# 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

ERKNet
The European Rare Kidney Disease Reference Network

european society for paediatric nephrology

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Université de Paris

# Congenital nephrotic syndrome

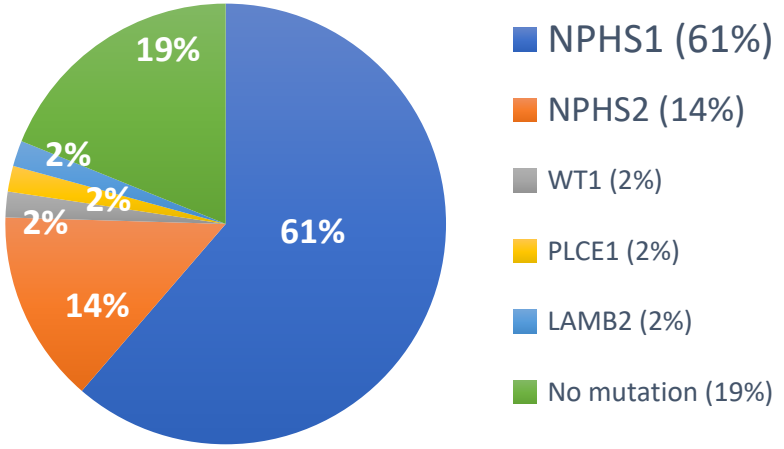
## Definition

- Nephrotic-range proteinuria and oedema that manifests *in utero* or during the first 3 months of life

## Etiologies

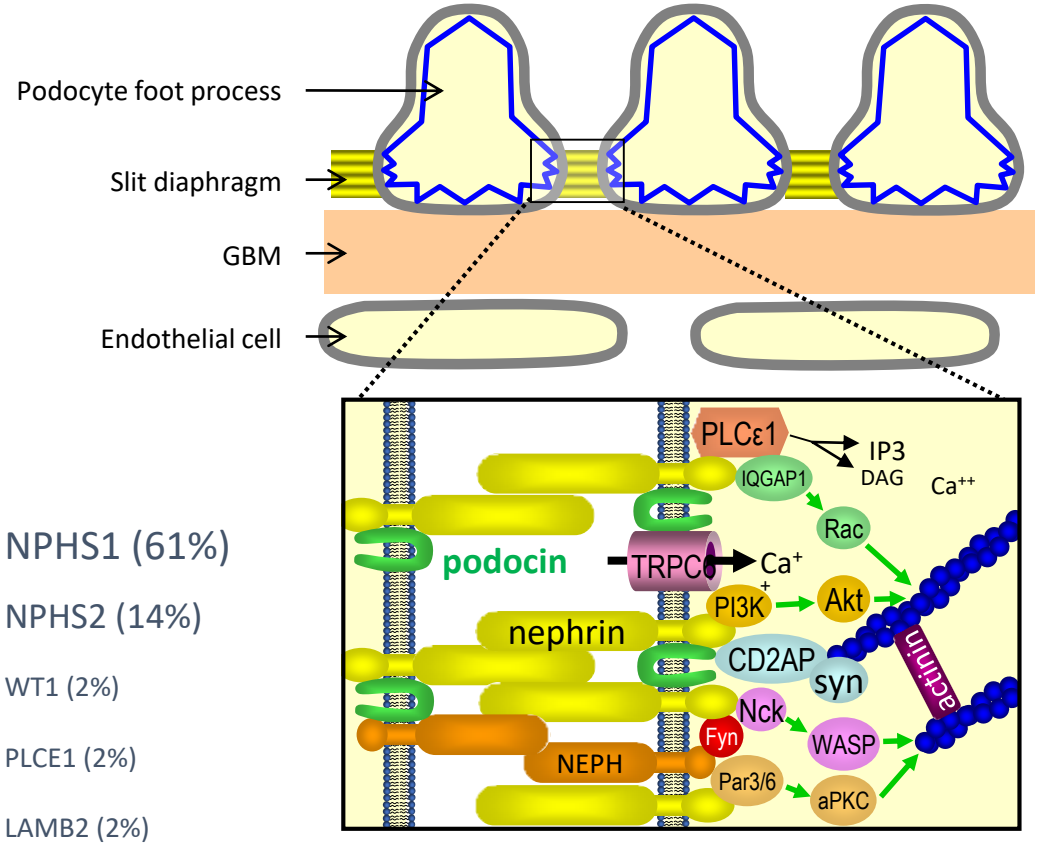
### Podocyte gene pathogenic variants (60–70%)

- *NPHS1* (nephrin)
- *NPHS2* (podocin)
- *PLCE1*
- *WT1*
- *LAMB2*




### Congenital infections

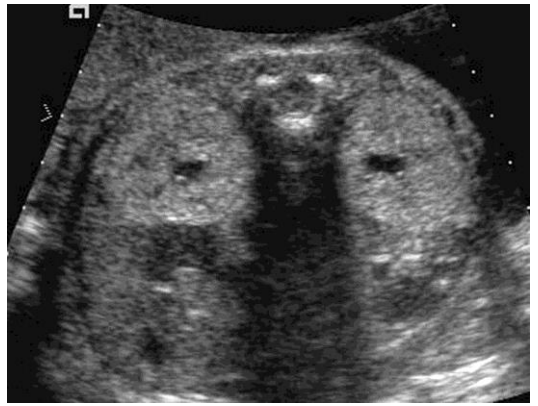
### Maternal allo-immune disease

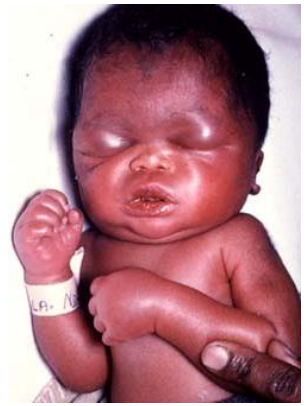


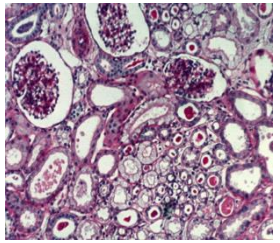

*Holmberg, Pediatr Nephrol 1995*
*Machuca et al. J Am Soc Nephrol 2010*

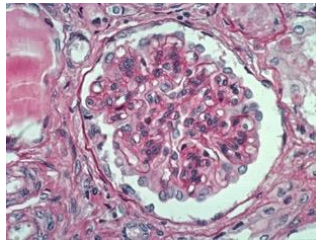
# Congenital nephrotic syndrome

- **Diagnosis**
  - Antenatal onset – 3 months
  - Enlarged hyperechoic kidneys
  - Increased $\alpha$-FP
  - Enlarged placenta >25% BW
  - **Massive Pu,** anasarca
  - Variable kidney function at birth
- **Histology**
  - **Tubular dilation (Finnish CNS)**
  - **MCD/FSGS or DMS**









*Holmberg, Pediatr Nephrol 1995*
*Machuca et al. J Am Soc Nephrol 2010*

# Congenital nephrotic syndrome

- **Prone to severe complications**
  - **hemodynamic instability**
  - recurrent **infections**
  - **thromboses**
  - impaired growth

- **Most children with CNS progress to kidney failure within a few years**

- 1965-1973: mean survival 7.6 months (0-26)
- Causes of death: infection or hemodynamic collapse, thromboses

*Holmberg, Pediatr Nephrol 1995*
*Machuca et al. J Am Soc Nephrol 2010*

# Congenital nephrotic syndrome

- **Finnish-type nephrotic syndrome**
  - 1/8.000 Finland > 0.5/100.000 Europe/USA
  - *NPHS1* = nephrin: Fin major and Fin minor
  - > 200 variants in non-Finnish populations + other genes

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

**Preemptive bilateral nephrectomy (# 7 kg)**

↓

**Dialysis (PD ++)**

↓

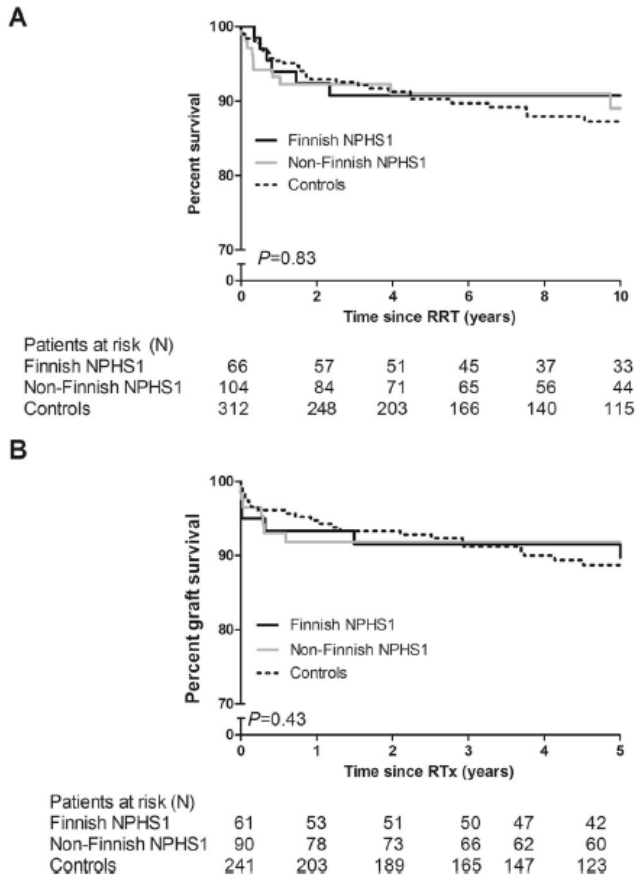
**Kidney transplantation (# 9 kg)**

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

# Congenital nephrotic syndrome

- **Before active treatment**
  - mean survival 7.6 months (0-26)
- **After active treatment**
  - >90% transplanted with similar renal and overall survival to other transplanted children
- **More recent data**
  - successful treatment using a conservative approach involving optimized nutrition and medications without preemptive nephrectomy

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




*Holmberg et al., Pediatr Nephrol 1995*
*Holtta et al. Pedaitr Nephrol 2016*

# Management of congenital nephrotic syndrome: CPR

## Core Group

**Pediatric Nephrologists and geneticists:**

**Olivia Boyer,** Paris, France

Franz Schaefer, Heidelberg, Germany

Dieter Haffner, Hannover, Germany

Detlef Bockenhauer, London, UK

Tuula Hölttä, Helsinski, 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, (pediatrc endocrinologist, France), Pierre Ronco (adult nephrologist, France), Rukshana Shroff (UK), Anne Smits (pharmacologist, Belgium), Yincent Tse (UK), Lore Willem (ethicist, Belgium), Alexia Florimont (France, patient representative and nurse).

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

# Management of congenital nephrotic syndrome: CPR

## 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

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

X moderate

X strong

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

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

# Management of congenital nephrotic syndrome: CPR

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 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/

Nature Reviews | Nephrology

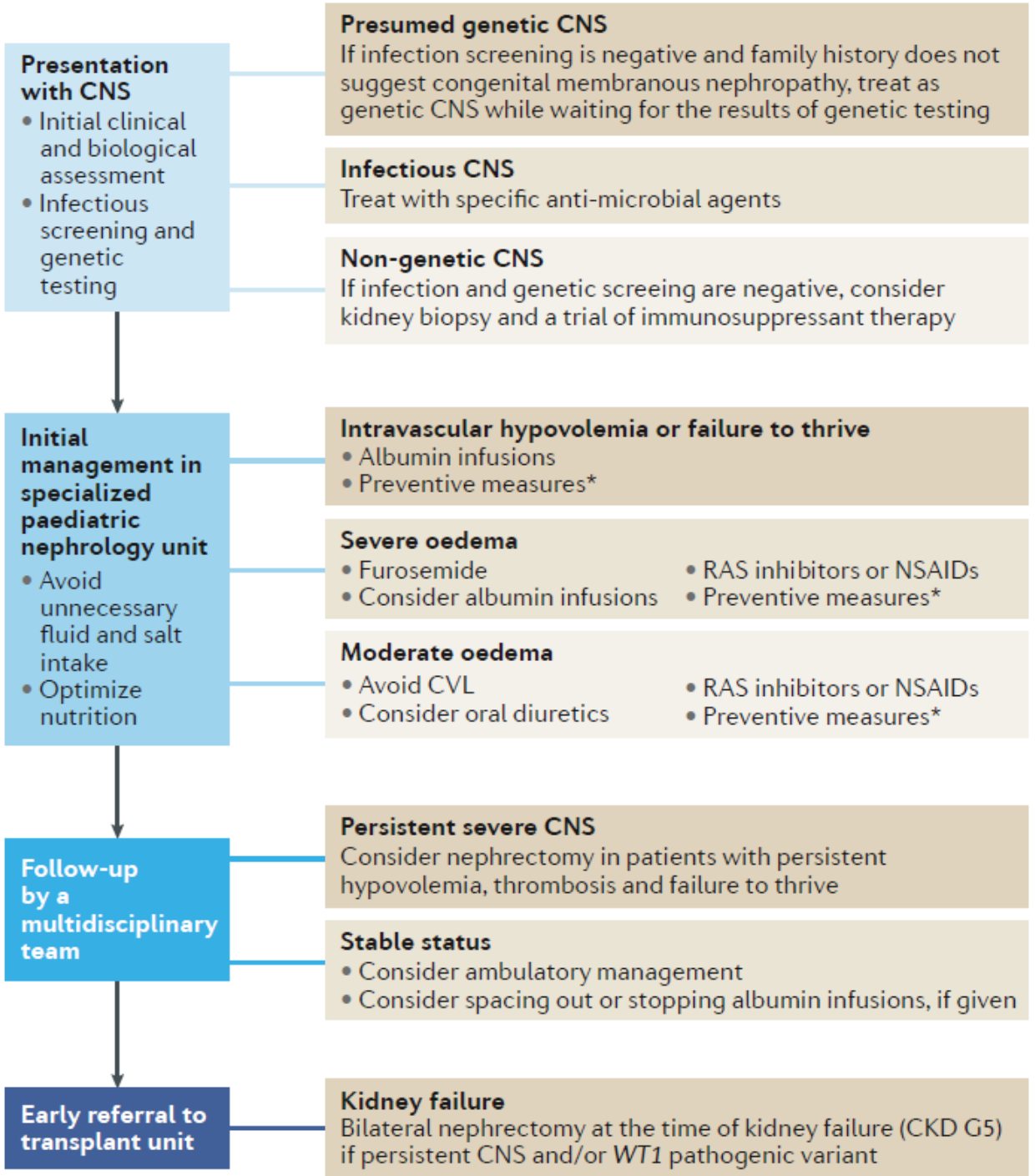
Manuscript number NRNEPH-20-093 Boyer Consensus Statement 14|10|20

# 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** → may require daily albumin infusions via a central venous line (CVL) and intensive symptomatic treatments to avoid complications.

- **Management should be adapted to the clinical severity of the condition with the aim of maintaining intravascular euvolemia and adequate nutrition, as well as preventing complications**

- **No RCTs** → we propose an opinion-based clinical practice recommendation and management algorithm for children with CNS




*Boyer et al. Nat Rev Nephrol 2020. in press*

# Multidisciplinary management

- We recommend rapid referral to **specialized teams in tertiary pediatric nephrology** centers and management by **multidisciplinary teams, including:**
  - neonatologists
  - pediatric nephrologists
  - pediatric nephrology nurses
  - pediatric renal dieticians
  - pediatric surgeons
  - child and/or youth psychologists
  - social workers.

- When children with CNS are managed outside of a transplant facility, we recommend that they are **introduced to a transplant center early as their CKD progresses** with the aim of minimizing time on dialysis and facilitating the transplant process.

# Recommendations for diagnosis

**HISTORY**

- Family history: consanguinity, history of CNS...
- Prenatal and perinatal history: increased amniotic fluid alphafetoprotein, fetal edema, oligohydramnios and placental weight >25% of newborn weight
- Patient history: fever, pain, swelling, fatigue

**FIRST LINE EVALUATION**

- Growth chart: length, weight, head circumference
- Blood pressure
- **Physical examination: volemia, oedema** (e.g. ascites, pericardial & pleural effusions)
- Blood biochemistry: blood count, levels of sodium, chloride, magnesium, creatinine, urea, protein, albumin, cholesterol, fasting triglycerides and glucose
- **TSH and T4**
- **IgG**
- **ionized calcium**, phosphate, alkaline phosphatase, PTH, 25(OH) vitamin D3
- Ultrasound of abdomen & pleural space, cardiac ultrasound (effusions and left ventricular mass)

**DIET**

Assessment and advice from a renal dietician on salt, potassium, calorie & protein intake.

*Lipska et al. Eur J Hum Genet 2020*
*Boyer et al. Nat Rev Nephrol 2020. in press*

# Recommendations for diagnosis

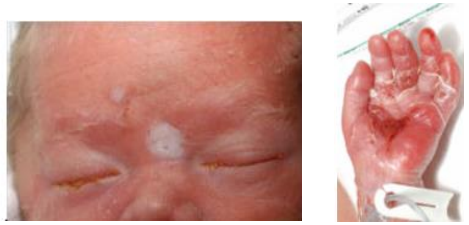
## EXTENDED EVALUATION

- Evaluation of **dysmorphic features and skeletal abnormalities, genital examination, ophthalmological examination, hearing test**
- **Full neurological examination** +/- MRI

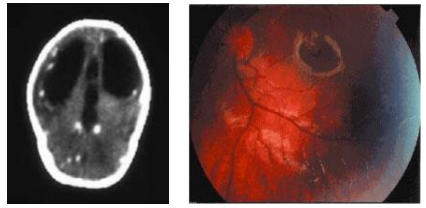
- **Serology** for syphilis, toxoplasmosis, CMV, rubella, measles, HBV, HCV, HSV1, HSV2, HZV, HIV and Bordetella pertussis (if the mother or infant has not already been screened for these infections).

- Further screening in **selected patients in endemic areas or in the case of clinical suspicion**: malaria, anti-nuclear antibodies, serum complement (C3 and C4), anti-neutral endopeptidase (NEP) antibodies, amino-acids (for diagnosis of glutaric aciduria type I or sialic acid storage disease) and/or mercury levels.

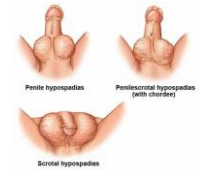
Congenital syphilis



Toxoplasmosis

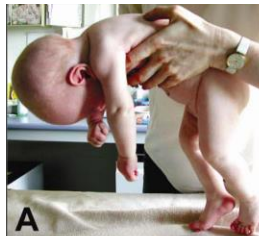


DDS/Frasier

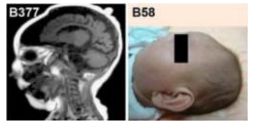


Pierson

Mitochondrial disease




Galloway Mowat

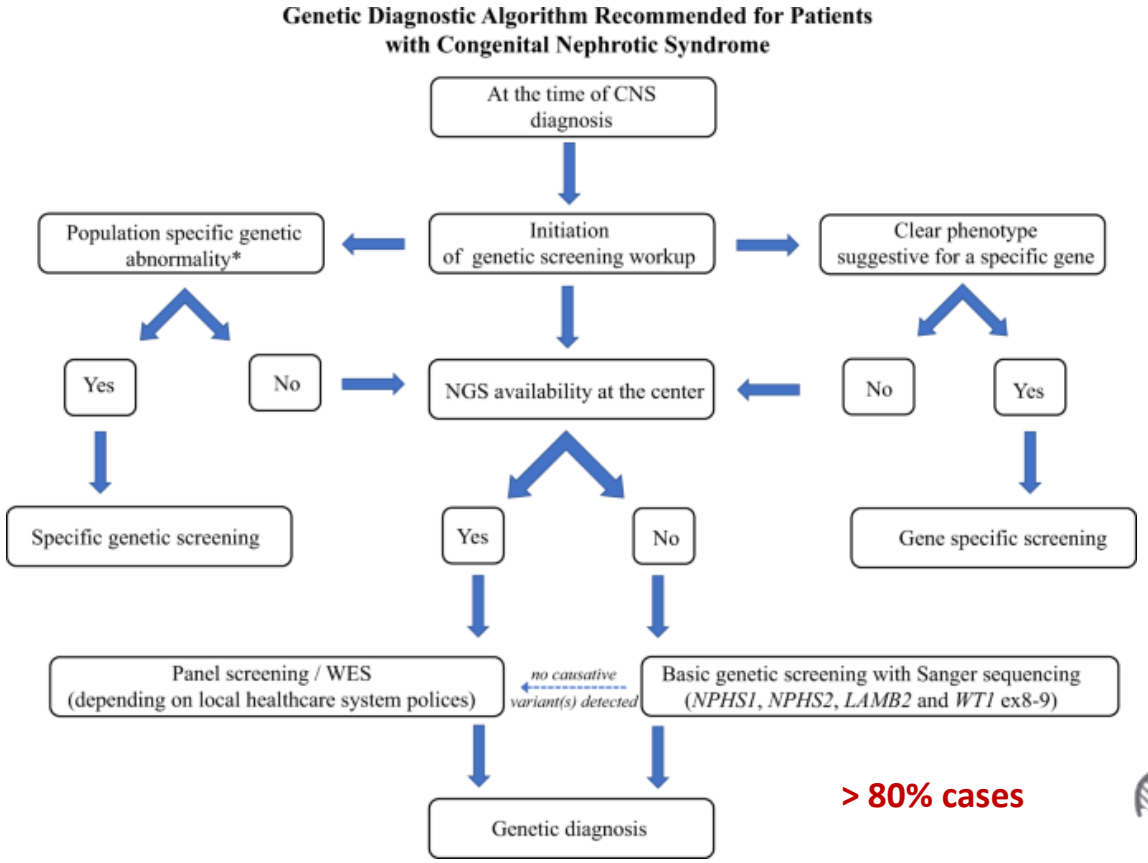



*Lipska et al. Eur J Hum Genet 2020*
*Boyer et al. Nat Rev Nephrol 2020. in press*

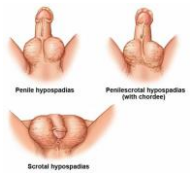
# Recommendations for diagnosis

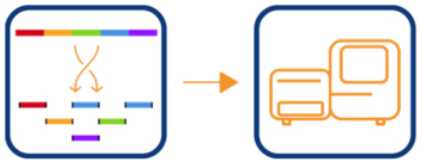
- We recommend **comprehensive genetic screening comprising all podocytopathy-related genes** as a first-line diagnostic measure in every patient with CNS.
- We recommend providing **genetic counseling promptly**.

Finland → *NPHS1*




DDS → *WT1*





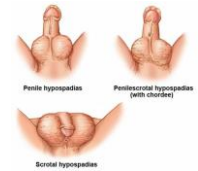
**> 80% cases**

*Lipska et al. Eur J Hum Genet 2020*
*Boyer et al. Nat Rev Nephrol 2020. in press*

# Recommendations for specific management of genetic forms

- ***WT1 :*** We recommend **karyotype testing** to be performed in each CNS patient with **ambiguous genitalia** and in each **phenotypic female with a causative *WT1* variant**.

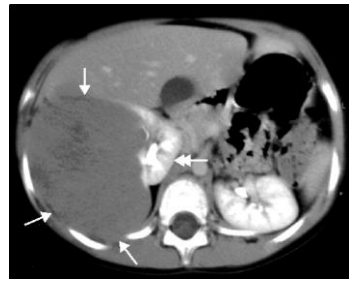
DDS → WT1




+ evaluation for urogenital malformations

+ oncological surveillance for Wilms tumor and gonadoblastoma

  - children with exonic variants should be monitored for Wilms tumor with **abdominal US performed every 3 months until the age of 7 years.**
  - After reaching ESKD, **bilateral nephrectomy** should be considered to prevent the development of Wilms tumor, in particular in individuals carrying truncating variants.
  - In 46,XY phenotypic girls (i.e., complete gonadal dysgenesis), we recommend **bilateral gonadectomy** due to increased gonadoblastoma risk.



+ endocrine management

*Lipska et al. Kidney Int 2014*
*Lipska et al. Eur J Hum Genet 2020*
*Boyer et al. Nat Rev Nephrol 2020. in press*

# Recommendations for specific management of genetic forms

- The vast majority of respond neither to standard steroid treatment nor to intensified immunosuppressive treatment.
- We recommend **not to use immunosuppressive regimens** but to use RAAS blockade.

- ***NPHS2:***
  - **Cardiac evaluation** : cardiac anomalies shown in 89% of patients with the c.412C>T(p.(Arg138*)) variant.

- **CoQ10-related mitochondriopathies** (*COQ2, COQ6,* and *PDSS2* genes)
  - **Complete and repeated** screening for extrarenal manifestations
  - In case of a non-informative NGS result, muscle or skin biopsies may be needed for measuring mitochondrial enzyme activity. Kidney biopsy with EM allows quantitative and qualitative analysis of mitochondria.
  - Early **CoQ10 supplementation** 15–30 to 50 mg/kg/day in 3 administrations
  - May improve proteinuria and sometimes neuromuscular complaints
  - Leukocyte CoQ10 levels can be normal, not helpful for monitoring therapy


- ***LAMB2* (Pierson):**
  - Detailed **ophthalmological** examination
- ***SGPL1***
  - Investigation of **adrenal insufficiency**.

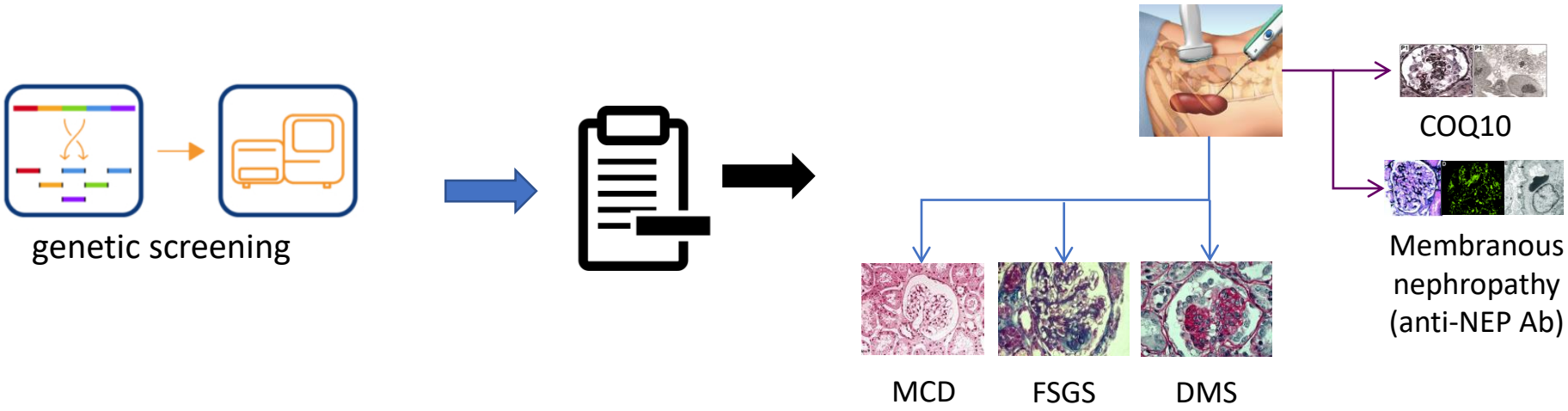
*Lipska et al. Kidney Int 2014*
*Lipska et al. Eur J Hum Genet 2020*
*Boyer et al. Nat Rev Nephrol 2020. in press*

# Recommendations for diagnosis

- **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 in whom comprehensive genetic testing has not yielded a molecular diagnosis.**

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

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




*Lipska et al. Eur J Hum Genet 2020*
*Boyer et al. Nat Rev Nephrol 2020. in press*

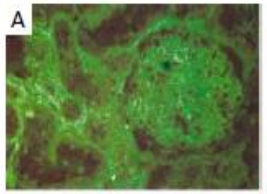
# Recommendations for management of non-genetic CNS

- **We do not recommend using immunosuppressive drugs to treat children with CNS.**
- If comprehensive genetic testing and screening for secondary forms of CNS yield negative results, kidney biopsy and a trial of immunosuppressive therapy may be considered in selected cases

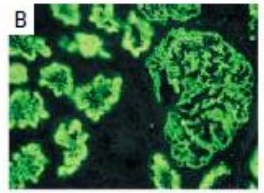
- We suggest considering **congenital membranous nephropathy due to anti-NEP antibodies** in patients who have kidney failure at presentation, transient proteinuria that resolves spontaneously or siblings with transient proteinuria at birth.

- **We recommend treating patients with infection-related CNS with specific anti-microbial agents and performing genetic screening in these patients.**
  - **Eg:** Congenital Syphilis → penicillin G
  - CMV → gancyclovir followed by valganciclovir

**Id IF on Nl kidney with maternal serum**




Before pregnancy




During pregnancy

*Debiec, NEJM 2002*

*Lipska et al. Eur J Hum Genet 2020*
*Boyer et al. Nat Rev Nephrol 2020. in press*

**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

**Non-genetic CNS**

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

*Boyer et al. Nat Rev Nephrol 2020. in press*

# Recommendations for management: general approach

- Rapid referral of children with CNS to a specialized pediatric nephrology unit.

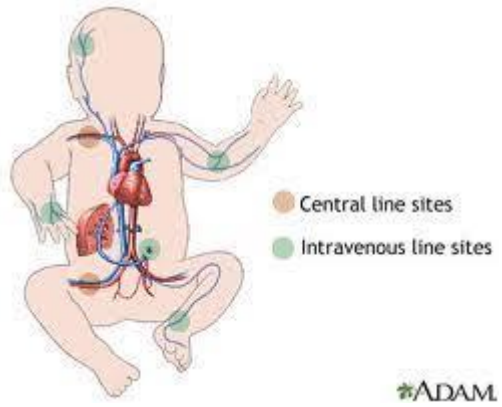
- Given the wide variation in clinical findings in infants with CNS, we recommend **individualized therapy** with a number of key objectives:
  - **preserve all central and peripheral arteries and veins** for potential dialysis access;
  - avoid peripherally inserted catheters and unnecessary venipunctures;
  - **optimize fluid, protein and caloric intake**;
  - minimize administration of **salt-containing** fluids;
  - **prevent thrombosis**, particularly in patients with a CVL or hypovolemia;
  - and **treat infection** when clinically suspected by starting empiric antibiotics before culture results are available.

*Lipska et al. Eur J Hum Genet 2020*
*Boyer et al. Nat Rev Nephrol 2020. in press*

# Recommendations for fluid and albumin administration

- When possible, we recommend **avoiding central venous lines** in children with CNS due to the high risk of thrombosis. If a central venous access is **required for repeated albumin infusions, we recommend administering prophylactic anticoagulation for as long as the line is in place**

- **Vascular preservation** for hemodialysis access (CVL/AV fistulas)




*Lipska et al. Eur J Hum Genet 2020*
*Boyer et al. Nat Rev Nephrol 2020. in press*

# Recommendations for fluid and albumin administration

- We recommend **avoiding intravenous fluids and saline**. Oral fluid intake should be concentrated if necessary to avoid marked oedema.

  - assessment of volume status : underfill versus overfill
  - **salt restriction**
  - **fluid restriction** in case of hyponatremia and in the most severe cases of edema

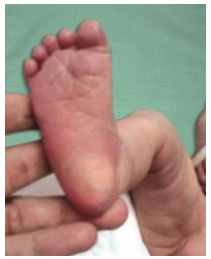
Fluid prescription should primarily be used to **provide adequate nutrition**. Intake of fluid should be limited, when feasible, by using **concentrated high-calorie formulas** to meet age-related energy needs, **guided by the advice of expert renal dieticians.**

Intravenous albumin is the treatment of choice for acute symptomatic hypovolemia (see below).

*Lipska et al. Eur J Hum Genet 2020*
*Boyer et al. Nat Rev Nephrol 2020. in press*

# Recommendations for fluid and albumin administration

- 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.**



Some centers administer IV albumin only when deemed clinically indicated, whereas others use regular albumin infusion protocols (1-4 g/kg/day).

Potential **advantages** of regular albumin infusions :

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

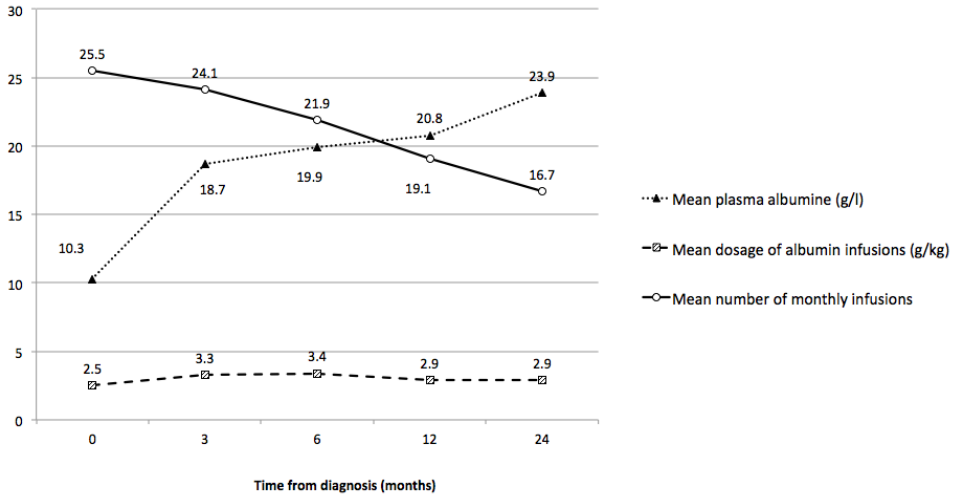
**Disadvantages** :

- 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

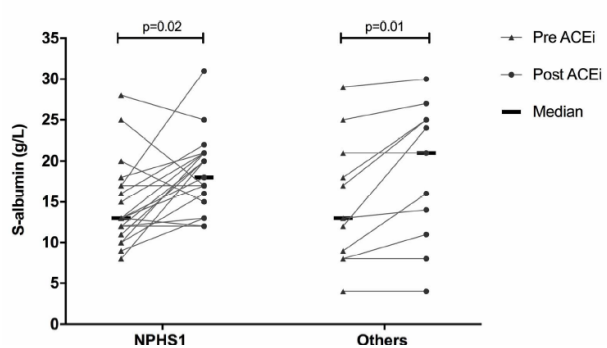
*Lipska et al. Eur J Hum Genet 2020*
*Boyer et al. Nat Rev Nephrol 2020. in press*

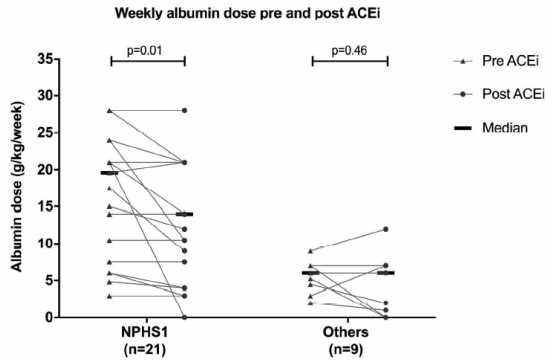
# Albumin tapering/discontinuation is possible before nephrectomy

- 96% patients received albumin infusion at diagnosis




- 96% patients received albumin infusion at diagnosis




- **Possible discontinuation of albumin infusions in 10/55 (18%)** children with normal eGFR, stable clinico-biological features
- **Median age 11 mo [5-29], median duration 26.5 mo [5-47]**

*Bérody, (…) Boyer. NDT 2018*

- **ACEi 59%** (started at 28-81 days) **and NSAIDs in 7**
- **pre/post-ACEi: 70% increase in S-Alb by median 6 g/l (3-8) with reduction of weekly albumin infusions dose by 1 (0-4) g/kg/week**

*Dufek, Holtta (…) Shroff. NDT 2018*

# Albumin tapering/discontinuation is possible before nephrectomy

- **7 children** (Newcastle UK)
  - 1.5-6 g/kg/d => ↓ frequency => discontinuation (5)
  - Stable clinico-biological features and serum albumin > 20 g/l

*Coulthard, Ped Nephrol 1989*
*Reynolds, Ped Nephrol 2015*

**Spontaneous remissions of CNS (*NPHS1*)**

**from 11 days to 10 months of age [24–26].**

Banton, Arch Dis Child 1990 (Consett, Durham, UK)

Smith, Arch Dis Child 1991 (Birmingham, UK)

Jarmolinski, abstract ESPN 2011 (Poland)

More unpublished cases

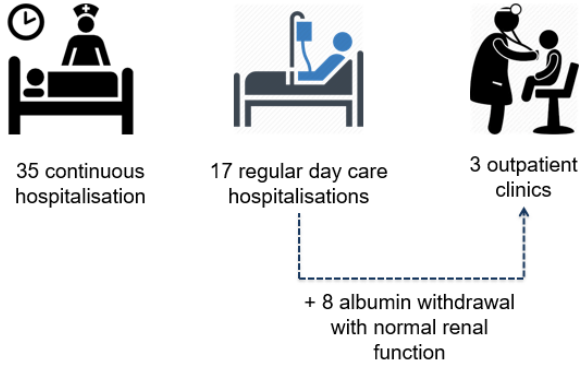
# Ambulatory management is possible before nephrectomy

- **7 children** (Newcastle UK)
  - 1.5-6 g/kg/d => ↓ frequency => discontinuation (5)
  - Serum albumin > 20 g/l
  - **Parental education program of home IV albumin administration via a CVL**
  - Infusion duration 2-3h
  - **Stay in hospital = 27-77 days**
  - **Home administration: 17d - 2 years**
  - ACEi + indomethacin, no Nx in the 5

  more recent patients
  - **0 line sepsis**

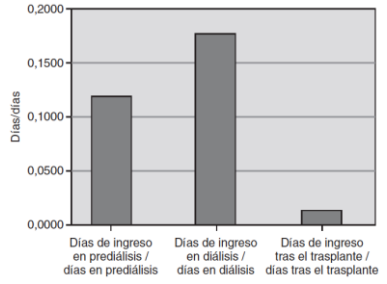
*Coulthard, Ped Nephrol 1989*
*Reynolds, Ped Nephrol 2015*

- **19/55 (35%) discharged before ESKD (QOL ++)**
- **Median age = 8 months [2-24]**




*Bérody, (…) Boyer. NDT 2018*

- **12 % of hospitalization/outpatient vs. 18% in dialysis**
- **0.5 day/8 days vs. 1 day/5.5 days**




*Canalejo González. An Pediatr 2006*

- **20% children home albumin infusions**

*Dufek, Holtta (…) Shroff. NDT 2018*

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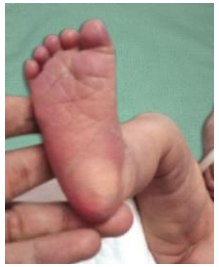
# Recommendations for fluid and albumin administration

- We recommend using **albumin infusions based on clinical indicators of hypovolemia** (including oliguria, acute kidney injury, 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.**



Most of the infused albumin is lost in the urine within hours
Purpose of albumin infusion : not to normalize serum albumin levels but to **support intravascular volume and reduce extravascular fluid retention** **in patients with symptomatic hypovolemia**

- Some children with no or minimal symptoms do well without regular albumin infusions.
- Others may need frequent albumin infusions to prevent the clinical consequences of hypovolemia and failure to thrive. In the latter, we recommend basing the frequency and dosage of albumin infusion on the **clinical indicators of hypovolemia**, rather than on serum albumin levels.
- In patients with severe disease, 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**.

# Recommendations for the use of diuretics

- **If albumin infusions are given**, we suggest administering **a dose of furosemide (0.5-2 mg/kg) at the end of each infusion** unless the patient has marked hypovolemia and/or hyponatremia.

- We recommend using diuretics in patients with signs of **intravascular fluid overload** (as evidenced by good peripheral perfusion and high blood pressure in combination with edema) and preserved kidney function.

- **furosemide (0.5–2 mg/kg per dose**, IV or orally up to 6 times daily; maximum 10 mg/kg per day) unless intravascular hypovolemia.
- Dosages >6 mg/kg per day should not be given for > one week.
- Infusions over 5-30 minutes to minimize ototoxicity.

*Lipska et al. Eur J Hum Genet 2020*
*Boyer et al. Nat Rev Nephrol 2020. in press*

# Recommendations for anti-proteinuric therapy

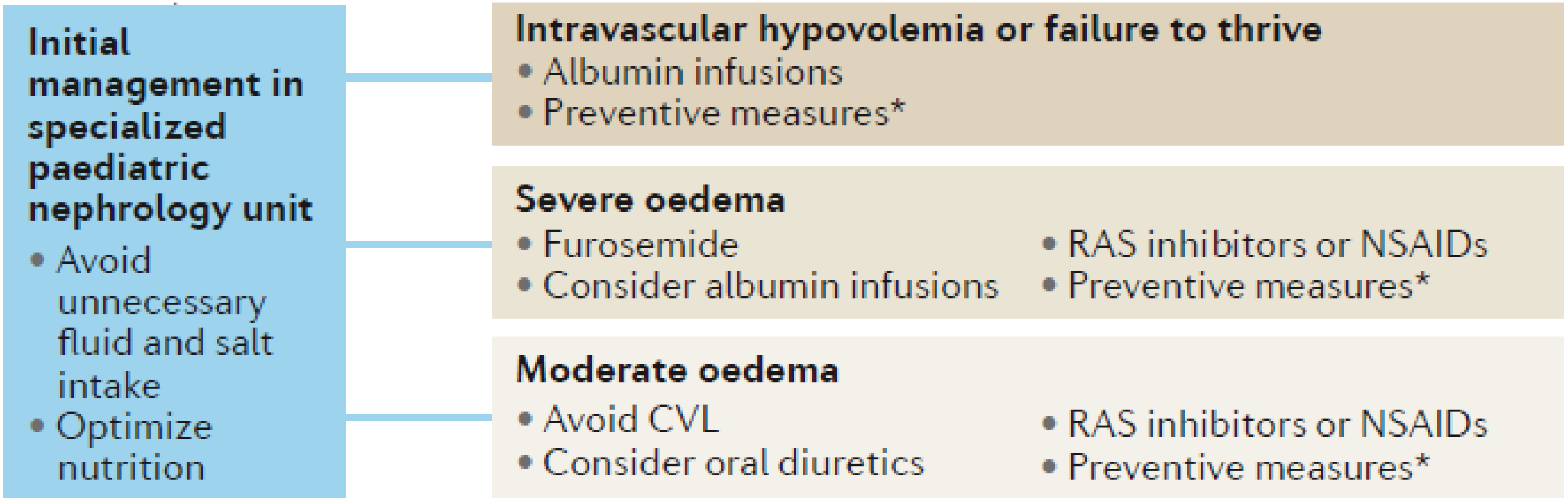
- We recommend administering **RAAS-blocking therapy such as ACE inhibitors or ARBs in children with CNS aged > 4 weeks.**

- Starting with the **short-acting** ACEi **captopril**, escalating the dosage from 0.01 to 0.5 mg/kg per dose in children younger than 3 months (maximum dosage of 2 mg/kg/day). Older infants should receive 0.15–3 mg/kg per dose (maximum dosage of 6 mg/kg/day).
- We **do not recommend combining ACEi and ARBs** due to the increased risk of AKI.

- In the case of poor responsiveness to RAASi, we suggest considering **indomethacin** dosed incrementally from 0.5 to 3 mg/kg/day.
- We recommend stopping prostaglandin inhibitors if no clinical benefit (▲serum albumin levels and/or ▼ edema) is apparent after 2 to 4 weeks.

- In case of **vomiting or diarrhea**, RAASi, indomethacin and diuretics must be stopped due to the high risk of intravascular volume depletion and AKI.

*Lipska et al. Eur J Hum Genet 2020*
*Boyer et al. Nat Rev Nephrol 2020. in press*




*Boyer et al. Nat Rev Nephrol 2020. in press*

# Recommendations for nephrectomies

- **We do not recommend performing routine early nephrectomies in children with CNS.**

Retrospective studies : no difference in long-term outcomes with these two strategies.

*Lipska et al. Eur J Hum Genet 2020*
*Boyer et al. Nat Rev Nephrol 2020. in press*

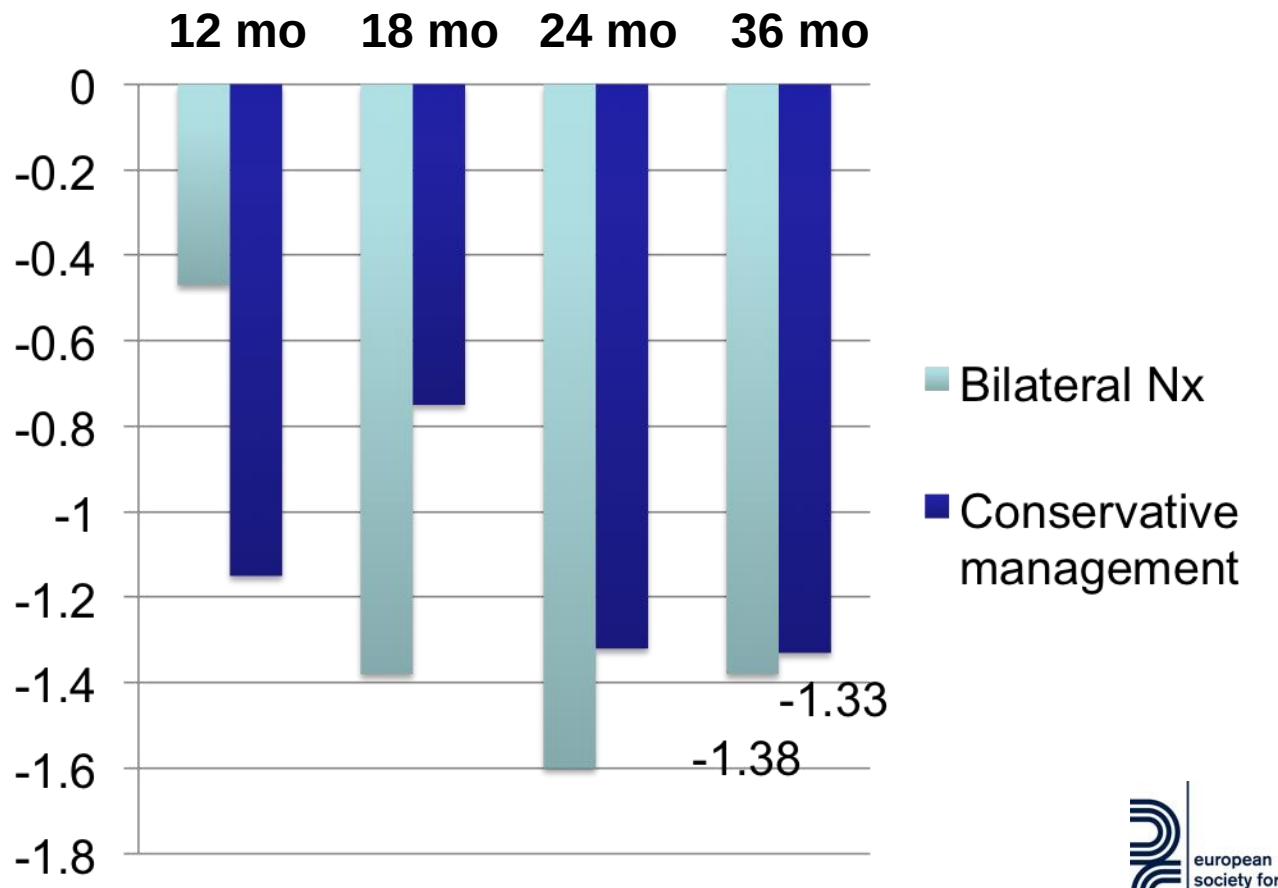
# Similar complication rates with/without systematic nephrectomy

| Berody et al, NDT 2018 | Dufek, Holtaa et al., NDT 2018 |
|---|---|
| French nationwide retrospective study (18 centres) | European retrospective study (22 centres – ESPN dialysis WG) |
| **55 consecutive children**<br>▪ NPHS1 (nephrin): 65%<br>▪ NPHS2 (podocine): 7%<br>▪ WT1 : 7%<br>▪ No identified mutation: 16% | **80 children**<br>▪ NPHS1 (nephrin): 69%<br>▪ NPHS2 (podocine): 1%<br>▪ WT1 : 11% (analyzed separately)<br>▪ Others : 19% |
| **Median age at ESKD (n=36) : 10.5 months**<br>**54 months in case of conservative care**<br>12 months in case of preemptive bilateral nephrectomy | **Median age at ESKD:**<br>**45 months in case of conservative care**<br>8 months in case of preemptive bilateral nephrectomy |
| 2.41 bacterial invasive infections/patient/yr < published series | **48% vs. 47%** (p= 0.95) CVL infections<br>**54% vs. 53%** (p = 0.94) septic episodes |
| 0.25 catheter thromboses/patient and 3 prenatal ischemic cerebral accidents | **16% vs. 12%** (p = 0.70) CNS-related thromboses |
| **4%** died in conservative management<br>**20%** in ESKD/RRT<br>**16/170 in RRT in the ESPN/ERA-EDTA registry** | 16% children died at a median age of 8 months (4-33) |

*Holtta, Pediatr Nephrol 2016*

# Similar complication rates with/without systematic nephrectomy

## Height (SDS)

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*Dufek, Holtta (…) Shroff. NDT 2018*

# Recommendations for nephrectomies

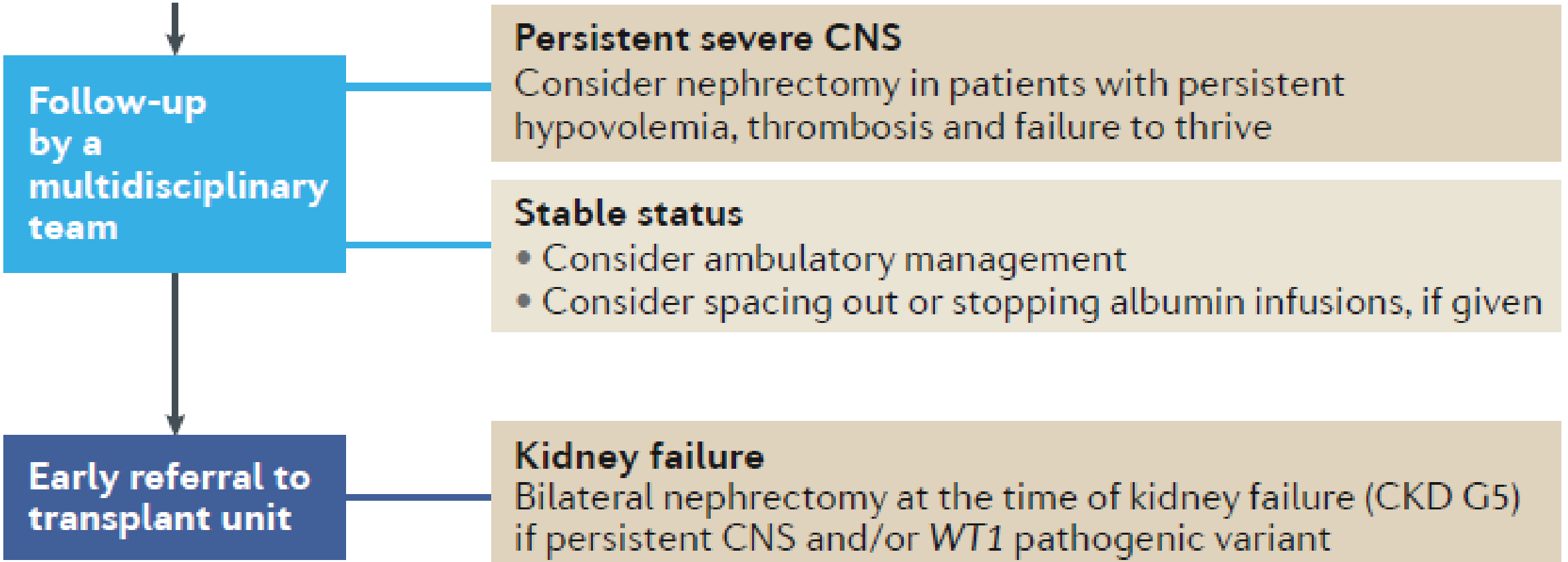
- **We do not recommend performing routine early nephrectomies in children with CNS.**

Retrospective studies : no difference in long-term outcomes with these two strategies.

- We suggest considering unilateral or bilateral nephrectomy in patients with severe complications including failure to thrive, thrombosis and/or difficulty in maintaining intravascular euvolemia despite optimization of conservative treatment.
- We recommend performing **bilateral nephrectomies before kidney transplantation in patients with persisting nephrotic syndrome and/or a *WT1* dominant pathogenic variant.**

- When possible, we recommend **ambulatory management** to increase QOL, decrease risk of nosocomial infections and reduce treatment costs.

*Lipska et al. Eur J Hum Genet 2020*
*Boyer et al. Nat Rev Nephrol 2020. in press*




*Boyer et al. Nat Rev Nephrol 2020. in press*

# Recommendations for prevention of complications

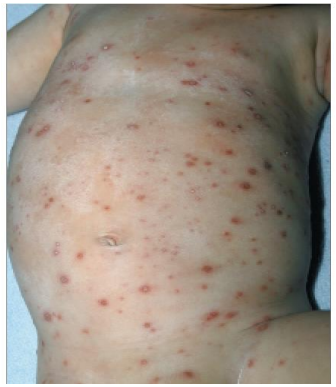
## Thrombosis prophylaxis

- **Preventive anticoagulation** during states of increased thrombosis risk (risk of dehydration, inserted central lines …) and/or in case of a prior thrombosis.

## Infection prophylaxis and management

- 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 for 5-7 days starting within 7-10 days of exposure.
- We recommend treatment of VZV infection with IV high-dose aciclovir for 7-10 days.



*Lipska et al. Eur J Hum Genet 2020*
*Boyer et al. Nat Rev Nephrol 2020. in press*

# Recommendations for prevention of complications



## Nutrition, growth and metabolism

- We recommend provision of a diet with a **high energy (130 kcal/kg/day) and protein (4g/kg/day)** content but **low salt content (<0.5-3g/day depending on the patient age).**

- We recommend initiating **growth hormone treatment** in patients with persistent height growth failure despite adequate nutrition.
- We recommend supplementing **with levothyroxine (T4)** in case of hypothyroidism.
- We recommend close monitoring of ionized calcium, 25-OH-D3 and PTH levels and supplementing with **cholecalciferol or decalcifediol and calcium (250-500 mg/day) in the case of abnormal levels.**

- There is insufficient evidence to recommend treatment of dyslipidemia in CNS.

*Lipska et al. Eur J Hum Genet 2020*
*Boyer et al. Nat Rev Nephrol 2020. in press*

# Recommendations for prevention of complications

## Anemia prevention and management

- We recommend **monitoring and treating iron deficiency** and administering **erythropoietin** in patients who have anemia despite iron supplementation.

- We recommend close monitoring of the reticulocyte count as a marker of erythropoiesis and response to therapy. Persistent anemia after 4 weeks of iron and erythropoietin therapy requires further evaluation for other possible contributing factors, such as **copper, ceruloplasmin or vitamin B12 deficiency, and appropriate treatment.**

*Lipska et al. Eur J Hum Genet 2020*
*Boyer et al. Nat Rev Nephrol 2020. in press*

# Recommendations for management of ESKD

- We recommend that use of dialysis in children with CNS **follows the general guidelines** for kidney replacement therapy in infants and children.

- **Genetic counseling** prior to parental kidney donation in genetic forms.
  - **Carriers of a heterozygous variant in an AR gene can be kidney donors.**
  - Mind intra- and inter-family variability, and age-dependent penetrance: *WT1* and *NPHS2* +++

*Lipska et al. Eur J Hum Genet 2020*
*Boyer et al. Nat Rev Nephrol 2020. in press*

# Recommendations for management of ESKD

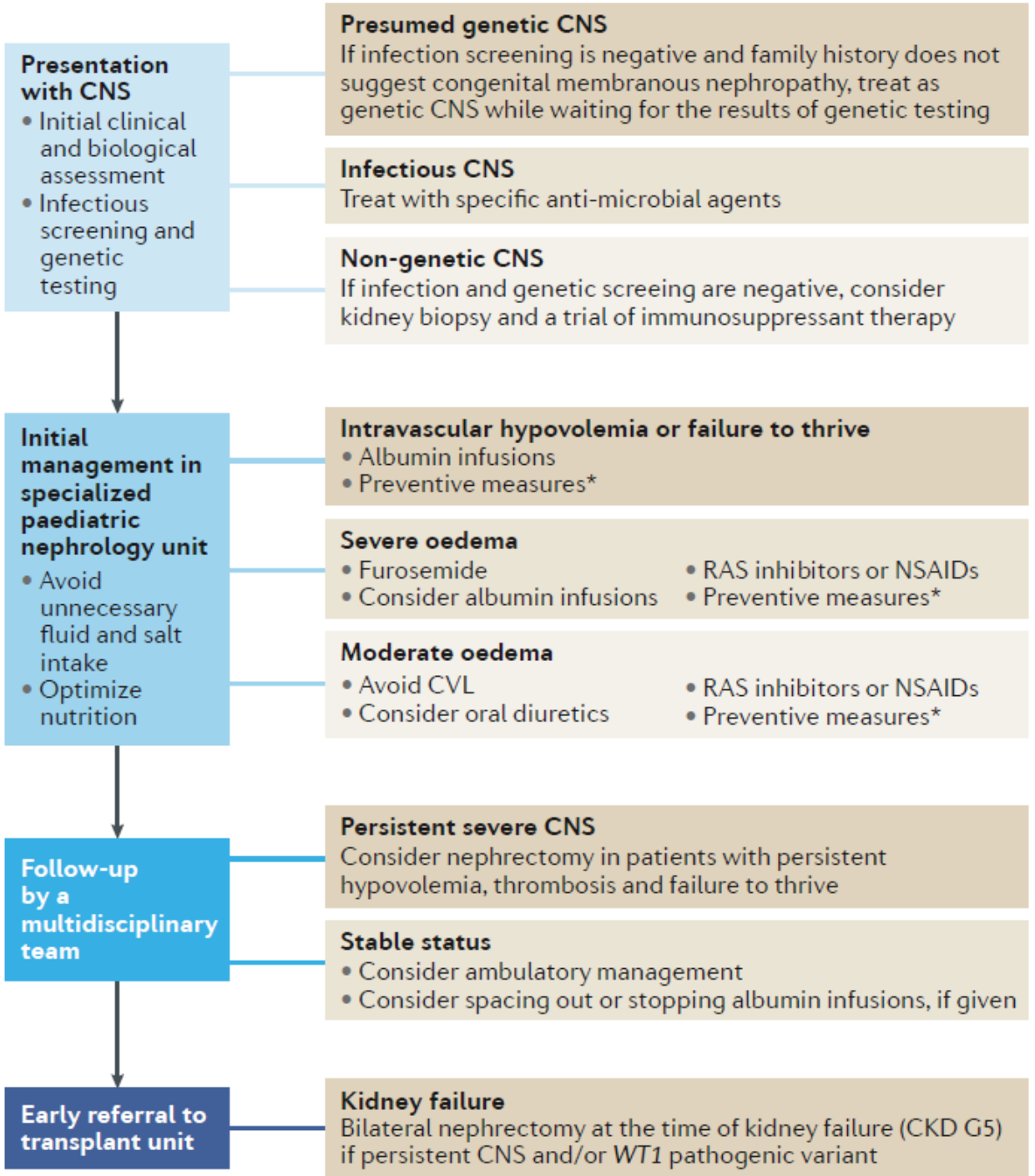
- **In children with post-transplant proteinuria, we recommend considering antibody-mediated disease and antibody reduction strategies (*i.e.* plasmapheresis and immunosuppressive drugs).**

  - Mild post- KTx proteinuria is not rare and can be related to : graft rejection, *de novo* glomerulopathy, infection or drug toxicity
  - **Almost all *de novo* glomerulopathy in children with Fin-major *NPHS1* variants**: occurs in 25-35% of them and 70% have detectable **anti-nephrin Abs**

  → daily PEx, methylprednisolone pulses and oral cyclophosphamide or rituximab

  - Few cases reported with *NPHS2* variants, no Abs : might be multifactorial.

*Lipska et al. Eur J Hum Genet 2020*
*Boyer et al. Nat Rev Nephrol 2020. in press*




*Boyer et al. Nat Rev Nephrol 2020. in press*

# Acknowledgements

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

# MCQs

How would you manage a 16 month-old infant with CNS (*NPHS1* compound heterozygous variants)

With slight lower limb edema and is satisfactory growth (weight 9.5 kg), few ENT infections and serum creatinine of 25 µmol/L (0.3 mg/dL)
receiving the following treatment :
two weekly albumin infusions, captopril, warfarin, calcium and vitamin D.

A- Bilateral nephrectomy and peritoneal dialysis

B- Pre-emptive kidney transplantation

C- Hospital discharge and ambulatory management

D- Unilateral nephrectomy and add indomethacin

E- Transfer to a long-stay center for children

# MCQs

You are following a 9-month-old girl for a CNS whose treatment is :
- on a central venous line: albumin x2/week, IVIGs x1/week,
- orally: warfarin, captopril, L-thyroxin, vitamin D, calcium.

She consults for a fever of 38°5, well tolerated. The examination is unremarkable apart from an acute right otitis media.

What is your immediate therapeutic attitude?

A- return home, antipyretics, monitoring
B- return home, antipyretics and amoxicillin
C- Paracentesis, antipyretics and adapted oral antibiotics at home
D- hospitalization, antipyretics and clinical monitoring
E- hospitalization, antipyretics, blood and urine tests and intravenous antibiotics

# Next Webinars

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Date: **15 Dec 2020**

Speaker: **Pierre Ronco**

Topic**: Membranous Nephropathy**

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