



Speaker: Olivia Boyer
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53rd ESPN annual meeting, Amsterdam ESPN workig group for glomerulopathies

Date: 16 september 2021

Topic: Congenital nephrotic syndrome: ERKNet-
ESPN consensus recommendations



Congenital nephrotic syndrome

- **Proposed management (1984)**
 - Daily albumin infusions (CVL)
 - Prevention and management of comorbidities
 - Infections, thromboses, anemia, hypothyroidism, ...
 - Nutrition, GH
 - ACEi / NSAIDs: indometacine

Preemptive bilateral nephrectomy (# 7 kg)



Dialysis (PD ++)



Kidney transplantation (# 9 kg)



Mahan et al. *J Pediatr* 1984
Holmberg, *Pediatr Nephrol* 1995



Nephrol Dial Transplant (2018) 1–10
doi: 10.1093/ndt/gfy015



Treatment and outcome of congenital nephrotic syndrome

Sandra Bérody¹, Laurence Heidet^{1,2,3}, Olivier Gribouval³, Jérôme Harambat⁴, Patrick Niaudet^{1,2,3}, Veronique Baudouin^{2,5}, Justine Bacchetta⁶, Bernard Boudailliez⁷, Maud Dehennault⁸, Loïc de Parscau⁹, Olivier Dunand¹⁰, Hugues Flodrops¹¹, Marc Fila¹², Arnaud Garnier¹³, Ferialle Louillet¹⁴, Marie-Alice Macher⁵, Adrien May¹⁵, Elodie Merieau¹⁶, Françoise Monceaux¹⁷, Christine Pietrement¹⁸, Caroline Rousset-Rouvière¹⁹, Gwenaëlle Roussey²⁰, Sophie Taque²¹, Julie Tenenbaum¹², Tim Uliniski^{2,22}, Rachel Vieux²³, Ariane Zaloszyc²⁴, Vincent Morinière³, Rémi Salomon^{1,2,3} and Olivia Boyer^{1,2,3}

Nephrol Dial Transplant (2019) 34: 1369–1377
doi: 10.1093/ndt/gfy165
Advance Access publication 21 June 2018



Management of children with congenital nephrotic syndrome: challenging treatment paradigms

Stephanie Dufek¹, Tuula Holtta², Agnes Trautmann³, Elisa Ylinen², Harika Alpay⁴, Gema Ariceta⁵, Christoph Aufricht⁶, Justine Bacchetta⁷, Sevcen A. Bakkaloglu⁸, Aysun Bayazit⁹, Rumeysa Yasemin Cicek¹⁰, Ismail Dursun¹¹, Ali Duzova¹², Mesiha Ekim¹³, Daniela Iancu¹⁴, Augustina Jankauskiene¹⁵, Günter Klaus¹⁶, Fabio Paglialonga¹⁷, Andrea Pasini¹⁸, Nikoleta Printza¹⁹, Valerie Said Conti²⁰, Maria do Sameiro Faria²¹, Claus Peter Schmitt³, Constantinos J. Stefanidis²², Enrico Verrina²³, Enrico Vidal²⁴, Karel Vondrak²⁵, Hazel Webb¹, Argyroula Zampetoglou²², Detlef Bockenhauer¹, Alberto Edefonti¹⁷ and Rukshana Shroff¹
on behalf of the ESPN Dialysis Working Group

More recent data (2018)

successful treatment using a conservative approach involving optimized nutrition and medications **without preemptive nephrectomy**

Bérody, (...) Boyer. *NDT* 2018
Dufek, Holtta (...) Shroff. *NDT* 2018

Core Group

Pediatric nephrologists and geneticists:

Olivia Boyer, Paris, France

Franz Schaefer, Heidelberg, Germany

Dieter Haffner, Hannover, Germany

Detlef Bockenhauer, London, UK

Tuula Hölttä, Helsinki, Finland

Elena Levtchenko, Leuven, Belgium

Beata S Lipska-Ziętkiewicz, Gdańsk, Poland

Fatih Ozaltin, Ankara, Turkey

Marina Vivarelli, Rome, Italy

Neonatologist: Sandra Bérody, Paris, France

Pediatric nephrology nurse: Hazel Webb, London, UK

Patient representative



External expert group

Gema Ariceta (Spain), Justine Bacchetta (France), Jan Ulrich Becker (pathologist, Germany), Carsten Bergmann (Germany), Francesco Emma (Italy), Elisabeth Hodson (Australia), Elsa Kermorvant (neonatologist, France), Agnès Linglart, (pediatric endocrinologist, France), Pierre Ronco (adult nephrologist, France), Rukshana Shroff (UK), Anne Smits (pharmacologist, Belgium), Vincent Tse (UK), Lore Willem (ethicist, Belgium), Alexia Florimont (France, patient representative and nurse).

External voting panel: (Delphi method)

ESPN WG on Glomerular Diseases

Evidence review (Dr Tanja Wlokowski, ERKNet)

- **27 relevant PICO questions**
- **1,367 results but no randomized clinical trials**
- **54 articles** are referenced in the consensus statement

No RCTs → consensus statement



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

X
moderate

X
strong

RIGHT statement
<http://www.right-statement.org/>

AAP grading system
<https://www.aap.org/>

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



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 Ozaltin³ • Tuula Hölttä⁴ • Detlef Bockenhauer⁵ • Sandra Bérody⁶ • Elena Levchenko⁷ • Marina Vivarelli⁸ • Hazel Webb⁵ • Dieter Haffner^{9,10} • Franz Schaefer¹¹ • Olivia Boyer^{6,12}

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

CONSENSUS STATEMENT

OPEN



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

Olivia Boyer^{1,2}, Franz Schaefer³, Dieter Haffner^{4,5}, Detlef Bockenhauer⁶, Tuula Hölttä⁷, Sandra Bérody¹, Hazel Webb⁶, Marie Heselden⁸, Beata S. Lipska-Ziętkiewicz^{9,10}, Fatih Ozaltin¹¹, Elena Levchenko¹² and Marina Vivarelli¹³

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



WELCOME TO

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

Date: 01 December 2020

Topic: Management of congenital nephrotic syndrome:
consensus recommendations

Speaker: Olivia Boyer

Moderator: Francesco Emma



Evidence-based clinical management in pediatric
nephrology
IPNA Virtual Scientific Workshop; March 29-31, 2021

Date: 29 March 2021

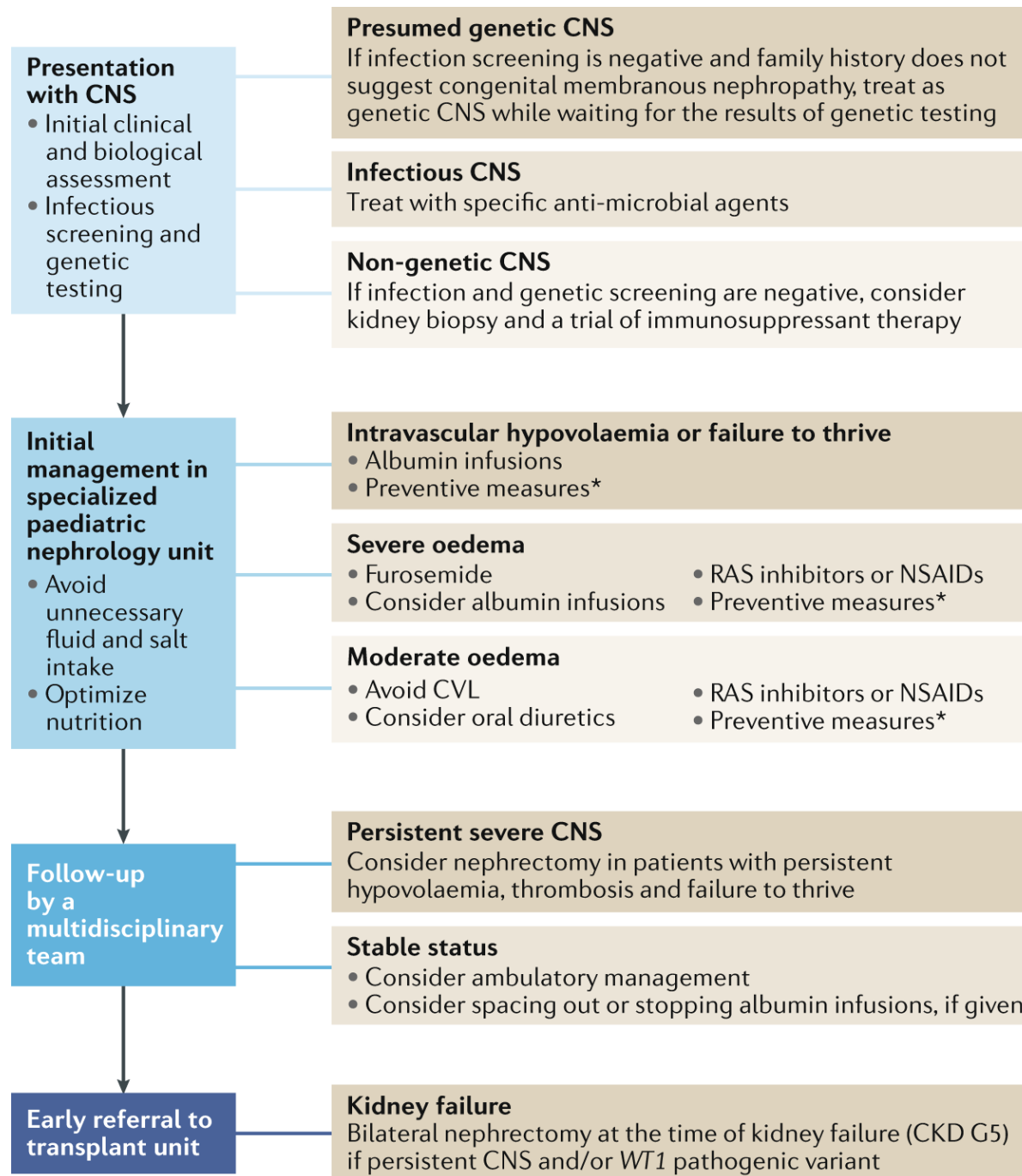
Topic: Management of congenital
nephrotic syndrome: consensus
recommendations

Speaker: Olivia Boyer



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

<https://theipna.org/workshop/>





Presentation with CNS

- Initial clinical and biological assessment
- Infectious screening and genetic testing

Presumed genetic CNS

If infection screening is negative and family history does not suggest congenital membranous nephropathy, treat as genetic CNS while waiting for the results of genetic testing

Infectious CNS

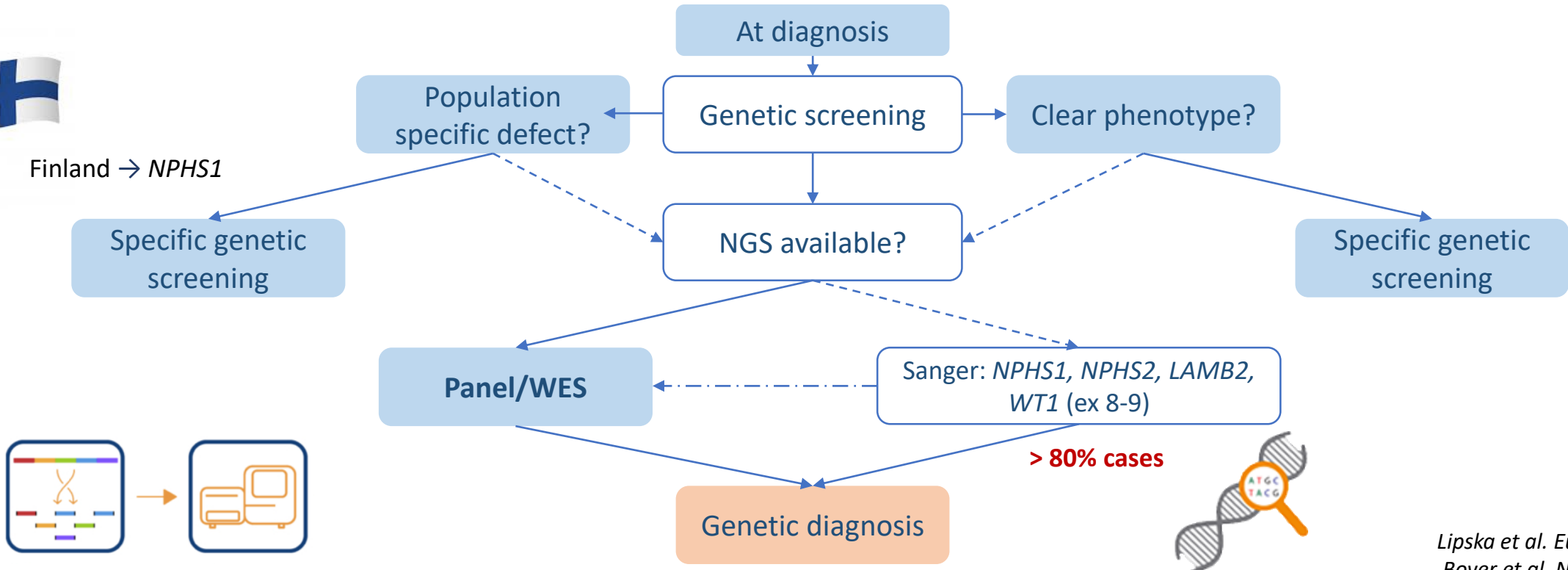
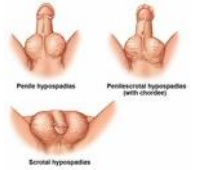
Treat with specific anti-microbial agents

- We recommend **comprehensive genetic screening comprising all podocytopathy-related genes**
- We recommend providing **genetic counseling promptly**.



Finland → *NPHS1*

DDS → *WT1*





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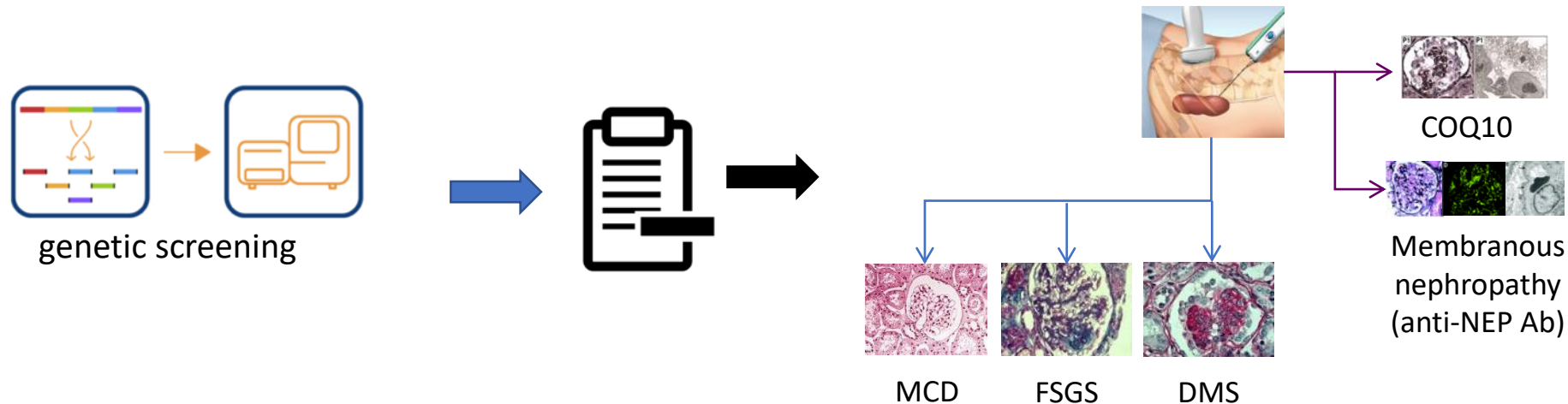
Non-genetic CNS

If infection and genetic screening are negative, consider kidney biopsy and a trial of immunosuppressant therapy

- **We do not recommend routine kidney biopsy in patients with CNS.** We suggest kidney biopsy be considered only in patients with sporadic, non-syndromic disease with negative comprehensive genetic testing

Genetic screening will identify the underlying genetic abnormality in >85% of patients

→ noninvasive molecular diagnostic methods have replaced KBx in these patients.





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Initial management in specialized paediatric nephrology unit

- Avoid unnecessary fluid and salt intake
- Optimize nutrition

Intravascular hypovolaemia or failure to thrive

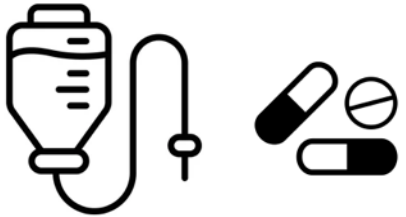
- Albumin infusions
- Preventive measures*

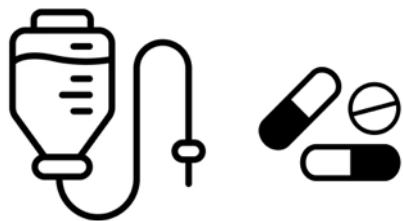
Severe oedema

- Furosemide
- Consider albumin infusions
- RAS inhibitors or NSAIDs
- Preventive measures*

Moderate oedema

- Avoid CVL
- Consider oral diuretics
- RAS inhibitors or NSAIDs
- Preventive measures*





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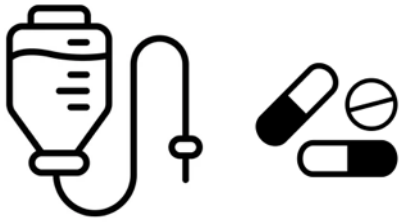
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Preliminary remarks

- **CNS encompasses a wide spectrum of clinical phenotypes that should be managed with different approaches :**
 - **If no or minimal symptoms** → avoid aggressive and potentially dangerous treatments,
 - **If anasarca and hemodynamic compromise** → daily albumin infusions via a CVL and intensive symptomatic treatments
- **Management should be adapted to the clinical severity of the condition with the aim of maintaining intravascular euvoemia and adequate nutrition, as well as preventing complications**





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- We recommend using **albumin infusions based on clinical indicators of hypovolemia** (including oliguria, AKI, prolonged capillary refill time, tachycardia, hypotension and abdominal discomfort) or upon failure to thrive. **We do not recommend administering albumin infusions in children with CNS based on serum albumin levels.**

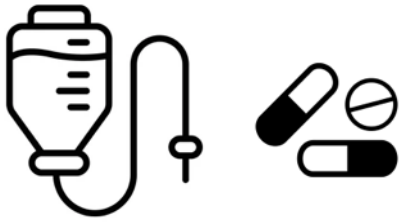
Potential **advantages** of regular albumin infusions :

- support growth and psychomotor development
- stabilize intravascular volume and minimize edema



Disadvantages :

- need for a CVL
- increased risk of infection and/or thrombosis (may endanger future hemodialysis access)
- prolonged hospitalization and associated costs
- impacts on QOL and school attendance



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- Some children do well without any albumin infusion (7/135 in European series)

Albumin discontinuation is possible before nephrectomy

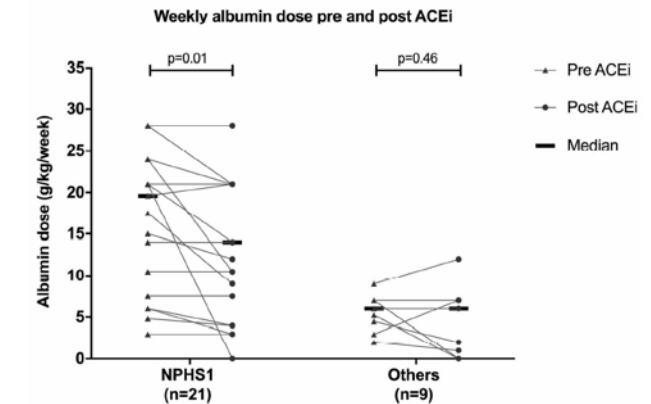
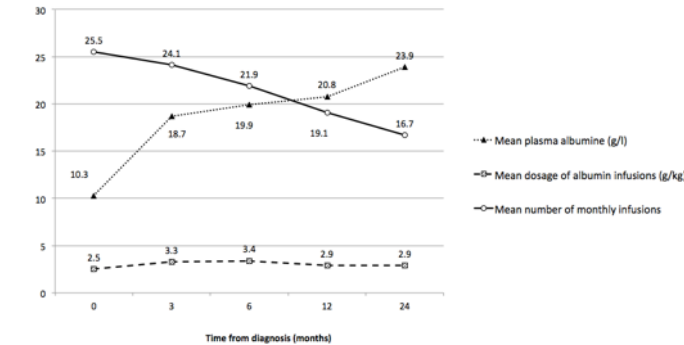
- 10/55 (18%) and 5/7 (70%) children with normal eGFR and stable status

Age 1-29 months; for up to 47 months

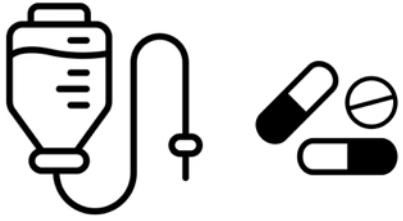
Or albumin tapering

- pre/post-ACEi: 70% increase in S-Alb with reduction of weekly albumin infusions dose
- Some cases of spontaneous remission

- Ambulatory management is possible before nephrectomy



Bérody, (...) Boyer. NDT 2018
 Dufek, Holtta (...) Shroff. NDT 2018
 Coulthard, Ped Nephrol 1989
 Reynolds, Ped Nephrol 2015
 Banton, Arch Dis Child 1990
 Smith, Arch Dis Child 1991
 Canalejo González. An Pediatr 2006



Initial management in specialized paediatric nephrology unit

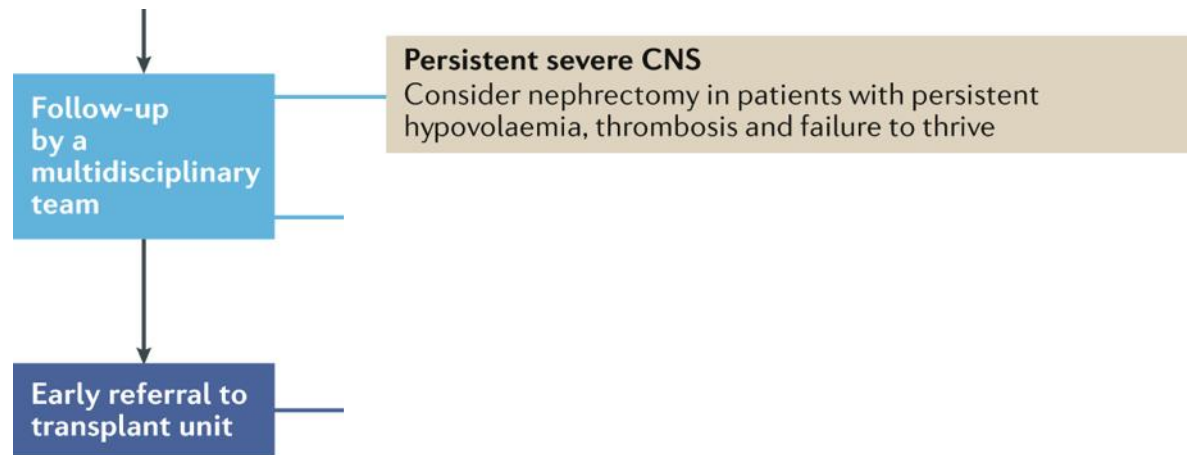
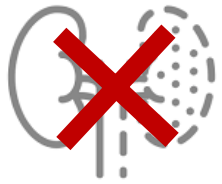
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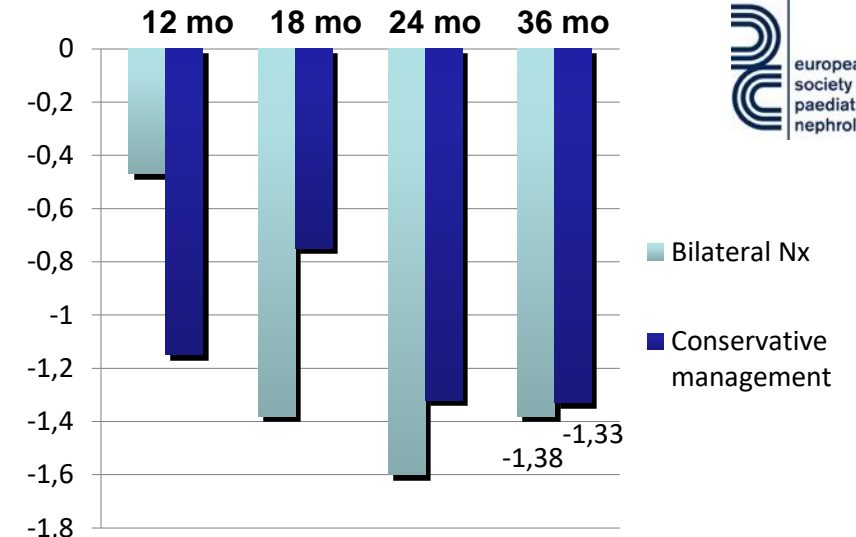
- Daily albumin infusions of up to **1-4 g/kg** may be initiated.
- In stable patients or when CKD progresses, **albumin dose may be reduced and infusions might subsequently be made less frequent or even stopped**.

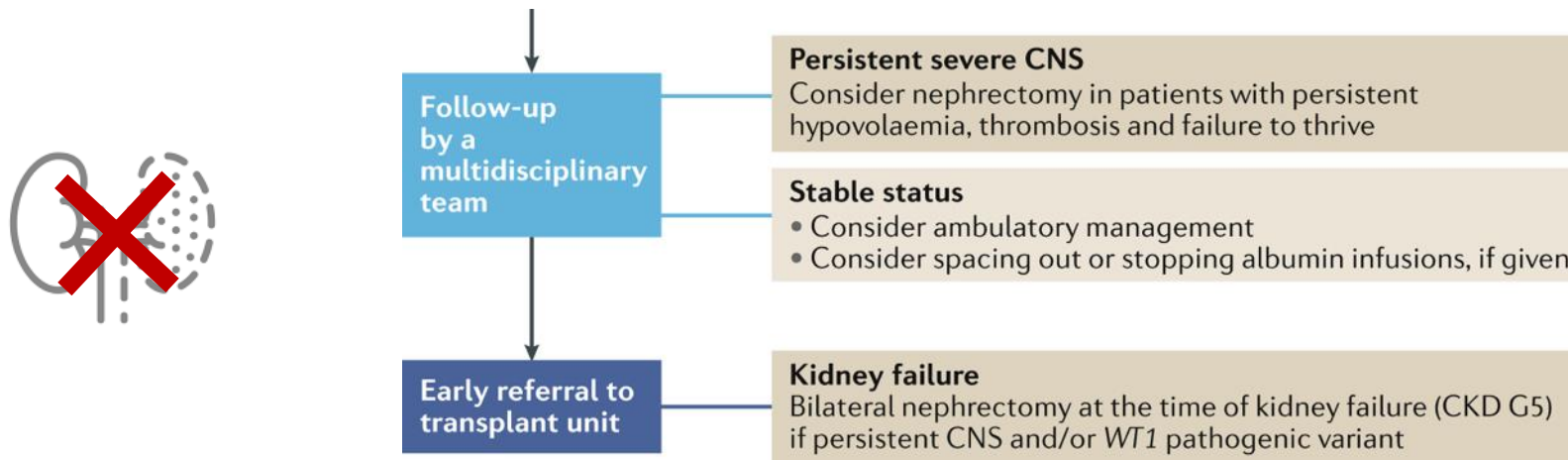


- **We do not recommend performing routine early nephrectomies in children with CNS.**
- Retrospective studies : no difference in CNS complications with these two strategies.

- **48% vs. 47%** ($p = 0.95$) CVL infections
- **54% vs. 53%** ($p = 0.94$) septic episodes
- **16% vs. 12%** ($p = 0.70$) CNS-related thromboses
- **4%** died in conservative management vs. **20%** in ESKD/RRT

Height (SDS)

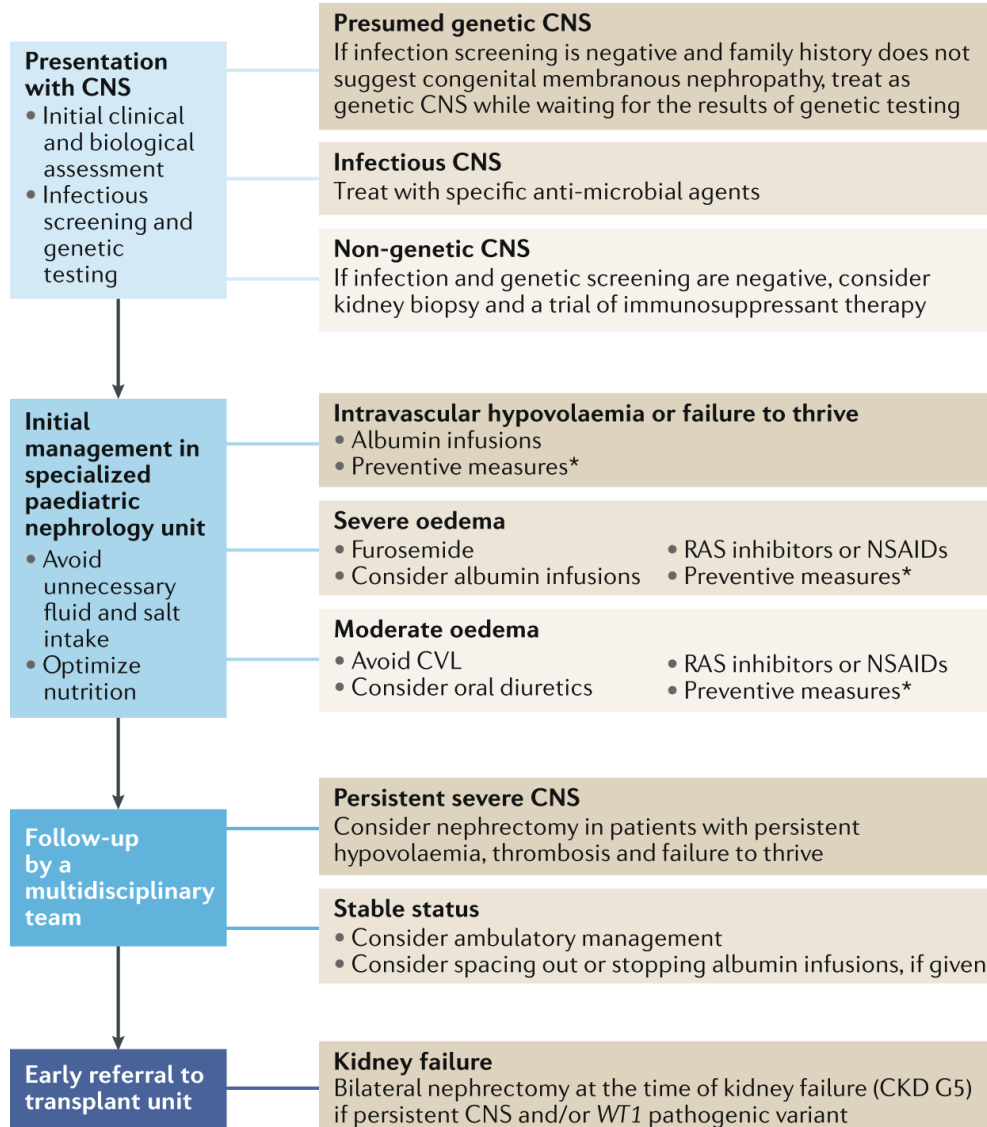




- We do not recommend performing routine early nephrectomies in children with CNS, but only to consider them in case of persistent severe CNS
- We recommend performing **bilateral nephrectomies before kidney transplantation in patients with persisting nephrotic syndrome and/or a WT1 dominant pathogenic variant.**



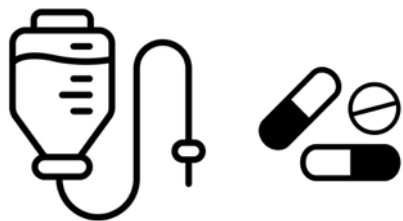
Core Group



External expert group

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External voting panel: (Delphi method)
ESPN WG on Glomerular Diseases



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Preventive measures

- **Preventive anticoagulation** during states of increased thrombosis risk (hypovolemia, CVL...) and/or if prior thrombosis.
- No antibiotic prophylaxis; but **prompt antibiotics if suspected** bacterial infection
- IVIg in patients with low serum IgG levels and **recurrent or severe infections**
- **Vaccinations**++, including vaccinating against encapsulated bacteria and VZV, and influenza vaccine annually
- In the case of **exposure to chickenpox** in non-immunized children: specific VZV IVIGs or oral acyclovir
- We recommend treatment of **VZV infection with IV high-dose aciclovir**
- **Diet:** high energy (130 kcal/kg/day) and protein (4g/kg/day) content but **low salt content**
- **Other: iron, EPO, calcium, vitamin D, levothyroxine (T4), growth hormone where appropriate**
- There is insufficient evidence to recommend treatment of dyslipidemia in CNS.

