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# Perinatal Diagnosis, Management, and Follow-up of Cystic Renal Diseases
## A Clinical Practice Recommendation With Systematic Literature Reviews

Charlotte Gimpel, MB, BChir, MA; Fred E. Avni, MD, PhD; Carsten Bergmann, MD, PhD; Metin Cetiner, MD; Sandra Habbig, MD; Dieter Haffner, MD, PhD; Jens König, MD; Martin Konrad, MD, PhD; Max C. Liebau, MD; Lars Pape, MD, PhD; Georg Rellensmann, MD; Andrea Titieni, MD; Constantin von Kaisenberg, MD, PhD; Stefanie Weber, MD, PhD; Paul J. D. Winyard, BM, BCh, MA, PhD; Franz Schaefer, MD, PhD

**IMPORTANCE** Prenatal and neonatal cystic kidney diseases are a group of rare disorders manifesting as single, multiple unilateral, or bilateral cysts or with increased echogenicity of the renal cortex without macroscopic cysts. They may be accompanied by grossly enlarged kidneys, renal oligohydramnios, pulmonary hypoplasia, extrarenal abnormalities, and neonatal kidney failure. The prognosis is extremely variable from trivial to very severe or even uniformly fatal, which poses significant challenges to prenatal counseling and management.

**OBJECTIVE** To provide a clinical practice recommendation for fetal medicine specialists, obstetricians, neonatologists, pediatric nephrologists, pediatricians, and human geneticists by aggregating current evidence and consensus expert opinion on current management of cystic nephropathies before and after birth.

**METHODS** After 8 systematic literature reviews on clinically relevant questions were prepared (including 90 studies up to mid-2016), recommendations were formulated and formally graded at a consensus meeting that included experts from all relevant specialties. After further discussion, the final version was voted on by all members using the Delphi method. The recommendations were reviewed and endorsed by the working groups on inherited renal disorders of the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) and European Society for Paediatric Nephrology (ESPN); the German Society of Obstetrics and Gynecology (DGGG), German Society of Perinatal Medicine (DGPM), and German Society of Ultrasound in Medicine (DEGUM); and the alliance of patient organizations, PKD International.

**RECOMMENDATIONS** The group makes a number of recommendations on prenatal and postnatal imaging by ultrasound and magnetic resonance imaging, genetic testing, prenatal counseling, in utero therapeutic interventions, and postnatal management of prenatal and neonatal cystic kidney diseases, including provision of renal replacement therapy in neonates. In addition to detailed knowledge about possible etiologies and their prognosis, physicians need to be aware of recent improvements and remaining challenges of childhood chronic kidney disease, neonatal renal replacement therapy, and intensive pulmonary care to manage these cases and to empower parents for informed decision making.

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Supplemental content

**Author Affiliations:** Author affiliations are listed at the end of this article.

**Corresponding Author:** Charlotte Gimpel, MB, BChir, MA, Department of General Pediatrics, Adolescent Medicine and Neonatology, Center for Pediatrics at Medical Center–University of Freiburg, Faculty of Medicine, University of Freiburg, 79106 Freiburg, Germany (charlotte.gimpel@uniklinik-freiburg.de).

Cystic kidney diseases can manifest anytime from early pregnancy to adulthood and include multicystic dysplastic kidneys (MCDK), cystic dysplasia, polycystic kidney disease, and numerous syndromic conditions. The incidence of these conditions varies widely from 0.44 cases per 10 000 births for neonatal-onset polycystic kidney disease[1] to 4.1 cases per 10 000 births for MCDK.[1,2]

Some cystic renal disorders are life limiting (eg, Meckel-Gruber syndrome or bilateral MCDK), and some have a grave prognosis, especially if associated with early-onset oligohydramnios. Chronic kidney disease is a common feature but varies greatly in severity and time of onset. Initial presentation frequently occurs with enlarged or hyperechogenic kidneys, with cysts only developing later. There is some overlap of these intrinsic kidney diseases with congenital anomalies of the kidney and urinary tract (eg, cystic dysplasia). However, it is important to differentiate urinary tract obstruction as urological interventions are usually not required in cystic diseases.

Because the prognosis may be grave, prenatal detection of cystic renal diseases currently often leads to termination of pregnancy.[1] However, owing to the low incidence and heterogeneity of presentations, there are few controlled studies to guide counseling and management. In addition, major advances in the treatment of neonatal renal failure in the last decades have significantly improved survival. Therefore, the aim of this clinical practice recommendation is to aggregate current evidence and expertise as guidance for clinicians managing prenatal and neonatal cystic kidney disease.

After completion of systematic literature reviews on 8 clinically relevant questions based on 90 studies up to mid-2016, recommendations were formulated and formally graded at a consensus meeting that included experts from all relevant specialties. After further discussion, the final version was voted on by all members using the Delphi method. The recommendations were reviewed and endorsed by the working groups on inherited renal disorders of the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) and European Society for Paediatric Nephrology (ESPN); the German Society of Obstetrics and Gynecology (DGGG), German Society of Perinatal Medicine (DGPM), and German Society of Ultrasound in Medicine (DEGUM); and the patient organization PKD International.

Details of the systematic literature reviews and structured consensus procedure are given in the eMethods (eTable 1 and eTable 2) and eAppendix in the Supplement. **Table 1** lists the definitions of different levels of evidence and strength of recommendations. The following sections summarize our recommendations, which are given in italics.

### Key Points

**Question** How should prenatal and neonatal cystic kidney disease be treated according to the best available evidence?

**Findings** Eight systematic literature reviews (90 studies) revealed an extremely variable etiology and prognosis of perinatal cystic kidney disease, with ultrasound being the most useful diagnostic tool but some evidence for focused genetic diagnostics and/or complementary magnetic resonance imaging. While most prenatal therapeutic interventions lack adequate evidence, postnatal prognosis has improved with neonatal intensive care and renal replacement therapy for neonates, which is now an established therapeutic option.

**Meaning** These clinical practice guidelines delineate current evidence in managing perinatal cystic nephropathies and stress the need for multiprofessional counseling by adequately specialized obstetricians and pediatricians, as well as shared decision making in moderate to severe cases.

**Table 1. Grading of Evidence and Recommendations[a]**

| Grade | Level | Recommendation |
|---|---|---|
| **Quality of Evidence** | | |
| High | A | Further research is very unlikely to change our confidence in the estimate of effect. |
| Moderate | B | Further research is likely to have an important influence on our confidence in the estimate of effect and may change the estimate. |
| Low | C | Further research is very likely to have an important influence on our confidence in the estimate of effect and is likely to change the estimate. |
| Very low | D | Any estimate of effect is very uncertain. |
| **Strength of Recommendation** | | |
| Strong | 1 | Based on the available evidence, the intervention is very likely to have greater benefit than harm. |
| Weak/ discretionary | 2 | Based on the available evidence, the intervention will probably have greater benefit than harm, but patients may take a different view. |
| Consensus | NA | Recommendations based on clinical expertise of the guideline group owing to the lack of directly relevant studies. |

Abbreviation: NA, not applicable.

[a] Adapted from the study by Guyatt et al.[3]

## Imaging

Ultrasound is the first-line diagnostic procedure for detecting, classifying, and following up on prenatal renal cystic disease and for defining renal pathology, assessing amniotic fluid volume, and detecting associated anomalies. Because many cystic kidney diseases manifest initially as hyperechogenic kidneys without visible cysts, their differential diagnosis should be considered together. The most likely etiology and differential diagnosis of different ultrasound findings and consensus recommendations for prenatal follow-up intervals (*Recommendation 1.1*), indication for magnetic resonance imaging (MRI) (*Recommendation 1.2*), and timing of postnatal imaging (*Recommendation 1.3*) are given in **Table 2**.

In selected cases, MRI may add valuable information, especially if there is oligohydramnios, unusual location, or appearance of cysts or malformations of other organs (Table 2). However, regional availability and expertise in fetal MRI is still variable. eTable 3 in the Supplement lists a systematic literature review of fetal MRI for genitourinary tract imaging. In suspected very early-onset autosomal dominant polycystic kidney disease (ADPKD) or when dominant gene defects (eg, *HNF1B* [OMIM 189907]) mutations) are found, imaging of asymptomatic first-degree relatives can be helpful.

## Genetic Testing

Genetic defects have an important role in most pediatric cystic nephropathies. Currently, monogenic diseases can be identified in

Table 2. Different Patterns of Prenatal Renal Cystic Disease, With Likely Etiology and Recommendations for Perinatal Imaging

| | Solitary Renal Cyst | Multiple Unilateral Cysts | Bilateral Cysts and/or Hyperechogenicity Without Oligohydramnios | Bilateral Cysts and/or Hyperechogenicity With Oligohydramnios |
|---|---|---|---|---|
| Most likely diagnosis | Single cortical cyst | MCDK | Bilateral cystic dysplasia (with or without obstruction) | ARPKD, syndromes, or bilateral (cystic) dysplasia |
| Differential diagnosis | • Dilated dysplastic upper pole of a duplex kidney<br>• Segmental multicystic dysplastic kidney<br>• Extrarenal cyst (eg, adrenal gland)<br>• Cystic tumor<br>• Beginning of a polycystic kidney disease | • Cystic dysplasia (with or without obstruction)<br>• Unilateral start of polycystic kidney disease<br>• Unilateral start of other cystic disease (see the 2 columns on the right) | • *HNF1B* mutation<br>• ARPKD<br>• ADPKD<br>• Bardet-Biedl syndrome<br>• Meckel-Gruber syndrome<br>• Other genetic abnormalities and syndromes[a]<br>• Infantile nephronophthisis<br>• Tubular dysgenesis<br>• Metabolic diseases[b]<br>• Drug toxicity[c]<br>• Lower urinary tract obstruction | • Bilateral MCDK<br>• Lower urinary tract obstruction (urethral valves)<br>• ADPKD (especially with 2 hypomorphic mutations)<br>• Bardet-Biedl syndrome<br>• Meckel-Gruber syndrome<br>• Metabolic diseases[b]<br>• Other syndromes and genetic abnormalities[a] |
| Further pathologies to exclude | See the Multiple Unilateral Cysts column. By definition, there should be no other related pathology | • Malformations of the contralateral kidney<br>• Inadequate compensatory hypertrophy of the contralateral kidney<br>• Malformations of the genital tract[d]<br>• Organ screening[e,f] | Complete organ screening, especially CNS and cardiac malformations | Complete organ screening, especially CNS and cardiac malformations |
| *Recommendation 1.1 (consensus strength, evidence level D): Intervals for prenatal follow-up* | Follow-up ultrasound after 4-6 wk during pregnancy to exclude newly developed cysts. Consequently, a confirmed single cyst does not require regular follow-up | Follow-up ultrasound after 4 wk. Subsequent follow-up intervals dependent on contralateral hypertrophy and amniotic fluid volume | Repeated ultrasound scans every 4 wk until end of pregnancy unless higher frequency indicated for obstetric reasons[g] | Repeated ultrasound scans every 4 wk until end of pregnancy unless higher frequency indicated for obstetric reasons[g] |
| *Recommendation 1.2 (consensus strength, evidence level C): Need for fetal MRI* | Not needed unless cyst appears unusual regarding echopattern or size. Consider MRI if suspicion of tumor | Not needed for typical MCDK. Whenever MCDK appears unusual in size or echogenicity, MRI can add information. Also, the following features are usually easier to detect on MRI:<br>• Small cystic lesions in the contralateral kidney<br>• Accompanying malformations of the gastrointestinal tract, the ureters, or genital tract<br>• In ectopic MCDK, MRI helps to differentiate from coccygeal teratoma | MRI adds valuable information regarding CNS malformations | Recommended MRI, especially in cases of oligohydramnios there is a significant advantage for imaging fetal kidneys and CNS by MRI because ultrasound quality can be severely compromised by the lack of amniotic fluid |
| Optimal timing of prenatal MRI | The later MRI is done, the better quality will be | If needed, MRI should be performed in the third trimester | MRI has better accuracy after 28-30 wk of pregnancy but may be helpful earlier if termination of pregnancy is being considered | Fetal MRI should be performed as early as possible; however, accuracy is low before 24 wk and increases with later gestational age |
| *Recommendation 1.3 (consensus strength, evidence level C): Postnatal imaging* | Renal ultrasound should be performed within 4 wk after birth unless there is clinical concern | Renal ultrasound should be performed ideally between days 3 and 7 of life to confirm diagnosis and focus on the contralateral kidney, as well as additional genital malformations | Renal ultrasound should be performed within the first week of life to confirm diagnosis. Additional imaging may be required for the CNS (eg, molar tooth sign in Joubert syndrome, periventricular cystic lesions in Zellweger syndrome), liver, pancreas, and genital tract | Renal ultrasound should be performed within the first few days of life to confirm diagnosis. Additional imaging may be required for the CNS, liver, pancreas, and genital tract |

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ARPKD, autosomal recessive polycystic kidney disease; CNS, central nervous system; MCDK, multicystic dysplasia of the kidney; MRI, magnetic resonance imaging.

[a] For example, chromosomal rearrangements or trisomies.

[b] For example, carnitine palmitoyltransferase deficiency type II or glutaric acidemia type II.

[c] For example, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers.

[d] Although these may be difficult to detect prenatally.

[e] Multicystic dysplasia of the kidney can be part of a more complex malformation syndrome (eg, vertebral, anal, cardiac, tracheal, esophageal, renal, and limb anomalies [VACTERL]).

[f] Multicystic dysplasia of the kidney is rarely caused by an underlying *HNF1B* mutation.

[g] For example, growth retardation or (suspected) placental insufficiency.

50% to 70% of children with 2 or more renal cysts and/or increased cortical echogenicity.[4] In fetuses with extrarenal anomalies, chromosomal rearrangements or aberrations are not uncommon[1]; however, genetic pathology is rare for solitary cysts with normal renal parenchyma, unilateral MCDK, or cystic dysplasia, especially without other malformations.

The broad phenotypic and genetic heterogeneity of cystic nephropathies and cystic dysplasia makes gene panel next-generation sequencing a powerful alternative to time-consuming and expensive single-gene sequencing, which may remain preferable for cases with a specific presumptive diagnosis.[5] Whole-exome analysis with subsequent filtering for cystic kidney disease genes is

becoming less costly, but interpretation may still pose challenges. Additional testing may be necessary to detect copy number variations, such as heterozygous deletions (eg, *HNF1B*) or defects in complex genomic regions not fully covered by whole-exome analysis or most gene panels (eg, *PKD1* [OMIM 601313]).

Establishing a genetic diagnosis in a fetus or infant can have far-reaching consequences. For example, genetic testing (1) can lead to earlier diagnosis and avoid unnecessary diagnostic procedures (eg, renal biopsy); (2) may establish a definite diagnosis, which can be psychologically helpful (however, sometimes it may also increase anxieties); (3) can point to renal and extrarenal comorbidities or highlight possible future complications (eg, maturity-onset diabetes of the young [MODY5, OMIM 137920] and autism spectrum disorders in patients with *HNF1B* deletions, or risk of progressive blindness in patients with *NPHP5* [OMIM 609254] mutations), which allows focused screening and sometimes prevention but may cause unnecessary anxiety; (4) can enable informed genetic counseling about recurrence risk for future children; (5) may influence the parents' decision on continuation of pregnancy in case of a grave prognosis; and (6) may in the future provide guidance for personalized medical management.

In our view, genetic testing should always be offered to families facing early-onset bilateral cystic kidney disease, and the medical and ethical implications should be discussed openly. Especially for prenatal testing, the physician must respect the principles of beneficence and respect for autonomy (ie, the parents' values and beliefs and their perspective on their interests) and should implement only those clinical strategies authorized after informed consent.[6] All of the following remarks presume that this kind of detailed and respectful genetic counseling has taken place and that local legislation is respected.

In practical terms, prenatal and preimplantation genetic diagnosis is feasible if the underlying genotype has been previously identified in an affected family member.[7] For pregnancies without a previously diagnosed index case, prenatal genetic testing can be effective, but sequence variations of unknown pathogenicity can cause uncertainty. Moreover, many cystic kidney diseases lack a clear-cut genotype-phenotype association, with large heterogeneity even within a family. Despite these limitations, DNA storage should be readily offered, especially if results could influence family planning.

## Recommendations for Prenatal Genetic Testing

*Recommendation 2.1 (consensus strength, evidence level D): It is important to offer nondirective counseling whenever genetic testing is considered for cases of prenatal cystic kidney disease.*

This will often also require multiprofessional support for the family (see the Prenatal Assessment section).

### Unilateral Cystic Kidney Disease

*Recommendation 2.2 (consensus strength, evidence level C): For fetuses with solitary cysts or multiple unilateral cysts, only consider prenatal or postnatal genetic testing when there are extrarenal manifestations.*

Renal cystic disease may be part of a multisystem syndromic disorder where extrarenal pathology may have major influence on prognosis and outcome (eg, chromosomal aberrations or Bardet-Biedl syndrome). However, without extrarenal manifestations, the identification of a genetic defect is very unlikely.

### Bilateral Cystic Kidney Disease

*Recommendation 2.3 (consensus strength, evidence level C): For fetuses with bilateral cystic kidney disease and/or bilateral hyperechoic or enlarged kidneys, consider prenatal genetic testing irrespective of the presence of oligohydramnios and/or extrarenal malformations.*

However, the relevance of results of genetic testing for informed decision making needs to be established beforehand; otherwise, postnatal testing should be preferred because of the lower risk of complications.

### Postmortem Analysis

*Recommendation 2.4 (consensus strength, evidence level C): After intrauterine fetal death or termination of pregnancy, offer postmortem genetic analysis or DNA storage because test results may influence family planning and diagnostic procedures in subsequent pregnancies.*

Sensitivity and specificity of subsequent genetic diagnostic tests benefit greatly from available DNA of the family's index patient. If the family declines genetic analysis, recommend DNA storage.

## Recommendations for Postnatal Genetic Testing

### Solitary Renal Cyst

*Recommendation 2.5 (consensus strength, evidence level C): In children with a solitary cyst in one kidney with normal renal parenchyma and without extrarenal manifestations, we do not recommend genetic testing on a routine basis because of the very low risk of genetic disease.*

### Unilateral Cystic Kidney Disease

*Recommendation 2.6 (consensus strength, evidence level C): For children with unilateral multicystic kidney disease and adequate hypertrophy and normal parenchyma of the contralateral kidney, we do not recommend genetic testing in the absence of extrarenal manifestations because of the low risk of specific genetic disease and the good prognosis.*

However, if extrarenal symptoms are present, this may point to a genetically determined syndromic disorder, and genetic testing should be considered.

### Bilateral Cystic Kidney Disease

*Recommendation 2.7 (consensus strength, evidence level C): For patients with 2 or more renal cysts and/or bilaterally increased echogenicity of the renal cortex of any age, genetic testing should be offered, especially if the result could influence further family planning and/or when an individual benefit from knowledge is expected.*

# Prenatal Assessment

## General Prognosis of Prenatally Detected Cystic Renal Disease

A systematic literature review of prognostic studies is summarized in **Table 3** (evidence level C). In summary, prenatally detected solitary cysts (with normal surrounding renal parenchyma) are rare and overwhelmingly have a good prognosis. However, they may occasionally be the first manifestation of more severe cystic renal disease or occur together with multiple extrarenal malformations,

Table 3. Summary of Evidence on Prognosis of Prenatally Detected Cystic Kidney Disease

| No. of Studies | Quality Assessment | | | | | | Effect | | | Quality | Importance[a] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Study Design | Risk of Bias | Inconsistency | Indirectness | Imprecision | Other Considerations | No. of Events/ Deaths | No. of Patients | Rate, % | | |
| **Solitary Cysts** | | | | | | | | | | | |
| Death | | | | | | | | | | | |
| 2 Studies[1,8] | Registry/ population study | Not serious | Serious[b] | Not serious | Not serious | None | 4 | 37 | 11 | Medium | 6 |
| Spontaneous resolution | | | | | | | | | | | |
| 1 Study[8] | Cohort | Not serious | NA | Not serious | Serious | None | 25 | 28 | 89 | Low | 6 |
| Revised diagnosis | | | | | | | | | | | |
| 1 Study[8] | Cohort | Not serious | NA | Not serious | Serious | None | 1 | 28 | 4 | Low | 5 |
| **Multiple Unilateral Cysts and/or Unilateral Increased Echogenicity** | | | | | | | | | | | |
| Death | | | | | | | | | | | |
| 4 Studies[9-12] | Case series | Not serious | Not serious | Not serious | Serious[c] | None | 13 | 177 | 7 | Low | 7 |
| MCDK only | | | | | | | | | | | |
| 6 Studies[2,13-17] | Registry/ case series | Not serious | Not serious | Not serious | Serious[c] | None | 73 | 572 | 13 | Medium | 8 |
| Impaired renal outcome in survivors | | | | | | | | | | | |
| 1 Study[9] | Case series | Not serious | NA | Not serious | Serious | Serious[d] | 1 | 52 | 2 | Very low | 5 |
| **Bilateral Cysts and/or Bilateral Hyperechoic Kidneys (Oligohydramnios Not Specified)** | | | | | | | | | | | |
| Death | | | | | | | | | | | |
| 5 Studies[9,12,18-20] | Cohort/ case series | Not serious | Not serious | Not serious | Serious | None | 95 | 118 | 81 | Low | 7 |
| Only hyperechogenicity and cysts | | | | | | | | | | | |
| 1 Study[21] | Case series | Not serious | NA | Not serious | Serious[e] | None | 22 | 30 | 73 | Low | 6 |
| Only polycystic disease | | | | | | | | | | | |
| 1 Study[1] | Registry | Not serious | NA | Not serious | Not serious | None | 17 | 27 | 63 | Medium | 6 |
| Only bilateral MCDK | | | | | | | | | | | |
| 3 Studies[2,16,22] | Registry/ case series | Not serious | Serious | Not serious | Not serious | None | 160 | 290 | 55 | Medium | 6 |
| Impaired renal outcome in survivors | | | | | | | | | | | |
| 2 Studies[9,18] | Case series | Not serious | Not serious | Not serious | Serious | Serious[d] | 9 | 13 | 69 | Very low | 5 |
| **Bilateral Cysts and/or Bilateral Hyperechoic Kidneys With Oligohydramnios** | | | | | | | | | | | |
| Death | | | | | | | | | | | |
| 6 Studies[10,11,23-26] | Cohort/ case series | Not serious | Not serious | Not serious | Serious | None | 54 | 71 | 76 | Low | 5 |
| Only isolated hyperechogenic kidneys | | | | | | | | | | | |
| 1 Study[27] | Case series | Not serious | NA | Not serious | Serious[e] | None | 20 | 22 | 90 | Very low | 4 |
| Only bilateral MCDK | | | | | | | | | | | |
| 2 Studies[13,14] | Case series | Not serious | Not serious | Not serious | Serious[e] | None | 27 | 27 | 100 | Low | 5 |
| Only hyperechogenicity and cysts | | | | | | | | | | | |
| 1 Study[28] | Case series | Not serious | NA | Not serious | Serious[e] | None | 20 | 21 | 95 | Low | 5 |
| Impaired renal outcome in survivors | | | | | | | | | | | |
| 2 Studies[23,24] | Case series | Not serious | Not serious | Not serious | Serious | Large effect | 7 | 7 | 100 | Low | 4 |
| **Bilateral Cysts and/or Bilateral Hyperechoic Kidneys Without Oligohydramnios** | | | | | | | | | | | |
| Death | | | | | | | | | | | |
| 7 Studies[11,14,26-30] | Case series | Not serious | Not serious | Not serious | Serious[e] | None | 8 | 89 | 9 | Low | 7 |
| Impaired renal outcome in survivors | | | | | | | | | | | |
| 2 Studies[27,30] | Cohort/ case series | Not serious | Not serious | Not serious | Serious[f] | None | 6 | 25 | 34 | Low | 5 |
| Spontaneous resolution | | | | | | | | | | | |
| 3 Studies[11,27,30] | Cohort/ case series | Not serious | Not serious | Not serious | Serious[g] | Serious[h] | 11 | 35 | 31 | Low | 5 |

(continued)

Table 3. Summary of Evidence on Prognosis of Prenatally Detected Cystic Kidney Disease (continued)

| No. of Studies | Quality Assessment | | | | | | Effect | | | Quality | Importance[a] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Study Design | Risk of Bias | Inconsistency | Indirectness | Imprecision | Other Considerations | No. of Events/ Deaths | No. of Patients | Rate, % | | |
| **Bilateral Cysts/Bilateral Hyperechoic Kidneys With Extrarenal Anomalies** | | | | | | | | | | | |
| Death | | | | | | | | | | | |
| 4 Studies[1,9,18,19] | Registry/ cohort | Not serious | Not serious | Not serious | Serious[e] | None | 288 | 383 | 75 | Low | 7 |
| Only Meckel-Gruber syndrome | | | | | | | | | | | |
| 1 Study[31] | Registry | Not serious | NA | Not serious | Serious[e] | None | 158 | 191 | 83 | Low | 7 |
| Only bilateral MCDK | | | | | | | | | | | |
| 3 Studies[14,16,17] | Case series | Not serious | Not serious | Not serious | Serious[g] | None | 24 | 28 | 86 | Low | 5 |
| Only hyperechogenicity and cysts | | | | | | | | | | | |
| 1 Study[21] | Case series | Not serious | NA | Not serious | Serious[e] | None | 15 | 18 | 83 | Low | 5 |
| Impaired renal outcome in survivors | | | | | | | | | | | |
| 1 Study[18] | Cohort | Not serious | NA | Not serious | Serious | None | 19 | 22 | 86 | Low | 4 |

Abbreviations: MCDK, multicystic dysplastic kidneys; NA, not applicable.

[a] Range of 1 to 9, where 9 is the highest level of importance.

[b] Four deaths were all in the same study. Also, they were all due to termination of pregnancy (2 with additional multiple malformations, 1 with chromosomal syndrome, and 1 with non–chromosomal syndrome).

[c] Most deaths unrelated to disease in that kidney.

[d] No details on renal function.

[e] Majority of deaths are by termination of pregnancy.

[f] Short follow-up.

[g] Low patient numbers.

[h] Publication bias suspected.

leading to termination of pregnancy, which were the only deaths in this group. Isolated multiple unilateral cysts with contralateral compensatory hypertrophy and without associated anomalies have an excellent prognosis. In cases with associated anomalies, outcome is mainly determined by other organ involvement, contralateral renal disease, and/or the particular syndrome complex. Fetuses with bilateral kidney cysts or hyperechogenic kidneys without oligohydramnios have good survival but significant risk of long-term renal disease. Fetuses with bilateral kidney cysts or hyperechogenic kidneys with oligohydramnios have poorer survival, especially with early onset of oligohydramnios, due to neonatal respiratory disease and longer-term renal dysfunction. Fetuses with bilateral cysts or hyperechogenic kidneys with concomitant extrarenal malformations have a mixed prognosis depending mainly on other organ involvement and the underlying syndrome, varying from extremely poor (eg, Meckel-Gruber syndrome) to an often mild renal phenotype (eg, Bardet-Biedl syndrome).

## Predicting Individual Prognosis

Classification into unilateral/bilateral disease and presumed diagnosis helps to stratify patients' prognosis, along with the identification of comorbidities and complications. The presence of oligohydramnios is an important prognostic feature even after adjustment for disease type and multiple anomalies.[18] While earlier onset of oligohydramnios is associated with worse outcome,[23-25] the distinction between oligohydramnios and anhydramnios is less helpful.[24] Further imaging and laboratory parameters that might help define individual prognosis are examined below.

*There is insufficient evidence to make recommendations on prenatal lung assessment as a means to predict postnatal mortality and morbidity in children with renal oligohydramnios (no grading).*

Data for predicting postnatal outcome by prenatal lung assessment come mainly from patients with premature rupture of membranes, diaphragmatic hernias, and/or congenital heart defects. However, renal oligohydramnios should be considered separately (eg, because enlarged kidneys further constrain lung growth, amniotic fluid movement, and postnatal inflation). They can also distort the thoracic to abdominal circumference ratio.[32] Unfortunately, few studies analyzed renal patients separately, and some did not include neonatal survivors (eTable 4 in the Supplement). Three-dimensional lung volume was the best predictor of pulmonary hypoplasia in renal oligohydramnios in one study,[32] followed by 2-dimensional thoracic area to heart area ratio. Magnetic resonance imaging lung volume measurements may be helpful, especially if oligohydramnios hampers ultrasound, but MRI was not superior to oligohydramnios in predicting outcome in the only published study.[33] Studies of pulmonary perfusion either by conventional Doppler ultrasound[34,35] or after maternal hyperoxygenation have also not included renal survivors. Meta-analysis could not confirm that the amniotic lecithin to sphingomyelin ratio predicts lung maturity.[36]

*There is insufficient evidence to make recommendations on prenatal renal function tests as a means to predict postnatal renal outcome for fetuses with cystic kidney disease (no grading).*

Fetal urinary electrolytes have been used to estimate renal function in lower urinary tract obstruction. However, their predictive power is poor, the bladder is not usually enlarged and easy to puncture in cystic diseases, and postrenal obstruction produces different electrolyte patterns than cysts of the collecting ducts, tubules, or glomeruli. Therefore, fetal blood sampling by cordocentesis, which has a slightly higher complication rate than amniocentesis or chorionic villus sampling,[37] is more suitable. eTable 5 in the Supplement summarizes studies on prenatal renal function tests for the prediction of postnatal renal function that include nonobstructive nephropathies. While higher serum $\beta_2$-microglobulin reflects glomerular damage and correlates with postnatal serum creatinine levels

to some degree, sensitivity and specificity for distinguishing mild from moderate or severe renal disease are suboptimal. Especially in diseases where renal function may decline over the course of pregnancy (eg, ARPKD), normal fetal $\beta_2$-microglobulin does not preclude later severe renal failure.[38]

## Counseling

*Recommendation 3.1 (consensus strength, evidence level D): In case of oligohydramnios, parents should be offered counseling by a fetal medicine specialist and a neonatologist; irrespective of the presence of oligohydramnios, parents of fetuses with bilateral cystic renal disease should be offered counseling by a pediatric nephrologist.*

Because of the broad spectrum of prognoses and diverse possible therapeutic interventions (eg, ventilation, different dialysis modalities, and transplantation), interdisciplinary counseling is extremely important. In severe cases, this will require repeated consultations with several specialists and psychosocial support.[39] High parental anxiety is often encountered even in less severely affected fetuses because of difficulties in pinpointing the prognosis after first examination and common preconceptions about dialysis; therefore, even families facing unilateral disease often find pediatric nephrological counseling helpful. Contact with patient organizations, which exist for several cystic nephropathies and genetic renal diseases in general on a national and international level, should be offered.

Where termination of pregnancy is locally available, nondirective counseling should be provided, aiming to give a realistic prospect of outcome. The visual analog scale shown in the eFigure in the Supplement may be helpful for this. When termination of pregnancy is offered, postnatal palliative care should always also be offered as an equal option.

## Therapeutic Interventions

### Corticosteroids

*Recommendation 3.2 (consensus strength, evidence level C): Despite the lack of evidence on the use of corticosteroids in late preterm pulmonary hypoplasia to improve pulmonary outcome, a single course of 2 doses is reasonable for this indication owing to the potential benefit.*

There is overwhelming evidence that corticosteroids can enhance lung maturation in threatened preterm delivery before 34 weeks' gestation, and it is recommended in multiple national guidelines.[40-45] A recent meta-analysis[46] also demonstrated benefits on respiratory morbidity for infants born late preterm (34-36 weeks' gestation) and before planned cesarean delivery at 37 weeks or later. Postnatal glucose levels should be monitored owing to the significantly higher rate of neonatal hypoglycemia.[47] While there is some concern about the adverse effects of repeated courses of corticosteroids, a single course is considered safe.[41] Corticosteroids have been used routinely before delivery of fetuses with congenital diaphragmatic hernia, with supporting evidence from animal models of diaphragmatic hernia.[48] For oligohydramnios-induced pulmonary hypoplasia, findings in a rabbit model suggested that corticosteroids in late gestation may improve outcome.[49] While animal data raised concern about their effect on the number of glomeruli,[50] nephrogenesis is largely complete in the late preterm period; therefore, we believe that a first course for pulmonary hypoplasia is reasonable even after 34 weeks' gestation.

### Serial Amnioinfusions

*There is insufficient evidence to make a recommendation on serial amnioinfusions for renal oligohydramnios (no grading).*

Serial percutaneous amnioinfusions have been studied mainly for spontaneous premature rupture of membranes, for which they may reduce mortality and pulmonary hypoplasia.[51,52] However, there is already an increased risk of infection in this setting, which is probably not elevated further. Amnioinfusions into previously intact membranes are commonly complicated by iatrogenic premature rupture of membranes, premature labor, and miscarriage.[53] In addition, infection and injury to fetus or mother are potential risks. The procedure should be considered only for pulmonary palliation because it does not improve renal function.

For renal oligohydramnios, there is a recent study using an amnioport device for serial amnioinfusions[54] and only case reports for serial percutaneous amnioinfusions (eTable 6 [evidence level D] in the Supplement). Because of the unknown balance of risks and benefits, results of a planned prospective study should be awaited.[54]

### Induction of Early Delivery

*Recommendation 3.3 (consensus strength, evidence level D): Do not offer early delivery for kidney reasons.*

There is no logical benefit on renal function from early delivery. On the contrary, prematurity should be avoided because it poses additional perinatal risks, and lower body weight can complicate treatment of renal dysfunction. Oligohydramnios may cause cord compression and fetal distress during labor, requiring obstetric management.

## Delivery in Hospital With Specialized Neonatal Care

*Recommendation 3.4 (consensus strength, evidence level D): In all cases with anticipated pulmonary problems (ie, oligohydramnios from early pregnancy), delivery should be planned in a hospital with high-level neonatal care (including availability of high-frequency oscillatory ventilation and inhaled nitric oxide therapy).*

*For fetuses with bilateral cystic renal disease without oligohydramnios, consider delivery in a hospital with easy access to a pediatric nephrologist.*

*Patients with unilateral cystic renal disease and healthy contralateral kidney generally do not require specialized neonatal care due to renal disease.*

Because of the wide spectrum of renal function impairment and secondary consequences, such as pulmonary hypoplasia, the place of delivery should be planned after individual risk assessment. Management of severely affected children will require an experienced team of neonatologists, pediatric nephrologists, and pediatric radiologists, as well as pediatric surgeons, urologists, and anesthetists. Also, complex decisions about offering palliative or intensive care or choosing dialysis modality may benefit from additional input from ethical experts and psychosocial support of the family (see the Postnatal Management section). In the initial neonatal phase, management of pulmonary complications is usually paramount, but nephrological assessment should not be delayed too long because treatment decisions may take some time to prepare and a number of children require dialysis soon after birth.

# Postnatal Management

Similar to the wide variety of prenatal presentations of cystic renal disease, a broad spectrum of postnatal morbidity is encountered.

While management of mild cases may focus mainly on ultrasound examination, severe cases require a multidisciplinary team, including neonatologists and pediatric nephrologists with expertise in neonatal kidney failure. Involvement of a geneticist may also be helpful (see the Genetic Testing section).

## Assessment in the Neonatal Period

*Recommendation 4.1 (consensus strength, evidence level C): Neonates with a prenatal diagnosis of a solitary kidney cyst should be seen for ultrasound examination within the first 4 weeks of life.*

This will confirm the diagnosis or identify further cysts due to the greater sensitivity of postnatal ultrasound in detecting smaller cysts or abnormalities of the contralateral kidney.

*Recommendation 4.2 (consensus strength, evidence level C): Neonates with prenatally diagnosed unilateral cystic kidney disease/hyperechogenic kidneys should be examined by ultrasound between the third and seventh days of life.*

Despite enormous advances in prenatal ultrasound, there is still a considerable proportion of children in whom the prenatal diagnosis of unilateral cysts has to be revised postnatally, usually to severe ureteropelvic junction obstruction.[22] Confirmation of the diagnosis is advised within the first week of life as severe obstruction may require surgical management. Because urine production only reaches normal quantities slowly after delivery, ultrasound before the third day of life may underestimate ureteric obstruction.

*Recommendation 4.3 (consensus strength, evidence level C): There is no need to perform blood tests for renal function in children with unilateral cystic disease and a normal contralateral kidney with adequate compensatory hypertrophy.*

Adequate compensatory hypertrophy is defined as renal volume above the 95th percentile (corrected for gestational age), which may take until the end of the first year of life to develop. Inadequate compensatory hypertrophy and other urogenital abnormalities should be excluded by postnatal ultrasound because they are the main risk factors for renal damage (albuminuria, hypertension, or renal function impairment) in patients with congenital solitary kidneys.[55] In case of the absence of other urogenital malformations and adequate contralateral hypertrophy, measurement of serum creatinine is unlikely to reveal impaired renal function. Micturating cystogram or scintigraphy is only indicated if there are clues toward further pathology, such as ureteric dilation, suspicion of MCDK in only one pole of a duplex kidney, or additional symptoms (eg, urinary tract infections). Patients require long-term follow-up for repeated ultrasound scans and measurements of proteinuria and blood pressure.

*Recommendation 4.4 (consensus strength, evidence level C): In patients at risk for neonatal renal failure (oligohydramnios or bilateral renal involvement), urine output should be monitored from birth.*

Serum creatinine and electrolyte levels and acid/base status should be monitored regularly but are largely influenced by maternal kidney status until 48 hours after birth. In addition to confirmatory postnatal ultrasound, renal function should be assessed with adequate time lag to allow clearance of maternal creatinine. Children with collecting duct abnormalities, such as ARPKD, are particularly at risk of hyponatremia and metabolic acidosis. Dialysis may need to be initiated after a few days or weeks of life depending on fluid overload and uremia. Peritoneal dialysis is the method of choice for most neonates.

## Current Prognosis of Children With Severely Impaired Kidney Disease From Birth

Individual prognosis of cystic renal disease is related to both underlying disease and comorbidities, with poorest outcomes in neonates after renal oligohydramnios (**Table 4** [evidence level D]). In 6 single-center studies, 24 out of 42 neonates died, but life-supporting therapy was not offered or was discontinued in at least 5. Owing to the small cohort sizes, it is difficult to distinguish the effects of age at onset of renal oligohydramnios, presence of associated malformations, and level of postnatal care on survival. Also, respiratory support and dialysis techniques have improved in recent years; therefore, outcome may now be better.

More detailed but very heterogeneous patient and organ outcome data are available for children with ARPKD (Table 4). In 4 current national registries and retrospective cohort studies, neonatal survival after birth with ARPKD was 88%, and 1-year survival was 78% (evidence level C). In 5 epidemiological studies with a mean follow-up time of 5 years, portal hypertension occurred in 15% to 86% (mean, 36%), and liver transplantation was performed in 0% to 50% (mean, 11%) of patients.

## Renal Replacement Therapy From Infancy

Solid epidemiological evidence is available regarding outcomes of renal replacement therapy (RRT) in neonates and infants for all indications (including 10%-15% with cystic kidney disease) (**Table 5**). Two international registries evaluated patient survival in 362 children started on long-term RRT in the first month of life since 2000; patient survival was 81% at 2 years, 79% at 3 years, and 76% at 5 years.[67,71] This compares with 85% 3-year survival among 182 children started on RRT from the second to the 12th month of life.[71] Neurological comorbidities increased the risk of death 5-fold. While van Stralen et al[67] did not demonstrate differing survival across 4 diagnosis groups, mortality was higher in children with polycystic kidney disease than in those with obstructive nephropathy in an American cohort.[71] Patient and graft survival after renal transplantation has also improved over time, including recipients aged 0 to 2 years,[74] even though transplantation is usually delayed until the child has reached about 10 kg. Results of further studies on neurological development, growth, and hospital admissions are summarized in eTable 7 in the Supplement. In resource-limited countries, pediatric renal replacement mortality is higher, especially when low public health expenditure limits provision of specialized pediatric renal services.[75]

*Recommendation 4.5 (level 2 strength, evidence level B): Renal replacement therapy should be offered to neonates with life-threatening kidney failure due to cystic renal disease.* Depending on individual circumstances, it can be appropriate to opt against RRT and pursue a palliative care plan.

Renal replacement therapy should now be considered an established therapy even in neonates because available data show marked improvement of survival in the last decades, with survival rates similar to those of older children.

However, concomitant conditions limiting life expectancy and/or quality of life independent of kidney function should be considered in the decision-making process. While most pediatric nephrologists recommend RRT as standard of care even for neonates and many families choose this treatment for their children,

Table 4. Summary of Evidence on Prognosis of Postnatal Cystic Renal Disease

| No. of Studies | Quality Assessments | | | | | | Effects | | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Study Design | Risk of Bias | Inconsistency | Indirectness | Imprecision | Other Considerations | No. of Events/ Survivors | No. of Patients | Event Rate/ Survival Rate, % (Range) | | |
| **Prognosis After Live Birth With Cystic Renal Disease and Renal Oligohydramnios** | | | | | | | | | | | |
| Overall survival | | | | | | | | | | | |
| 6 Studies[23-27,56] | Mainly single-center case | Very serious | Not serious | Not serious | Serious[a] | None | 18 | 42 | 43 (25 to 66) | Low | Medium |
| **Prognosis of Neonatal ARPKD** | | | | | | | | | | | |
| Neonatal survival | | | | | | | | | | | |
| 4 Studies[57-60] | Cohort studies | Not serious | Not serious[b] | Not serious | Not serious | None | 353 | 403 | 88 (82-96) | Medium | Medium |
| 2 Studies[61,62] | Historical cohort studies | Not serious | Serious[c] | Not serious | Serious[c] | None | 63 | 125 | 50 (25-87) | Low | Low |
| 1-y Survival of neonatal survivors | | | | | | | | | | | |
| 4 Studies[57-60] | Cohort studies | Not serious | Not serious[b] | Not serious | Not serious[b] | None | 315 | 353 | 89 (85-92) | Medium | Medium |
| 2 Studies[61,62] | Historical cohort studies | Not serious | Not serious | Not serious | Not serious | None | 42 | 63 | 67 (62-78) | Medium | Low |
| Survival until end of observation | | | | | | | | | | | |
| 4 Studies[57-60] | Cohort studies | Not serious | Not serious[b] | Not seriosu | Not serious[d] | None | 323 | 416 | 78 (70-81) | Medium | Medium |
| 3 Studies[61-63] | Historical cohort studies | Not serious | Serious[c] | Not serious | Serious[c] | None | 139 | 235 | 59 (23-87) | Low | Low |
| Hypertension | | | | | | | | | | | |
| 6 Studies[57,58,62-65] | Cohort studies | Not serious | Not serious | Not serious | Not serious | None | 307 | 470 | 65 (55-73) | Medium | Medium |
| Chronic kidney disease | | | | | | | | | | | |
| 4 Studies[57,58,63,65] | Cohort studies | Not serious | Not serious | Not serious | Serious[e,f] | None | 183 | 352 | 52 (42-65) | Low | Medium |
| End-stage renal disease | | | | | | | | | | | |
| 7 Studies[57-60,62,63,65] | Cohort studies | Serious[f] | Serious[f] | Not serious | Not serious | None | 128 | 588 | 22 (10-74) | Low | Medium |
| Renal transplantation | | | | | | | | | | | |
| 5 Studies[57,60,63-65] | Cohort studies | Serious[f] | Not serious | Not serious | Not serious | None | 64 | 421 | 15 (5-55) | Low | Low |
| Portal hypertension | | | | | | | | | | | |
| 5 Studies[57,58,60,63,65] | Cohort studies | Serious[g] | Not serious | Not serious | Serious[h] | None | 134 | 375 | 36 (15-86) | Low | Low |
| Variceal bleed | | | | | | | | | | | |
| 6 Studies[57,58,60,62,65,66] | Cohort studies | Not serious[g] | Not serious | Not serious | Not serious | None | 37 | 368 | 10 (4-27) | Low | Low |
| Cholangitis | | | | | | | | | | | |
| 4 Studies[58,60,65,66] | Cohort studies | Serious[i] | Not serious | Not serious | Serious[j] | None | 22 | 306 | 7.2 (4-25) | Low | Medium |
| Liver transplantation | | | | | | | | | | | |
| 5 Studies[57,58,60,65,66] | Cohort studies | Serious[f,g] | Not serious | Not serious | Not serious | None | 37 | 337 | 11 (2-50) | Low | Low |

Abbreviation: ARPKD, autosomal recessive polycystic kidney disease.

[a] All studies have low patient numbers; inclusion of patients with other malformations varies.

[b] Despite varying inclusion criteria (eg, clinical/only genetically confirmed cases).

[c] Early neonatal deaths missed by tertiary hospital in pre–ultrasound era.

[d] Despite varying length of follow-up.

[e] Very variable definitions of chronic kidney disease.

[f] Dependent on follow-up time.

[g] Higher incidence in studies focusing on patients with congenital hepatic fibrosis.

[h] Very variable definitions of portal hypertension.

[i] Not reported in many studies (unclear if none occurred or simply not reported).

[j] Cholangitis and sepsis of other origin often hard to distinguish clinically.

Table 5. Summary of Evidence on Prognosis After Starting Renal Replacement Therapy for Any Renal Disease Before Age 24 Months

| No. of Studies | Quality Assessment | | | | | | Effect | | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Study Design | Risk of Bias | Inconsistency | Indirectness | Imprecision | Other Considerations | No. of Events/ Survivors | No. of Patients | Event Rate/ Survival Rate, % (Range) | | |
| **1-y Survival** | | | | | | | | | | | |
| 3 Studies[67-69] | Cohort studies (after 2000) | Not serious | Not serious | Not serious | Not serious[a] | [b] | 874 | 1007 | 87 (83-88) | Medium | High |
| 2 Studies[69,70] | Cohort studies (before 2000) | Not serious | Not serious | Not serious | Not serious[a] | [b] | 120 | 143 | 84 (79-86) | Low | Medium |
| **2-y Survival** | | | | | | | | | | | |
| 3 Studies[67-69] | Cohort studies (after 2000) | Not serious | Not serious | Not serious | Not serious[a] | [b] | 813 | 1007 | 81 (80-81) | Medium | High |
| 2 Studies[69,70] | Cohort studies (before 2000) | Not serious | Not serious | Not serious | Not serious[a] | [b] | 111 | 143 | 78 (68-81) | Low | Medium |
| **3-y Survival** | | | | | | | | | | | |
| 4 Studies[67-69,71] | Cohort studies (after 2000) | Not serious | Not serious | Not serious | Not serious[a] | [b] | 1000 | 1287 | 78 (73-88) | Medium | High |
| 4 Studies[23,69,70,72] | Cohort studies (before 2000) | Not serious | Not serious | Not serious | Not serious[a] | [b] | 509 | 687 | 74 (68-80) | Medium | Medium |
| **5-y Survival** | | | | | | | | | | | |
| 3 Studies[67-69] | Cohort studies (after 2000) | Not serious | Not serious | Not serious | Not serious[a] | [b] | 638 | 1007 | 63 (58-78) | Medium | High |
| 2 Studies[69,70] | Cohort studies (before 2000) | Not serious | Not serious | Not serious | Not serious[a] | [b] | 109 | 143 | 76 (68-79) | Low | Medium |
| **Survival Until End of Study** | | | | | | | | | | | |
| 4 Studies[67-69,71] | Cohort studies (after 2000) | Not serious | Not serious | Not serious | Not serious[a] | [b] | 1049 | 1329 | 79 (74-83) | Medium | Medium |
| 5 Studies[23,69,70,72,73] | Cohort studies (before 2000) | Not serious | Not serious | Not serious | Not serious[a] | [b] | 620 | 864 | 72 (66-78) | Medium | Medium |
| **Temporary Return of Native Kidney Function** | | | | | | | | | | | |
| 5 Studies[23,26,27,58,59] | Cohort studies | Not serious | Not serious | Not serious | Not serious | None | 105 | 1869 | 6 (2-8) | Medium | Medium |
| **Renal Transplant by End of Study** | | | | | | | | | | | |
| 5 Studies[67-69,71,72] | Cohort studies (after 2000) | Not serious | Serious[c] | Not serious | Serious[d] | None | 668 | 1219 | 55 (49-80) | Medium | Medium |
| 2 Studies[68,72] | Cohort studies (before 2000) | Not serious | Not serious | Not serious | Serious[d] | None | 217 | 416 | 52 (49-60) | Medium | Medium |

[a] Despite varying definitions of age at starting renal replacement therapy (<1 month, <1 year, and <2 years) and some studies excluding hemodialysis patients.

[b] Survival not stratified for primary diagnosis in most studies.

[c] Historical cohorts cannot be separated out for the studies by Muller et al[38] and Brownfoot et al.[41]

[d] Rate of transplant highly dependent on survival rate and length of follow-up.

the lifelong burden of disease is considerable for affected children and their caregivers. The decision on initiation, withholding, or discontinuation of RRT should be carefully evaluated in a shared decision-making process with all involved disciplines and the parents. A formalized ethical decision-making framework can give useful guidance in this process.[76,77]

## ARTICLE INFORMATION

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**Author Affiliations:** Department of General Pediatrics, Adolescent Medicine and Neonatology, Center for Pediatrics at Medical Center–University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany (Gimpel); Department of Pediatric Radiology, Jeanne de Flandre Mother and Child Hospital, University of Lille, Lille, France (Avni); Department of Medicine IV at Medical Center–University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany (Bergmann); Center for Human Genetics, Bioscientia, Ingelheim, Germany (Bergmann); Department of Pediatrics II, University Hospital Essen, Essen, Germany (Cetiner); Department of Pediatrics and Center for Molecular Medicine, University Hospital of Cologne, Cologne, Germany (Habbig); Department of Pediatric Kidney, Liver and Metabolic Diseases, Hannover Medical School, Hannover, Germany (Haffner, Pape); Department of General Pediatrics, University Children's Hospital, Münster, Germany (König, Konrad, Rellensmann, Titieni); Department of Pediatrics and Center for Molecular Medicine, University Hospital of Cologne, Cologne, Germany (Liebau); Nephrology Research Laboratory, Department II of Internal Medicine, University Hospital of Cologne, Cologne, Germany (Liebau); Department of Obstetrics and Gynecology, Hannover Medical School, Hannover, Germany (von Kaisenberg); Department of Pediatrics, University Hospital Marburg, Marburg, Germany (Weber); UCL Great Ormond Street Institute of Child Health, University College London, London, England (Winyard); Division of Pediatric Nephrology, Center for Pediatrics and Adolescent Medicine, Heidelberg University Hospital, Heidelberg, Germany (Schaefer).

**Author Contributions:** Dr Gimpel had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
*Study concept and design:* Gimpel, Bergmann, Cetiner, Haffner, Konrad, Liebau, Pape, Titieni, Winyard, Schaefer.
*Acquisition, analysis, or interpretation of data:* Gimpel, Avni, Bergmann, Cetiner, Habbig, Haffner, König, Liebau, Pape, Rellensmann, von Kaisenberg, Weber, Winyard, Schaefer.
*Drafting of the manuscript:* Gimpel, Avni, Cetiner, Habbig, Haffner, Konrad, Liebau, Pape, Rellensmann, von Kaisenberg, Weber, Schaefer.
*Critical revision of the manuscript for important intellectual content:* All authors.
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*Administrative, technical, or material support:* Gimpel, Bergmann, Cetiner, Habbig, König, Konrad, Liebau, Rellensmann, von Kaisenberg, Winyard, Schaefer.
*Study supervision:* Bergmann, Cetiner, Konrad, Liebau, von Kaisenberg, Winyard, Schaefer.

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