Speaker: Olivia Boyer

Hôpital Necker, Paris

Institut Imagine

olivia.boyer@aphp.fr

IPNA-AsPNA Junior Master Class, New Delhi
26-27 November 2022

Date: November 26th 2022

Topic: **Congenital Nephrotic Syndrome**

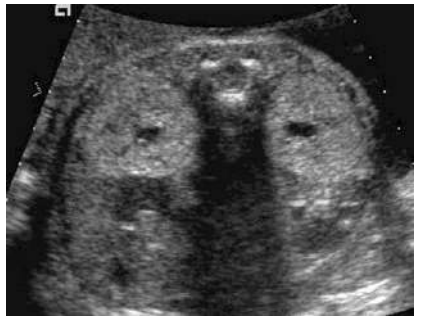
Congenital nephrotic syndrome

Definition

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

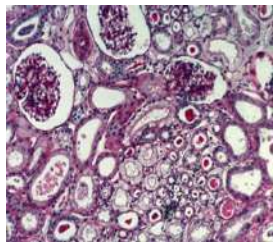
Etiologies

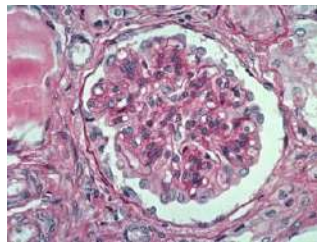
- **Podocyte gene pathogenic variants (85%)**
  - *NPHS1* (nephrin): 61%
  - *NPHS2* (podocin): 14%
  - *WT1* : 2%
  - *LAMB2*: 2%
  - *PLCE1*: 2%
- Congenital infections
- Maternal allo-immune disease



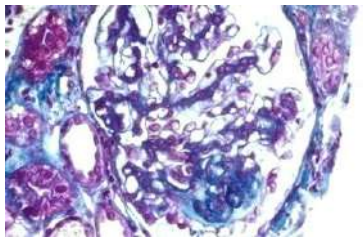
Prenatally:
Enlarged hyperechoic kidneys
Increased α-FP

Enlarged placenta
>25% BW
Massive Pu, anasarca
Variable GFR

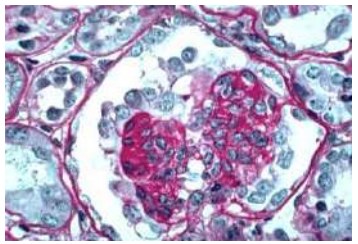




Tubular dilations and mesangial hypercellularity (Finnish CNS)



MCD/FSGS



DMS

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

Non-syndromic causes of genetic CNS

NPHS1 (nephrin)- Finland

1/8000 in Finland > 1/47000

2 recurrent mutations (98%):

Fin-major et Fin-minor

No expression of nephrin

Normal GFR at birth – ESKD ≅ 2 yrs (to adulthood)

25-35% post-Tx de novo autoimmune-mediated NS due to antinephrin Ab deposition in the kidney graft.

Other populations

> 200 variants (missense ++)

Mutation rate in CNS : 78%

No post-Tx Pu

NPHS2 (podocin)

14 % of cases of CNS (MCD/FSGS)

NPHS1 : early onset: **1st week of life**

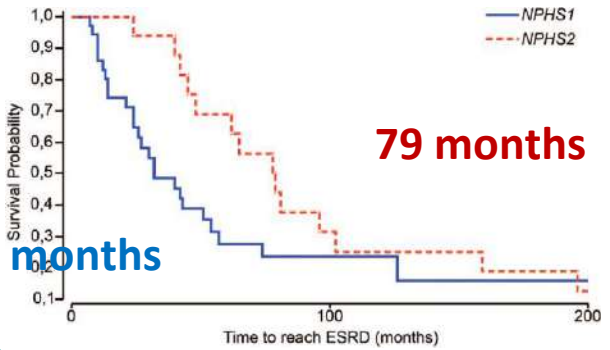
NPHS2 : later onset (median **29 days**)

CNS < 1 wk: 74% *NPHS1* – 11% *NPHS2*

CNS > 1 month: 16% *NPHS1* – 37% *NPHS2*

Childhood SRNS +++ & adult SRNS

ESKD ≅ 6-7 years



79 months

32 months

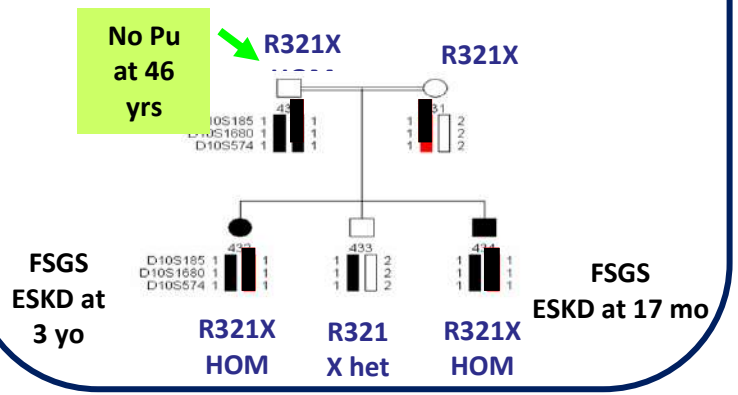
NPHS3 (PLCE1)

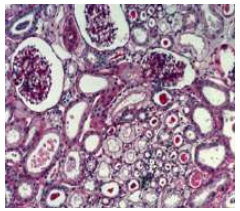
- Onset : 2 mo (CNS) to 4 yrs (SRNS)
- FSGS or DMS **(+/- neonatal CKD)**
- ESKD < 7 yrs
- **INCOMPLETE PENETRANCE**

⇒ *Oligogenic inheritance?*

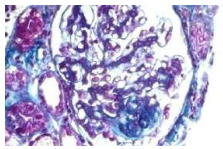
⇒ *Modifier genes?*

⇒ *environnemental factors?*



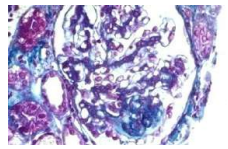


mesangial hypercellularity, hyperlobulated capillary tufts and microcystic dilation of proximal and distal tubules with diffuse podocyte foot process effacement.

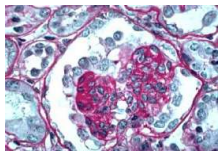


FSGS

Kestila et al., Mol Cell 1998
Philippe et al., KI 2008
Machuca et al. JASN 2010

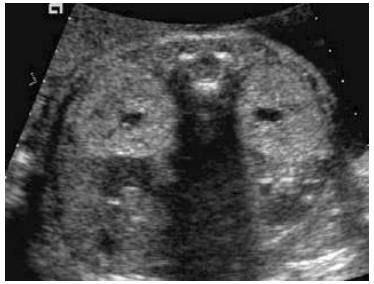


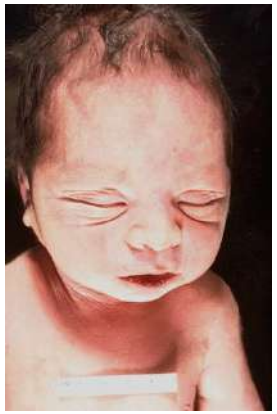
FSGS



Diffuse mesangial sclerosis

WT1 mutations (AD) and Denys Drash or Frasier syndrome





WT1-related NS

Congenital, infantile or childhood NS

5% of girls (46XX) with hereditary SRNS

Peak of onset at **4–12 months**, then regular distribution among adolescents and young adults.

Mostly *de novo*, some with AD inheritance

CKD may be present at birth/AN (Potter)
Time to ESKD ≅ 2.7 (exonic) vs 9.2 yrs (intronic variant)

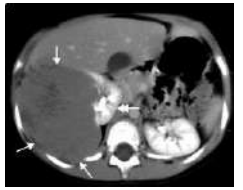
Monitor kidney US/3 months until 7 years of age

Karyotype (phenotypic girls)

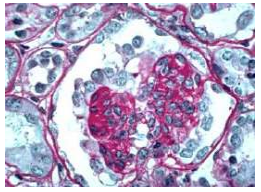
Lipska et al. Kidney Int 2014
Lipska et al. Eur J Hum Genet 2020

Denys Drash

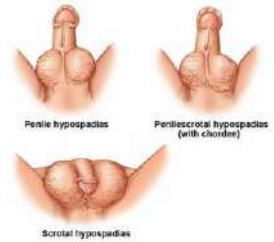
Variant in exons 8 and 9



Wilm's

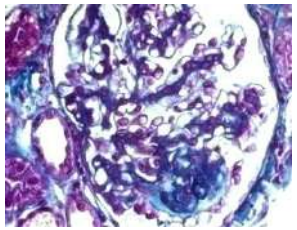


DMS



Male pseudo-hermaphroditism

Gonadoblastoma
Streak gonades



FSGS

Splice site variant in intron 9

Frasier

Other syndromic causes of genetic CNS

Pierson

LAMB2

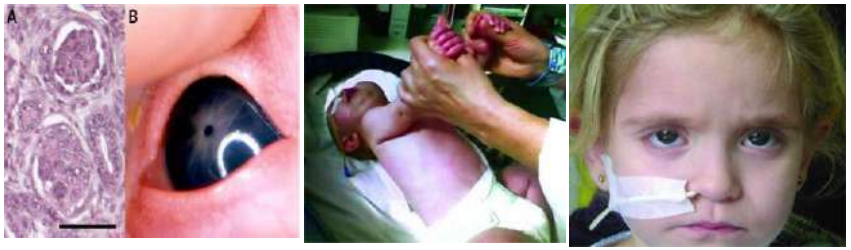
DMS (or FSGS)

microcoria and hypoplasia of the ciliary and pupillary muscles.

early death.

Survivors : neurodevelopmental delay and visual loss.

Also cause isolated CNS



Zenker , Hum Mol Genet 2004

Wuhl, Am J Hum Genet 2007

Galloway-Mowatt

WDR73, OSGEP, TP53RK, TPRKB, GON7, LAGE3, YRDC, NUP107, WDR4, NUP133

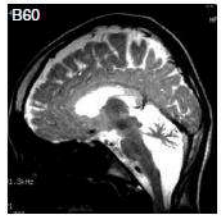
FSGS or DMS, variable age at ESKD

Pre or post-natal microcephaly

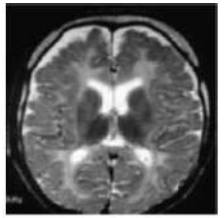
DD, hypotonia, seizures

Cortical and cerebellar atrophy

Gyration (lissencephaly/pachygyria) and myelination defects



Polymicrogyria and diffuse cerebellar atrophy



Reduced myelination of the white matter

Boyer. Ped Nephrol 2021

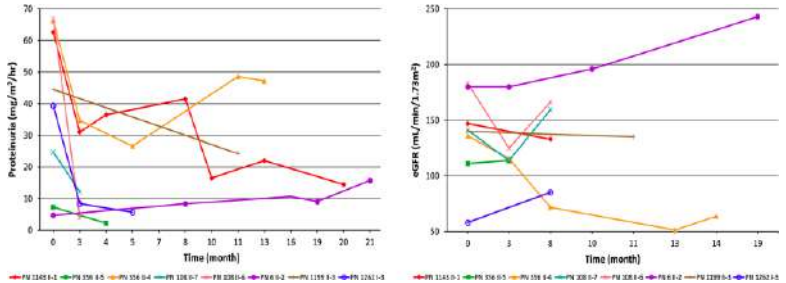
Mitochondriopathies (COQ10)

PDSS2, COQ2, COQ6

± Deafness, seizures, ataxia, DD

Leigh, encephalopathy, MOF

COQ10 supplementation: may ↓ Pu ± deafness

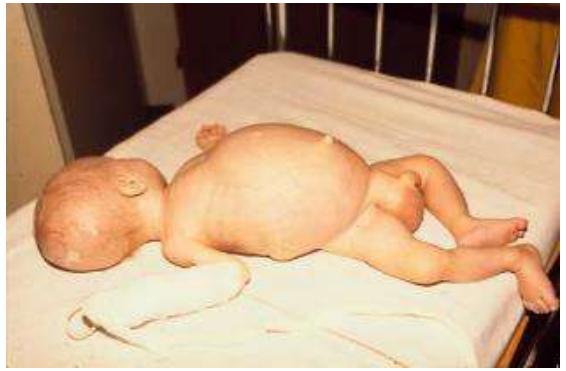


Atacama et al., Ped Nephrol 2017

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**

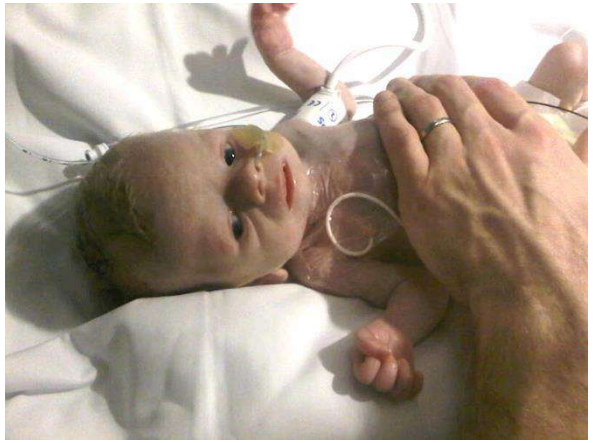


- 1965-1973: mean survival 7.6 months (0-26)
- Causes of death: infection or hemodynamic collapse, thromboses

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 ++)

↓

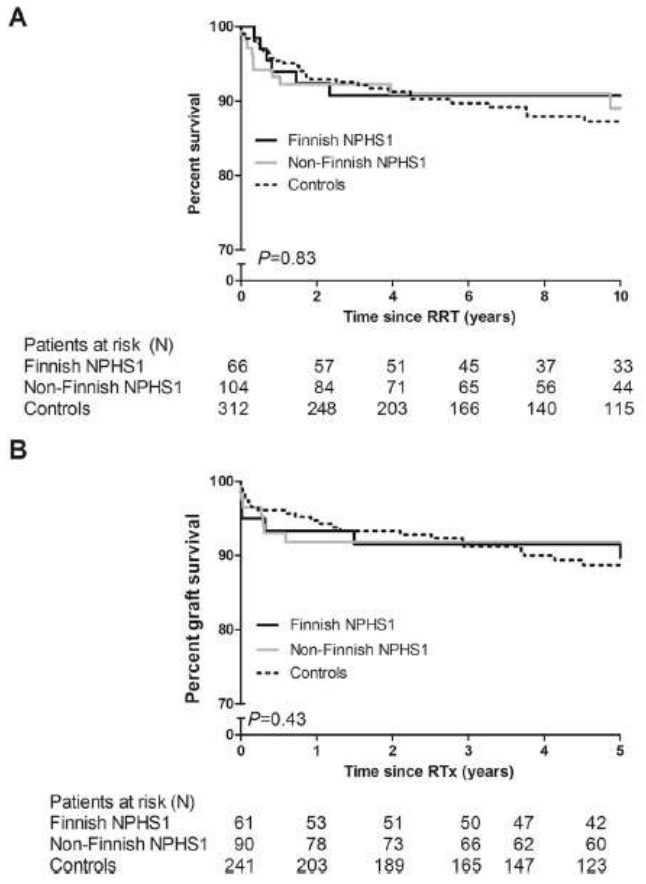
Kidney transplantation (# 9 kg)

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



ESPN/ERA-EDTA Registry

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

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

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*

Follow-up by a multidisciplinary team

Persistent severe CNS
Consider nephrectomy in patients with persistent hypovolaemia, thrombosis and failure to thrive

Stable status
- Consider ambulatory management
- Consider spacing out or stopping albumin infusions, if given

Early referral to transplant unit

Kidney failure
Bilateral nephrectomy at the time of kidney failure (CKD G5) if persistent CNS and/or *WT1* pathogenic variant

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/

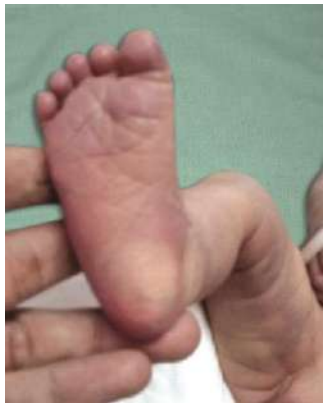
https://www.erknet.org/fileadmin/files/user_upload/2020-12-02_Boyer_CNS.pdf

Presentation with CNS
- Initial clinical and biological assessment
- Infectious screening and genetic testing

Diagnostic work-up

History:
- Family: consanguinity, history of CNS...
- Prenatal and perinatal history: increased amniotic fluid alphafetoprotein, fetal edema, placental weight >25% BW

First line evaluation:
- **Physical examination: volemia, oedema** (e.g. ascites, pericardial & pleural effusions)
- Blood biochemistry, Ca, TSH, FT4, IgG
- **Dietary assessment**



Boyer et al. Nat Rev Nephrol 2021

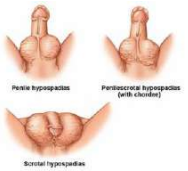
Presentation with CNS
- Initial clinical and biological assessment
- Infectious screening and genetic testing

History:
- Family: consanguinity, history of CNS...
- Prenatal and perinatal history: increased amniotic fluid alphafetoprotein, fetal edema, placental weight >25% BW

First line evaluation:
- **Physical examination: volemia, oedema**
- Blood biochemistry, Ca, TSH, FT4, IgG
- **Diet**

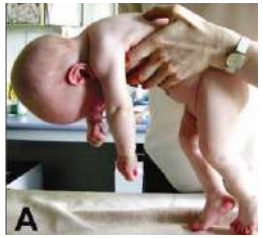
Extended evaluation:
- **Dysmorphia, skeletal/genital/ophthalmological examination, hearing test**
- **Full neurological examination** +/- MRI
- **Infection screening +/- immunological tests (NEP..)**

DDS/Frasier

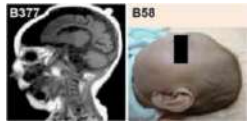


Pierson

Mitochondrial disease



Galloway Mowat



Lipska et al. Eur J Hum Genet 2020
Boyer et al. Nat Rev Nephrol 2021

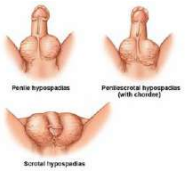
Presentation with CNS
- Initial clinical and biological assessment
- Infectious screening and genetic testing

History:
- Family: consanguinity, history of CNS...
- Prenatal and perinatal history: increased amniotic fluid alphafetoprotein, fetal edema, placental weight >25% BW

First line evaluation:
- **Physical examination: volemia, oedema**
- Blood biochemistry, Ca, TSH, FT4, IgG
- **Diet**

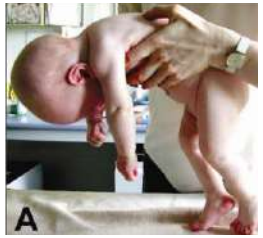
Extended evaluation:
- **Dysmorphia, skeletal/genital/ophthalmological examination, hearing test**
- **Full neurological examination** +/- MRI
- **Infection screening +/- immunological tests (NEP..)**

DDS/Frasier

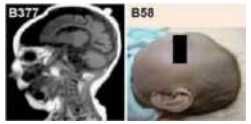


Pierson

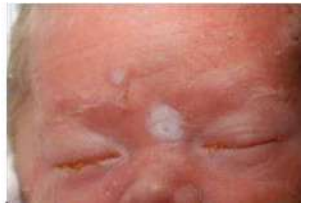
Mitochondrial disease

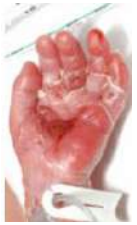


Galloway Mowat

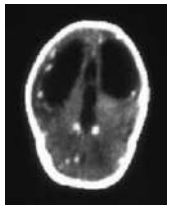


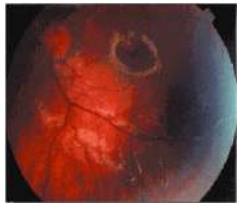
Congenital syphilis





Toxoplasmosis





Lipska et al. Eur J Hum Genet 2020
Boyer et al. Nat Rev Nephrol 2021

Presentation with CNS
- Initial clinical and biological assessment
- Infectious screening and genetic testing

Infectious CNS
Treat with specific anti-microbial agents

Penicillin G

Pyrimethamine

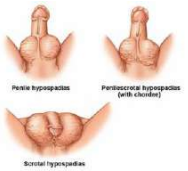
Gancyclovir

History:
- Family: consanguinity, history of CNS...
- Prenatal and perinatal history: increased amniotic fluid alphafetoprotein, fetal edema, placental weight >25% BW

First line evaluation:
- **Physical examination: volemia, oedema**
- Blood biochemistry, Ca, TSH, FT4, IgG
- **Diet**

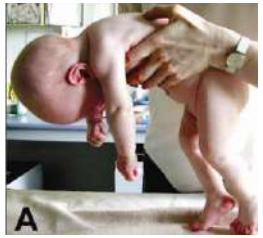
Extended evaluation:
- **Dysmorphia, skeletal/genital/ophthalmological examination, hearing test**
- **Full neurological examination** +/- MRI
- **Infection screening +/- immunological tests (NEP..)**

DDS/Frasier

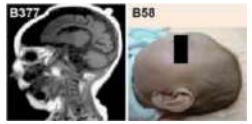


Pierson

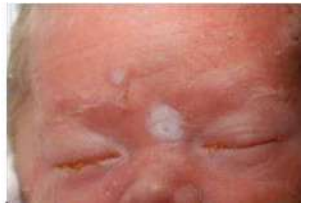
Mitochondrial disease

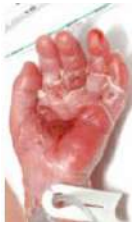


Galloway Mowat

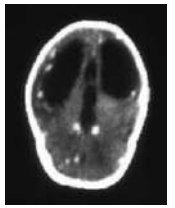


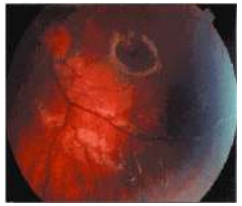
Congenital syphilis





Toxoplasmosis





Lipska et al. Eur J Hum Genet 2020
Boyer et al. Nat Rev Nephrol 2021

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

History:
- Family: consanguinity, history of CNS...
- Prenatal and perinatal history: increased amniotic fluid alphafetoprotein, fetal edema, placental weight >25% BW

First line evaluation:
- **Physical examination: volemia, oedema** (e.g. ascites, pericardial & pleural effusions)
- Blood biochemistry, Ca, TSH, FT4, IgG
- **Diet**

Extended evaluation:
- **Dysmorphia, skeletal/genital/ophthalmological examination, hearing test**
- **Full neurological examination** +/- MRI
- **Infection screening +/- immunological tests (NEP..)**

Lipska et al. Eur J Hum Genet 2020
Boyer et al. Nat Rev Nephrol 2021

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*

At diagnosis

Genetic screening

Population specific defect?

Clear phenotype?

Specific genetic screening

NGS available?

Specific genetic screening

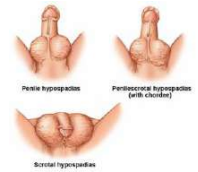
Panel/WES

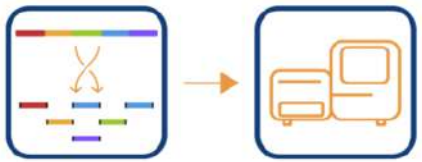
Sanger: *NPHS1, NPHS2, LAMB2, WT1* (ex 8-9)

> 80% cases

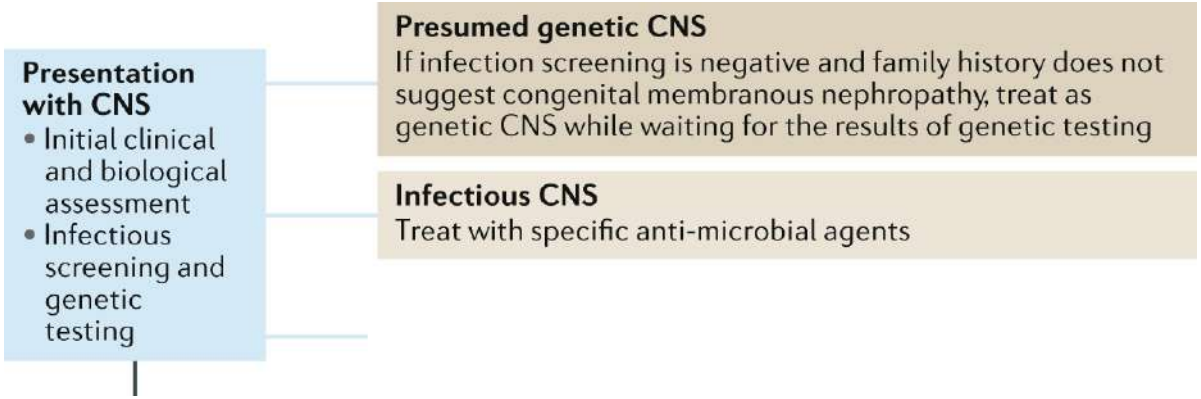
Genetic diagnosis

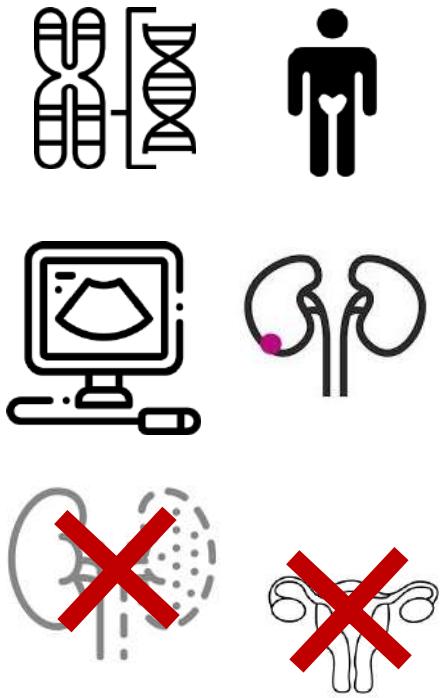
DDS → *WT1*





Lipska et al. Eur J Hum Genet 2020
Boyer et al. Nat Rev Nephrol 2021





- ***WT1* gene specific-management:**
  - **karyotype testing** in each CNS patient with **ambiguous genitalia** and in each **phenotypic girl with a pathogenic *WT1* variant**.

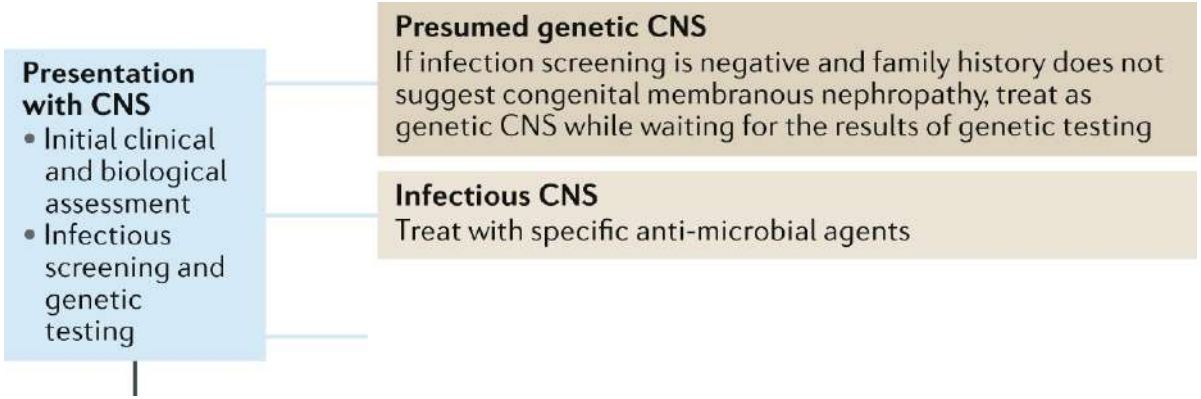
+ evaluation for **urogenital** malformations

+ oncological surveillance for **Wilms tumor and gonadoblastoma**

- **abdominal US performed every 3 months until the age of 7 years**
- **bilateral nephrectomy** at time of ESKD
- **bilateral gonadectomy in** 46,XY phenotypic girls (i.e., complete gonadal dysgenesis)

+ **endocrine** and **psychological** management

Lipska et al. Kidney Int 2014
Lipska et al. Eur J Hum Genet 2020
Boyer et al. Nat Rev Nephrol 2021



- **CoQ10-related mitochondriopathies** (*COQ2, COQ6,* and *PDSS2* genes)
  - **Complete and repeated** screening for extra-renal manifestations
  - In case of a non-informative NGS result, **muscle, skin, and/or kidney biopsies** may be needed.
  - Early **CoQ10 supplementation** 15–30 to 50 mg/kg/day in 3 administrations
  - May improve proteinuria and sometimes neuromuscular complaints

- **The vast majority of genetic CNS** respond neither to steroids nor to intensified immunosuppressive treatment.
- We recommend **not to use immunosuppressive regimens** but to use RAASi

and other preventive measures

Lipska et al. Eur J Hum Genet 2020
Boyer et al. Nat Rev Nephrol 2021

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

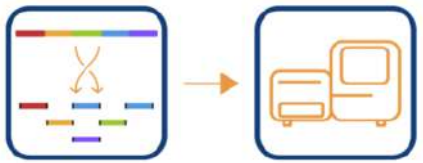
Infectious CNS
Treat with specific anti-microbial agents

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

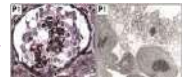
- **We do not recommend routine kidney biopsy in patients with CNS.** We suggest kidney biopsy be considered **only in patients with sporadic, non-syndromic disease with negative comprehensive genetic testing or if GFR < 30 ml/min/1.73m^2**

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

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

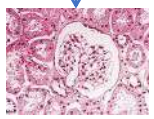


genetic screening



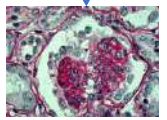
COQ10

Membranous nephropathy (anti-NEP Ab)



MCD

FSGS



DMS

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

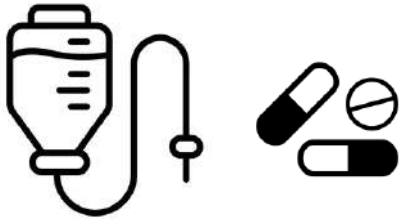
Initial management in specialized paediatric nephrology unit
- Avoid unnecessary fluid and salt intake
- Optimize nutrition

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*

Boyer et al. Nat Rev Nephrol 2021

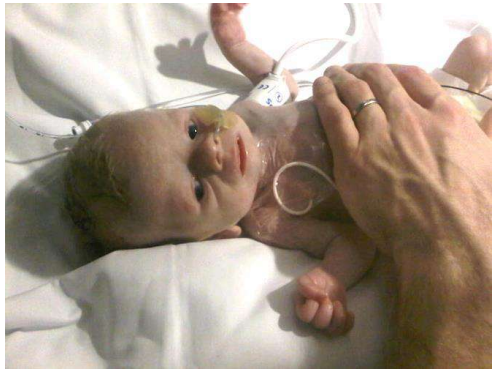


Initial management in specialized paediatric nephrology unit
- Avoid unnecessary fluid and salt intake
- Optimize nutrition

Intravascular hypovolaemia or failure to thrive
- Albumin infusions
- Preventive measures*

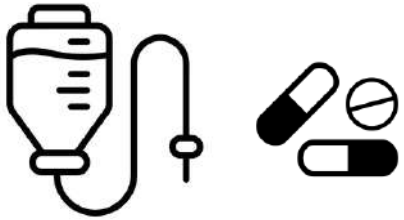
Severe oedema
- Furosemide
- Consider albumin infusions
- RAS inhibitors or NSAIDs
- Preventive measures*

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



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 euvolemia and adequate nutrition, as well as preventing complications**

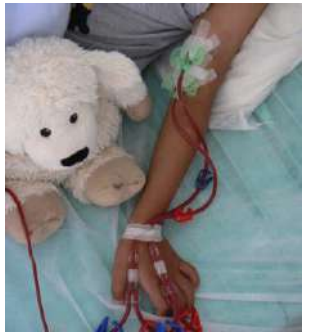


Initial management in specialized paediatric nephrology unit
- Avoid unnecessary fluid and salt intake
- Optimize nutrition

Intravascular hypovolaemia or failure to thrive
- Albumin infusions
- Preventive measures*

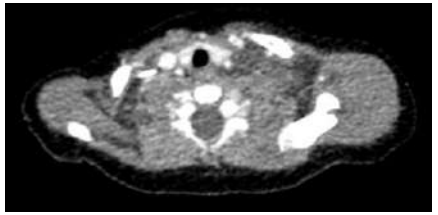
Severe oedema
- Furosemide
- Consider albumin infusions
- RAS inhibitors or NSAIDs
- Preventive measures*

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

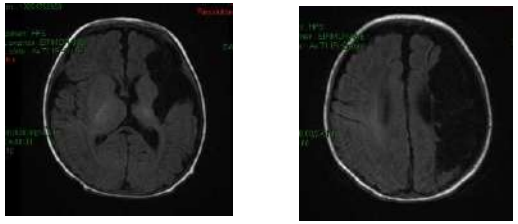


- When possible, we recommend **avoiding central venous lines** in children with CNS due to the high risk of thrombosis. If a central venous access is **required for repeated albumin infusions, we recommend administering prophylactic anticoagulation for as long as the line is in place**

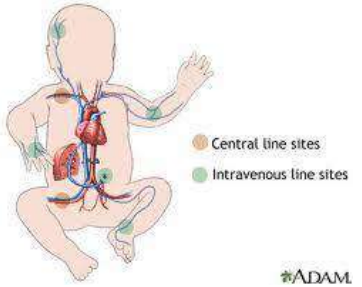
- **Vascular preservation** for hemodialysis access (CVL/AV fistulas)



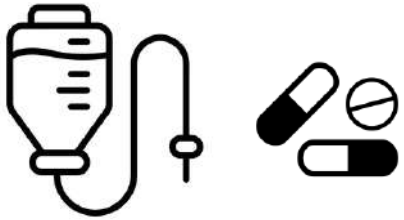
Thrombosis of the left brachio-cephalic trunk in an infant with CNS

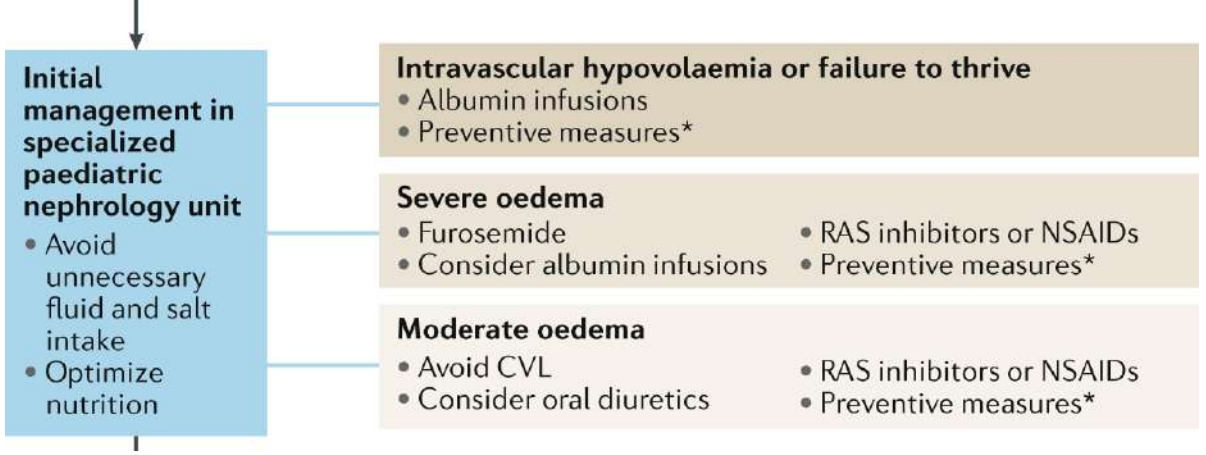


Prenatal ischemic cerebral accidents in an infant with CNS



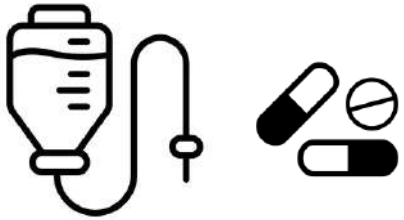
Boyer et al. Nat Rev Nephrol 2021





- We recommend **avoiding intravenous fluids and saline**.
- Oral fluid intake should be concentrated if necessary to avoid marked oedema (expert renal dieticians).
- **Salt restriction**
- **Fluid restriction** in case of hyponatremia and in the most severe cases of edema

Boyer et al. Nat Rev Nephrol 2021

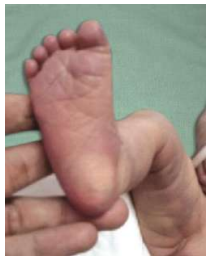


Initial management in specialized paediatric nephrology unit
- Avoid unnecessary fluid and salt intake
- Optimize nutrition

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*

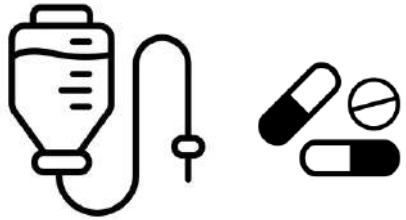


- We recommend using **albumin infusions based on clinical indicators of hypovolemia** (including oliguria, AKI, prolonged capillary refill time, tachycardia, hypotension and abdominal discomfort) or upon failure to thrive. **We do not recommend administering albumin infusions in children with CNS based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

Lipska et al. Eur J Hum Genet 2020
Boyer et al. Nat Rev Nephrol 2021

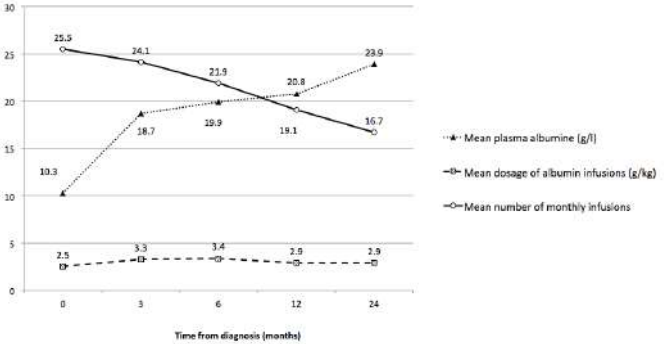


Initial management in specialized paediatric nephrology unit
- Avoid unnecessary fluid and salt intake
- Optimize nutrition

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*



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

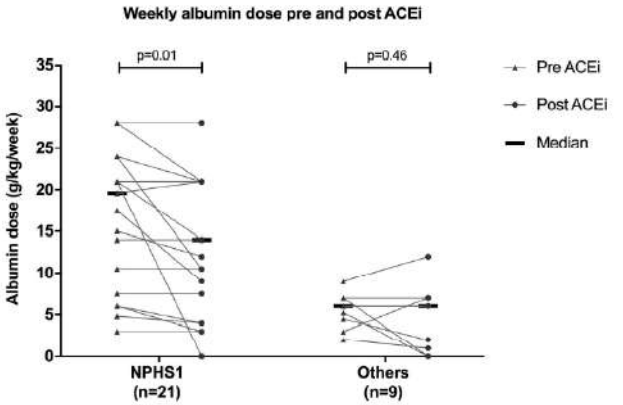
Albumin discontinuation is possible and safe before nephrectomy

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

  Age 1-29 months; for up to 47 months

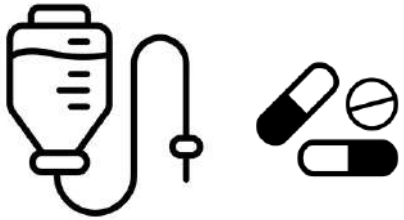
Or albumin tapering

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



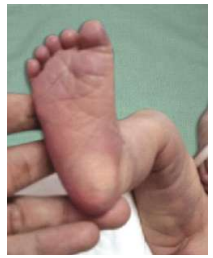
- **Ambulatory management is possible before nephrectomy**

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



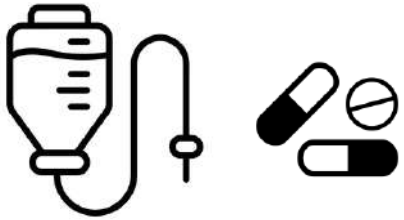
Initial management in specialized paediatric nephrology unit
- Avoid unnecessary fluid and salt intake
- Optimize nutrition

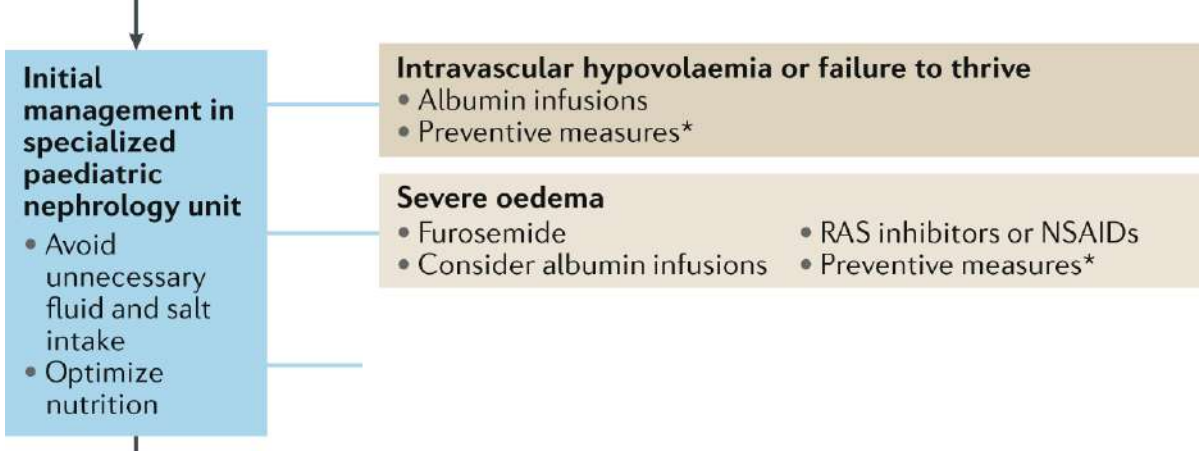
Intravascular hypovolaemia or failure to thrive
- Albumin infusions
- Preventive measures*

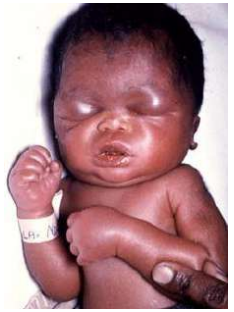


In case of hypovolemia or failure to thrive

- 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**.



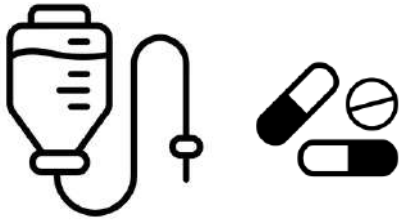




In case of severe oedema

- We recommend using diuretics in patients with signs of **intravascular fluid overload** (as evidenced by good peripheral perfusion and high blood pressure + edema) and preserved kidney function.
- **furosemide (0.5–2 mg/kg per dose**, up to 6 times daily; max 10 mg/kg per day) NOT if intravascular hypovolemia.
- Infusions over 5-30 minutes to minimize ototoxicity.

Lipska et al. Eur J Hum Genet 2020
Boyer et al. Nat Rev Nephrol 2021

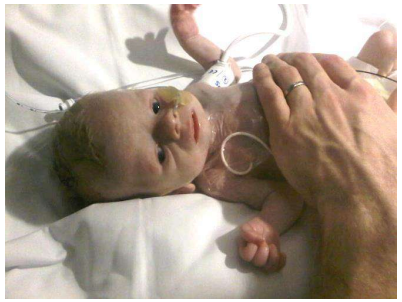


Initial management in specialized paediatric nephrology unit
- Avoid unnecessary fluid and salt intake
- Optimize nutrition

Intravascular hypovolaemia or failure to thrive
- Albumin infusions
- Preventive measures*

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

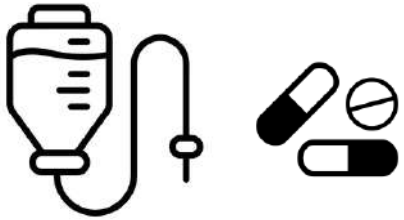
Moderate oedema
- Avoid CVL
- Consider oral diuretics
- RAS inhibitors or NSAIDs
- Preventive measures*

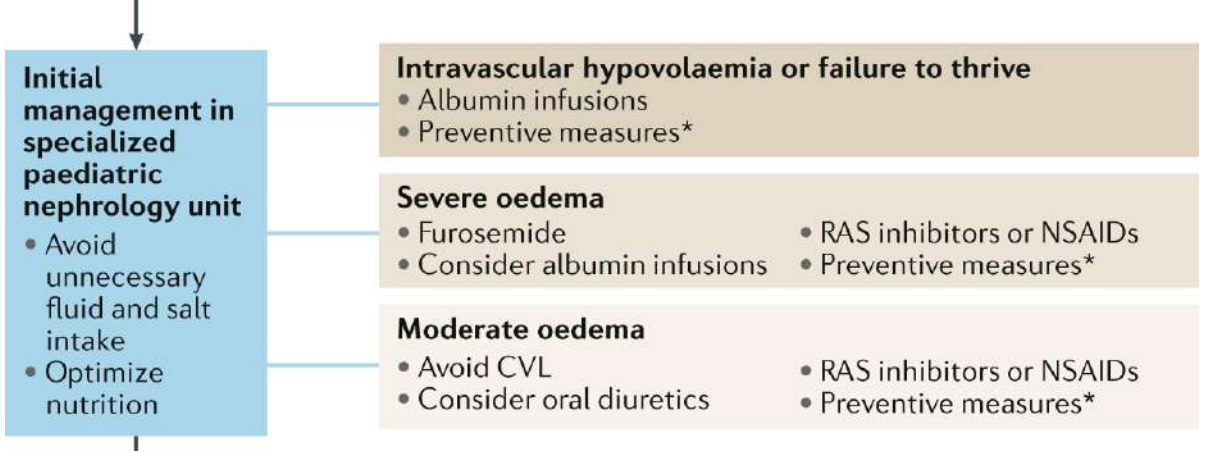


In case of moderate oedema

- Avoid CVL
- **+/- oral diuretics**

Lipska et al. Eur J Hum Genet 2020
Boyer et al. Nat Rev Nephrol 2021





RAASi or NSAIDs

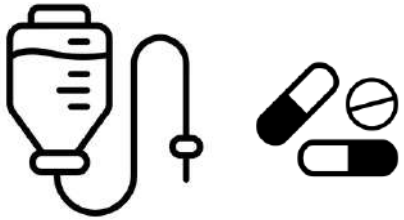
- We recommend **RAAS-blocking therapy (ACEi or ARBs) in children with CNS aged > 4 weeks.**

- Suggest starting with the **short-acting** ACEi **captopril**, dosed incrementally
- 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.
- 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, thromboses and AKI.

Lipska et al. Eur J Hum Genet 2020
Boyer et al. Nat Rev Nephrol 2021

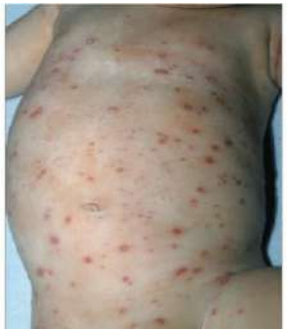


Initial management in specialized paediatric nephrology unit
- Avoid unnecessary fluid and salt intake
- Optimize nutrition

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*



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.

Lipska et al. Eur J Hum Genet 2020
Boyer et al. Nat Rev Nephrol 2021

Follow-up by a multidisciplinary team

Persistent severe CNS
Consider nephrectomy in patients with persistent hypovolaemia, thrombosis and failure to thrive

Early referral to transplant unit

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

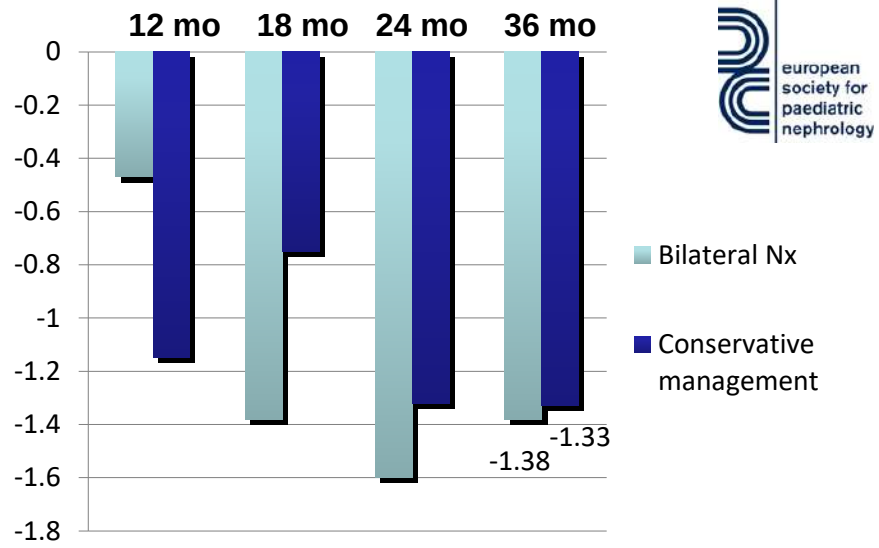
Retrospective studies : no difference in CNS complications with these two strategies.

european society for paediatric nephrology

Société de Néphrologie Pédiatrique

- **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

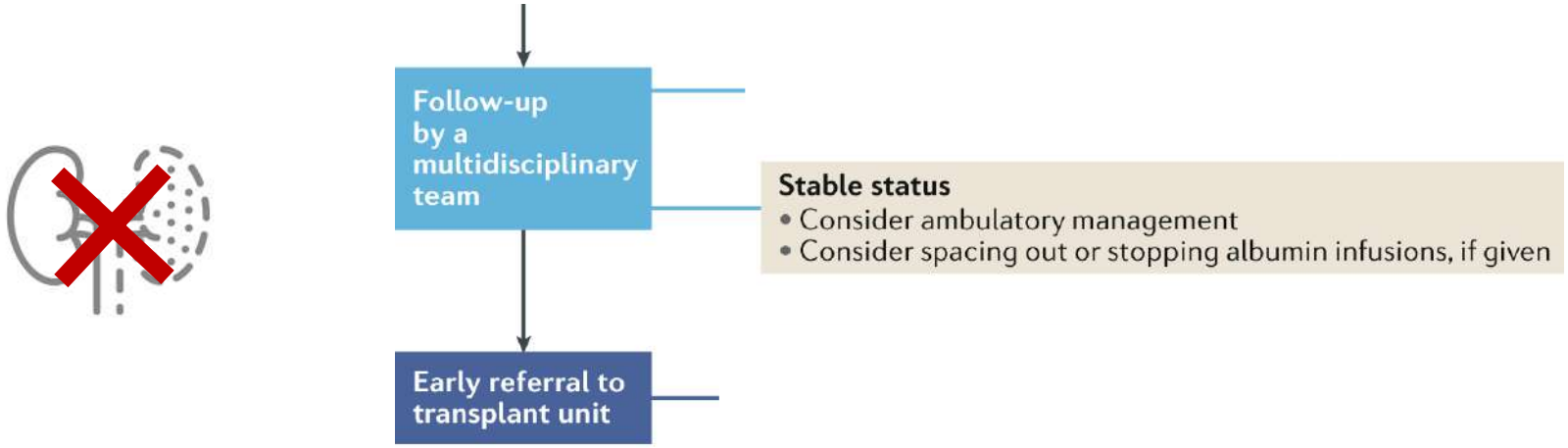
Height (SDS)



european society for paediatric nephrology

Bérody, (…) Boyer. NDT 2018

Dufek, Holtta (…) Shroff. NDT 2018

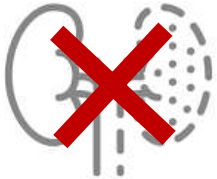


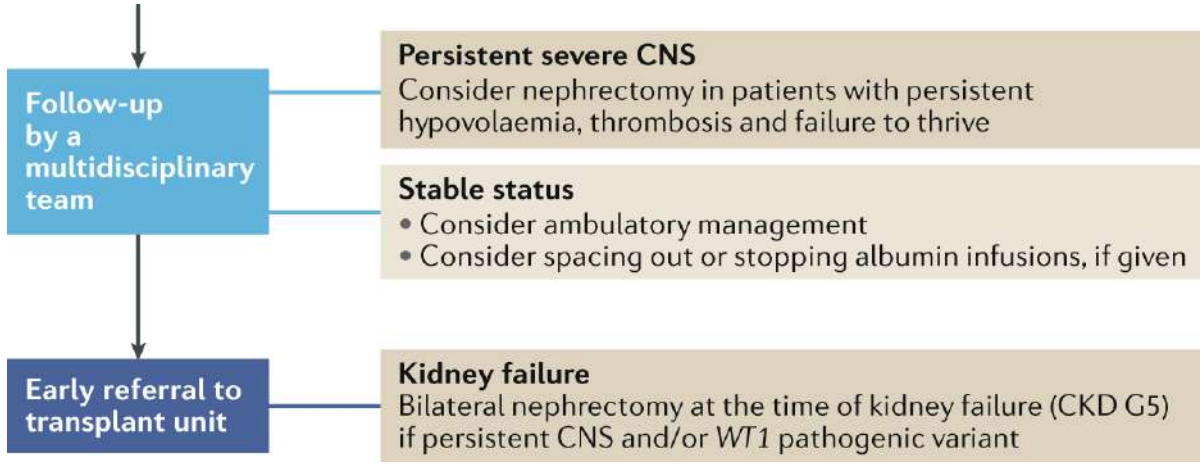
- **We do not recommend performing routine early nephrectomies in children with CNS.**

- In stable children, we recommend **ambulatory management** to increase QOL, decrease risk of nosocomial infections and reduce treatment costs and spacing out or stopping albumin infusions if given

Bérody, (…) Boyer. NDT 2018

Dufek, Holtta (…) Shroff. NDT 2018



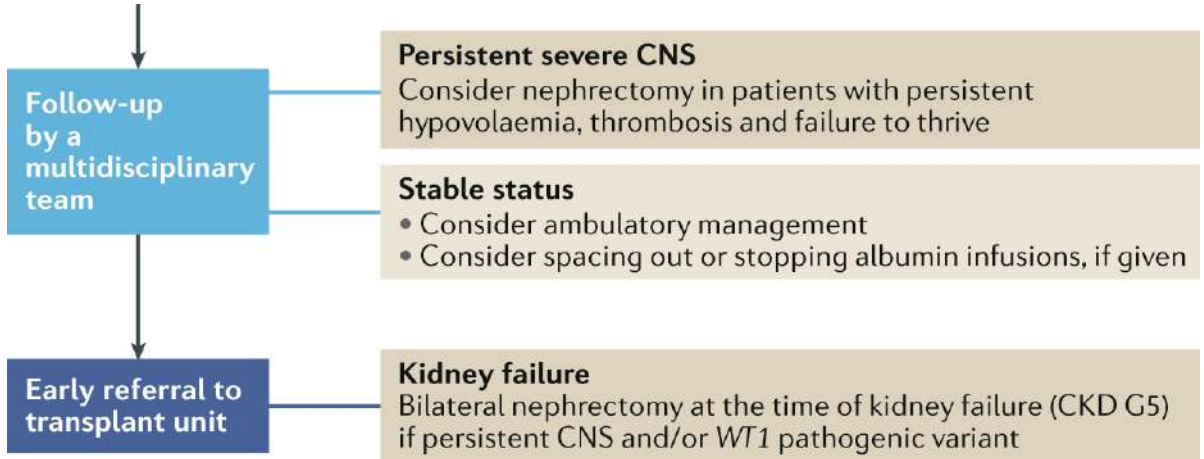


- **We do not recommend performing routine early nephrectomies in children with CNS, but only to consider them in case of <u>persistent severe CNS</u>**

- We recommend performing **bilateral nephrectomies before kidney transplantation in patients with persisting nephrotic syndrome and/or a *WT1* dominant pathogenic variant.**

Bérody, (…) Boyer. NDT 2018

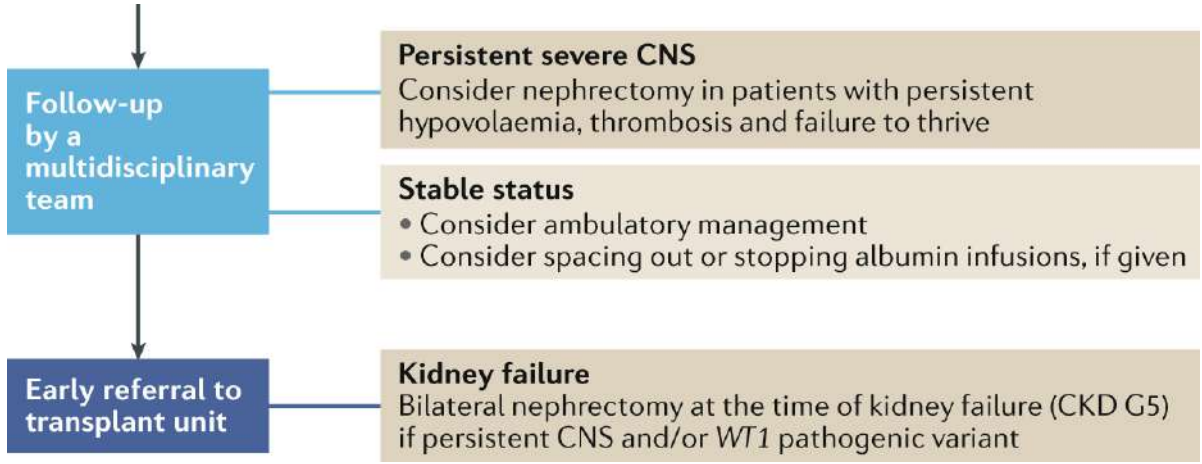
Dufek, Holtta (…) Shroff. NDT 2018



- 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 2021



- **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, infection or drug toxicity

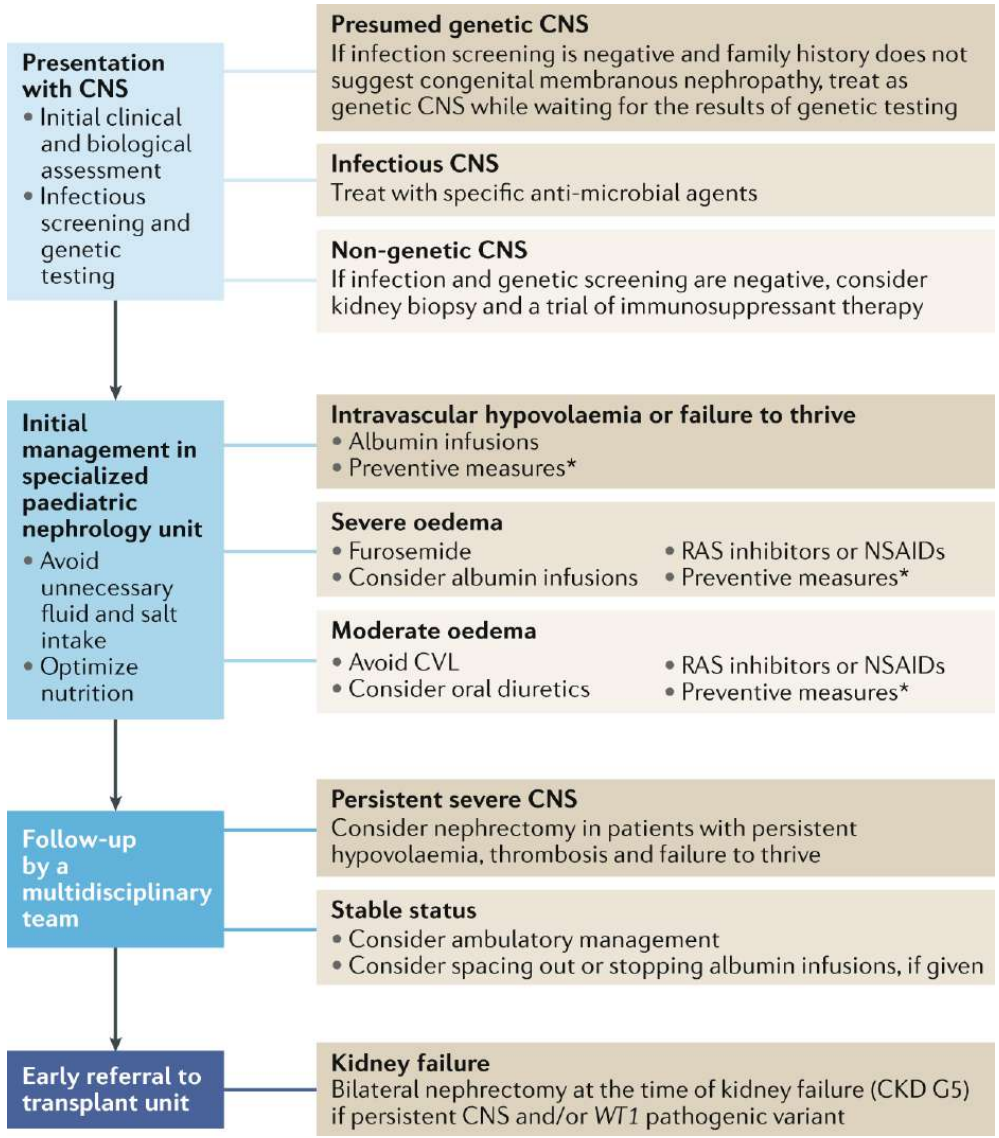
  - **Almost all *de novo* glomerulopathy in children with Fin-major *NPHS1* variants**: occurs in 25-35% of them and 70% have detectable **anti-nephrin Abs**

  → 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 2021

Acknowledgements



Core Group

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), Yincent Tse (UK), Lore Willem (ethicist, Belgium), Alexia Florimont (France, patient representative and nurse).

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