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Management of Congenital Nephrotic Syndrome: Consensus Recommendations by 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, Beata S Lipska-Ziętkiewicz[8,9], Fatih Ozaltin10, Elena Levtchenko[11], Marina Vivarelli[12].

Affiliations:
1. Department of Pediatric Nephrology, Reference center for Idiopathic Nephrotic Syndrome in Children and Adults, Imagine Institute, Paris University, Necker Hospital, APHP, 75015 Paris, France
2. Laboratory of Hereditary Kidney Diseases, Imagine Institute, INSERM U1163, Paris Descartes University, Paris, France
3. Division of Pediatric Nephrology, Center for Pediatrics and Adolescent Medicine, Heidelberg, Germany.
4. Department of Pediatric Kidney, Liver and Metabolic Diseases, Children's Hospital, Hannover, Germany, Hannover Medical School
5. Center for Congenital Kidney Diseases, Center for Rare Diseases, Hannover Medical School, Hannover, Germany
6. UCL Department of Renal Medicine and Renal Unit, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK
7. Department of Pediatric Nephrology and Transplantation, The New Children's Hospital, HUS Helsinki University Hospital, Helsinki, Finland
8. Clinical Genetics Unit, Department of Biology and Medical Genetics, Medical University of Gdańsk, Poland
9. Centre for Rare Diseases, Medical University of Gdańsk, Poland
10. Department of Pediatric Nephrology and Nephrogenetics Laboratory, Hacettepe University Faculty of Medicine, Ankara, Turkey
11. Division of Pediatric Nephrology, Department of Pediatrics, University Hospitals Leuven; Department of Development & Regeneration, University of Leuven, Belgium
12. Division of Nephrology and Dialysis, Department of Pediatric Subspecialties, Bambino Gesù Pediatric Hospital Istituto di Ricerca e Cura a Carattere Scientifico (IRCCS), Rome, Italy

Corresponding author:
Olivia Boyer
Department of Pediatric Nephrology, Reference center for Idiopathic Nephrotic Syndrome in Children and Adults, Imagine Institute, Paris University, Necker Hospital, APHP,
149 rue de Sèvres, 75015 Paris, France
+33142192648

Beata S Lipska-Ziętkiewicz : https://orcid.org/0000-0002-4169-9685
Fatih Ozaltin: https://orcid.org/0000-0003-1194-0164
Dieter Haffner https://orcid.org/0000-0002-9601-7813
Elena Levtchenko https://orcid.org/0000-0002-8352-7312

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ABSTRACT (198 words)

Congenital nephrotic syndrome (CNS) is a heterogeneous group of disorders characterized by nephrotic-range proteinuria, hypoalbuminemia and edema manifesting *in utero* or during the first three months. Rarely caused by congenital infections or allo-immune maternal disease, it is mostly due to podocyte genetic defects. CNS management is very challenging since patients are prone to severe complications such as hemodynamic compromise, infections, thromboses, impaired growth and end-stage kidney disease. In this consensus paper, experts from the European Reference Network for Kidney Diseases (ERKNet) and the European Society for Paediatric Nephrology (ESPN) summarize the current evidence and present clinical practice recommendations. Prompt genetic screening and counseling are recommended, while routine kidney biopsy is not. We provide guidance for symptomatic treatment of CNS including renin-angiotensin system inhibitors, diuretics, anticoagulation, and infection prophylaxis. Therapeutic management should be adapted to the clinical severity of the condition, aiming at maintenance of intravascular euvolemia and adequate nutrition, at prevention of complications such as infections, thrombosis, psychomotor delay and failure to thrive, and at vasculature preservation (*i.e.* protection of all central and peripheral arteries and veins). We do not recommend performing routine early nephrectomies but suggest considering them in patients with severe complications despite optimal conservative treatment, and before transplantation in patients with persisting nephrotic syndrome and/or a *WT1* dominant pathogenic variant.

INTRODUCTION

Congenital nephrotic syndrome (CNS) is a heterogeneous group of disorders characterized by nephrotic-range proteinuria and edema manifesting *in utero* or during the first three months of life [1]. CNS can be rarely caused by congenital infections or allo-immune maternal disease, but is mostly due to genetic defects [2]. Several genes have been implicated in the etiology of isolated CNS (mainly *NPHS1* encoding nephrin [3,4], *NPHS2, WT1* and *PLCE1*) or in less common syndromic forms of the disease (mostly *WT1, LAMB2*) [5,6]. Because pathogenic variants in these genes alter the physiology of podocytes, highly specialized epithelial cells and main components of the glomerular filter, genetic forms of nephrotic syndrome are now referred to as podocytopathies [2].

Patients with CNS are prone to severe complications such as hemodynamic problems, recurrent infections, thromboses and impaired growth. Most children progress to end stage kidney disease (ESKD) within a few years [1,7–11]. Before the eighties, the mean patient survival was reported to be 7.6 months (0-26), most infants dying from infection or hemodynamic collapse[9]. In 1995, an aggressive treatment including dialysis, early nephrectomies and transplantation was proposed which dramatically improved survival [1]. However, numerous reports have emerged since of successful conservative treatment using only optimized nutrition and medications, leading to a different treatment approach [12,13].

In 2018 a joint initiative of the European Reference Network for Rare Kidney Diseases (ERKNet) and the European Society for Paediatric Nephrology (ESPN) established a Work Group to develop guidelines for clinical diagnostics, management and treatment of CNS. Because evidence is frequently missing or inadequate in CNS management, this article is a consensus paper based on expert opinion rather than a clinical practice guideline. The genetic aspects of the hereditary forms of CNS are discussed further in a separate open access article[14].

METHODOLOGY

We have followed the RIGHT (Reporting Items for practice Guidelines in HealThcare) statement for Practice Guidelines [15]. Three groups were assembled: a core leadership group, an external expert group, and a voting panel. The core group comprised 9 members of the European Reference Network for Rare Kidney Diseases (ERKNet) and the European Society for Paediatric Nephrology (ESPN) including pediatric nephrologists, and renal geneticists, as well as a neonatologist, a renal nurse and a patient representative. The individual expertise and responsibilities of the core group members are given in **Supp. Table 1**. The external expert group included 6 pediatric nephrologists, an adult nephrologist, a renal geneticist, a renal pathologist, a pediatric pharmacologist, a neonatologist, a pediatric endocrinologist, an ethicist, a nurse and a patient representative. Experts were asked by e-questionnaire to provide a level of agreement on a 5-point scale (strongly disagree, disagree, neither agree/disagree, agree, strongly agree) (Delphi method). Recommendations that did not reach a consensus level of at least 70% were modified after discussion within a voting panel of 35 pediatric nephrologists from the ESPN nephrotic syndrome working group and reviewed again by the experts and the Core group until a consensus level of at least 70% was achieved.

Developing the PICO questions

We developed PICO (Patient or Population covered, Intervention, Comparator, Outcome) questions [16]:

- *Population covered:* children with CNS, (defined as onset of nephrotic syndrome within the first three months of life), before and after start of renal replacement therapy (dialysis, renal transplantation).

- *Intervention and comparators:* treatment compared with no treatment or other treatment.

- *Outcomes addressed:* recommendations for diagnosis, treatment and follow-up of children with CNS.

Literature search

The following key words were used to identify suitable studies until December 2018: nephrotic syndrome, congenital nephrotic syndrome, Galloway Mowat Syndrome, Pierson Syndrome, Frasier Syndrome, Denys Drash Syndrome. The search retrieved 1367 results (no randomized clinical trial) and 54 articles were referenced here. Further details and a summary of the publications used for this consensus statement are given in the Supplementary material (**Suppl. Table 2)**.

DIAGNOSTIC MANAGEMENT

Box 1 Recommendations for diagnosis

- **We recommend that all CNS patients be managed by a multidisciplinary team.**
- **We recommend performing an initial diagnostic work-up including medical history, clinical and biological evaluation of CNS complications and associated extra-renal features (Table 1).**
- **We recommend comprehensive genetic screening comprising all podocytopathy-related genes as a first-line diagnostic measure in every CNS patient.**
- **We recommend providing genetic counseling promptly in families with past history of a CNS or prenatal signs of CNS.**
- **We suggest kidney biopsy be considered only in sporadic, non-syndromic cases, in whom comprehensive genetic testing has not yielded a molecular diagnosis.**

Multidisciplinary team management

We recommend that all CNS patients be referred to specialized teams in tertiary pediatric nephrology centers and managed by a multidisciplinary team including neonatologists, pediatric nephrologists, pediatric nephrology nurses, pediatric renal dieticians, pediatric surgeons, child and/or youth psychologists, and social workers. Indeed, the psychosocial pressure often experienced by families with a child with CNS must be taken into account for the successful management of these children. All members of the multidisciplinary team must be trained in child care. For children managed outside of a transplant facility, we recommend that they be introduced to a transplant centre early, as the CKD evolves, to minimize the dialysis period required and to facilitate the transplant process.

Initial diagnostic work-up

In infants with CNS, we recommend performing the initial diagnostic work-up as presented in Table 1 and Box 1. In addition, extended diagnostic work-up aimed at identification of extra-renal manifestations of the hereditary forms of CNS should be considered. The list of possible signs and symptoms of syndromic forms of CNS is presented and discussed further in a published open access article[14].

Genetic testing

Identification of a genetic cause establishes the etiology of the disease, informs the management, especially with regards to potentially associated problems, such as Wilms tumor or neurological involvement and enables genetic counseling of the family. Further detailed phenotype-genotype considerations are presented in a separate document[14].

We recommend genetic screening as a first-line diagnostic measure in every CNS patient. The preferred method of genetic testing is massive-parallel sequencing, with rapid whole exome sequencing (WES) being the method of choice. In countries where rapid WES is not yet clinically available, the usage of an extended podocytopathy gene panel is recommended due to the wide range of phenotypic variability and genetic heterogeneity of the disease [4,5,17–20]. The minimum set of genes to be tested should include *NPHS1, NPHS2, WT1, PLCE1* and *LAMB2.* In CNS, screening of *NPHS1, NPHS2, WT1* and *LAMB2* will uncover underlying genetic abnormalities in >80% of the patients [4,5,17–19,21,22]. A dozen of other, less commonly mutated, genes account for an additional ~5% of diagnoses. Clinical presentation suggestive of a particular syndromic form of CNS or ethnicity associated with a founder pathogenic variant may lead to direct testing of the associated causative gene.

In families with past history of CNS, recurrence risk counseling by a clinical geneticist/clinical counselor should be promptly provided. The decision regarding prenatal diagnosis including pre-implantation diagnostics should be discussed in light of the local financial, social and legal setting[23].

The gene-specific management of CNS is detailed elsewhere[14]. Notably, children with exonic *WT1* pathogenic variant must be monitored for Wilms tumor by performing abdominal ultrasound every 3 months till the age of 7[24].

Histopathology

Given the fact that in patients with CNS, genetic screening will uncover underlying genetic abnormalities in >85% of cases (see above), noninvasive molecular diagnostic methods have largely replaced kidney biopsy in these patients[4,5,17–19,21,22]. We do not recommend routine kidney biopsy in patients with CNS. Kidney biopsy may be indicated in cases where a genetic diagnosis could not be established, or in cases with compromised kidney function where it can be informative in establishing rare diagnoses (i.e. congenital membranous nephropathy due to anti-NEP antibodies, other glomerulopathies) and in estimating the prognosis.

The following findings would suggest an underlying mitochondrial disease: nystagmus, retinitis pigmentosa, visual impairment or loss, sensorineural deafness, developmental delay, cognitive impairment, hypotonia, seizure, encephalopathy, cardiomyopathy, feeding difficulties, live failure, progressive muscle weakness, diabetes mellitus, lactic acidemia, increased serum creatinine kinase, anemia, pancytopenia, and in these patients, we suggest to initiate a therapeutic trial of coenzyme Q10 even before the results of genetic testing, and to discontinue it if no improvement is observed after 4 to 6 weeks[14].

THERAPEUTIC MANAGEMENT

Box 2 Recommendations for fluid and albumin administration

- We recommend rapid referral of children with CNS to a specialized pediatric nephrology unit, due to the complexity of disease and fluid management.

- We recommend avoiding intravenous fluids and saline, while oral fluid intake should be concentrated if necessary to avoid marked edema.

- We recommend using albumin infusions based upon 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.

- 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 as long as the line is in place (see below).

The experts recognize and emphasize that CNS encompasses a wide spectrum of clinical phenotypes that should be managed with different approaches in specialized units. Indeed, some newborns/infants present with no or minimal symptoms and should be spared aggressive and potentially dangerous treatments whereas others are critically ill with massive proteinuria, anasarca and hemodynamic compromise and may require daily albumin infusions via a central venous line (CVL) and intensive symptomatic treatments to avoid complications. Therefore, management should be adapted to the clinical severity of the condition, aiming at the maintenance of intravascular euvolemia, adequate nutrition and at the prevention of complications (Box 2). As is typical for such a rare disease, there is considerable variability in clinical practice with some centres aiming to avoid intensive treatment. The expert group recognizes that there are no conclusive clinical data, such as randomized clinical trials, that allow the definition of a treatment algorithm. Treatment decisions should be made in conjunction with the family of the affected child and will be influenced by individual centre experience, as well as by the wishes of the family. Especially in developing countries, intensive treatment may not be feasible due to financial constraints.

General approach

We recommend rapid referral of children with CNS to a specialized pediatric nephrology unit (Box 2).

Children with CNS are often born prematurely and amniotic fluid may be meconium stained but ventilator therapy is rarely needed. Pregnancy is usually uneventful.

The clinical findings in a small infant with undiagnosed CNS may vary from a stable condition with only moderate edema to severe hemodynamic compromise necessitating intensive support. Individualized therapy is thus needed, serving the following key objectives:

- Preserve all central and peripheral arteries and veins from damage for potential dialysis access: avoid peripherally inserted catheters and unnecessary venipunctures[25]

- Optimize fluid, protein and caloric intake

- Minimize administration of salt-containing fluids

- Prevent thrombosis, particularly in patients with CVL or hypovolemia

- Treat infection when clinically suspected by starting empiric antibiotic before the results of cultures. C-reactive protein and leukocyte levels cannot be considered reliable indicators of septicemia in CNS patients.

Fluid Management

There are no studies investigating specific treatments for edema in CNS. Recommendations that have been made for the treatment of edema in NS in general apply also to CNS. These focus around the assessment of volume status (over- versus underfill, reviewed in [26]), and salt restriction. Fluid restriction is advocated for hyponatremia and in the most severe cases of edema.

Fluid prescription should primarily account for the need to provide adequate nutrition. Fluid intake should be restricted only as much as feasible by using concentrated high-calorie formulas to meet age-related energy needs, guided by expert renal dietician advice.

For acute symptomatic hypovolemia, intravenous albumin is the treatment of choice (see below).

Albumin infusions

The use of albumin infusions in CNS children varies between centers. While some administer intravenous albumin infusions only when deemed clinically indicated, others use regular albumin infusion protocols (1-4 g/kg/day). Proposed advantages of regular albumin infusions are 1) replacement of lost protein to support growth and psychomotor development, 2) stabilization of intravascular volume, and 3) minimization of edema [1]. Arguments proposed against the regular use are 1) need for central line with risk of infection and/or thrombosis of large vessels endangering future hemodialysis access, 2) need for prolonged hospitalization (although home administration has been reported [27], and 3) cost. Recent retrospective studies show no apparent difference in long-term outcome with these two strategies [12,13]. Most of the infused albumin is lost in the urine within hours. Therefore, the purpose of albumin infusion is not the normalization of serum albumin levels but the support of intravascular volume and the reduction of extra-vascular fluid retention in patients with

symptomatic hypovolemia. The latter can be suggested in the presence of prolonged capillary refill time, tachycardia, hypotension, oliguria, and abdominal discomfort. In addition, quality of life and school attendance should be taken into account.

The experts acknowledge that some children with no or minimal symptoms do well without regular albumin infusion and do not need any CVL. Others may need frequent albumin infusions to prevent clinical consequences of hypovolemia and failure to thrive. In the latter, we recommend basing the frequency and dosage of albumin infusion on clinical indicators (see above) rather than on serum albumin levels. In the most severe cases, daily infusions of up to 1-4 g/kg may be initiated. In stable patients or when CKD progresses, albumin dosage may be reduced and infusions may then be spaced out and even stopped [12,13].

Vascular access

When possible, we recommend avoiding central venous lines in children with CNS due to the high risk of thrombosis. However, when regular albumin infusions are inevitable, a CVL becomes necessary. If a central venous access is unavoidable, we recommend administering prophylactic anticoagulation as long as the line is in place (see below). We also recommend avoiding peripherally inserted catheters and unnecessary venipunctures to preserve arteries and veins from damage for the potential creation of arteriovenous fistula[25].

Box 3 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 albumin 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, high blood pressure in combination with edema) and preserved renal function.**

- **We recommend using furosemide at 0.5 to 2 mg/kg per dose intravenously or orally up to 6 times daily (maximum 10 mg/kg per day) dependent on the degree of edema and achieved diuresis unless the patient has evidence of intravascular hypovolemia. We recommend NOT giving dosages above 6 mg/kg per day for periods longer than one week. We recommend administering infusions slowly to minimize ototoxicity.**

- **If a potassium-sparing diuretic is preferred, we recommend epithelial sodium channel (ENaC) inhibitors such as amiloride over mineralocorticoid inhibitors (spironolactone).**

Diuretics

Diuretics should be used with caution (only in case of intravascular fluid overload as evidenced by good peripheral perfusion and high blood pressure) since they could induce/increase hypovolemia and promote thrombosis (Box 3).

Diuretics improve edema/fluid control and allow adequate nutrition in most children with CNS, especially when given in conjunction with albumin infusions [10]. We recommend considering an intravenous bolus of furosemide (0.5-2 mg/kg) at the end of each albumin infusion [10,28] in the absence of marked hypovolemia and/or hyponatremia.

In patients with severe edema, we recommend to commence furosemide at dosages of **0.5 to 2 mg/kg per dose intravenously or orally up to 6 times daily (maximum 10 mg/kg per day)** , based on the degree of edema and achieved diuresis. Adequate monitoring, *i.e.* assessment of fluid status, electrolytes (hypokalemia, hyponatremia), blood pressure and renal function (diuresis and eGFR) is required. High doses of furosemide (>6 mg/kg/day) should NOT be given for periods longer than 1 week, and infusions should be administered over 5-30 minutes in order to avoid hearing loss [29–31]. Furosemide must be stopped in case of anuria.

In stable patients, furosemide may be given orally at doses of 2-5 mg/kg/day in combination with a thiazide and/or potassium-sparing diuretic such as amiloride or spironolactone with appropriate monitoring. Experimental evidence suggests that proteases in the urine such as plasmin [32] directly activate the epithelial sodium channel (ENaC) and thus contribute to salt retention and edema formation [26,32,33]. Since this direct activation of ENaC is independent of the mineralocorticoid receptor (MCR), it will not be affected by MCR blockers, such as spironolactone. Therefore, if potassium-sparing diuretics are used, blockers of ENaC, such as amiloride, are preferable.

Box 4 Recommendations for antiproteinuric therapy

- **We recommend administering RAAS-blocking therapy such as ACEi or ARBs in children with CNS aged > 4 weeks.**
- **ACE inhibition should be started 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 .**
- **We do not recommend combining ACEi and ARBs, due to the potentially increased risk of AKI**

- **In case of poor responsiveness to RAAS blockade we suggest considering the use of prostaglandin inhibitors (indomethacin dosed incrementally from 0.5 to 3 mg/kg per day) as add-on treatment.**
- **We recommend stopping prostaglandin inhibitors if there is no apparent clinical benefit (increase in serum albumin and/or reduction in edema) after 2 to 4 weeks.**
- **In case of extra-renal volume losses such as vomiting and diarrhea, routine treatment with RAASi, prostaglandin inhibitors and diuretics must be discontinued due to the high risk of intravascular volume depletion and AKI.**

Anti-proteinuric agents

RAAS antagonists (Angiotensin-Converting Enzyme inhibitors (ACEi) or angiotensin type I receptor blockers (ARBs)) lower glomerular protein loss by a dose-dependent hemodynamic effect, *i.e.* preferential dilatation of the efferent arteriole [34]. In adults and older children with proteinuric nephropathies, 30-50% proteinuria reduction can typically be achieved with these drug classes [35].

In CNS the clinical effect of RAAS inhibition is usually moderate. In a recent retrospective study in children with CNS, serum albumin levels increased moderately (by median 6 g/L) and albumin infusion frequency was reduced in some, albeit not all, CNS children treated with RAAS inhibitors [12].

When possible, RAAS inhibition should be avoided before 4 weeks of age post-term to circumvent interference with physiological RAAS functions in early postnatal tissue growth [36] and/or long-lasting hypotension and oliguric acute renal failure [37] (Box 4). The short-lasting ACEi Captopril is preferred in young infants due to its short half-life.

RAAS inhibition should be started at a very low dose and gradually escalated under frequent monitoring of proteinuria, urine output, serum creatinine and potassium to the maximally effective and tolerated dose. The recommended captopril-dosing scheme for infants younger than three months is 0.01-0.5 mg/kg/dose with a maximum daily dosage of 2 mg/kg. Older infants should receive 0.15–3 mg/kg per dose, with a maximum dosage of 6 mg/kg per day. If a therapeutic effect is observed, children in stable condition may be switched to long-acting ACEi (e.g. ramipril 0.1-0.2 mg/kg o.d.) or ARB (e.g. candesartan 0.2-0.4 mg/kg o.d.).

There is no evidence to suggest that combined ACE inhibition and AT1 receptor blockade might provide more effective proteinuria reduction than maximized ACEi or ARB

monotherapy in children with CNS. We do not recommend this combination due to increased risk of hypotension and AKI [38,39].

Prostaglandin inhibitors (also called Cyclooxygenase inhibitors or COXi) can lower proteinuria by affecting renal perfusion and reducing intraglomerular pressure via suppressing renin production in the juxtaglomerular apparatus [40]. The efficacy of prostaglandin inhibitors in children with CNS is unclear due to their common co-administration with other interventions, *i.e.* ACEi/ARBs and/or unilateral nephrectomy. Combined treatment with ACEi and indomethacin resulted in increased serum protein levels and sufficient growth and development in 4 out of 5 children with CNS [41]. In a recent retrospective study, serum albumin increased similarly in 7 children with co-administration of ACEi and indomethacin as in 35 children with ACEi monotherapy [12].

To avoid adverse effects such as oliguric renal failure and erosive gastritis, non-selective COXi, such as indomethacin, should be started after the end of the neonatal period (>4 weeks of age) and dosed incrementally from 0.5 mg/kg/day to a maximum of 3 mg/kg/day. COXi should be stopped in case of advanced CKD (stage 4-5). Co-treatment with H2 blockers and/or proton pump inhibitors is recommended. Alternatively, selective COX2 inhibitors such as celecoxib can be considered to minimize gastrointestinal side effects.

Treatment with diuretics, RAASi, NSAIDs should be stopped in case of hypovolemia since they increase the risk for AKI and thrombosis [42]. Parents must be informed about this procedure.

Box 5 Recommendations for nephrectomies

- **We do NOT recommend performing routine early nephrectomies.**
- **We suggest considering unilateral or bilateral nephrectomy in patients with severe complications including failure to thrive, thrombosis and/or difficulties to maintain intravascular euvolemia despite optimization of conservative treatment.**
- **We recommend performing bilateral nephrectomies in patients with persisting nephrotic syndrome and/or *WT1* dominant pathogenic variant before renal transplantation**

Nephrectomies

In a commonly used treatment protocol, bilateral nephrectomy is performed and dialysis initiated when the infant weights around 7-9 kg (6-12 months of age) followed by renal transplantation a few months later (upon attainment of 10 kg body weight). The mortality of

these infants on dialysis is low (6-11 %)[43,44] and the risk of thrombotic events and septic infections is reduced after nephrectomy. However, many clinicians provide conservative therapy without nephrectomies. Recent retrospective studies show no apparent difference in outcome between these different treatment approaches [12,13]. Therefore, an individualized, stepwise approach with prolonged conservative management is an appropriate alternative to early bilateral nephrectomies and dialysis in many children with CNS.

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

Ambulatory management

We recommend ambulatory management whenever possible, to increase quality of life and decrease nosocomial infections and treatment costs. Acknowledging that patients with CNS are at risk of sudden deterioration, especially with acute infections, a recent retrospective study demonstrated no apparent difference in in complications and long-term outcome for patients treated as in- or out-patients [13]. If albumin is given regularly, home administration by the parents has been shown to be feasible and safe [27].

Box 6 Recommendations for management of non-genetic CNS

- **We do NOT recommend using immunosuppressive drugs to treat children with CNS.**

- **If comprehensive genetic testing, kidney biopsy and screening for secondary forms of CNS yield negative results, a trial of immunosuppressive therapy may be considered in selected cases**

- **We suggest considering antibody-removing treatment strategies in the presence of persistent severe congenital membranous nephropathy due to anti-NEP antibodies.**

- **We recommend treating infection-related CNS with specific anti-microbial agents and also performing genetic screening in these patients.**

Treatment of non-genetic CNS

Based on the fact that CNS is most frequently caused by genetic abnormalities that are not susceptible to immunosuppressive agents, we do not recommend using immunosuppressive drugs to treat children with CNS. Anecdotal reports suggested improvement of proteinuria upon therapy with steroids and/or cyclosporine A. However, these patients were usually co-treated with ACEi [45–47]. Even spontaneous remission has been reported in some cases [48]. Negative genetic testing and infection screening results, and kidney biopsy should be obtained before considering immunosuppression [46,49]. If comprehensive genetic testing and screening for secondary forms of CNS yield negative results, a trial of immunosuppressive therapy may be considered in selected cases.

A small number of infants presenting with a clinical picture of CNS may have congenital membranous nephropathy due to a maternal variant in a gene encoding for a podocyte protein named neutral endopeptidase (NEP). During pregnancy, the mother becomes sensitized by the fetal NEP and produces anti-NEP antibodies that can damage the offspring's podocytes leading to nephrotic proteinuria [50,51]. The IgG anti-NEP titres become more elevated in subsequent pregnancies, determining a clinical picture ranging from no symptoms in the first child or a miscarriage, to non-nephrotic transient proteinuria, or severe CNS with renal failure in subsequent children. Albuminuria may persist and significant renal failure can develop over time [50]. As the causes of this disease are the anti-NEP antibodies of maternal origin that progressively decrease, proteinuria is transient. In severe cases however, an exchange transfusion can eliminate the pathogenic antibodies and prevent further renal damage. The mothers of these children should plan subsequent pregnancies at the lowest possible level of anti-NEP antibodies to prevent fetal podocyte damage [52]. This can be achieved with plasmapheresis and IVIGs. Anti- NEP antibodies [51,52] should be tested in the following CNS settings: 1) renal failure at presentation; 2) OR transient proteinuria at birth that spontaneously resolves within a few weeks; 3) OR CNS and positive family history for siblings with congenital MN or with transient proteinuria at birth; 4) OR membranous nephropathy on renal biopsy. In all cases the mother should be tested as well. Samples can be sent to Prof. Pierre Ronco and Dr. Hanna Debiec (Inserm U1155, Hôpital Tenon, Paris, France) after sending a brief clinical synopsis to verify the indication.

We recommend treating infection-related CNS with specific anti-microbial agents and also performing genetic screening in these patients.

- **Congenital Syphilis** has re-emerged in developing countries after years of declining incidence [53]. Renal involvement in untreated newborns and infants can vary from mild proteinuria to nephrotic syndrome, hematuria or acute renal failure, and might be the only presentation of the disease [54]. However, extra-renal features (anemia, jaundice, hepatosplenomegaly, cutaneous lesions, neurological symptoms) are more frequent symptoms of the disease. The diagnosis is based on the detection of antibodies against *Treponema Pallidum* and T. pallidum hemagglutination assay (TPHA). Treatment consists of penicillin G (50,000 U/kg IV q 12 hours ($\leq$ 1 week of age), q8 hours (> 1 week), q6 hours (> 1 month), or benzathine penicillin G 50,000 U/kg, IM, q24 hours, x10-15 days [53].

- **Congenital cytomegalovirus (CMV) infection.** While over 90% of congenital CMV infections are asymptomatic, CNS has been reported among other more common disease presentations (convulsion, paraplegia, sensory type of deafness, absence of light reflexes, pulmonary and cutaneous lesions). The diagnosis is based on a positive PCR reaction showing the presence of viral DNA in urine and/or saliva. Treatment consists of ganciclovir 6 mg/kg, q 12 hours x15-21 days, followed by valganciclovir 15 mg/kg, q 12 hours x6 weeks. Of note, plasma concentration show large variation in newborns and the standard dose frequently fails to achieve the recommended target ganciclovir AUC_{0-24} of 40-50 μg*h/ml [55].

- Other rare infection-associated CNS were described in patients with congenital toxoplasmosis, hepatitis B and rubella [56]. HIV frequently causes nephropathy with proteinuria or nephrotic syndrome in children and adults, however, no patient with HIV-related CNS has been described so far.

- Patients with presumed infection-associated CNS may have an associated pathogenic gene variant and should be tested for the underlying genetic causes [57].

Box 7 Recommendations for monitoring and preventive measures

Thrombosis Prophylaxis

- **We suggest that preventive anticoagulation be considered during states of increased thrombosis risk in patients with CNS (acute illness, risk of dehydration, inserted central lines, thrombocytosis > 750.000/ml).**

Infection Prophylaxis and management

- **We suggest not to administer antibiotic prophylaxis routinely in children with CNS but to start prompt antibiotic treatment in case of a suspected bacterial infection.**

- **We suggest that immunoglobulin infusions should be considered in case of low serum IgG levels and/or recurrent and/or severe infections.**

- **We recommend to follow the vaccination schedule recommended for healthy children including vaccinating against encapsulated bacteria and VZV, and administering the influenza vaccine annually.**

- **In case of exposure to chickenpox in non-VZV-immunized children, we recommend prophylactic treatment with oral acyclovir for 5-7 days when started 7-10 days after exposure to chickenpox and to consider specific VZV IVIGs.**

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

Nutrition, growth and metabolism

- **We recommend provision of a diet with high energy (130 kcal/kg/d) and protein (4g/kg/d) but low salt content (<1-3g/day depending on the patient age).**

- **We recommend initiating growth hormone treatment in case of persistent stature growth failure despite adequate nutrition.**

- **We recommend substituting levothyroxine (T4) in case of hypothyroidism.**

- **We recommend close monitoring of ionized calcium, 25-OH-D3 and PTH in children with CNS, and supplementing oral D3-vitamin (cholecalciferol) or 25-OH-D3-vitamin (decalcifediol) and calcium (250-500 mg/day) in case of low 25-OH-D3 and/or low ionized calcium and/or elevated PTH.**

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

Anemia prevention and management

- **We recommend monitoring and treating iron deficiency, and administering erythropoietin in case of 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 .**

MONITORING AND PREVENTIVE MEASURES

We recommend to regularly monitor and prevent complications of CNS including acute complications (hypovolemic and hypervolemic crisis, intermittent hypertensive and thromboembolic events, bacterial and viral infections) and/or development of chronic consequences of the disease including hypertension, dyslipidemia, hypothyroidism, hypomagnesemia, hypocalcemia, vitamin D deficiency, bone disease, growth failure, progressive CKD and side effects of medications, as well as complications of prematurity (hyperbilirubinemia etc.) **(Table 1).**

Thrombosis prophylaxis

Patients with CNS are at risk of developing venous or arterial thromboembolic complications (including renal, cerebral, pulmonary vessels) that may be life threatening [58]. In CNS, the

thrombotic risk is multifactorial and includes a disease-related hypercoagulability, underlying thrombophilic predisposition and treatment-related risks. An inserted central venous line is a strong pro-thrombotic risk factor in the nephrotic state and should be avoided whenever possible. In CNS, the hypercoagulability is related to an imbalance between pro and anticoagulant factors [59–61]: urinary leakage of circulating factors (antithrombin III and plasminogen) and low molecular weight factors (IX, XI) result in compensatory synthesis by the liver of high molecular weight coagulant factors: fibrinogen, factor V, VII, VIII and X [62]. Moreover, patients with CNS are deficient for pituitary adenylate cyclase-activating polypeptide (PACAP) due to urinary losses of PACAP bound to ceruloplasmin [63]. PACAP is the major inhibitor of megakaryopoiesis and of platelet activation[63]. These findings theoretically justify the administration of platelet aggregation blockers in these patients.

We suggest that preventive anticoagulation be considered in all children with CNS and a prior thrombosis, or during states of increased thrombosis risk (acute illness, risk of dehydration, inserted central lines, thrombocytosis > 750.000/ml) (Box 7). The goal of antithrombotic therapy is to prevent formation and local extension of thrombosis, embolism, recurrence, and long-term complications. There is no randomized controlled trial demonstrating the safety and efficacy of pharmacologic thromboprophylaxis. Preventive anticoagulation appears to be efficacious in preventing cerebral thromboses in children with CNS [1], though in a recent retrospective outcome study the incidence of thrombotic events was unchanged by anti-thrombotic prophylaxis[12]. Agents that have been used include heparin, vitamin K antagonist, and aspirin [60,61]. Infusion of antithrombin III (ATIII; 50 units/kg) before the placement of a central venous catheter is recommended[10]. Due to reduced ATIII levels, anticoagulation with low molecular weight heparins may be ineffective. Long-term warfarin prophylaxis (target INR 2-2.5) has been used for CNS patients with central venous lines. No significant increase in the risk of bleeding has been reported[10]. Aspirin may induce acute kidney injury. Several novel anticoagulants have recently been approved for use in adults, and are now undergoing pediatric trials [58,64]. Where needed, magnesium and calcium supplements should be given to avoid very low levels that may promote thromboses [65].

Infection prophylaxis and management

Antibiotics

Infections are a major concern in children with CNS, and the primary cause of death in children with CNS [1,10,12,13]. Because of urinary losses of IgG and complement opsonins, children with CNS are prone to infections caused by encapsulated bacteria such as pneumococci. However, prophylactic antibiotics are not routinely indicated since several studies have not shown a significant reduction in the rate of sepsis [1,11,13,66]. Appropriate therapeutic antibiotics should be started promptly in patients with proven or suspected acute bacterial infection[1].

Immunoglobulin infusions

Patients with CNS may have extremely low levels of circulating immunoglobulin G (IgG), due to urinary loss, and should therefore be considered, as agammaglobulinemic patients from other causes, extremely prone to developing infections. However, the use of prophylactic intravenous immunoglobulins is much debated. The arguments against systematic infusions include 1) the rapid urinary loss following infusion (up to 50% of infused IgGs are lost in 30 hours [67,68]; 2) commercial immunoglobulin preparations contain low IgG titres against bacteria mainly responsible for the septic episodes (staphylococci, streptococci, gram-negative bacteria)[1,10]; 3) the cost of immunoglobulin preparations. However, a trend to reduced infection rates was observed with the use of prophylactic immunoglobulin infusions[13].

IVIG may be useful to treat septic episodes combined with parenteral antibiotics in children with low plasma IgG levels [10]. Preventive IVIG infusions may be considered in case of low plasma total IgG levels AND/OR recurrent and/or severe infections as in other cases of secondary hypogammaglobulinemia (https://bestpractice.bmj.com/topics/en-us/1058).

Vaccination

Vaccination should follow the recommended schedule for healthy children including vaccinating against encapsulated bacteria (especially meningococcal, H. Influenza and pneumococcal) and VZV [69,70], and administering the influenza vaccine annually. There is some evidence that oral acyclovir may reduce the risk of chickenpox when given within 7-10 days of exposure for a duration of 7 days [71]. In case of exposure to chickenpox in non-VZV-immunized children, we recommend prophylactic treatment with oral acyclovir for 5-7 days within 7-10 days after exposure to chickenpox and to consider specific VZV IgG.

Susceptible patients, *i.e.* those with hypogammaglobulinemia and not immunized or without any history of chickenpox may be given a dose of Varicella zoster immunoglobulins (VZIG) as soon as possible, which may be effective up to 10 days post-exposure. *(Food and Drug Administration. FDA approves VariZIG for reducing chickenpox symptoms. Silver Spring, MD: Food and Drug Administration; 2012).* However VZIG is not ubiquitously available.

The diagnosis of VZV infection relies on clinical features +/- VZV PCR of a vesicle. Of note, in these patients specific antibody titers are not informative as long as nephrotic-range proteinuria persists and are unreliable in children receiving IVIG infusions. We recommend treatment of VZV infection with intravenous high-dose acyclovir for 7-10 days.

Other preventative measures

Nutrition, growth and metabolism

We recommend provision of a diet with high energy (130 kcal/kg/d) and protein (4g/kg/d) but low salt content : <1g/day in infants < 1 year of age, <2g/day in children 1-3 y of age, <3 g/day in children > 3 years of age [10]. Patients should be followed by an expert dietician. Enteral tube feeding or gastrostomy should be considered in patients with insufficient oral intake. Fluid restriction should not compromise caloric intake.

There is no evidence for pervasive growth hormone (GH) deficiency in CNS and growth failure is likely related to nutritional deficiencies and CKD. If the former have been excluded, GH (0.045-0.05 mg/kg/day s.c.) may be administered from 6 months of age onward in children whose height is < 3rd percentile and height velocity <25th percentile, and eGFR ≤ 60 ml/min*1.73m^2 [72]. Since a persistently reduced growth rate will ultimately result in short stature, GH therapy may also be considered in children with height between the 3rd and 10th percentile who have low height velocity (< 25th percentile) that persists beyond 3 months in infants and beyond 6 months in children with growth potential, provided that other potentially treatable risk factors for growth failure have been adequately addressed[72].

Hypothyroidism in CNS is due to urinary loss of thyroxine-binding proteins. Therefore, we recommend measuring free-levothyroxine (fT4) and TSH at disease onset and treat as indicated by lab testing[1].

Nephrotic children have low 25-OH-D3 levels due to urinary loss of vitamin D-binding protein. Total serum calcium levels underestimate calcium content in the presence of hypoalbuminemia. Thus, estimation of vitamin D deficiency is not accurate. We recommend close monitoring of ionized calcium, 25-OH-D3 and PTH in children with CNS, and supplementing oral D3-vitamin (cholecalciferol) or 25-OH-D3-vitamin (decalcifediol) and calcium (250-500 mg/day) in case of low 25-OH-D3 and/or low ionized calcium and/or elevated PTH. Reduced ionized-calcium levels and elevated PTH levels indicate the need for vitamin D and calcium supplementation [10]. Vitamin D supplementation has been shown to correct the vitamin deficiency in nephrotic children [73].

Some experts suggest considering statins when fasting LDL-cholesterol is persistently >160 mg/dl (4.1 mmol/l) [74,75] or earlier (>130 mg/dl (3.4 mmol/l)), in case of additional cardiovascular risk factors [76].

Anemia prevention and management

Successful correction of anemia in nephrotic syndrome depends on the underlying causes that may be one of a combination of the following: urinary losses of erythropoietin, iron, transcobalamin and transferrin (transferrin saturation and ferritin level are unreliable in CNS), vitamin B12 and/or copper deficiency, and/or ACEi toxicity [77]. Iron deficiency anemia should be treated with iron supplementation. A trial of erythropoietin therapy should be considered in patients with anemia after correction of iron deficiency since massive urinary losses are expected in CNS, and the efficacy and safety of recombinant human erythropoietin in the treatment of anemia in nephrotic syndrome has been described in children [77,78]. Increased doses are often required due to the urinary losses[77]. Subcutaneous administration of EPO might be superior to IV. 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 .

Box 8 Recommendations for management of end-stage kidney disease
- **We recommend managing dialysis in children with CNS following the general guidelines for renal replacement therapy in infants and children.**

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

MANAGEMENT OF END-STAGE KIDNEY DISEASE

A retrospective case note review by members of the ESPN Dialysis Working Group reported a comparable overall complication rate in infants with CNS and infants with other primary renal diseases, specifically regarding the peritonitis rate, dialysis technique survival, the growth and transplantation rates[43]. Peritoneal dialysis is the modality of choice since it preserves central venous access; however, hemodialysis is an alternative with comparable outcomes in children with CNS. In patients with autosomal recessive disease, parental kidney donation is usually accepted. See [14] for further details.

Mild proteinuria after renal transplantation is not rare and can be related to several conditions including rejection, recurrence of primary glomerulopathy, de novo glomerulopathy, infection or drug toxicity[79]. Recurrence of nephrotic-range proteinuria has also been described in CNS patients after renal transplantation. Almost all of them have a homozygous *NPHS1* Fin-major (p.Leu41Aspfs) variant that leads to an early stop codon and total absence of nephrin in the native kidney. In this group, post-transplant de novo glomerulopathy occurs in 25-35% of the patients and at least 70% of them have detectable anti-nephrin antibodies caused by allo-immunization against the nephrin molecule in the kidney graft. Recurrence can appear at any time after transplantation, renal function is initially normal despite heavy proteinuria, and kidney biopsy reveals only mild histological changes with negative immunofluorescence [79–82]. Recurrence of nephrotic-range proteinuria in children of other genetic backgrounds is very rare and only one patient with anti-nephrin antibodies has been reported outside Finland; this patient carried a homozygous *NPHS*1 truncating variant (p.Glu189Ter*)* [83]. Successful treatment outcomes have been reported after treatment with daily plasma exchanges, methylprednisolone pulses, and oral cyclophosphamide or rituximab [80,83].

Early or late recurrence of nephrotic range proteinuria has also been reported in few patients (1-2%) with homozygous or compound heterozygous pathogenic variants in the podocin gene (*NPHS2*, especially p.Arg138Ter and p.Arg138Gln variants)[84]. The pathophysiology of the

post-transplant de novo glomerulopathy in patients with *NPHS2* pathogenic variants is unclear (antibodies not identified) and it might be multifactorial [85].

PRIMARY OUTCOME MEASURES

We recommend to aim for and monitor the following primary outcome measures:

- Normal growth, nutritional status, normal cognitive and motor development
- Preservation of vascular access (patent central veins and peripheral vessels for fistulae).
- Absence of thrombotic complications
- Absence of severe infections
- Absence of edema
- Normal blood pressure
- Euthyroidism
- Absence of anemia
- Minimized hospitalizations
- Good quality of life (absence of pain, ability to perform normal age-appropriate daily activities)

Patients with CNS are prone to develop severe complications including growth failure, cognitive delay, thromboses, hypothyroidism, infections, hypertension, and anemia, which may require frequent hospitalizations and considerably impair their quality of life. Therefore, we recommend regularly monitoring these complications and use them as outcome parameters.

ETHICAL CONSIDERATIONS

We recommend considering the following ethical issues when taking care of a child with CNS:

Decisions about intensive versus palliative treatments in neonates with severe and life-threatening disease should be made by a team of professionals in a family-centered shared decision-making framework leaded by the primary responsible physician [86,87]. In

patients with severe comorbidities and/or under circumstances with limited medical resources the decision to withhold treatment can be taken by the medical team after discussing with the families.

Specific literature on offering genetic testing to siblings of children with autosomal dominant disease (phenotypic heterogeneity in disease expression) in CNS is lacking. In general, genetic counseling of the family should precede genetic testing [88]. The testing for the known pathogenic variant found causative in the index patient in his/her asymptomatic siblings should be considered only in WT1-associated glomerulopathy as this is the only autosomal dominant disorder with variable expressivity and non-full penetrance that might manifest as CNS [89].

CONCLUSIONS AND PERSPECTIVES

In these recommendations, we provide guidance to multidisciplinary teams for the initial diagnostic work-up and monitoring of complications. We recommend prompt genetic screening and genetic counseling in all children with CNS. Routine kidney biopsy is not recommended but may be considered in sporadic, non-syndromic cases in whom comprehensive genetic testing has not yielded a molecular diagnosis. Therapeutic management should be adapted to the clinical severity of the condition, aiming at the maintenance of intravascular euvolemia, adequate nutrition and the prevention of complications such as infections, thrombosis, psychomotor delay and failure to thrive, and vasculature preservation. We recommend basing the use of albumin infusions upon clinical indicators of hypovolemia or upon failure to thrive, rather than on serum albumin levels. When possible, we recommend avoiding central venous lines due to the high risk of thrombosis. We provide guidance for symptomatic treatment of CNS including ACEi or ARBs, diuretics that should be used with caution, anticoagulation to be considered during states of increased thrombosis, vaccination, and IVIG infusions in selected cases. We do not recommend performing routine early nephrectomies but suggest considering them in patients with severe complications despite optimization of conservative treatment, and before transplantation in patients with persisting nephrotic syndrome and/or *WT1* dominant pathogenic variants. Various topics for future research are outlined in Box 9.

Box 9 Future research topics

- **Develop a comprehensive registry for children with CNS to evaluate the variations in treatment and natural history of the disease, including rare complications**
- **Evaluate the impact of CNS on schooling, social life and professional activity**
- **Evaluate the phenotype/genotype correlations**
- **Define the optimal indications, dose and frequency of albumin infusions to use once patients have achieved a stable disease state**
- **Evaluate the risk versus benefit ratio of symptomatic treatments such as anticoagulation, immunoglobulin infusion, vaccines …**

recommendations and evidence text and grading of recommendations and reviewed and/or edited the manuscript before submission.

Competing interest

The material is original research, has not been previously published and has not been submitted for publication elsewhere while under consideration. The authors declare there are no competing financial interests in relation to the work described.

Table 1: Initial work-up and follow-up for a child with CNS

	Initial work-up	Frequency during follow-up
FAMILY HISTORY		
Consanguinity, ethnicity, family history of CNS, early infantile deaths, unsolved neurological and renal disease of infancy.	✔	Ask for new/emerging family history details whenever eligible
PRE/PERINATAL HISTORY		
Enlarged prenatal nuchal translucency, increased amniotic fluid AFP, fetal edema, oligohydramnios and placental weight >25% of newborn weight	✔	
CLINICAL		
Evaluation of dysmorphic features and skeletal abnormalities, genital examination, ophthalmological examination, hearing test	✔	At presentation
Growth chart: height/length, weight, head circumference < 2 yrs.; calculation of BMI and annual height velocity	✔	Monthly in infants, every three months thereafter
Blood pressure (BP)	✔	At every visit
Patient history (fever episodes, pain, abdominal discomfort, swelling, fatigue, school attendance, adherence to medication)	✔	At every visit
Physical examination (including signs of edema (e.g. ascites, pericardial & pleural effusions), tetany, drug toxicity, skeletal status, and extrarenal features e.g. dysmorphic signs or ambiguous genitalia)	✔	At every visit
Full neurological examination & standardized assessment of cognitive status	✔	Every three months in infants, yearly thereafter or as appropriate
BIOCHEMISTRY		
Blood: CBC, sodium, chloride, albumin, ionized calcium, phosphate, magnesium, creatinine, urea, protein, albumin, cholesterol, fasting triglycerides & glucose	✔	Monthly in infants, thereafter every three months or as appropriate
Estimated GFR (Schwartz formula)	✔	Every three months (more frequently in CKD stage 4)
ALP, PTH	✔	Every three months, more frequently in advanced CKD (stage 4-5)
25(OH) vitamin D_3	✔	Every six months, yearly after age 12 months
TSH, free T4	✔	Monthly in infants, thereafter every three months or as appropriate
IgG	✔	Yearly or as appropriate
Vaccination status including blood titer tests		As appropriate
Serology for: syphilis, toxoplasmosis, CMV, rubella, measles, HBV, HCV, HSV1 and 2, HZV, HIV, Bordetella pertussis. In cases where this has not already been performed by screening in the mother or infant.	✔	
GENETIC TESTS	✔	Refer to Lipska-Ziętkiewicz et al.[14] for details

GENETIC COUNSELLING	✔	As appropriate
In selected patients (if clinical suspicion, endemic areas)**:** Malaria Anti-nuclear antibodies Serum complement (C3 and C4) Anti-neutral endopeptidase (NEP) antibodies Amino-acids : glutaric aciduria type I, sialic acid storage disease Mercury levels	✔	
DIETARY ASSESSMENT & Advice by a dietician including salt, K, caloric & protein intake	✔	Monthly in infants, thereafter every three months
IMAGING		
Ultrasound of abdomen & pleural space (renal echogenicity & size, ascites, effusions, thrombosis)	✔	Every 3 months till the age of 7 years in children with exonic *WT1* variant
Cardiac ultrasound (effusions, left ventricular mass)	✔	As appropriate
X-ray of the left knee: mineralization? & left wrist for bone age assessment in children aged >5 yrs.	✔	Yearly or as appropriate
ASSESSMENT FOR EXTRARENAL INVOLVEMENT (depending on the underlying disease, e.g. brain MRI)	✔	As appropriate
ASSESSMENT FOR POTENTIAL DRUG SIDE EFFECTS eg. Hearing loss (furosemide)	✔	As appropriate
RENAL HISTOLOGY (including LM, IF/IHC and EM)	✔ (not needed if causative pathogenic variant is known)	
PREPARATION FOR RENAL REPLACEMENT THERAPY (referral to dialysis/transplant center; preparation for dialysis including fistula creation & transplantation)	if eGFR < 30 ml/min/1.73m^2	If eGFR < 30 ml/min/1.73m^2

CBC, complete blood cell count; ALP, alkaline phosphatase; CKD, chronic kidney disease; PTH, parathyroid hormone; LM, light microscopy; IF, immunofluorescence; IHC: immunohistochemistry; EM, electron microscopy; eGFR, estimated glomerular filtration rate; n.a., not applicable

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SUPPLEMENTAL MATERIAL

Supp Table 1: Area or expertise and responsibilities of core group members

Supp Table 2 : Evidence review