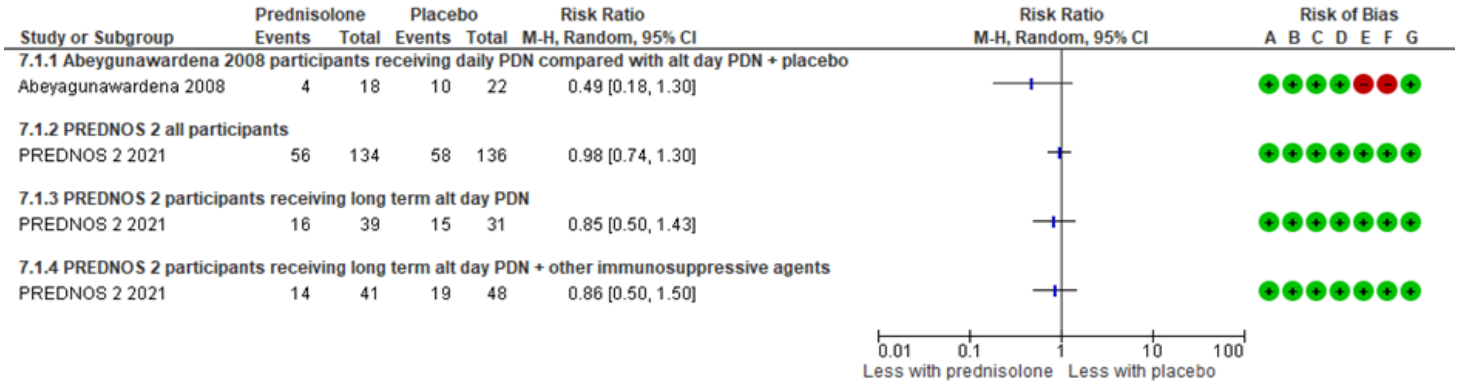
IPNA guidelines on SSNS in children: RELAPSE prevention

C Weak

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 for prevention of relapse

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



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

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.

IPNA guidelines on SSNS in children: maintenance therapy

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 or low-dose maintenance PDN** given as an alternate-day or a daily dose

Shared decision with parents

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**

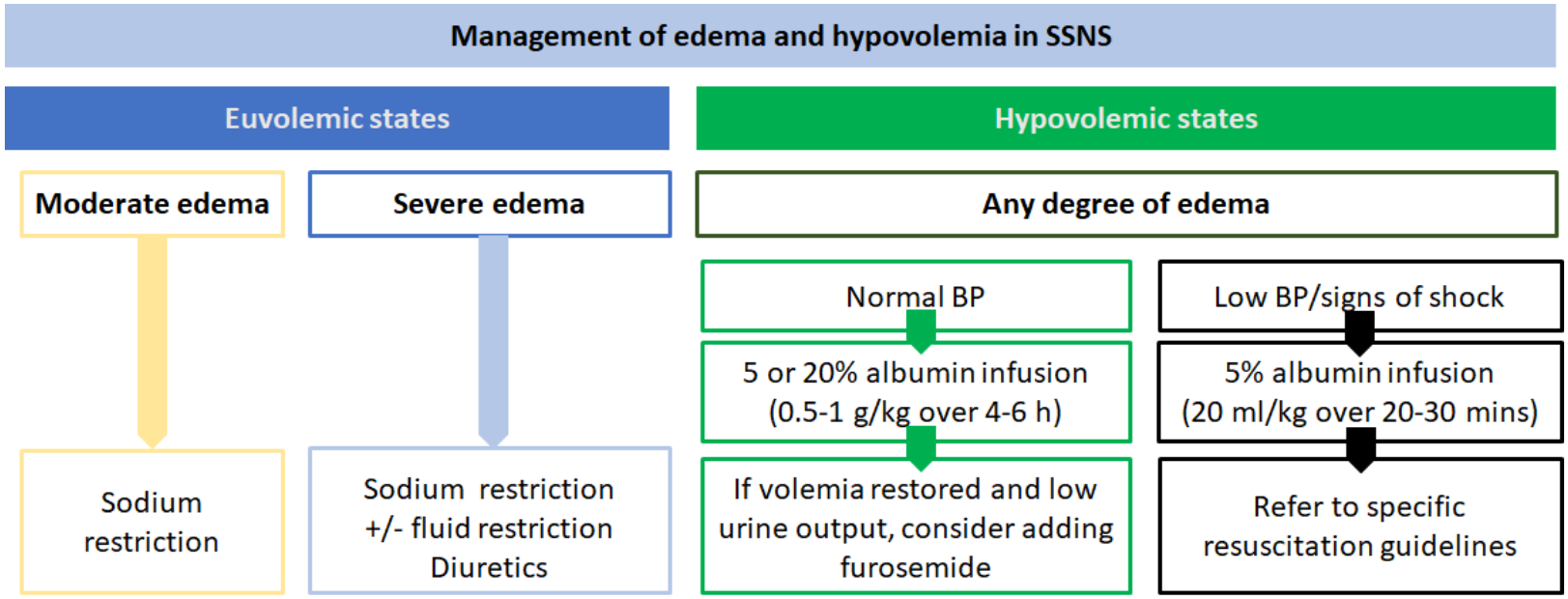
B Moderate

- 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 Moderate

- We recommend considering tapering and discontinuation of maintenance treatment in all children **in sustained remission for at least 12 months**

IPNA guidelines on SSNS in children: supportive therapy



In case of euvolemia, we **suggest treating moderate edema by low salt-diet only AVOID DIURETICS**

C
Weak

We **do <u>NOT</u> recommend routine prophylactic anticoagulative** or antiplatelet treatment for children and adolescents in the acute nephrotic stage, but only if identified increased risks : hypovolemia, hospitalisation, CVL, familial RF, past Hx, adolescent.

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Acknowledgements

IPNA

IPNA guideline Core Group

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Deidre Hahn ANZPNA Sydney, Australia
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Wendy Cook, patient representative

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Marina Vivarelli Roma

Agnes Trautmann Heidelberg

Société de Néphrologie Pédiatrique

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ORKiD

Necker Enfants Malades Hôpital Universitaire

imagine Institut des Maladies Génétiques

Université de Paris

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Ongoing guidelines

IPNA

- **IgAN and IgAV**: lead Marina Vivarelli, Koichi Nakanishi

Marina
Vivarelli
Roma
ESPN
IPNA

Koichi
Nakanishi
Okinawa
JSPN
IPNA

Join us in Calgary, Sept 7th 1-6 pm

- Pre-congress course on Guideline development
- And full presentation of the SSNS guideline

Evaluation of Immune and Vaccine Competence in Steroid-Sensitive Nephrotic Syndrome Pediatric Patients

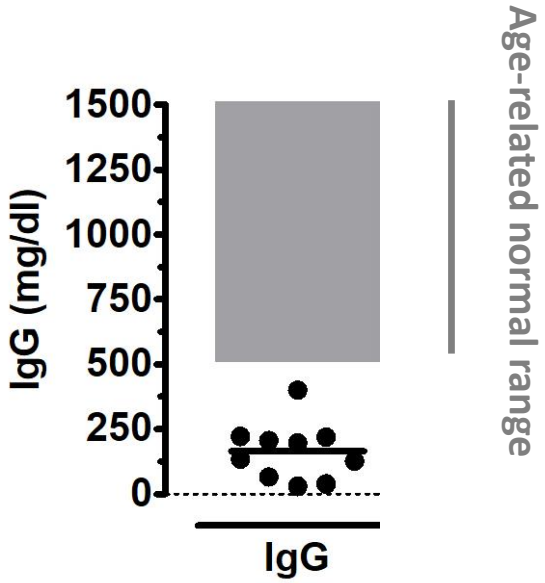
Marina Vivarelli – Manuela Colucci

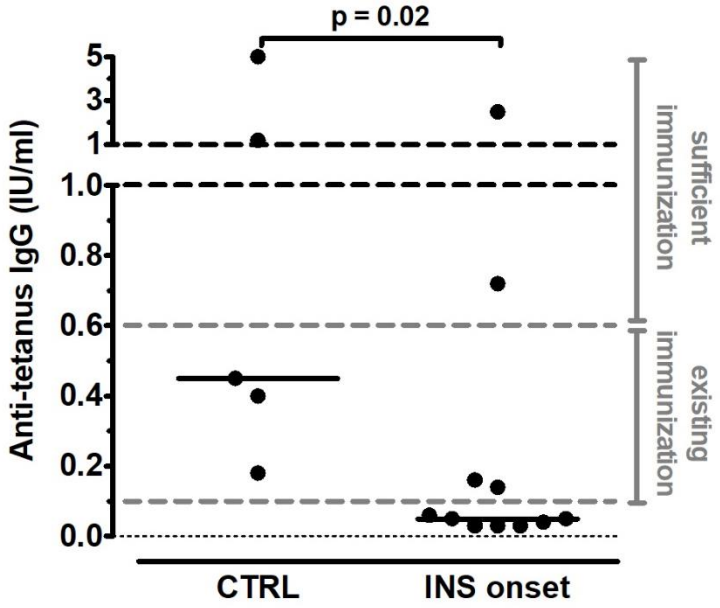
Study Design

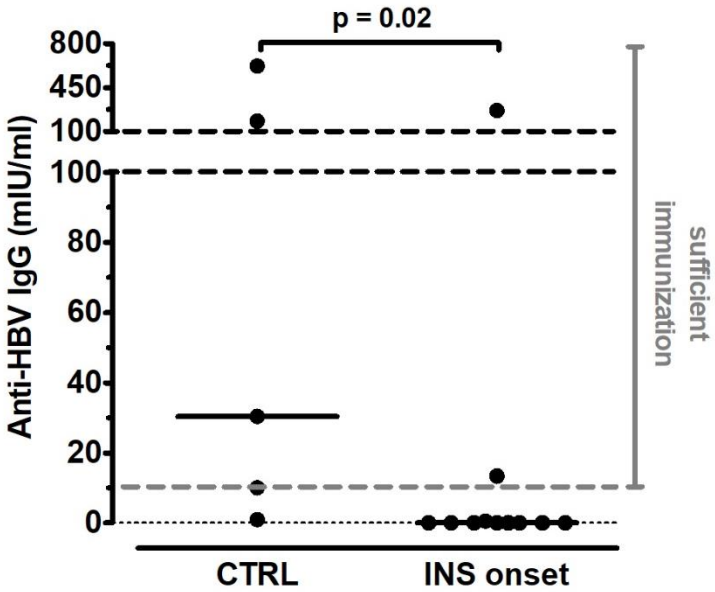
- Prospective observational cohort study
- Patients:
  - INS patients prospectively followed from disease onset and after introduction of steroid-sparing agents in those patients who develop FR/SDNS
  - FR/SDNS patients enrolled in a randomized controlled clinical trial evaluating the superiority of rituximab generic vs mycophenolate mofetil
  - age- and sex-matched healthy controls, to determine normal values of all the assessed parameters

- Aim: to determine the modifications of the immunological memory of INS patients induced by disease conditions alone and by the administration of different immunosuppressive agents, both oral and B-cell depleting, and to characterize the ability to maintain response to vaccinations and to potential infections in these patients.

Serum total and vaccine specific IgG are significantly reduced in steroid-sensitive nephrotic syndrome pediatric patients at onset



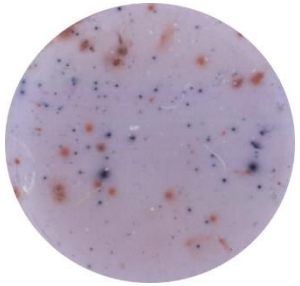




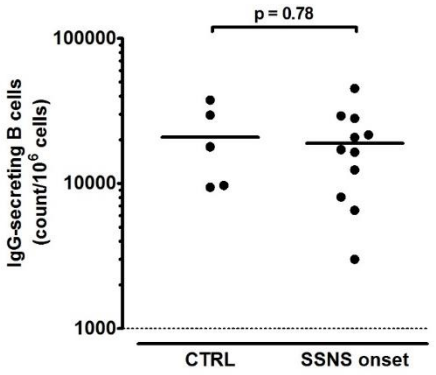
- All patients were previously vaccinated against tetanus and HBV as per national requirements.
- Serum total IgG levels were below the normal range and serum anti-tetanus and anti-HBV IgG were significantly reduced compared to age-matched healthy controls and below the sufficient protection level in most SSNS patients at disease onset.

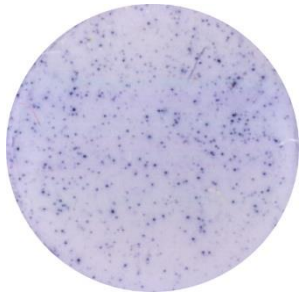
Colucci et al. *Frontiers in Immunology* 2019.

A competent memory B-cell response is observed in steroid-sensitive nephrotic syndrome pediatric patients at onset

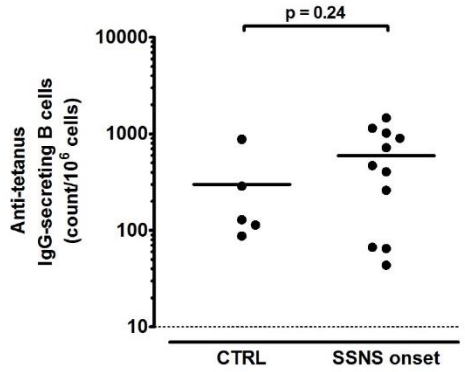


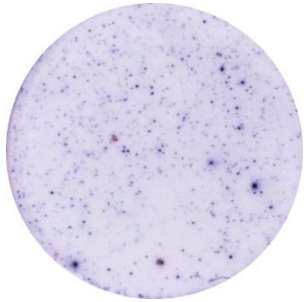
Total
IgG/IgM



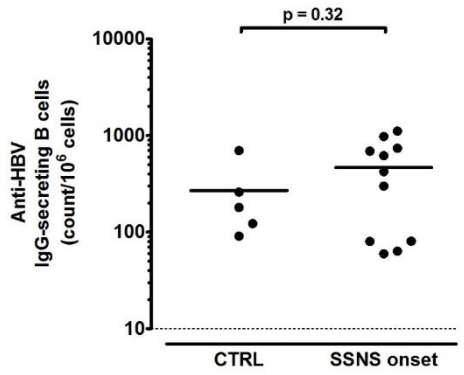


Anti-tetanus
IgG/IgM





Anti-HBV
IgG/IgM



- In contrast to the reduced levels of serum IgG, SSNS patients showed an intact B-cell memory pool, by evaluating by ELISPOT the total amount of total and vaccine-specific IgG-secreting B cells.

Colucci et al. *Frontiers in Immunology* 2019.

Conclusions

SSNS pediatric patients show a preserved immune and vaccine competence at disease onset, which can be efficiently evaluated by quantifying antigen-specific memory B cell response rather than by measuring serum IgG titers strongly affected by the intense proteinuria.

Ongoing

- Monitoring of immunological memory of INS patients from onset and following introduction of different immunosuppressive agents for relapsing patients (more than 30 enrolled patients)
- The RCT comparing the efficacy of RTX vs MMF is still ongoing (evaluation of the immunological memory is performed in parallel to clinical assessment)
- The obtained results are planned to be published in two different articles.

Membranous Nephropathy in Children

Dr. Julien Hogan
Dr. Claire Dossier
Hôpital Robert Debré, APHP, Paris
Université de Paris

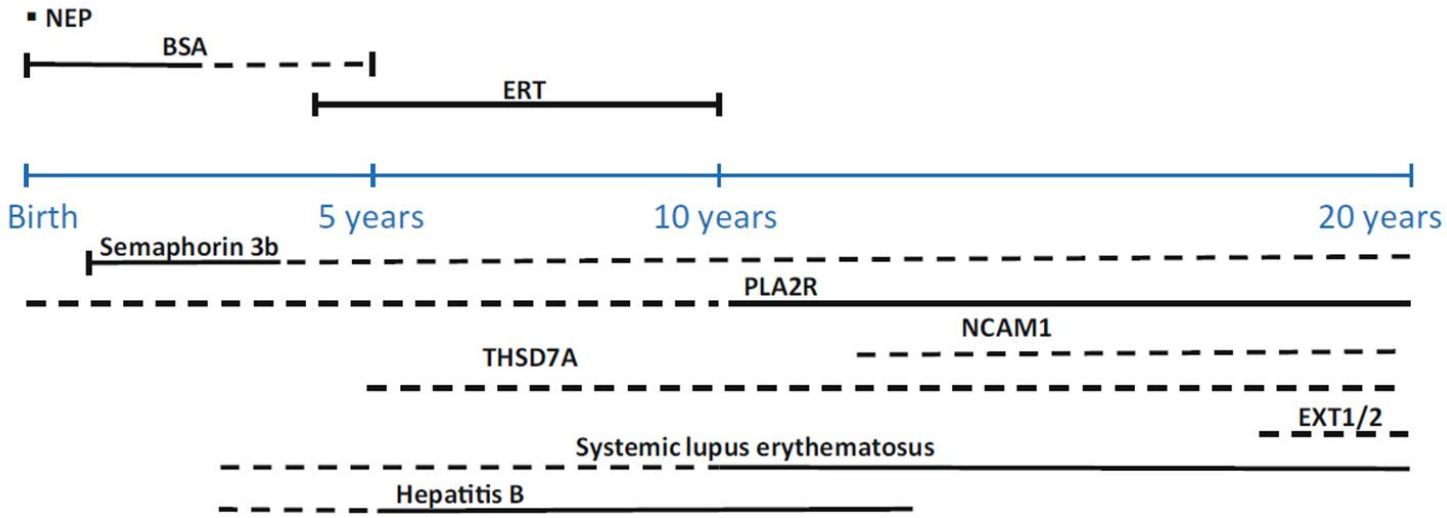
Dr. Marina Vivarelli
Ospedale Pediatrico Bambino Gesù, Roma

Pr. Pierre Ronco/Hanna Debiec, INSERM 1155
Sorbonne Université
Hôpital Tenon, Paris

Study rationale

- Membranous nephropathy is a rare condition in children
- Published data are mostly single center reports
- Lack of data on:
  - MN epidemiology in children
  - Treatment practicies and outcomes
  - Value of anti-PLA2R monitoring
- Need of large cohorts with clinical data and biopsy samples to assess the prevalence of recently discovered antigens and to discover new antigens.

Distribution of antigens according to age



Ronco P, Vivarelli M, Ayalon R & Debiec H Chapter 94.1 Pediatric Nephrology, 2021

Example: Discovery of Semaphorin 3B antigen

Flowchart of the discovery and validation cohorts

Discovery COHORT
70 biopsies of PLA2R-negative MN
MS/MS

↓

2 Sema3B-associated MN by MS/MS

↓

Both confirmed by IHC, + 1 additional case detected on screening 90 cases for Sema3B-associated MN and confirmed by MS/MS

FRENCH VALIDATION COHORT #1*
59 biopsies of MN

↓

2 Sema3B-associated MN by IF

FRENCH VALIDATION COHORT #2*
16 biopsies of MN by IF

↓

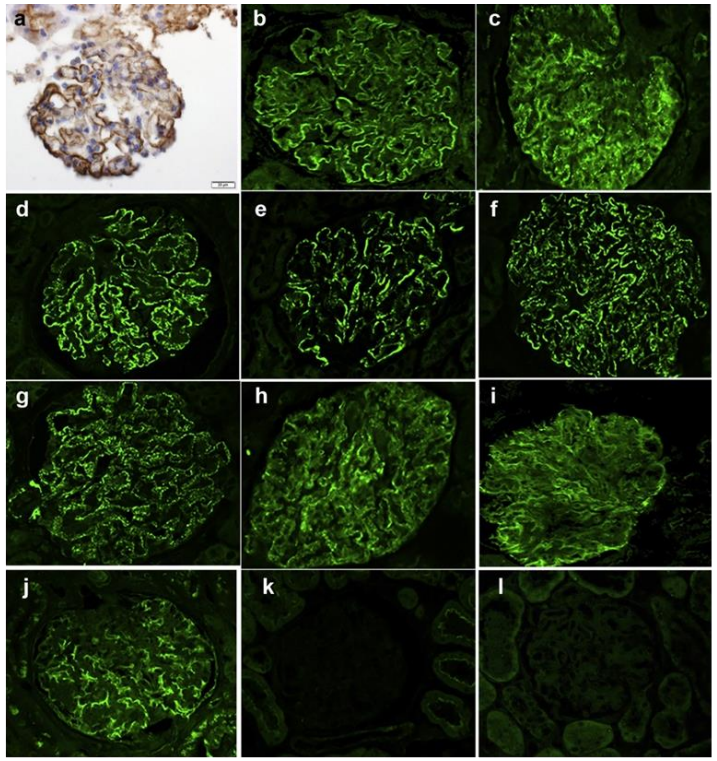
2 Sema3B-associated MN by IF

ITALIAN VALIDATION COHORT*
43 biopsies of MN by IF

↓

4 Sema3B-associated MN by IF

IHC and IF labeling of the paraffin biopsies from the European patients



c: Patient #5 at 1 year

d: Patient #5 at 19 years

e-j: All pediatric patients

Control cases:

k: PLA2R positive MN
i: PLA2R negative, Sema3b negative child

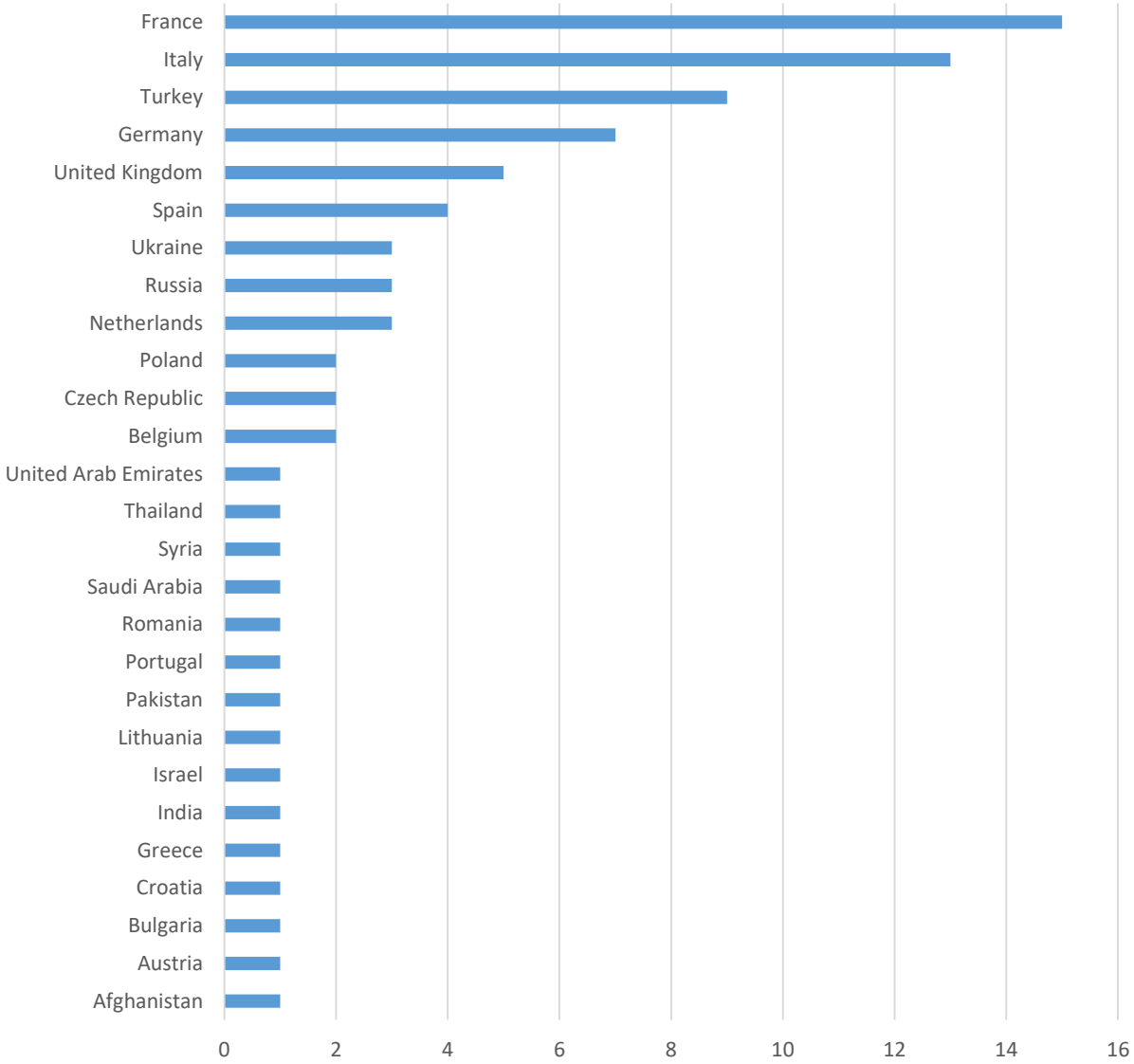
Kidney Int 2020, 98:1253

Study Objectives

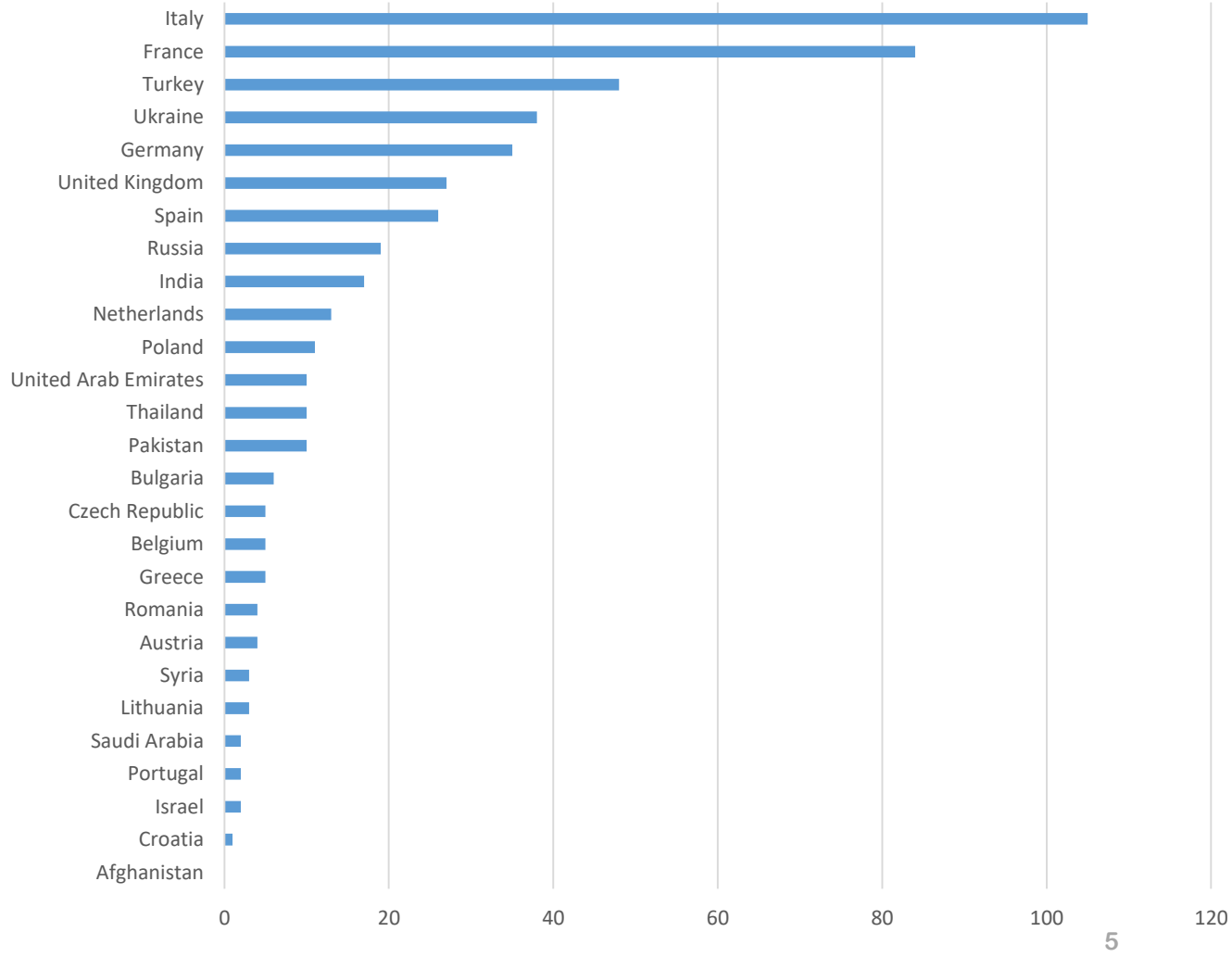
- **Objective 1:** To describe the epidemiology of membranous nephropathy in children in a large multinational cohort.
  - Population: All patients with MN (IMN and secondary MN)
  - Data collected: Demographics, clinical data, anti-PLA2R Ab at diagnosis
- **Objective 2:** To assess the oucomes of pediatric patients treated for IMN based on treatment regimen and immunological monitoring (anti-PLA2R Ab during follow-up).
  - Population: All patients with idiopathic MN
  - Additional data collected: Treatment regimen, outcomes (uPCR, serum albumin, eGFR, complications), immunological monitoring (anti-PLA2R Ab, B cell count if RTX…)
- **Objective 3:** Assess the prevalence of « new antigens » in children with IMN and create a tissue biobank of IMN without identified Ag for future discovery analysis.

Feasibility Survey

83 centers from 27 countries

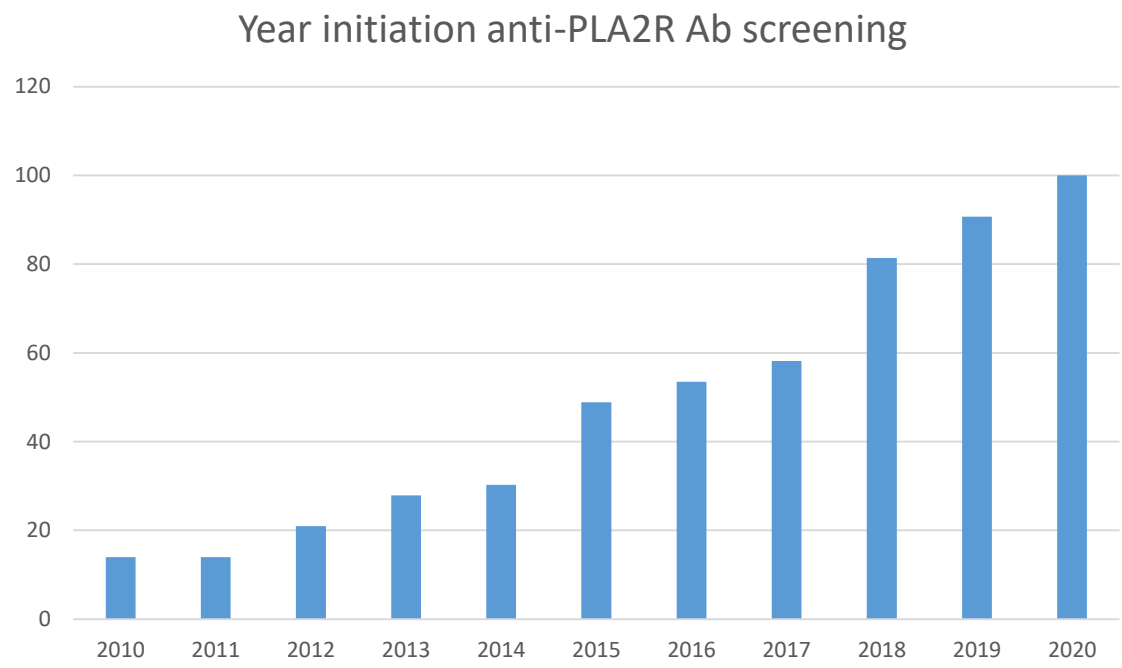


495 patients



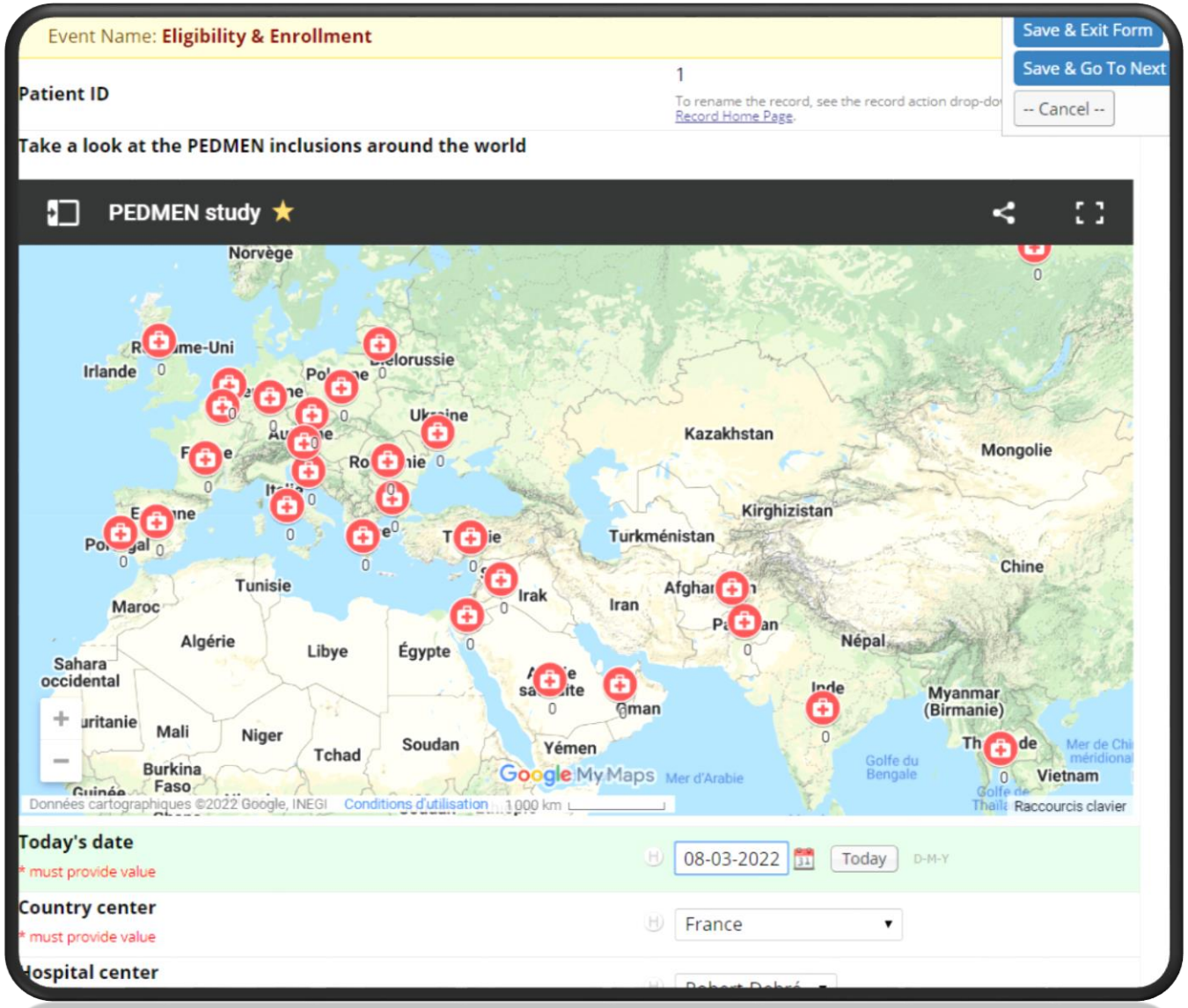
PLA2R Ab testing

19/83 centers (22%) do not screen for anti-PLA2R Ab at diagnosis



55/64 centers (86%) monitor anti-PLA2R Ab titers during follow-up

Data collection



7

Database

REDCap
Research Electronic Data Capture

Study 1
Study 2
Study 3

	Demographics & Diagnosis	**Biopsy results**	**Labs**	**Immune monitoring**	**Treatments**
		Biopsy results ...	**Labs** ...		
Data points	Baseline and last FU	All biopsies	Bx, M1,3,6,12,24, relapse, last FU	All assessments	Whole Follow up
Variables	**Demo**: Age, sex, race, country, zipcode **Clinical presentation:** Pu/NS, Hu, AKI, HTA, extrarenal symptomes **Biological presentation**: ANA, anti-dsDNA, low complement **Diagnosis:** IMN, Class V LN, other secondary MN **Outcome**: Complete remission(Y/N), kidney outcome (CKD, ESRD)	**Light microscopy:** GBM: Normal /prominent/spikes **IF:** IgG (subclasses), C3, C1q **Electronic microscopy** (Y/N) **Anti-PLA2R staining** (Y/N, if Y: Pos/Neg) **Anti-PLA2R Ab** (Y/N, if Y: Pos/Neg) **Other antigenes** ***Upload scanned pdf***	**Height** **Serum creatinine** **UPCr** **Serum Albumin**	**Anti-PLA2R Ab titers** *CD20 count in patients treated with anti-CD20*	**Treatments received:** Steroids (pulse) Calcineurin Inh. Anti-CD20 Cyclophosphamide RAS blockers Others **Start date/End date**

Biopsy samples with negative AntiPLAR staining and no anti-PLA2R Ab in serum
Possibility to send unstained slides to Paris for staining of all known antigens +/- discovery of new antigens

Next step

Patient ID	Eligibility & Enrollment	Baseline			Biopsy		Labs FU								Immune monitoring	Treatments
	Eligibility criteria	Demographics	Clinical & biological assessments	Diagnosis & outcomes	Histological patterns	Biopsy-banking	Labs baseline	Labs FU-M1	Labs FU-M3	Labs FU-M6	Labs FU-M12	Labs FU-M24	Remission & relapse	Labs last FU	Immuno-assessments	Treatments follow-up
1																
2																
3																
4																

OBJECTIVES:

- Finalyze database May 2022
- Set up access for all the sites and launch data collection in all participating centers (june 2022 – ESPN congress)

Aim 3 submitted to ESPN grant

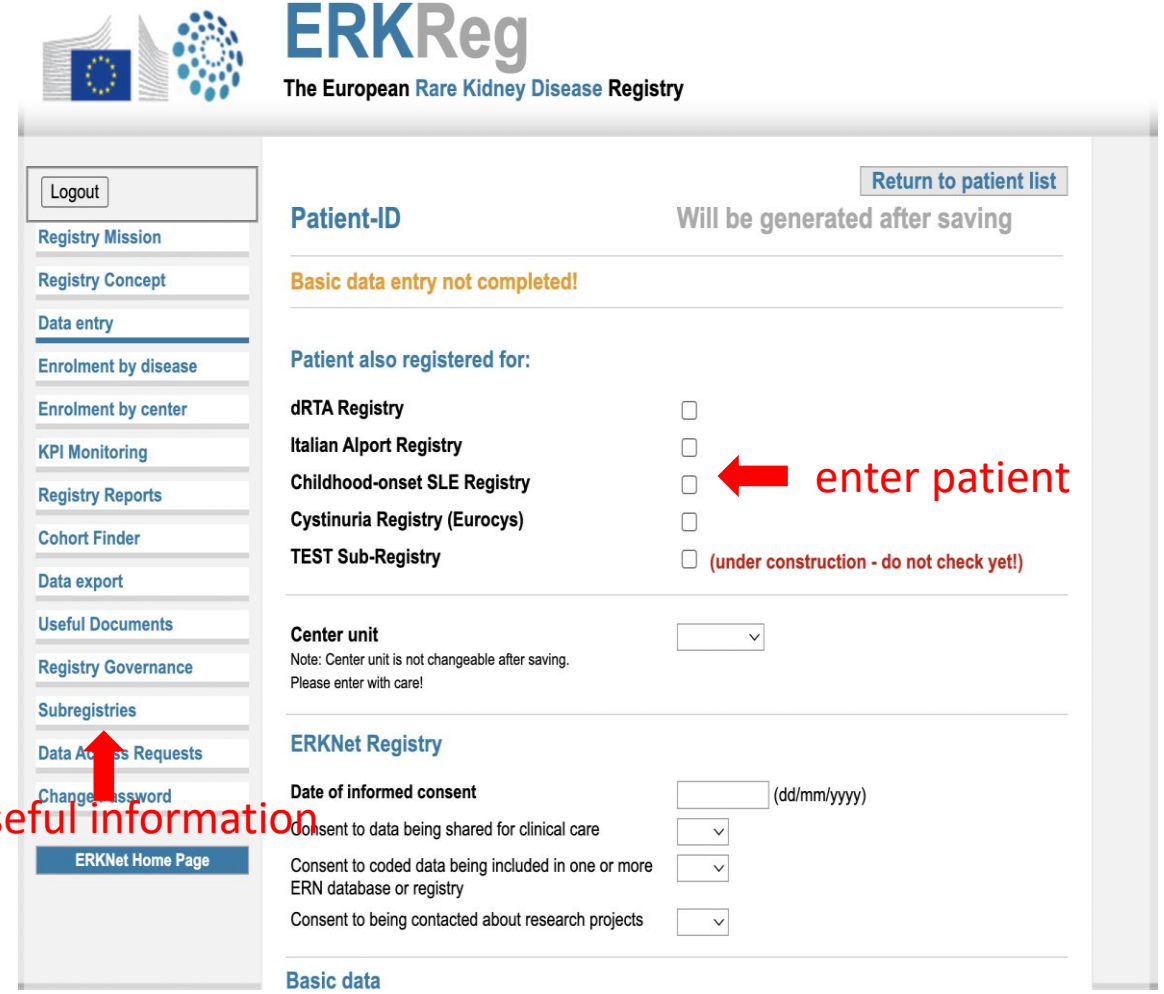
Reminder: IRB approved in France (centers from countries requesting a local IRB approval can be provided with study documents for submission)

ESPN-ERKNet Lupus nephritis registry

Scientific Committee:
Rezan Topaloglu, Eda Didem, Kurt Sukur (Ankara, Turkey)
Dieter Haffner, Adriana Suhlrie (Hannover, Germany)
Marina Vivarelli (Rome, Italy)
Tadej Avcin (Ljubljana, Slovenia)

european society for paediatric nephrology

ERKNet
The European Rare Kidney Disease Reference Network



Eligible patients

- Biopsy proven Lupusnephritis
- Childhood onset SLE, i.e. diagnosis <=18 years

ERKNet
The European Rare Kidney Disease Reference Network

european society for paediatric nephrology

What is the aim of the European registry?

- To create an European registry with large patient numbers to allow adequate statistical analyses of:

  -long term renal outcome and its determining factors in childhood onset LN (including transition)

  -disease and treatment associated comorbidities

- In order to allow benchmarking, develop research hypothesis, improve treatment and outcome

ERKNet
The European Rare Kidney Disease Reference Network

european society for paediatric nephrology

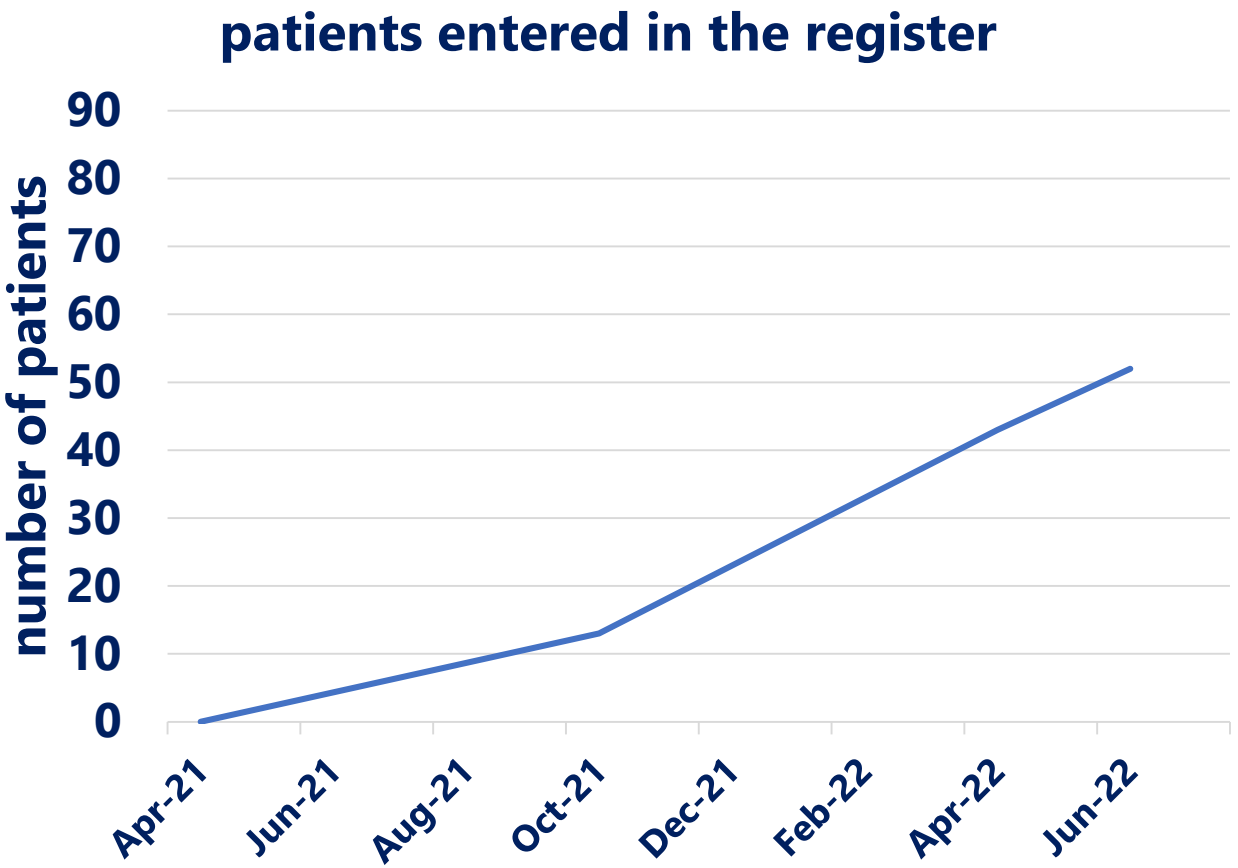
Visits:

- **Initial visit with yearly follow-ups** (at least for 5 years)
- **Basic data** (age, gender, weight, height, ethnicity, biopsy, activity index/SLEDAI)
- **Visit sheet** Blood results (renal function, immunology), urine results, complications (hypertension and consequential damages, steroid associated, disease associated),
- **Medication** (immunosuppressive, antihypertensive, others)
- **Extracorp. Therapy**

ERKNet
The European Rare Kidney Disease Reference Network

european society for paediatric nephrology

What happened so far?



- October 2021: 13 patients → today: 52 patients
- In total 100 patients with childhood onset LN registered in the main registry

→ Please check if you entred LN-patients to transfer them to the subregister

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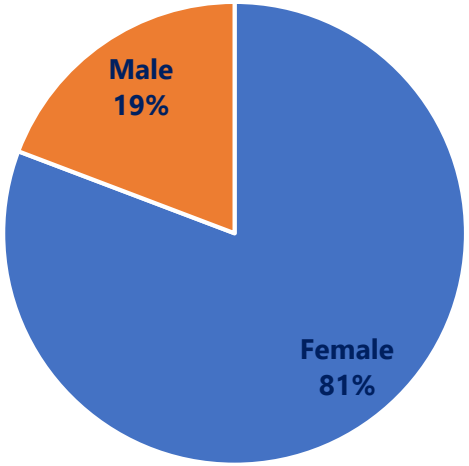
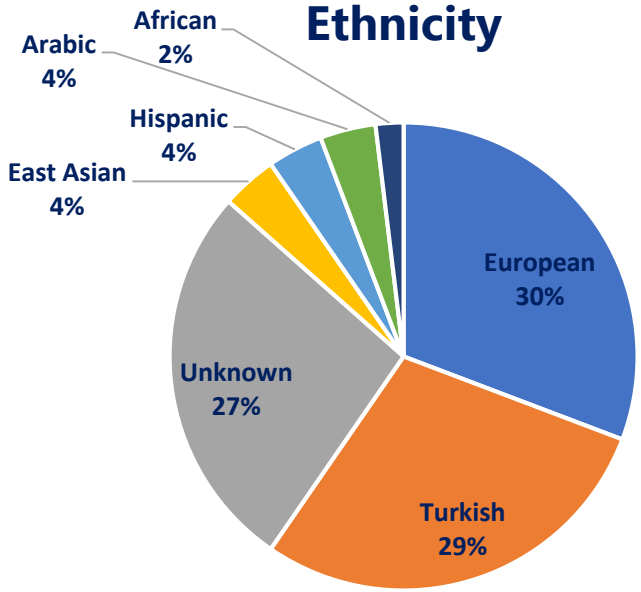
Gender

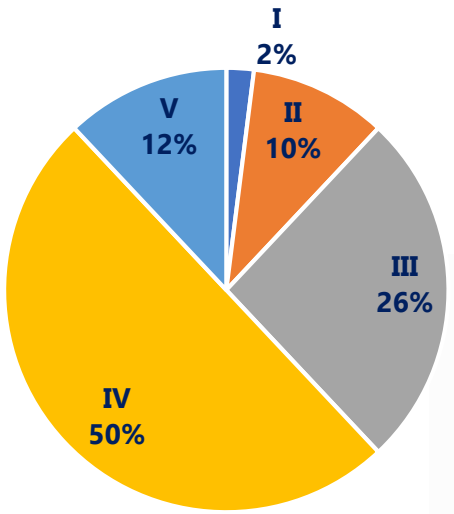


total patient	52	median (min-max)	unit
Age at first symptoms		12.5 (4.5-18.0)	years
low C3 (<0.85)	36 (71%)	0.38 (0.11-1.10)	g/l
low C4 (<0.14)	38 (76%)	0.04 (0.02-0.15)	g/l
elevated dsDNA antibodies	44 (86%)	300 (24-5888)	IU/ml

Ethnicity



Histopathology WHO



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What's new?

1) Reasonable ranges for parameters

Value	Unit	Normal value	Reasonable Range (min-max)
dsDNA-Antibody Titer	IU/ml	<5	0-6000
24h-Proteinuria	g/m^2/d	<0.1	0-20

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What's new?

2) Addendum: parameters asked **at time of diagnosis** (basic sheet)

- height, weight of the patient
- blood pressure
- blood results: Creatinine, Cystatin C, Albumin, blood count
- urine values: Urinary casts, Leukocyturia, Proteinuria

→ Centers which already entered patients will enter missing data

ERKNet The European Rare Kidney Disease Reference Network

european society for paediatric nephrology

What's new?

Eligible patients

- Biopsy proven Lupusnephritis
- Childhood onset SLE, i.e. diagnosis <=18 years
- Diagnosis 2015 or later

→ In order to gain more long term data

ERKNet
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european society for paediatric nephrology

What the future holds

1) Transfer eligible patients from the main registry

2) Enter new patients from other centres
   →Cooperations, online help desk sessions

ERKNet
The European
Rare Kidney Disease
Reference Network

european
society for
paediatric
nephrology

Contact

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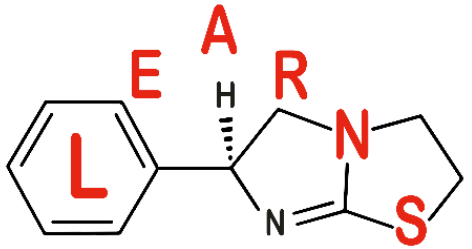
- Tanja.Wlodkowski@med.uni-heidelberg.de

Hôpital universitaire mère-enfant Robert-Debré

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

The NEPHROVIR-3 trial
&
LEARNS-2 trial project

Claire Dossier
Hôpital Robert-Debré, APHP, Paris
CRMR Syndrome Néphrotique

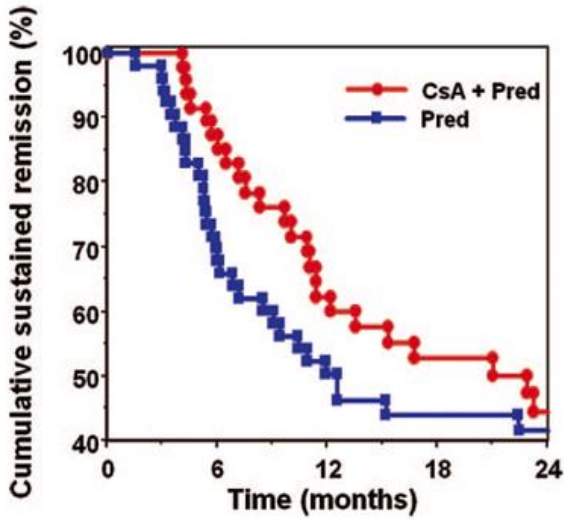


ESPN Ljubjana
Glomerular Disease Working Group

Challenges for the treatment of 1st flare INS

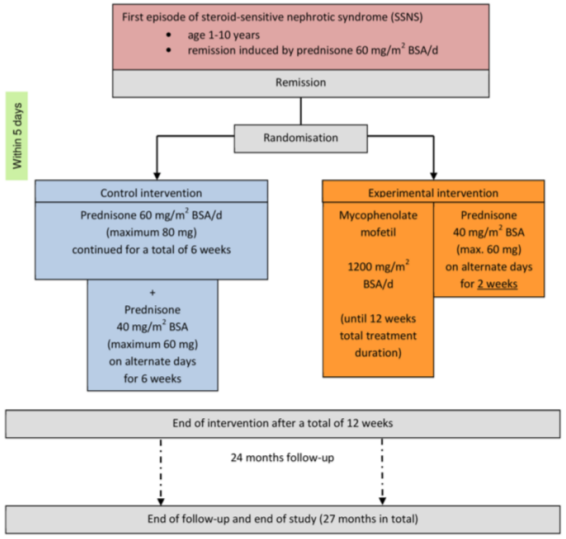
- Whatever the dose and duration of steroids
- 70- 80% relapse and 50% become Frequent Relapsers
- Add an Immunosuppressor at first flare ?

Cyclosporine

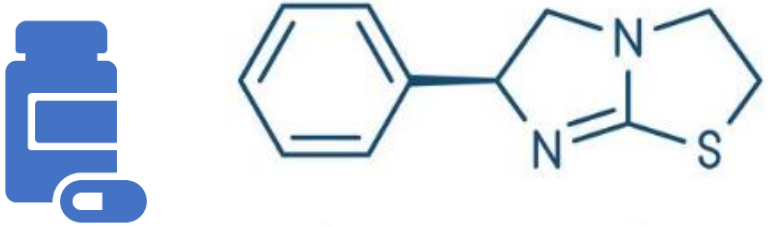


CJASN Hoyer 2006

MMF, INTENT study

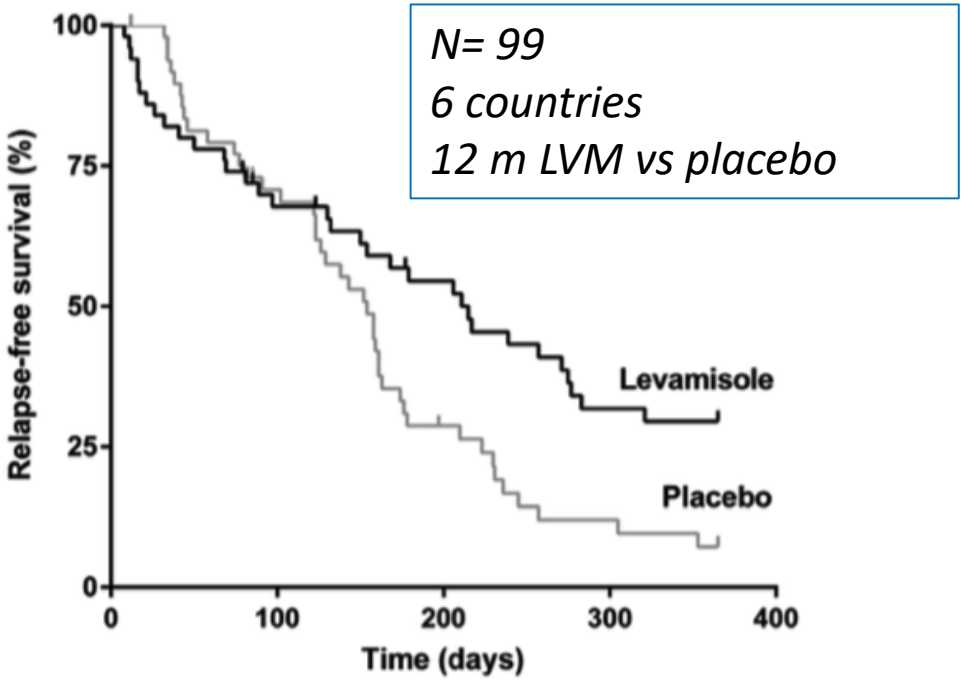


BMJ Open Ehren 2018



levamisole

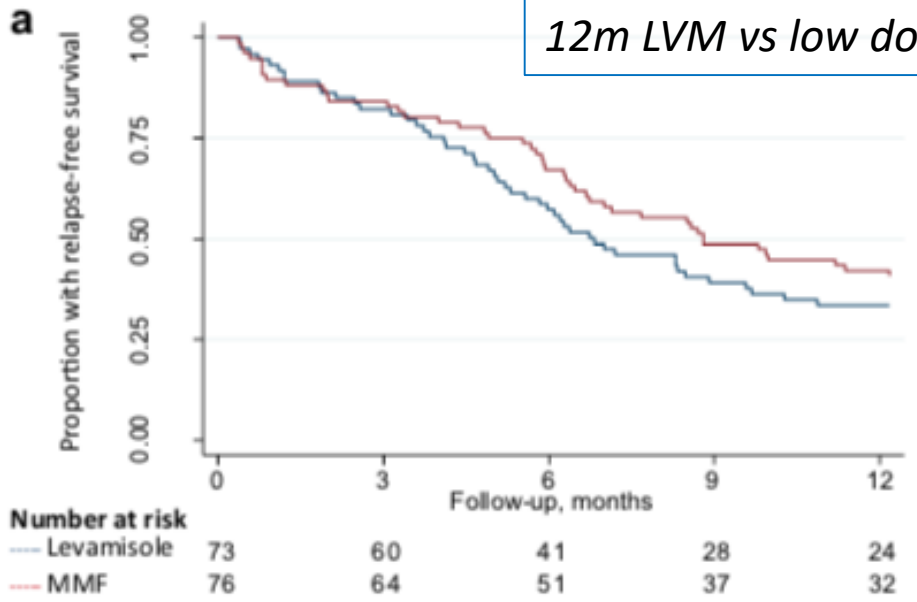
- Immunomodulatory - remanent – safe – low cost



N= 99
6 countries
12 m LVM vs placebo

KI Gruppen, 2017

N= 137
India
12m LVM vs low dose MMF



KI Sinha, 2019

NEPHROVIR-3 *Efficacy and safety of levamisole for maintaining remission after the first flare of INS in children*

✓A placebo-controlled, double-blind, superiority, randomized (1:1) clinical trial

✓*Primary Objective* : Assess the efficacy of levamisole, given at the posology of 2.5 mg/kg/48h, during 6 months, in addition to a 18 weeks-steroid therapy* in children at first flare of steroid sensitive nephrotic syndrome.

✓*Primary Endpoint* : Relapse-free survival at 12 months

**SNP Protocol (3990mg/m²)*

✓Multicentric in the NEPHROVIR network in the Paris Area

- ✓N=38 centers (35 general pediatric and 3 pediatric nephrology departments)
- ✓N= 20 centers for randomisation

N° EUDRACT 2016-002324-92, NCT02818738

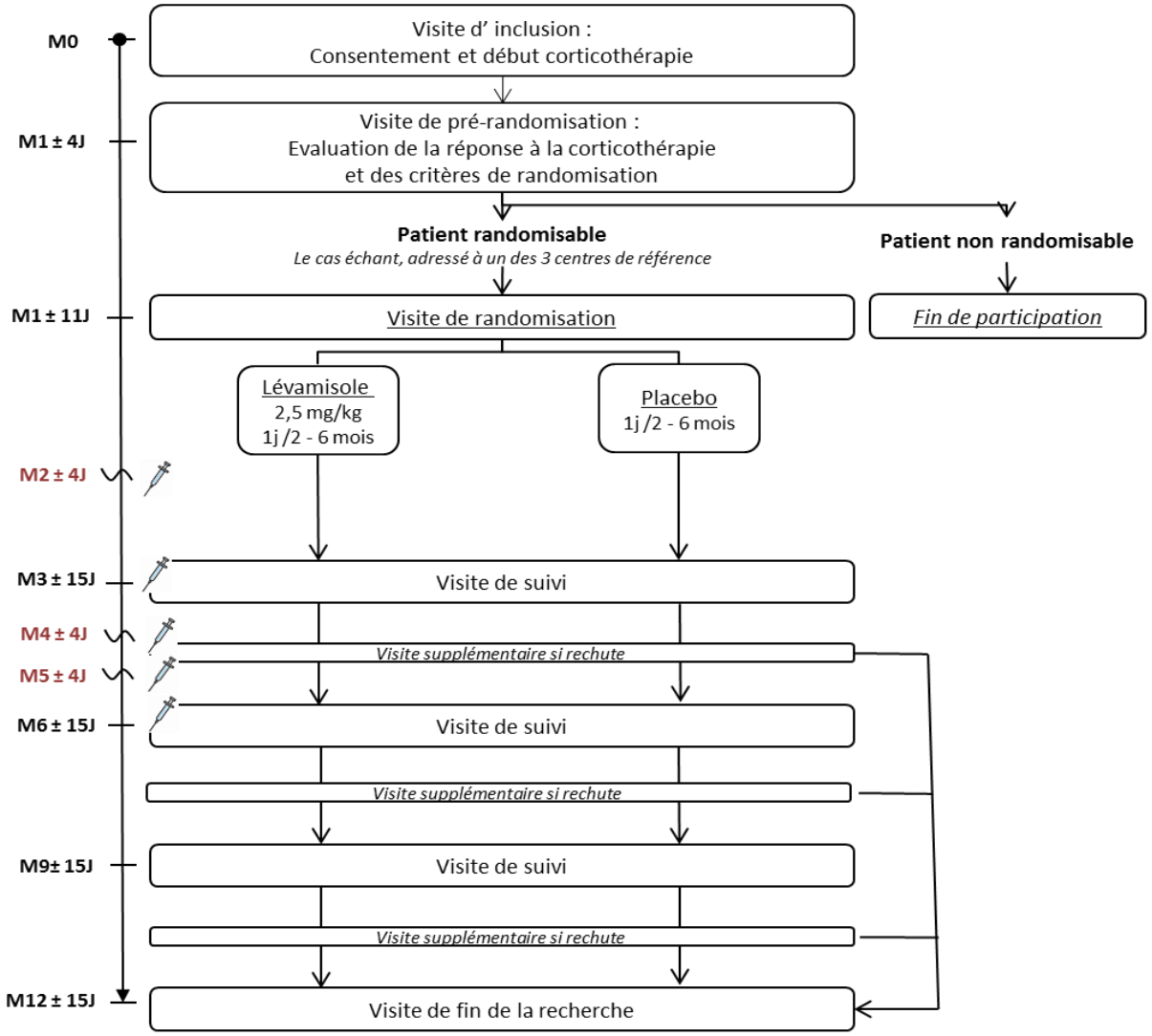
NEPHROVIR-3 Design

Main Inclusion criteria

- Age 2-16yrs
- First flare of NS
  - Albumine < 25 g/l
  - UPCR >0,20 g/mmol
- Normal C3 complement

Randomisation criteria

- Steroid Sensitivity after 4 weeks of oral prednisone or prednisolone
- Successful swallowing test with placebo 5 mg for children <6 yrs.
- Normal Neutrophile count

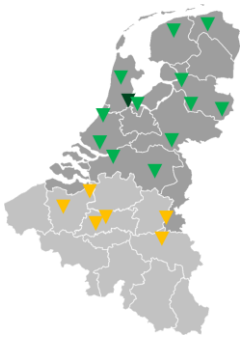


Surveillance de la tolérance hématologique et hépatologique

NEPHROVIR-3

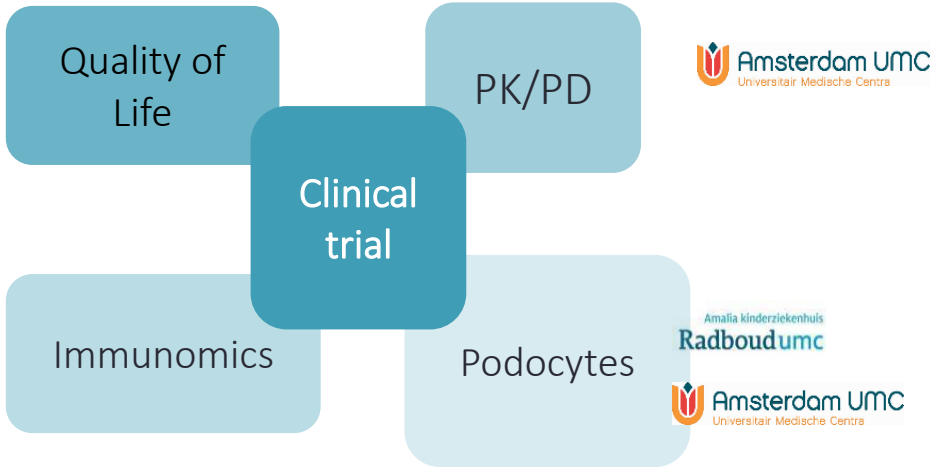
- 2015 Institutionnal funding
- 350 000^{E}
- Recruitment
  - 38 centers in Paris area
  - Sep 2017 to Feb 2020

	Planned	Completed
N inclusions	156	86
N randomisations	136	63
Duration of inclusions (m)	26	29



LEARNS

- Dutch Kidney Fundation Funding
- >1ME
- Recruitment (# 55-60 / 92)
  - 15 centers in NL + 5 in Belgium
  - Since 2018 to july 2022 ?



NEPHROVIR-3 : Relapse-free survival

OP-39

Saturday 25th

10:15 – 12:15

Best oral presentations session

Not yet published

NEPHROVIR-3 - LEARNS : Next steps …

- **The N3M24 study** : M24 Follow-up of randomized patients in the NEPHROVIR-3 trial in Paris

- LEARNS trial in The Netherlands and Belgium
  - End of inclusions : summer 2022
  - Primary End Point : summer 2023
  - M24 Follow-up

- Data sharing and **meta-analysis with the LEARNS study**

Thank you to Antonia Bouts and Floor Veltkamp for the successful collaboration

Thank you for your attention !

claire.dossier@aphp.fr

Update on ongoing studies

Matko Marlais
ESPN Glomerular Diseases Working Group
23rd June 2022

Original research

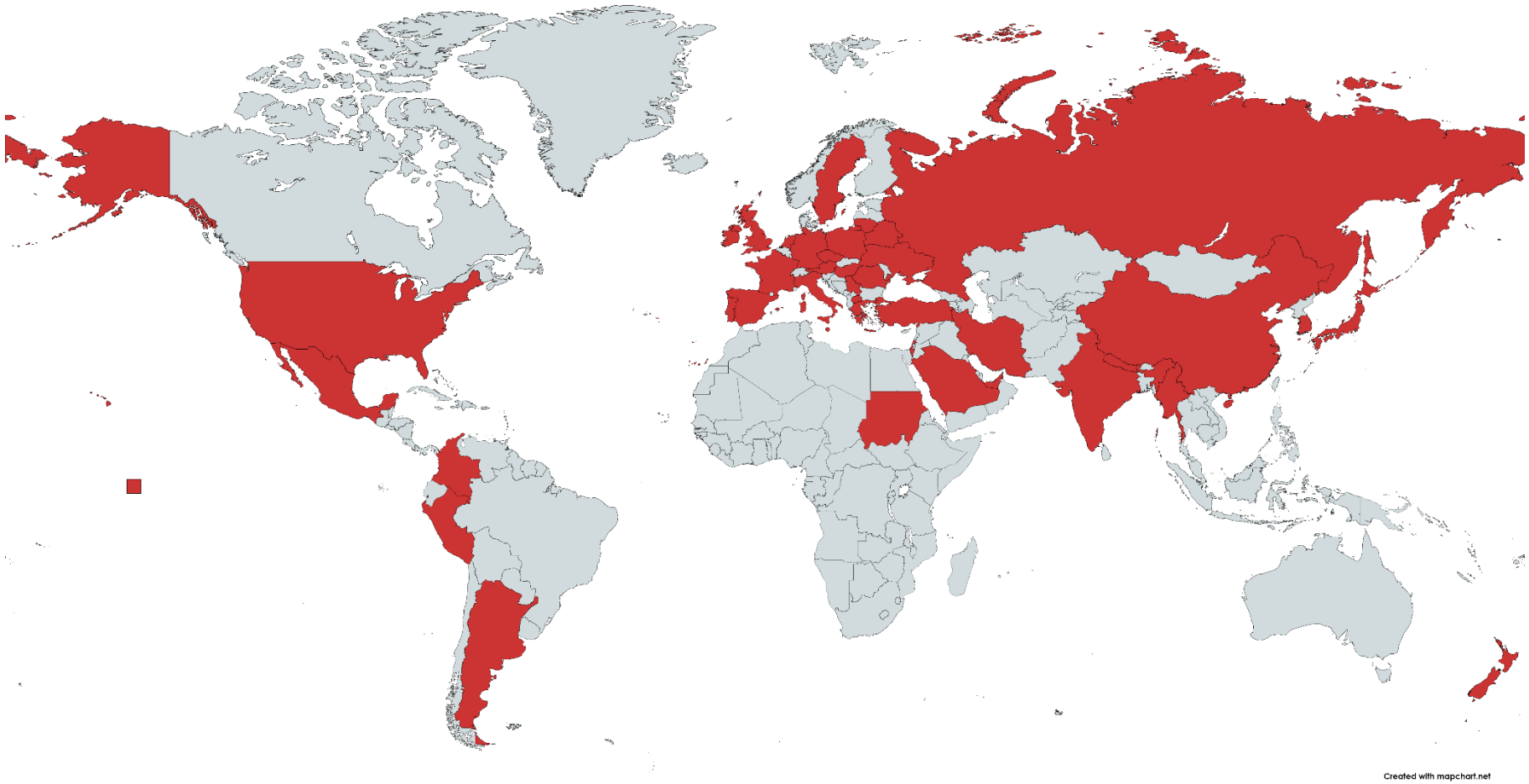
OPEN ACCESS

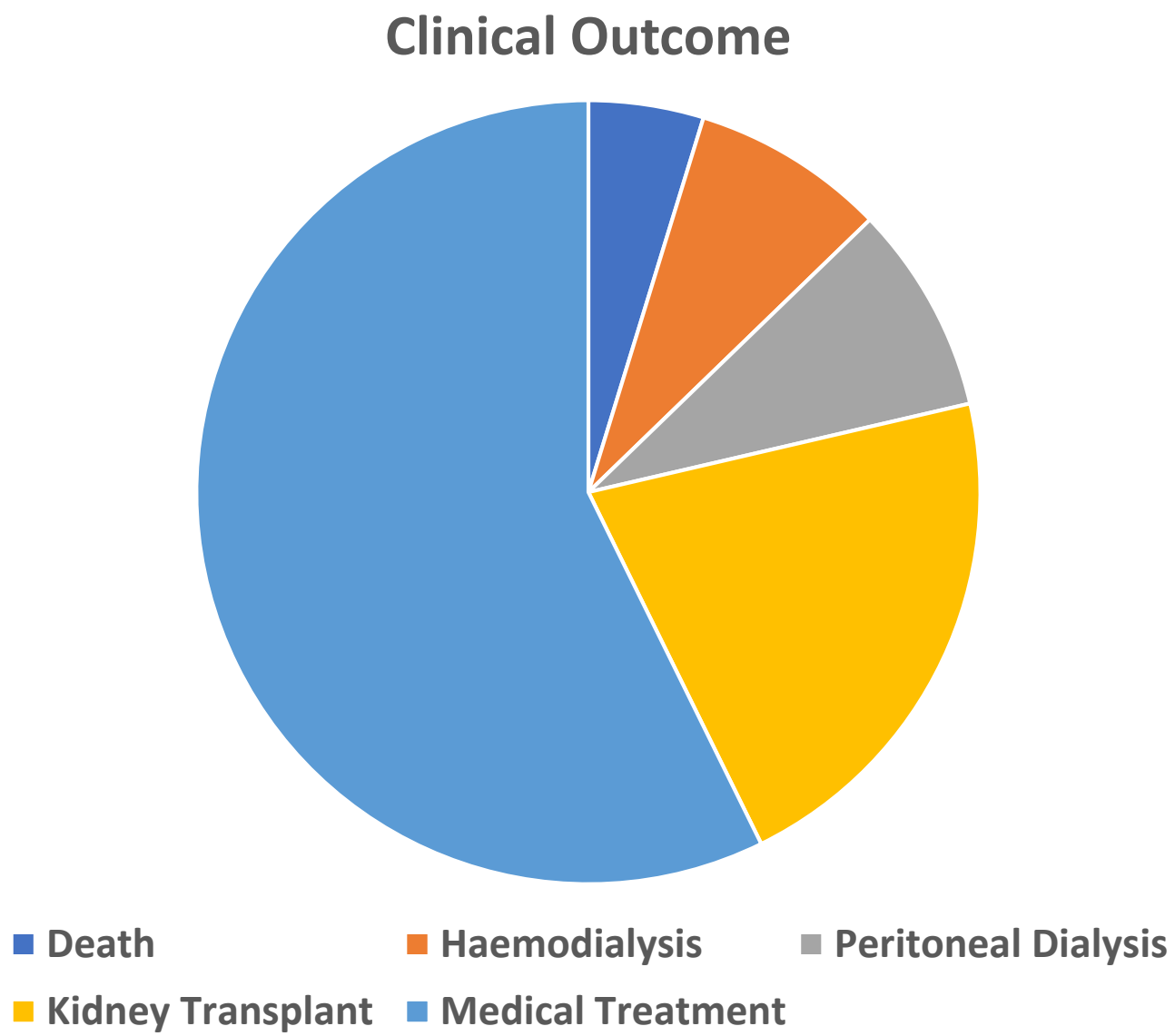
COVID-19 in children treated with immunosuppressive medication for kidney diseases

Matko Marlais ,[1,2] Tanja Wlodkowski,[3] Samhar Al-Akash,[4] Petr Ananin,[5] Varun Kumar Bandi,[6] Veronique Baudouin,[7] Olivia Boyer,[8] Luciola Vásquez,[9] Sukanya Govindan,[10] Nakysa Hooman,[11] Iftikhar Ijaz,[12] Reyner Loza,[13] Marta Melgosa,[14] Nivedita Pande,[15] Lars Pape,[16] Anshuman Saha,[17] Dmitry Samsonov,[18] Michiel F Schreuder,[19] Jyoti Sharma,[20] Sahar Siddiqui,[21] Rajiv Sinha,[22] Heather Stewart,[23] Velibor Tasic ,[24] Burkhard Tönshoff,[25] Katherine Twombley,[26] Kiran Upadhyay,[27] Marina Vivarelli,[28] Donald J Weaver,[29] Robert Woroniecki,[30] Franz Schaefer,[3] Kjell Tullus [2]

Clinical Factors and Adverse Kidney Outcomes in Children With ANCA-Associated Glomerulonephritis

Am J Kidney Diseases – Accepted, in Press


Created with mapchart.net


Clinical Outcome
Death
Haemodialysis
Peritoneal Dialysis
Kidney Transplant
Medical Treatment

	Required KRT at initial presentation		Required KRT at last known follow-up		P-value for difference (KRT requirement at latest follow-up)
	Yes	No	Yes	No	
N	119	207	132	194	
Female	75%	69%	78%	68%	**0.04**
Mean age at presentation (years ± SD)	12.1 ± 4.4	12.5 ± 5.4	11.9 ± 4.6	12.7 ± 5.3	0.2
ANCA MPO serotype	71%	64%	77%	60%	**0.001**
High income GDP	61%	66%	58%	68%	0.08
Peak Scr during initial presentation (µmol/l ± SD)	736 ± 345	173 ± 121	616 ± 333	218 ± 115	**<0.001**
	Organ involvement at presentation				
Respiratory tract	50%	42%	50%	41%	0.1
ENT	12%	17%	10%	19%	**0.03**
Skin	13%	32%	17%	30%	**0.008**
Musculoskeletal	9%	24%	18%	19%	0.8
Neurological	16%	8%	18%	6%	**<0.001**
Eye	5%	10%	7%	9%	0.4
	Induction treatment				
IV steroids	95%	80%	92%	81%	**0.009**
Rituximab	29%	27%	25%	29%	0.4
IV Cyclophosphamide	55%	57%	64%	56%	0.2
Plasma Exchange	57%	19%	44%	26%	**<0.001**
	Maintenance treatment				
Azathioprine	22%	27%	24%	27%	0.6
MMF	46%	45%	43%	47%	0.4
Rituximab	17%	17%	14%	19%	0.3

International Study of Takayasu Arteritis

- Retrospective study of clinical aspects and treatment in children with Takayasu arteritis
- Study run in collaboration with colleagues from North America
- Expressions of interest sent out through ESPN and IPNA
- Study also conducted in collaboration with rheumatologists
- 60 centres across 24 countries currently agreed to take part

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

european society for paediatric nephrology

Takayasu Arteritis

- Aim: to characterise Takayasu arteritis in a paediatric population: clinical presentation, investigations, treatment, and outcomes in an international multi-centre study
- Key research questions:
  - Prevalence of severe neurological presentation in TA/management of high BP
  - Clinical practice in the diagnosis/classification of TA in children
  - General epidemiology of paediatric TA

- Please get in touch if you are interested to know more about the study! Lancelot.Millar@univ.ox.ac.uk, Matko.Marlais@gosh.nhs.uk, Kjell.Tullus@gosh.nhs.uk

Some studies

Kjell Tullus

Consultant Paediatric Nephrologist

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Institute of Child Health

Dosing regimen of Rituximab in FRSDNS

Eugene Yu-hin Chan, HazelWebb, EllenLokmanYu, GianMarcoGhiggeri, MarkusJ.Kemper, AlisonLap-takMa, TomohikoYamamura, AditiSinha, ArvindBagga, JulienHogan, ClaireDossier, MarinaVivarelli, IsaacDeshengLiu, KoichiKamei, KenjiIshikura, PriyaSharma and KjellTullus

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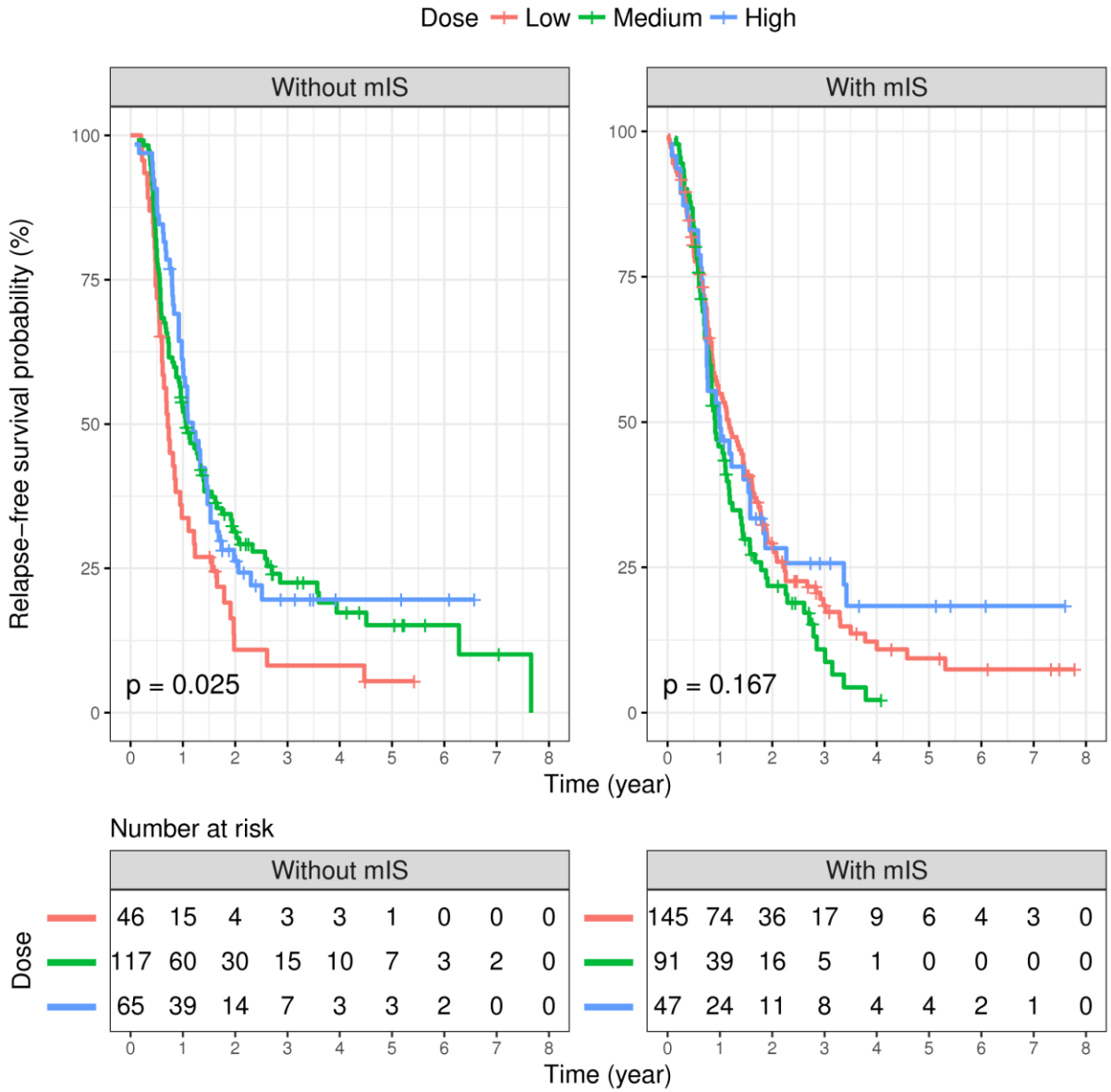
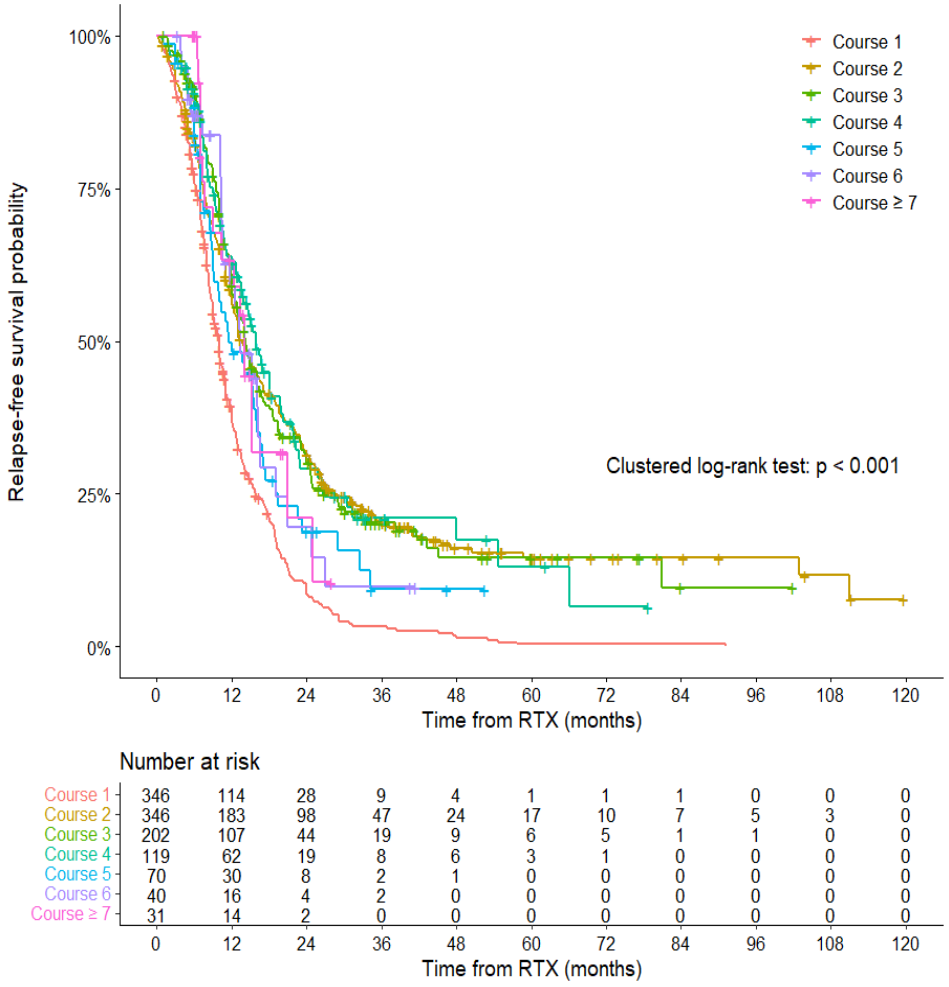


Kidney International 2019

Repeat doses if Rituximab Safety and efficacy

Eugene Yu-hin Chan FHKAM(Paed)[1,2,3*], Ellen LM Yu MSc[4], Andrea Angeletti PhD[5,6], Zainab Arslan MSc[3], Biswanath Basu MD[7], Olivia Boyer PhD[8], Chang-Yien Chan PhD[9,10], Manuela Colucci PhD[11], Guillaume Dorval PhD[8], Claire Dossier MD[12], Stefania Drovandi MD[5,13], Gian Marco Ghiggeri MD[5], Debbie S. Gipson MD[14], Riku Hamada MD[15], Julien Hogan PhD[16], Kenji Ishikura PhD[17,18], Koichi Kamei PhD[19], Markus Kemper MD[20], Alison Lap-tak Ma FRCPCH[1,2], Rulan S. Parekh MS[21], Seetha Radhakrishnan FRCPC[21], Priya Saini FRCPC[21], Qian Shen PhD[22], Rajiv Sinha MD[23], Chantida Subun MD[3], Sharon Teo FRACP[10], Marina Vivarelli MD[24], Hazel Webb BSc[3], Hong Xu PhD[22], Hui Kim Yap MD[9,10], Kjell Tullus FRCPCH[3*]

Increasing efficacy with increasing number of doses



JASN 2022

No increased side-effects with increasing number of doses.

Neither short-term nor any more hypogammaglobulinaemia or infections

Rituximab in SRNS

249 children with SRNS failing on a CNI

3 month

20% complete and 12.5% partial response

6 month

23% complete and 18.5% partial response

Lasted up to 24 month

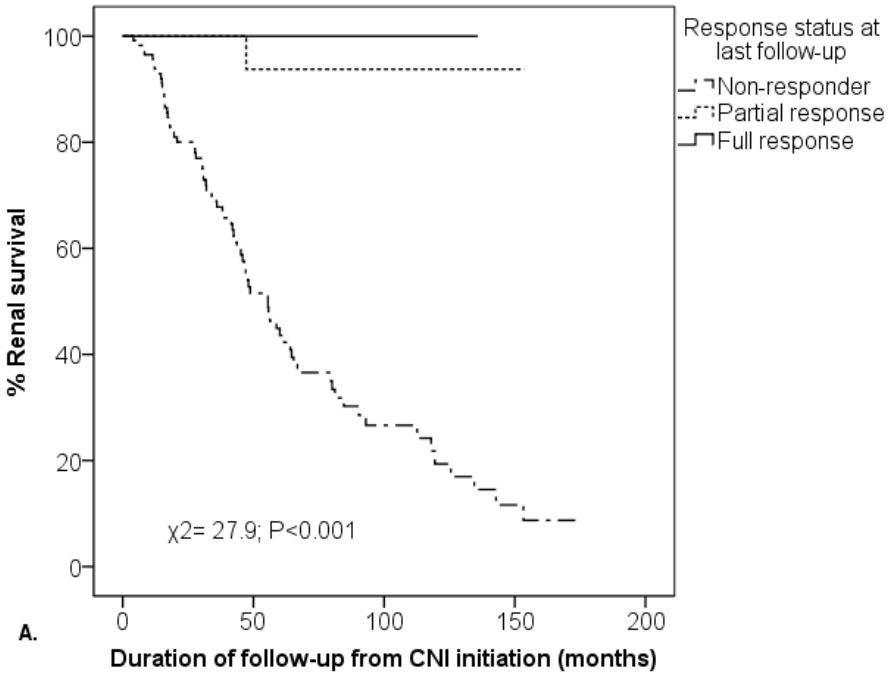
CNI in mendelian SRNS

Georgia Malakasioti MD[1], Daniela Iancu MD[2], Anastasiia Milovanova MD[3], Alexey Tsygin MD[3], Tomoko Horinouchi MD, PhD[4], China Nagano MD, PhD[4], Kandai Nozu MD, PhD[4], Koichi Kamei MD, PhD[5], Shuichiro Fujinaga MD, PhD[6], Kazumoto Iijima MD, PhD[7], Hee Gyung Kang MD[8], Seon Hee Lim MD[9], Rajiv Sinha MD[10], Biswanath Basu MD[11], William Morello MD[12], PhD, Giovanni Montini MD[12, 13], Aoife Waters MD[14], Olivia Boyer MD[15], Zeynep Yürük Yıldırım MD[16], Sibel Yel MD[17], İsmail Dursun MD[17], Hugh J McCarthy PhD, FRACP[18], Marina Vivarelli MD[19], Larisa Prikhodina MD, PhD[20], Martine T P Besouw MD[21], Eugene Yu-hin Chan FHKAM (Paed)[22], Wenyan Huang MD, PhD[23], Markus J. Kemper MD[24], Sebastian Loos MD[24], Chanel Prestidge MBChB, FRACP[25], William Wong MBChB, FRACP[25], Galia Zlatanova MD[26], Rasmus Ehren MD[27], Lutz Weber MD[27], Hassib Chehade MD[28], Nakysa Hooman MD[29], Marcin Tkaczyk MD, PhD[30], Małgorzata Stańczyk PhD[30], Kjell Tullus MD[14], on behalf of the CNI in Monogenic SRNS Study Investigators[31]

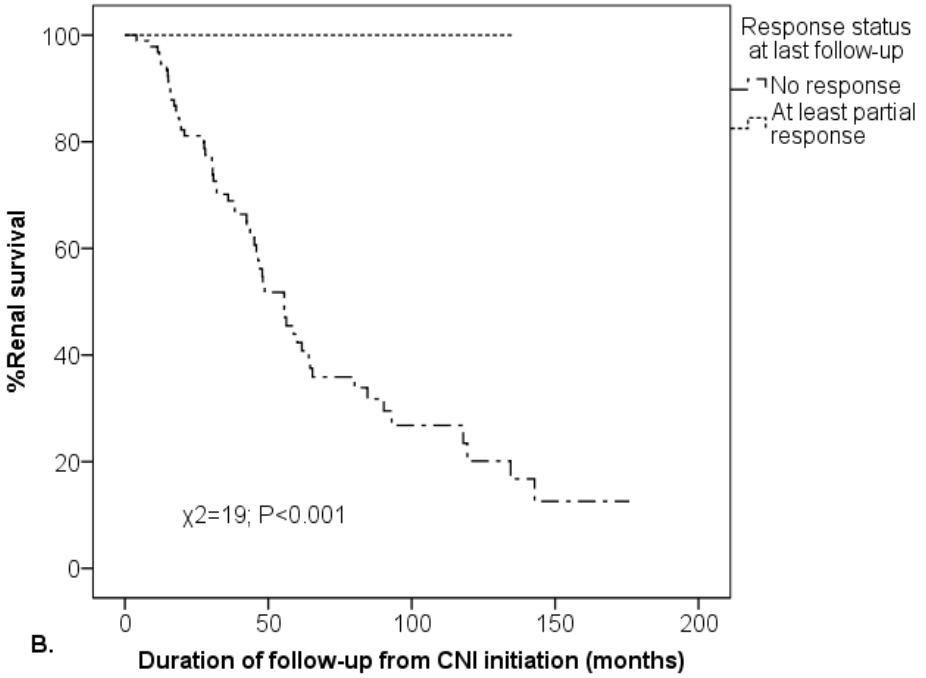
Pathogenic (N=122) or possibly pathogenic (N=19) genotypes

After 6 months of treatment and at last visit, 27.6% and 22.5% of all subjects respectively, demonstrated partial or full response.

Submitted


% Renal survival
100
80
60
40
20
0
0
50
100
150
200
Duration of follow-up from CNI initiation (months)
χ2= 27.9; P<0.001
Response status at last follow-up
Non-responder
Partial response
Full response

A.


%Renal survival
100
80
60
40
20
0
0
50
100
150
200
Duration of follow-up from CNI initiation (months)
χ2=19; P<0.001
Response status at last follow-up
No response
At least partial response

B.

International cohort of 382 children with lupus nephritis – presentation, treatment and outcome at 24 months

Chiara De Mutiis[1], Scott E Wenderfer[2], Biswanath Basu [3] , Arvind Bagga[4], Alvaro Orjuela[2], Tanmoy Sar[3], Amita Aggarwal [5] , Avinash Jain[6], Hui-Kim Yap[7], Sharon Teo[8], Shuichi Ito[9] , Ai Ohnishi[9], Naomi Iwata[10], Ozgur Kasapcopur[11], Mehmet Yildiz[11], Audrey Laurent [12], Antonio Mastrangelo[13] , Masao Ogura[14] , Yuko Shima[15], Pornpimol Rianthavorn[16], Clovis A. Silva[17], Vitor Trindade[17], Alessandra Gianviti[18], Miyazono Akinori[19], Riku Hamada[20], Junya Fujimura[21], Shogo Minamikawa[21], Naohiro Kamiyoshi[21], Hiroshi Kaito[21], Shingo Ishimori[22], Francesco Iannuzzella[23], Kjell Tullus[24].

. Rheumatology 2022 May 30;61(6):2563-2571
Submitted

Complete remission