Pediatric Nephrology
https://doi.org/10.1007/s00467-024-06328-2

REVIEW

Diagnosis and management of primary hyperoxalurias: best practices

Mini Michael[1] · Elizabeth Harvey[2] · Dawn S. Milliner[3] · Yaacov Frishberg[4] · David J. Sas[5] · Juan Calle[6] · Lawrence Copelovitch[7] · Kristina L. Penniston[8] · Jeffrey Saland[9] · Michael J. G. Somers[10] · Michelle A. Baum[10]

Received: 13 November 2023 / Revised: 7 February 2024 / Accepted: 16 February 2024

Abstract

The primary hyperoxalurias (PH 1, 2, and 3) are rare autosomal recessive disorders of glyoxylate metabolism resulting in hepatic overproduction of oxalate. Clinical presentations that should prompt consideration of PH include kidney stones, nephrocalcinosis, and kidney failure of unknown etiology, especially with echogenic kidneys on ultrasound. PH1 is the most common and severe of the primary hyperoxalurias with a high incidence of kidney failure as early as infancy. Until the recent availability of a novel RNA interference (RNAi) agent, PH care was largely supportive of eventual need for kidney/liver transplantation in PH1 and PH2. Together with the Oxalosis and Hyperoxaluria Foundation, the authors developed a diagnostic algorithm for PH1 and in this report outline best clinical practices related to its early diagnosis, supportive treatment, and long-term management, including the use of the novel RNAi. PH1-focused approaches to dialysis and kidney/liver transplantation for PH patients with progression to chronic kidney disease/kidney failure and systemic oxalosis are suggested. Therapeutic advances for this devastating disease heighten the importance of early diagnosis and informed treatment.

Keywords Primary hyperoxalurias · Primary hyperoxaluria type 1 · PH · RNA interference agent · Kidney transplant · Combined liver-kidney transplant · Nephrocalcinosis · Nephrolithiasis

Introduction

The primary hyperoxalurias (PH) are rare autosomal recessive disorders of glyoxylate metabolism resulting in hepatic overproduction of oxalate. Excess oxalate is excreted by the kidneys and can precipitate as insoluble calcium oxalate crystals causing urolithiasis, nephrocalcinosis, and progressive kidney impairment requiring dialysis and kidney/liver transplantation. Three types of PH (PH1, PH2, and PH3) have been molecularly characterized [1, 2]. PH1 is caused by mutations in the *AGXT* gene encoding the liver-specific enzyme alanine:glyoxylate aminotransferase and is the most common and severe form of PH with the highest incidence of kidney failure [3]. PH2 is caused by mutations in the *GRHPR* gene encoding the enzyme glyoxylate reductase/hydroxypyruvate reductase which is not liver-specific.

Michael J. G. Somers and Michelle A. Baum contributed equally as final or last authors.

✉ Mini Michael
mmichael@bcm.edu

[1] Division of Pediatric Nephrology, Baylor College of Medicine, Texas Children's Hospital, Houston, USA

[2] Division of Pediatric Nephrology, Hospital for Sick Children, University of Toronto, Toronto, Canada

[3] Pediatrics and Medicine, Mayo Clinic, Rochester, USA

[4] Division of Pediatric Nephrology, Shaare Zedek Medical Center, Jerusalem, Israel

[5] Division of Pediatric Nephrology and Hypertension, Mayo Clinic, Rochester, MN, USA

[6] Department of Kidney Medicine, Cleveland Clinic, Cleveland, USA

[7] Division of Nephrology, The Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, USA

[8] Department of Urology, University of Wisconsin School of Medicine, Madison, USA

[9] Division of Pediatric Nephrology and Hypertension, Mount Sinai Kravis Children's Hospital, New York, NY, USA

[10] Division of Nephrology, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA

Published online: 16 May 2024

Kidney stones are common in PH2, and kidney failure has been described [4]. PH3 is caused by mutations in *HOGA1* encoding 4-hydroxy-2-oxoglutarate aldolase type 1 predominantly expressed in the liver and kidney [5]. PH3 causes recurrent urolithiasis, often in early childhood, with kidney failure rarely ensuing [6].

Until the recent introduction of liver-directed RNAi therapy to reduce oxalate production, PH care was largely supportive of eventual need for transplantation in PH1 and sometimes PH2. With the advent of effective oxalate-lowering therapy other than transplantation, the need for early diagnosis and treatment to potentially prevent end organ damage becomes more compelling. We present suggested best practices intended to complement the recently published OxalEurope and ERKNet expert consensus clinical practice recommendations for PH [7]. Additionally, we provide recommendations for the diagnosis and treatment of PH at all stages of the disease, including best practices for dialysis and transplantation, and we comment on PH2 and PH3 and their diagnosis and management.

Methods

In 2020, the Oxalosis and Hyperoxaluria Foundation charged a group of international experts in PH (nephrologists, urologists, basic scientists, nurses, dieticians, and geneticists) with creating best-practice guidance for PH patient care. Due to its rarity, randomized controlled clinical trials in PH are few, all with small patient numbers. Hence, in addition to published literature, the group also used a structured review of clinical diagnosis and management to define best practices by Delphi techniques [8]. Cochrane Library, MEDLINE, and Embase databases were searched with the terms "primary hyperoxaluria type 1," "primary hyperoxaluria type 2," "primary hyperoxaluria type 3," "oxalosis" in combination with the terms "pathophysiology," "diagnosis," "treatment," "dialysis," "transplant," "liver and kidney transplantation," "liver only and kidney only transplantation," and "novel agents" to identify citations since January 1, 2010, for expert review, supplemented by commonly referenced or noteworthy older publications identified by group members.

Diagnosis of primary hyperoxaluria

An algorithm for PH diagnosis is provided (Fig. 1) [9].

PH diagnosis is strongly considered in patients with recurrent calcium oxalate stones, nephrocalcinosis, progressive chronic kidney disease (CKD) of unknown etiology, or a family history of stones and CKD. Younger age at onset, larger stone burden, and nephrocalcinosis increase the likelihood of underlying genetic disorders such as PH. PH should also be suspected when a kidney biopsy shows parenchymal calcium oxalate crystals under polarized light.

Urinary oxalate (Uox) > 0.5 mmol (45 mg)/day/1.73 m^2 body surface area (BSA), in the absence of secondary sources of oxalate, is consistent with PH. In children, 24-h Uox should be corrected to 1.73 m^2 BSA. However, due to challenges with timed urine collection, random urine ox/creatinine ratios are often used, and to interpret Uox results, age-specific normal values are referenced (Table 1) [10, 11]. Since oxalate is cleared by kidney excretion, Uox in PH patients with markedly reduced GFR may be < 0.5 mmol (45 mg)/day/1.73 m^2 BSA. Plasma oxalate (Pox), though elevated in all patients with kidney failure, is even higher in those with PH and can help differentiate PH from other kidney disease [12–15]. A laboratory with experience in oxalate assays should be used. Moreover, the processing of samples to measure Pox can be challenging, and reference values vary depending on the assay used and the reference laboratory. Hence, clinicians must be aware of these possible confounding variables in interpreting Pox measurements.

A presumptive diagnosis of PH by Uox or Pox is confirmed by molecular testing of *AGXT*, *GRHPR*, and *HOGA1* genes. Screening of siblings using targeted genetic testing [16] should ensue given their risk for severe disease even if asymptomatic [17]. Whenever genetic testing is performed, it is important for genetic counseling to be offered as well, optimally by a geneticist or certified genetics counselor who understands the ramifications of both positive and negative test results. In families known to be at risk for PH, the potential for prenatal diagnosis should be shared with families, and again genetic counseling accompanying results of fetal testing is paramount.

Management of PH (Box 1: M1–M11)

Fluids (M2)

Aggressive hydration lowers Uox by dilution, reducing the risk of calcium oxalate crystallization [9, 18]. Placement of a gastrostomy tube (g-tube) facilitates consistent fluid intake, particularly if achieving targeted hydration is problematic or the stone burden increases. A g-tube may also help achieve nutritional goals and assist with hydration and medication administration post-transplant [9, 19].

Box 1 Best practices for medical management of primary hyperoxaluria

M1: Maintain best possible GFR [9, 18]
1. Maintain brisk urine flow with hydration
2. Avoid dehydration
3. Limit exposure to nephrotoxins
M2: Fluid management [9, 18, 20]
1. Oral fluid intake 2–3 liters/m^2/BSA/day
2. If oral intake difficult (e.g. young infants, developmental delay), consider g-tube placement
3. If vomiting, diarrhea, or reduced oral/enteral intake use i.v. fluid for hydration
M3: Oral inhibitors of calcium oxalate crystallization in the urinary tract [18, 21–23]
1. Potassium citrate 1–2 meq/kg/day in children, 15–30 meq/day in adults divided bid or tid. Consider sodium citrate or sodium bicarbonate if eGFR < 30 ml/min/1.73 m^2
2. Magnesium as oxide, gluconate, or carbonate
M4: Diet [24, 25]
1. Avoid excess intake of high oxalate foods
2. Maintain recommended daily intake of calcium
3. Avoid high dose vitamin C supplementation (oxalate precursors)
M5: Monitor stone formation by clinical history and ultrasound at 6–12 month intervals
M6: Monitor kidney function by serum creatinine, or cystatin C at a minimum annually and more frequently as GFR declines: annually for stage 1–3a; 3–6 monthly for stage 3b; 3 monthly for stage 4; monthly for stage 5
M7: Reduction of hepatic oxalate production is the most definitive and effective management strategy for the prevention and management of oxalate damage (stones, progressive CKD, and oxalosis) and can be accomplished with:
a. Pharmacological doses of pyridoxine in PH1 with fully or partially sensitive variants
b. RNAi therapy in PH1 patients
c. Liver +/- kidney transplant in PH1 & PH2 with advanced CKD (Box 3)
M7a: Pyridoxine management:[26–28]
- Pyridoxine 5 mg/kg/day (maximum dose 1 gram daily) starting dose orally as a treatment trial in all patients with higher urine oxalate, followed by maintenance in pyridoxine responsive patients with genetically confirmed PH1; efficacy should be assessed in patients with mutations with no data on pyridoxine sensitivity
- Repeat 24-hour urine after 3 months. Pyridoxine responsiveness defined as ≥ 30% reduction in oxalate excretion. However, consider continuing pyridoxine if associated with any sustained decline ≥ 15% in Uox in the absence of toxicity.
- Continue pyridoxine indefinitely and despite kidney failure, should it occur, if responsive and/or if a pyridoxine sensitive mutation is confirmed
- For patients diagnosed with PH1 after kidney failure, consider pyridoxine use despite difficulty in assessing pyridoxine responsiveness

M7b: RNAi therapy [29–33]
- Following genetic confirmation of PH1, initiate RNAi therapy if available in patients who are not fully pyridoxine sensitive
- Continue RNAi therapy if there is evidence of effectiveness (normal or near normal Uox or > 30% reduction from baseline) and in patients with advanced CKD or who are dialysis dependent with documented reduction in plasma oxalate
- Choice of RNAi agent (lumasiran vs. nedosiran) should be determined based on experience and accessibility; even though relative efficacy not compared, separate trials on lumasiran and nedosiran showed similar effect in reducing urine oxalate levels
- Refer to product monograph for specific dosing instructions

M8: Monitor Pox and Uox levels every 3-6 months while on pyridoxine and/or RNAi therapy to ensure adherence to treatment and ongoing efficacy
M9: Oxalosis management principles and monitoring [13]
- Maintain Pox as low as possible through all CKD stages to reduce the risk of oxalosis
- Initiate dialysis in advanced CKD with a prescription to optimize oxalate removal (Box 2) and perform transplantation in a timely manner (Box 3)

M10: Measurement of Pox [34, 35]
- Monitor Pox to evaluate oxalosis risk and to assess dialysis adequacy according to CKD stage
  - CKD 1–3a: 6–12 monthly
  - CKD 3b: 6 monthly
  - CKD 4: 3 monthly
  - CKD 5: monthly (after the longest interdialytic interval in patients on dialysis)
- Hold supplemental vitamin C (if any) 24 hours prior to blood sampling
- Clinicians should be familiar with the assay used and expected reference ranges

M11: Clinical evaluation and diagnostic tests for oxalosis
- Clinical evaluation with careful history and physical exam at diagnosis then annually for CKD 1–3a, 3 monthly for CKD 3b–4, monthly for CKD 5
- Diagnostic tests at diagnosis then annually in CKD 3b–4, 6 monthly in CKD 5 and more frequently with symptoms
  - Kidneys: image for stones and nephrocalcinosis
  - Eyes: visual acuity and fundoscopy for oxalate deposition. Fundus photography for longitudinal comparison if available, balancing need for sedation with potential benefit. OCT better localizes oxalate crystals if available [36]
  - Heart: echocardiography. Strain imaging may be more sensitive to assess effects of oxalate deposition than standard echocardiography [37, 38]
  - Bone: image at diagnosis then as clinically indicated, and if bone pain or fractures occur. Radiological features of bone oxalosis may mimic secondary hyperparathyroidism and adynamic bone. Bone biopsies are not routinely performed [39–43]. MRI [44, 45], pQCT and high resolution pQCT [46, 47] are techniques under study. Plasma fibroblast growth factor 23 may also be monitored [48]

bid, twice a day; *BSA*, body surface area; *CKD*, chronic kidney disease; *eGFR*, estimated glomerular filtration rate; *MRI*, magnetic resonance imaging; *OCT*, optical coherence tomography; *PH1*, primary hyperoxaluria type 1; *PH2*, primary hyperoxaluria type 2; *pQCT*, peripheral quantitative computed tomography; *Pox*, plasma oxalate; *tid*, three times a day; *Uox*, urine oxalate

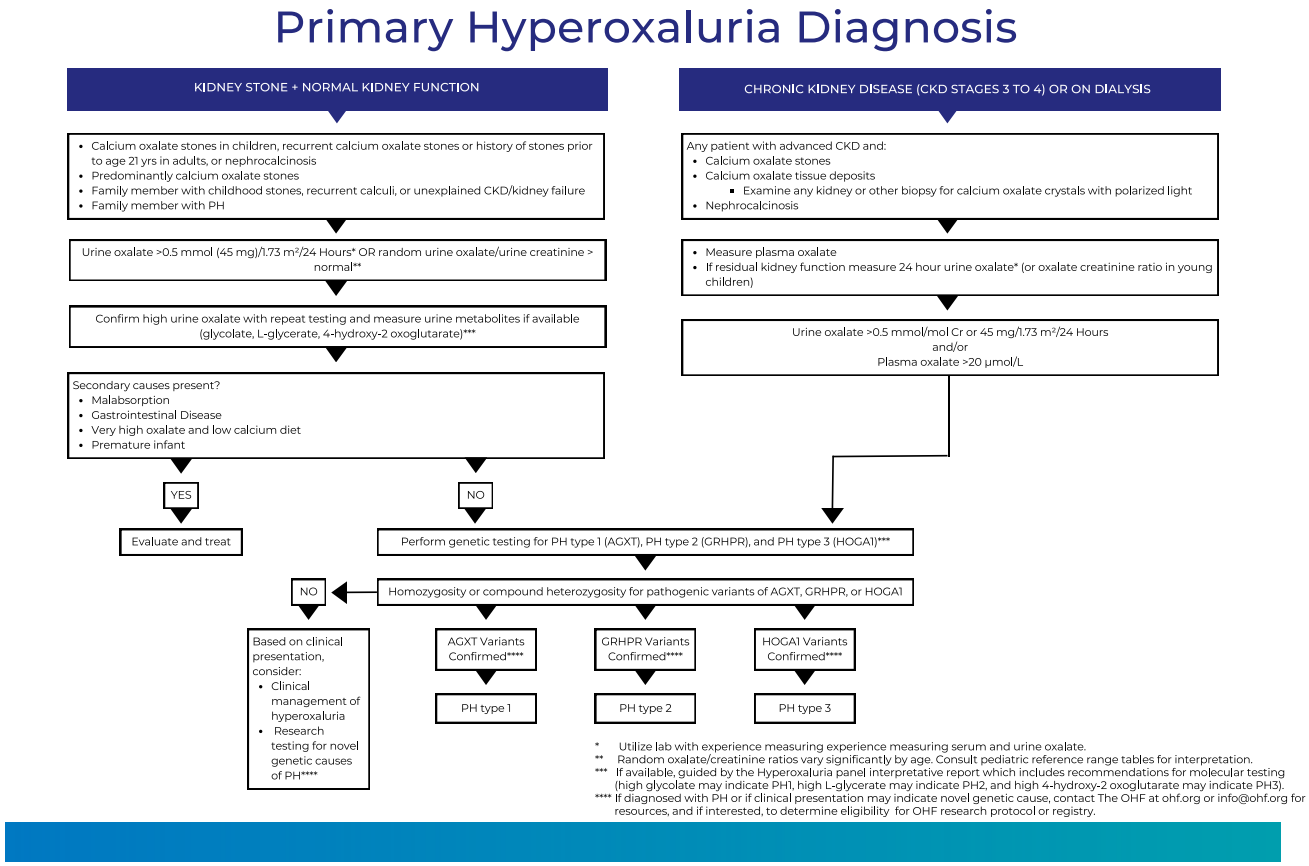

Fig. 1 Diagnostic evaluation for patients suspected to have primary hyperoxaluria (PH)

Table 1 Normal urinary oxalate/creatinine ratio by age of the child [11]

Age	Urine oxalate/creatinine ratio	
	mmol/mmol	mg/mg
< 6 months	< 0.37	< 0.29
6–23 months	< 0.26	< 0.20
2–5 years	< 0.14	< 0.22
6–12 years	< 0.08	< 0.06
≥ 13 years	< 0.04	< 0.03

Crystallization inhibitors (M3)

Potassium citrate and magnesium can reduce stone formation and kidney injury. Potassium citrate should be used as adjunctive therapy with hypocitraturia, elevated urinary supersaturation of calcium oxalate, or increasing stone burden. Pharmacologic dose citrate is necessary since augmenting dietary citrate is less effective in PH1 [18, 21, 22, 24]. Magnesium as oxide, gluconate, or carbonate is considered when there is low 24-h urine magnesium excretion, high supersaturation of calcium oxalate, or increasing stone burden [23]. Titrate crystallization inhibitor dose based on urine pH (goal pH 6.5–7.5), 24-h urine citrate levels or urine citrate/creatinine ratios if 24-h urine is not possible and if available, 24-h urine supersaturation profile.

Dietary oxalate (M4)

In PH, hepatic oxalate overproduction is profound, and dietary oxalate contributes only modestly to Uox excretion. Though limiting high oxalate foods is appropriate, strict avoidance is not beneficial [25].

Imaging (M5)

Given the propensity for nephrolithiasis with necessary urologic procedures in PH, periodic imaging of the kidneys and urinary tract is important to assess the efficacy of treatment to prevent new stone formation and to identify stones requiring intervention. In children and adolescents, ultrasound is the preferred imaging modality.

Therapies to lower hepatic oxalate production

Pyridoxine (M7a)

Pyridoxine, a co-factor in the hepatic oxalate pathway, reduces oxalate production in a subset of PH1 patients with *G170R*, *G41A*, *F152I*, and *I244T* mistargeting variants [26–28]. Pyridoxine treatment in *G170R* homozygosity may reduce Uox to normal or near normal levels, with Uox levels falling by 25–50% in *G170R* heterozygotes [49–51]. There is also clinical evidence for pyridoxine responsiveness in *F152I*, and pyridoxine sensitivity may characterize other missense mutations as well [2, 28] since most such pathogenic variants remain untested. Up to 20% of PH1 patients normalize Uox excretion with pyridoxine, and 30% may experience a partial response [24, 28, 49, 52, 53]. Pyridoxine is not effective in PH2 and PH3.

A pyridoxine trial is provided to all PH1 except those with known unresponsive *AGXT* mutations. A starting daily dose of at least 5 mg/kg is usually provided, with doses generally limited to < 10 mg/kg, with a maximum dose of 1000 mg daily. When kidney failure is present, pyridoxine response is difficult to assess, so therapy is provided unless there is a known unresponsive genetic mutation. Although high doses may be associated with peripheral neuropathy, pyridoxine is typically well tolerated and can be effective even in advanced CKD [54]. Patients taking > 10 mg/kg/day should have an annual assessment for peripheral nerve dysfunction.

New therapies

RNAi therapeutics

At this time, two commercially produced RNAi therapies for PH1 exist, and they are described briefly below. They have been approved by regulatory agencies based on clinical trials, and it is likely that more information about their most efficacious clinical use will be learned with ongoing real-world experience and clinical trial extension data. Detailed information about each drug such as dosing specifics or adverse sequelae are best found in each manufacturer's package insert for these preparations, as they reflect the information the manufacturer has shared to gain regulatory approval and are updated as required by these agencies. There is currently no data directly comparing different RNAi products for PH, and the choice of any specific RNAi is more likely to reflect local practice, drug availability, and individual patient parameters.

Lumasiran (M7b)

Lumasiran (Oxlumo™), the first liver-directed RNAi approved for the treatment of PH1 by regulatory agencies [29, 30], reduces Uox excretion independent of PH1 genotype. Lumasiran targets glycolate oxidase (GO), the enzyme converting glycolate into glyoxylate. Decreased hepatic production of glyoxylate reduces the generation of its primary downstream product oxalate while increasing upstream glycolate, which is soluble and readily excreted. Lumasiran is not effective in PH2 or PH3.

Administered subcutaneously, lumasiran reduces Uox and Pox in PH1 patients with normal kidney function, CKD, and on dialysis. In initial clinical trials, no serious side effects were noted, though long-term data is needed to assess longitudinal efficacy and safety as well as outcomes of kidney-only transplant under RNAi. With a reduction in Uox and Pox, supportive therapy may also be weaned [55].

Nedosiran

Nedosiran, a second hepatic RNAi therapy, uses GalNAc-targeting ligands to inhibit lactate dehydrogenase (LDHA), the enzyme that catalyzes the final step in oxalate production. In a double-blind study of nedosiran-treated PH1 patients ≥ 6 years old with GFR > 30 ml/min/1.73 m^2, mean Uox approached normal at six months. PH2 patients were also studied but demonstrated highly variable Uox excretion, and further studies are needed to determine efficacy in both PH2 and PH3 [56]. Nedosiran was well tolerated with no serious adverse effects. Nedosiran (Rivfloza™) was FDA approved in October 2023 for ages 9 and older, with GFR ≥ 30 ml/min/1.73 m^2.

Other treatments in development

Small molecule inhibitors of GO and LDHA such as stiripentol are the focus of ongoing study, as is CRISPR technology-assisted gene editing [57, 58]. See ClinicalTrials.gov and search for "primary hyperoxaluria" for current information.

Liver transplantation

Although liver transplantation restores oxalate production to normal in PH1 and substantially reduces oxalate production in PH2, it entails significant clinical risk, requires a live donor or use of an organ from an already-limited supply of deceased donor organs, and is very costly (refer to Panel 3 for Transplant Guidelines). Accordingly, for the management of PH patients with preserved kidney function, with the availability of RNAi therapy to reduce

hepatic overproduction of oxalate, liver transplantation is not recommended [59, 60].

Best practices for PH patients with advanced CKD and kidney failure

Ongoing injury from oxalate nephropathy in PH leads to progressive CKD, the risk of which is proportional to Uox excretion [61]. Kidney failure occurs in any PH type but is especially frequent in PH1. High Pox in PH patients with low GFR causes multisystem injury and complicates both dialysis and transplantation outcomes [62].

Oxalosis (M9–M11)

Oxalosis defines the deposition of calcium oxalate crystals in tissues of any organ system. Kidney (nephrocalcinosis), bone (sclerosis, impaired growth, bone pain, pathological fractures), eye (retinal deposits causing fibrosis, corneal deposits, optic disc atrophy, compromised visual acuity), bone marrow (erythropoiesis-stimulating agent resistant anemia), heart (cardiomyopathy, arrhythmias), blood vessels (ischemic cutaneous ulcers), nerves (peripheral neuropathy), and skin (livedo reticularis, subcutaneous nodules, cutaneous necrosis mimicking calciphylaxis) are commonly affected. As GFR declines, kidney oxalate clearance decreases, and Pox levels rise. Although nephrocalcinosis can occur at any time in PH due to high oxalate concentrations in the glomerular filtrate, extrarenal deposition of calcium oxalate occurs with Pox concentrations > 30–45 µmol/L that exceed the plasma saturation threshold [12, 15]. Pox concentrations in this range typically occur with GFR < 30 ml/min/1.73 m^2 and often occur earlier in PH1 [51]. Without therapy lowering hepatic oxalate production, early and intensive dialysis is needed at that point to reduce oxalosis.

With infantile oxalosis, the most severe PH1 form, kidney failure develops in the first months of life, and these children may develop severe oxalosis within months despite aggressive hemodialysis (HD) [15]. Although HD removes oxalate more efficiently than peritoneal dialysis (PD), neither treatment matches oxalate generation in the absence of therapy lowering hepatic oxalate production, leading inevitably to systemic oxalate deposition [12, 63, 64].

Since the risk of life-threatening complications from oxalosis increases progressively in PH patients with kidney failure, early transplantation has been a key goal prior to the availability of RNAi therapy.

Dialysis (Box 2: D1–D3)

Dialysis initiation (D1)

Pox in non-dialysis patients reflects the equilibrium between hepatic production and kidney elimination. Pox levels are normal or mildly elevated in PH patients with eGFR > 40 ml/min/1.73 m^2 but rise quickly with lower GFR [13]. With dialysis dependency, Pox levels reflect the complex interplay of hepatic production, residual kidney function, dialysis clearance, and tissue deposition [65].

To mitigate oxalosis risk, dialysis is started with Pox levels > 30–45 µmol/L or GFR < 30 ml/min/1.73 m^2 [15], recognizing that Pox levels at any given GFR vary between patients based on hepatic oxalate production, PH type, genotype, and treatments reducing oxalate production [24].

Infants represent a special group as their GFR is normally low at birth and increases over the first months of life. Serial monitoring of Pox and GFR is needed to assess how Pox levels change if kidney function improves or worsens.

Dialysis management (D2)

Hemodialysis frequency and duration

HD frequency and duration should be determined by Pox levels, as well as standard dialysis management parameters such as electrolyte and volume balance and dialysis adequacy. Without significant residual kidney function or effective therapy lowering oxalate production, a standard 3-day-per-week HD regimen is insufficient, as is peritoneal dialysis (PD) monotherapy.

The majority of Pox clearance occurs during the first 1–2 h of a dialysis session, followed by significant Pox rebound post-HD [66, 67, 73]. Thus, frequent dialysis treatments are more effective than less frequent but longer sessions [68]. Serial Pox measurement, estimation of daily oxalate generation, and measurement of oxalate dialysis clearance are important factors to consider when prescribing dialysis duration and frequency to prevent progressive oxalosis [73].

Peritoneal dialysis (D3)

Guidance on the role of PD in PH management is shown in D3.

Outside of an absolute lack of HD resources or as a rare adjunct to HD, PD is not recommended in PH in the

Box 2 Best practices for dialysis in primary hyperoxaluria patients with advanced CKD

D1: Initiation of Dialysis [13, 15, 24, 65]
- Pox > 30–45 µmol/L
- eGFR < 30 ml/min/1.73 m^2 in PH1; eGFR < 20 in PH2 and PH3
- If Pox is unknown in a patient with known or suspected PH in CKD 4–5, start dialysis while awaiting Pox, especially if oligoanuric. Obtain Pox as soon as possible, before dialysis initiation (if possible) or immediately before a dialysis session.
- In patients with suspected PH and rapidly progressive CKD or kidney failure, initiate pyridoxine while awaiting confirmation of diagnosis
- In infants with known PH1, monitor serum creatinine and Pox every 2 weeks and initiate dialysis if creatinine is higher than expected for age and Pox increases progressively to > 30–45 µmol/L

D2: Dialysis Frequency and Duration [66–72]
- Goal of dialysis is to reduce Pox and maintain at < 30–45 µmol/L for as much time as possible between dialysis sessions
- HD either intermittent or nocturnal is preferred due to better oxalate clearance in patients not on RNAi therapy or fully pyridoxine responsive
- HD 6–7 days per week is required in the absence of effective reduction of oxalate production by pyridoxine or RNAi therapy or residual kidney function
- Weekly hours of HD should be determined by Pox, degree of oxalosis, and residual kidney function, but not less than 12 hours/week if Pox > 30 µmol/L
- Goal is oxalate reduction ratio ≥ 50% per treatment; blood flow (dialytic clearance) ≥ 6–7 ml/kg/min per dialysis session in children
- Use a high flux dialyzer with surface area ≥ patient's BSA. In infants, smaller dialyzer if needed to keep extracorporeal volume < 10–15% of blood volume
- In children, blood flow rates of 150–200 ml/min/m^2 BSA (approximately 5–7 ml/kg/min) optimize oxalate removal [66]
- Optimal dialysate flow rate >2 times blood flow rate [67, 69]
- Home nocturnal HD has been shown to improve oxalosis symptoms in adults [70, 71]
- Predilution HDF does not substantially augment oxalate clearance in the era of high flux biocompatible filters [67], but there is no contraindication to its use. Minimal data exists on post-dilution HDF [72]

D3: Peritoneal Dialysis

PD monotherapy is not recommended but may be considered in the following circumstances:
- Adjunctive in combination with HD, if sufficient HD to achieve target Pox cannot be provided, keeping in mind the significant burden of concomitant PD and HD on quality of life for the patient and family and the small incremental increase in oxalate clearance achieved by PD [63, 66]
- PD monotherapy if hepatic oxalate production is well controlled by pyridoxine or RNAi therapy and Pox < 30 µmol/L; specific outcome data with this approach is not yet available [16, 26, 27, 29, 49, 50]
- PD monotherapy when the patient has sufficient residual kidney function to maintain Pox < 30 µmol/L
- Aggressive PD monotherapy if HD is not feasible. PD monotherapy should include:
  - Peritoneal equilibration testing to determine optimal dwell time
  - Pox monitored monthly. If Pox increasing, increase peritoneal solute clearance by increasing length of therapy, increasing cycle number, and/or addition of 1–2 daytime exchanges in patients on CCPD

BSA, body surface area; *CCPD*, continuous cycling peritoneal dialysis; *CKD*, chronic kidney disease; *eGFR*, estimated glomerular filtration rate; *HD*, hemodialysis; *HDF*, hemodiafiltration; *PD*, peritoneal dialysis; *PH1*, primary hyperoxaluria type 1; *PH2*, primary hyperoxaluria type 2; *PH3*, primary hyperoxaluria type 3; *Pox*, plasma oxalate

absence of oxalate-lowering therapy due to its inability to achieve sufficient oxalate clearance.

Transplantation (Box 3: T1–T7)

Transplant planning (T1)

Oxalosis risk increases as GFR decreases. In the absence of effective treatment to lower hepatic oxalate production, organ transplantation should be planned with eGFR < 45 ml/min/1.73 m^2 [24, 74].

Transplantation may not be feasible before initiation of dialysis in many PH1 patients, and previously undiagnosed patients may present with kidney failure. In such situations, transplantation timing depends on existing oxalosis and the potential for this burden to compromise allograft function.

With severe oxalosis and Pox levels > 70 µmol/L at diagnosis, treatment to lower Pox such as RNAi therapy should be commenced with aggressive dialysis initiated and maintained prior to transplantation to allow for mitigation of the systemic oxalate burden that may damage the kidney allograft post-transplant when oxalate stores are mobilized and excreted.

While delaying transplant until Pox falls below a supersaturation level of 30–45 µmol/L optimizes allograft protection, in most PH1 dialysis patients, this level is unachievable even with the addition of oxalate lowering therapy. The benefits of kidney transplantation outweigh the risks associated with continued months of dialysis unless there is evidence of severe oxalosis with Pox > 70 µmol/L [75]. Although three case reports suggest that bilateral native nephrectomies may decrease both the need for post-transplant HD and the risk for kidney allograft injury [76, 83], the benefit of this approach

in PH1 is unproven, and nephrectomy decisions should be individualized, weighing the kidney contribution to total oxalate burden against potential adverse surgical consequences (T1).

Policies defining medical eligibility for transplant listing and prioritization differ from country to country and are subject to regulatory review and revision. Transplant centers should maintain familiarity with such policies to advance timely transplant when medically eligible.

In PH, initial poor allograft GFR can predispose to significant early allograft injury from the pre-existing oxalate burden. Donor factors adding to the risk of delayed graft function include older donor age, smaller donor size, cold ischemia time, and distance of the donor's kidney from the recipient.

The ramifications of using a relative heterozygous for a pathogenic *AGXT* variant as a donor remain unclear. Although heterozygotes may have reduced AGT enzyme activity, they typically have normal Uox excretion and remain unaffected by stones or oxalate-related CKD. Good transplant outcomes from obligate heterozygote donors have been reported [77].

Transplantation in fully pyridoxine-responsive PH1 patients or those receiving RNAi therapy who have advanced CKD (Stage 4–5) (T2)

In PH patients responsive to pyridoxine or RNAi therapy, ongoing availability and adherence to these therapies should be ascertained prior to transplant.

With *G170R* variant homozygosity, isolated kidney transplantation with ongoing pyridoxine treatment can succeed [50]. In pyridoxine-responsive patients who do not normalize urine oxalate with pyridoxine or who manifest extensive oxalosis, liver-kidney transplant [50] or kidney transplant alone with RNAi therapy should be considered.

RNAi therapy appears highly effective in reducing hepatic oxalate production and has changed approaches to transplantation in PH1. Although current clinical experience with RNAi use and kidney-only transplant is limited [59], longitudinal effectiveness and pertinent long-term treatment concerns will be clarified by ongoing study of this now increasingly adopted approach. Similarly, the utility of RNAi as a "rescue" therapy when PH is newly diagnosed after kidney transplantation will need to be elucidated.

Transplantation without complete pyridoxine responsiveness or in the absence of available or effective RNAi therapy (T3)

PH1

In patients without complete pyridoxine responsiveness or access to effective RNAi therapy, liver-kidney transplantation is recommended, and isolated kidney transplantation is avoided. Studies have demonstrated up to six times higher rates of kidney allograft survival in liver-kidney vs. kidney-only transplantation at 5 years and 15 years post-transplant [78].

When liver-kidney transplants are done, either a sequential liver-kidney transplant (SLKT) or combined liver-kidney transplant (CLKT) approach may be used. With SLKT, the liver is transplanted first, followed by a kidney when oxalate metabolism becomes normal. In CLKT, both organs are transplanted at the same surgery. CLKT or SLKT appear equally effective and are recommended therapy for kidney failure in the absence of available RNAi therapy [78, 79].

PH2

To date, RNAi therapeutics have not been shown to be effective in PH2. Early reports suggest that Uox becomes normal after a combined liver-kidney transplant [80], and this treatment may benefit those with severe disease or extensive oxalosis. Some PH2 patients do well following kidney-only transplantation, however, so transplant type needs individualization (T4).

PH3

Progression to kidney failure has rarely been reported (T5).

Peri-operative and post-transplant management (T6–T7)

Peri-operative and immediate post-transplantation management, including fluid management and indications and timing for post-transplant dialysis, are outlined in T6.

When the transplanted kidney functions well, Pox levels decline quickly [15], but may remain above normal for months [81] depending on GFR, systemic oxalate burden, and hepatic graft function or completeness of response to RNAi therapy or pyridoxine.

With delayed kidney allograft function or inadequate urine output, Pox levels may stay high, and dialysis post-transplant may be needed to reduce Pox rapidly and may be the safest way to protect the allograft from oxalate injury. Serial monitoring of Pox in the immediate post-transplant period helps guide dialysis decisions, making the rapid turnaround of post-transplantation levels crucial to limit or avoid post-transplant dialysis. Typically, once Pox levels consistently remain < 20 µmol/L, dialysis is not needed [82]. Some centers prefer CKRT as the initial post-transplant modality as it allows for continuous oxalate removal without a concern for rebound to injurious levels.

Maintenance post-transplantation management is outlined in T7.

Box 3 Best practices for transplantation planning in primary hyperoxaluria patients with kidney failure

T1: Transplant planning [24, 74–77]

1. PH patients should be referred for transplant assessment in CKD 3b or 4, prior to Pox levels > 30–45 µmol/L
2. Selection of liver and kidney vs. kidney alone transplantation should be informed by PH type and treatment available to reduce hepatic oxalate production, its effectiveness, and reliability of its availability after transplant. See **T2–T5**
3. Recommend prompt transplantation in most patients to minimize oxalosis progression
4. Throughout the transplant workup period, optimize oxalate removal by dialysis and/or measures to lower hepatic oxalate production. Ideally, Pox should be < 60 µmol/L before proceeding to kidney transplant alone in the following circumstances: patients on RNAi therapy; pyridoxine sensitive PH1 patients; patients with PH2; and/or CLKT
5. Significant systemic oxalate burden may threaten kidney allograft function and may warrant delay until reduction of oxalate burden with intensive dialysis and/or use of agents to reduce hepatic oxalate production when available
6. Transplanting centers should have availability of rapid turnaround of Pox levels; ability to initiate HD/CKRT quickly if required post-transplant; and pathology expertise to discern oxalate crystals on biopsy specimens
7. Native nephrectomy either prior to or at the time of kidney transplant may be considered to protect the allograft from oxalate deposition from excretion of stored oxalate

T2: Transplantation in PH1 patients with CKD stages 4–5 with full pyridoxine responsiveness or those receiving RNAi treatment: [50, 59]

1. In the setting of full pyridoxine responsiveness or control of oxalate production with RNAi treatment, consider kidney-only transplant
2. Donation by donors with heterozygous mutation do not preclude kidney only donation

T3: Transplantation in PH1 in the absence of available or effective RNAi therapy or complete pyridoxine responsiveness [78, 79]

1. CLKT is recommended
2. SLKT or CLKT result in similar rates of patient and graft survival

- Local medical resources and expertise along with consideration of specific patient factors and the donor source should determine the choice of SLKT vs. CLKT

3. Deceased donor organs: regional and national policies may include PH-specific policies defining medical eligibility criteria for listing and prioritization of kidney, liver, and CLKT for both adult and pediatric patients
4. Attention to donor factors that could minimize delayed graft function such as donor age, size and geographical location to avoid prolonged cold ischemia time are important

T4: Transplantation in PH2 [80]

PH2 patients may do well following kidney only transplant, however, in those with significant oxalosis, liver transplantation may be considered, pending reports of additional experience.

T5: Transplantation in PH3

There are no reports of transplantation in PH3 and understanding of changes in oxalate metabolism in this PH type remain incomplete. Kidney only transplantation is recommended pending further evidence

T6: Peri-operative and early post-transplant management [15, 75, 81, 82]

1. Transplant recipients with Pox > 30 µmol/L should receive HD in the immediate pre-operative period to reduce the Pox level if suitable dialysis access is available
2. Transplant recipients should be kept adequately hydrated while NPO before transplantation to avoid effective volume contraction, while avoiding volume overload
3. Follow local immunosuppression protocols including induction and maintenance immunosuppression in cases of kidney-only transplant or CLKT. If there is delayed kidney allograft function, consider delay in the start of calcineurin inhibitors with use of an alternate induction protocol, or lower target drug levels if introduced early, to minimize nephrotoxicity
4. Ensure optimal hydration intraoperatively (2–3 L/m^2/day) if feasible to allow rapid clearance of oxalate as effective GFR is restored
5. Continue intravenous hydration (2–3 L/m^2/day) postoperatively after transplantation as tolerated with attention to overall fluid balance
6. Avoid use of furosemide or other loop diuretics in PH patients after transplantation when possible; use a thiazide diuretic if needed
7. Observe without dialysis if prompt allograft function achieved with excellent urine output from the transplant kidney (> 1–2 ml/kg/hr) in the immediate post-transplant period
8. Start dialysis promptly (CKRT or intermittent HD), if transplant urine output is sub-optimal (< 1 ml/kg/hr) and/or daily Pox monitoring is not feasible in patients with high pre-transplant Pox levels
9. Continue CKRT or daily HD until graft function is established and Pox is < 20 µmol/L. Ensure maintenance of adequate intravascular volume during dialysis

T7: Post-transplant maintenance, monitoring and management

1. Continue optimal hydration (2–3 L/m^2/day) after transplantation until Uox excretion remains consistently within the normal range

- 6–12 months or longer may be required to eliminate the excess oxalate, depending on pre-transplant systemic oxalate load

2. Recommend to monitor Pox levels. Suggested frequency is:

- Daily in the first post-transplant week if there is delayed graft function. Reduce to once weekly during the first month post-transplant; once monthly during months 2–4 post-transplant; every 3 months until 1 year post-transplant
- In kidney only transplant recipients receiving RNAi or pyridoxine treatment, Pox should be measured every 3 months thereafter
- With any occurrence of acute kidney injury, measure Pox level promptly, with follow up levels guided by results and ongoing kidney function

3. Recommend to monitor urine oxalate levels. Suggested frequency:

- Monthly for 6 months and then every 3 months during the first year
- In liver transplant or CLKT recipients, 6 monthly after the first year until consistently within the normal range
- In kidney only recipients receiving RNAi or pyridoxine treatment, 3 monthly indefinitely

4. Initiate crystallization inhibitors post kidney transplant when tolerated and continue until Uox normalizes (Box 1)

CKD, chronic kidney disease; *CKRT*, continuous kidney replacement therapy; *CLKT*, combined liver–kidney transplant; *eGFR*, estimated glomerular filtration rate; *HD*, hemodialysis; *NPO*, nothing by mouth; *PD*, peritoneal dialysis; *PH1*, primary hyperoxaluria type 1; *PH2*, primary hyperoxaluria type 2; *PH3*, primary hyperoxaluria type 3; *Pox*, plasma oxalate; *SLKT*, sequential liver–kidney transplant; *Uox*, urine oxalate

Pox is monitored at least weekly for 4 weeks post-transplant, and then at least monthly. By 6 months post-transplant, with stable Pox < 20 µmol/L, levels can transition to every 3 months until a year post-transplant, with this frequency maintained indefinitely for those treated with RNAi or pyridoxine. With any acute kidney injury and drop in GFR, Pox should be measured urgently.

Uox levels post-transplant reflect systemic oxalate burden going into transplantation. Brisk hydration (2–3 L/m^2/day) with crystallization inhibitor prescription is necessary until Uox is consistently normal. Uox should be assessed monthly for at least 6 months and then every 3 months until a year post-transplant, with this frequency maintained indefinitely for kidney-alone recipients treated with RNAi or pyridoxine. Uox should be measured every 6–12 months until normal following liver transplantation.

Patient advocacy groups that exist in many countries (for example Oxalosis and Hyperoxaluria Foundation in North America) are an invaluable resource for patients and families, providing support and education while promoting research and innovation. Contact information for such groups should be provided routinely. To locate details on patient advocacy organizations dedicated to primary hyperoxaluria like the Oxalosis and Hyperoxaluria Foundation, seek information through reputable sources or inquire with healthcare professionals and online forums.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00467-024-06328-2.

Acknowledgements We are grateful to the Oxalosis and Hyperoxaluria Foundation for convening the panel of international experts in PH. Kim Hollander, Executive Director, and Julie Bertarelli, Operations Coordinator, provided invaluable guidance and administrative support. We thank Maya Vaishnaw for design assistance with the diagnostic algorithm and graphic abstract.

Declarations

Conflict of interest *MM:* Alnylam Pharmaceuticals-served as site PI for use of lumasiran for PH1; PI longitudinal study (BONAPH1DE); Novo Nordisk Inc: served in the advisory board; *EH:* Research funding: Dicerna; Consulting fees, Advisory Board chair, speaker fees and travel funding from Alnylam; Consulting fees from Arbor Biotechnologies; *DM:* Research funding—Dicerna, Alnylam, OxThera; Advisory Boards—Synlogic, Mirum Pharmaceuticals, Consulting agreements—Oxthera, Dicerna, Alnylam; *YF*: Alnylam – consulting fees, research funding; Dicerna – travel grant to attend investigators' meeting; *DJS:* Received grant funding for research from Alnylam and Dicerna Pharmaceuticals; *JC:* None; *LC:* Nuwellis-Consultant; *KP:* None; *JS*: Alnylam: research funding, consulting fees, Novo-Nordisk: scientific advisory; *MJGS:* Advisory Boards for Alnylam Pharmaceuticals, Cantero Therapeutics, Dicerna Pharmaceuticals, and BioPorto. Chairs a Data Safety Monitoring Board for a clinical trial for Dicerna. Member of the Scientific Advisory Board of the Oxalosis and Hyperoxaluria Foundation; *MAB:* Novo Nordisk (previously Dicerna): scientific advisory, PI clinical trial Nedosiran; Alnylam: scientific advisory, PI longitudinal study (BONAPH1DE); Chinook: scientific advisory; Cantero (previously Orfan): scientific advisory; UpToDate: author and section editor.

References

1. Demoulin N, Aydin S, Gillion V, Morelle J, Jadoul M (2022) Pathophysiology and management of hyperoxaluria and oxalate nephropathy: a review. Am J Kidney Dis 79:717–727
2. Fargue S, Acquaviva Bourdain C (2022) Primary hyperoxaluria type 1: pathophysiology and genetics. Clin Kidney J 15(Suppl 1):i4–i8
3. Danpure CJ, Jennings R (1986) Peroxisomal alanine:glyoxylate aminotransferase deficiency in primary hyperoxaluria type I. FEBS Lett 201:20–24
4. Webster KE, Ferree PM, Holmes RP, Cramer SD (2000) Identification of missense, nonsense, and deletion mutations in the GRHPR gene in patients with primary hyperoxaluria type II (PH2). Hum Genet 107:176–185
5. Monico CG, Rossetti S, Belostotsky R, Cogal AG, Herges RM, Seide BM, Olson JB, Bergstrahl EJ, Williams HJ, Haley WE, Frishberg Y, Milliner DS (2011) Primary hyperoxaluria type III gene HOGA1 (formerly DHDPSL) as a possible risk factor for idiopathic calcium oxalate urolithiasis. Clin J Am Soc Nephrol 6:2289–2295
6. Martin-Higueras C, Garrelfs SF, Groothoff JW, Jacob DE, Moochhala SH, Bacchetta J, Acquaviva C, Zaniew M, Sikora P, Beck BB, Hoppe B (2021) A report from the European Hyperoxaluria Consortium (OxalEurope) Registry on a large cohort of patients with primary hyperoxaluria type 3. Kidney Int 100:621–635
7. Groothoff JW, Metry E, Deesker L, Garrelfs S, Acquaviva C, Almardini R, Beck BB, Boyer O, Cerkauskiene R, Ferraro PM, Groen LA, Gupta A, Knebelmann B, Mandrile G, Moochhala SS, Prytula A, Putnik J, Rumsby G, Soliman NA, Somani B, Bacchetta J (2023) Clinical practice recommendations for primary hyperoxaluria: an expert consensus statement from ERKNet and OxalEurope. Nat Rev Nephrol 19:194-211
8. Niederberger M, Spranger J (2020) Delphi technique in health sciences: a map. Front Public Health 8:457
9. Sas DJ, Harris C, Milliner DS (2019) Recent advances in the identification and management of inherited hyperoxalurias. Urolithiasis 47:79–89
10. Edvardsson VO, Goldfarb DS, Lieske JC, Beara-Lasic L, Anglani F, Milliner DS, Palsson R (2013) Hereditary causes of kidney stones and chronic kidney disease. Pediatr Nephrol 28:1923–1942
11. Edvardsson V, Sas D (2022) Urinary stone disease and nephrocalcinosis. In Emma F, et al (ed) Pediatric Nephrology, 8th edn. Springer, Cham
12. Marangella M, Petrarulo M, Vitale C, Daniele PG, Sammartano S, Cosseddu D, Linari F (1991) Serum calcium oxalate saturation in patients on maintenance haemodialysis for primary hyperoxaluria or oxalosis-unrelated renal diseases. Clin Sci (Lond) 81:483–490
13. Milliner DS, McGregor TL, Thompson A, Dehmel B, Knight J, Rosskamp R, Blank M, Yang S, Fargue S, Rumsby G, Groothoff J, Allain M, West M, Hollander K, Lowther WT, Lieske JC (2020) End points for clinical trials in primary hyperoxaluria. Clin J Am Soc Nephrol 15:1056–1065
14. Milliner DS, Cochat P, Hulton SA, Harambat J, Banos A, Dehmel B, Lindner E (2021) Plasma oxalate and eGFR are correlated in primary hyperoxaluria patients with maintained kidney function-data from three placebo-controlled studies. Pediatr Nephrol 36:1785–1793
15. Hoppe B, Kemper MJ, Bökenkamp A, Portale AA, Cohn RA, Langman CB (1999) Plasma calcium oxalate supersaturation in children with primary hyperoxaluria and end-stage renal failure. Kidney Int 56:268–274

16. Mandrile G, Beck B, Acquaviva C, Rumsby G, Deesker L, Garrelfs S, Gupta A, Bacchetta J, Groothoff J; OxalEurope Consortium/Erknet Guideline Workgroup On Hyperoxaluria (2023) Genetic assessment in primary hyperoxaluria: why it matters. Pediatr Nephrol 38:625–634
17. Sas DJ, Enders FT, Mehta RA, Tang X, Zhao F, Seide BM, Milliner DS, Lieske JC (2020) Clinical features of genetically confirmed patients with primary hyperoxaluria identified by clinical indication versus familial screening. Kidney Int 97:786–792
18. Pearle MS, Goldfarb DS, Assimos DG, Curhan G, Denu-Ciocca CJ, Matlaga BR, Monga M, Penniston KL, Preminger GM, Turk TM, White JR; American Urological Association (2014) Medical management of kidney stones: AUA guideline. J Urol 192:316–324
19. Gupta A, Somers MJG, Baum MA (2022) Treatment of primary hyperoxaluria type 1. Clin Kidney J 15(Suppl 1):i9–i13
20. Cochat P, Groothoff J (2013) Primary hyperoxaluria type 1: practical and ethical issues. Pediatr Nephrol 28:2273–2281
21. Leumann E, Hoppe B, Neuhaus T (1993) Management of primary hyperoxaluria: efficacy of oral citrate administration. Pediatr Nephrol 7:207–211
22. Meschi T, Maggiore U, Fiaccadori E, Schianchi T, Bosi S, Adorni G, Ridolo E, Guerra A, Allegri F, Novarini A, Borghi L (2004) The effect of fruits and vegetables on urinary stone risk factors. Kidney Int 66:2402–2410
23. Massey L (2005) Magnesium therapy for nephrolithiasis. Magnes Res 18:123–126
24. Cochat P, Hulton SA, Acquaviva C, Danpure CJ, Daudon M, De Marchi M, Fargue S, Groothoff J, Harambat J, Hoppe B, Jamieson NV, Kemper MJ, Mandrile G, Marangella M, Picca S, Rumsby G, Salido E, Straub M, van Woerden CS; OxalEurope (2012) Primary hyperoxaluria type 1: indications for screening and guidance for diagnosis and treatment. Nephrol Dial Transplant 27:1729–1736
25. Noori N, Honarkar E, Goldfarb DS, Kalantar-Zadeh K, Taheri M, Shakhssalim N, Parvin M, Basiri A (2014) Urinary lithogenic risk profile in recurrent stone formers with hyperoxaluria: a randomized controlled trial comparing DASH (Dietary Approaches to Stop Hypertension)-style and low-oxalate diets. Am J Kidney Dis 63:456–463
26. Singh P, Chebib FT, Cogal AG, Gavrilov DK, Harris PC, Lieske JC (2020) Pyridoxine responsiveness in a type 1 primary hyperoxaluria patient with a rare (atypical). Kidney Int Rep 5:955–958
27. Mandrile G, van Woerden CS, Berchialla P, Beck BB, Acquaviva Bourdain C, Hulton SA, Rumsby G; OxalEurope Consortium (2014) Data from a large European study indicate that the outcome of primary hyperoxaluria type 1 correlates with the AGXT mutation type. Kidney Int 86:1197–1204
28. Fargue S, Rumsby G, Danpure CJ (2013) Multiple mechanisms of action of pyridoxine in primary hyperoxaluria type 1. Biochim Biophys Acta 1832:1776–1783
29. Garrelfs SF, Frishberg Y, Hulton SA, Koren MJ, O'Riordan WD, Cochat P, Deschênes G, Shasha-Lavsky H, Saland JM, Van't Hoff WG, Fuster DG, Magen D, Moochhala SH, Schalk G, Simkova E, Groothoff JW, Sas DJ, Meliambro KA, Lu J, Sweetser MT, Garg PP, Vaishnaw AK, Gansner JM, McGregor TL, Lieske JC; ILLUMINATE-A Collaborators (2021) Lumasiran, an RNAi Therapeutic for Primary Hyperoxaluria Type 1. N Engl J Med 384(13):1216–1226. https://doi.org/10.1056/NEJMoa2021712. PMID: 33789010
30. Frishberg Y, Deschênes G, Groothoff JW, Hulton SA, Magen D, Harambat J, Van't Hoff WG, Lorch U, Milliner DS, Lieske JC, Haslett P, Garg PP, Vaishnaw AK, Talamudupula S, Lu J, Habtemariam BA, Erbe DV, McGregor TL, Cochat P; study collaborators (2021) Phase 1/2 study of lumasiran for treatment of primary hyperoxaluria type 1: a placebo-controlled randomized clinical trial. Clin J Am Soc Nephrol 16:1025–1036
31. Sas DJ, Magen D, Hayes W, Shasha-Lavsky H, Michael M, Schulte I, Sellier-Leclerc AL, Lu J, Seddighzadeh A, Habtemariam B, McGregor TL, Fujita KP, Frishberg Y; ILLUMINATE-B Workgroup (2022) Phase 3 trial of lumasiran for primary hyperoxaluria type 1: a new RNAi therapeutic in infants and young children. Genet Med 24:654–662
32. Hayes W, Sas DJ, Magen D, Shasha-Lavsky H, Michael M, Sellier-Leclerc AL, Hogan J, Ngo T, Sweetser MT, Gansner JM, McGregor TL, Frishberg Y (2023) Efficacy and safety of lumasiran for infants and young children with primary hyperoxaluria type 1: 12-month analysis of the phase 3 ILLUMINATE-B trial. Pediatr Nephrol 38:1075–1086
33. Michael M, Groothoff JW, Shasha-Lavsky H, Lieske JC, Frishberg Y, Simkova E, Sellier-Leclerc AL, Devresse A, Guebre-Egziabher F, Bakkaloglu SA, Mourani C, Saqan R, Singer R, Willey R, Habtemariam B, Gansner JM, Bhan I, McGregor T, Magen D (2023) Lumasiran for advanced primary hyperoxaluria type 1: phase 3 ILLUMINATE-C trial. Am J Kidney Dis 81(2):145-155.e1
34. Stokes F, Acquaviva-Bourdain C, Hoppe B, Lieske JC, Lindner E, Toulson G, Vaz FM, Rumsby G (2020) Plasma oxalate: comparison of methodologies. Urolithiasis 48:473–480
35. Stevens PE, Levin A; Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members (2013) Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Ann Intern Med 158:825–830
36. Derveaux T, Delbeke P, Walraedt S, Raes A, Van Laecke S, Leroy BP, De Zaeytijd J (2016) Detailed clinical phenotyping of oxalate maculopathy in primary hyperoxaluria type 1 and review of the literature. Retina 36:2227–2235
37. Lagies R, Beck BB, Hoppe B, Sreeram N, Udink Ten Cate FE (2013) Apical sparing of longitudinal strain, left ventricular rotational abnormalities, and short-axis dysfunction in primary hyperoxaluria type 1. Circ Heart Fail 6:e45–e47
38. Sas DJ, Enders FT, Gunderson TM, Mehta RA, Olson JB, Seide BM, Banks CJ, Dehmel B, Pellikka PA, Lieske JC, Milliner DS (2021) Natural history of clinical, laboratory, and echocardiographic parameters of a primary hyperoxaluria cohort on long term hemodialysis. Front Med (Lausanne) 8:592357
39. Fisher D, Hiller N, Drukker A (1995) Oxalosis of bone: report of four cases and a new radiological staging. Pediatr Radiol 25:293–295
40. Ben-Shalom E, Cytter-Kuint R, Rinat C, Becker-Cohen R, Tzvi-Behr S, Goichberg J, Peles V, Frishberg Y (2021) Long-term complications of systemic oxalosis in children-a retrospective single-center cohort study. Pediatr Nephrol 36:3123–3132
41. Julian BA, Faugere MC, Malluche HH (1987) Oxalosis in bone causing a radiographical mimicry of renal osteodystrophy. Am J Kidney Dis 9:436–440
42. Rootman MS, Mozer-Glassberg Y, Gurevich M, Schwartz M, Konen O (2018) Imaging features of primary hyperoxaluria. Clin Imaging 52:370–376
43. El Hage S, Ghanem I, Baradhi A, Mourani C, Mallat S, Dagher F, Kharrat K (2008) Skeletal features of primary hyperoxaluria type 1, revisited. J Child Orthop 2:205–210
44. Merz LM, Born M, Kukuk G, Sprinkart AM, Becker I, Martin-Higueras C, Hoppe B (2023) Correction to: three Tesla magnetic resonance imaging detects oxalate osteopathy in patients with primary hyperoxaluria type I. Pediatr Nephrol 38:2497–2498
45. Merz LM, Born M, Kukuk G, Sprinkart AM, Becker I, Martin-Higueras C, Hoppe B (2023) Three Tesla magnetic resonance imaging detects oxalate osteopathy in patients with primary hyperoxaluria type I. Pediatr Nephrol 38:2083–2092
46. Bacchetta J, Fargue S, Boutroy S, Basmaison O, Vilayphiou N, Plotton I, Guebre-Egziabher F, Dohin B, Kohler R, Cochat P (2010) Bone metabolism in oxalosis: a single-center study

using new imaging techniques and biomarkers. Pediatr Nephrol 25:1081–1089
47. Tonnelet D, Benali K, Rasmussen C, Goulenok T, Piekarski E (2020) Diffuse hypermetabolic bone marrow infiltration in severe primary hyperoxaluria on FDG PET. Clin Nucl Med 45(6):e296–e298
48. Bacchetta J, Boivin G, Cochat P (2016) Bone impairment in primary hyperoxaluria: a review. Pediatr Nephrol 31:1–6
49. Monico CG, Rossetti S, Olson JB, Milliner DS (2005) Pyridoxine effect in type I primary hyperoxaluria is associated with the most common mutant allele. Kidney Int 67:1704–1709
50. Lorenz EC, Lieske JC, Seide BM, Meek AM, Olson JB, Bergstralh EJ, Milliner DS (2014) Sustained pyridoxine response in primary hyperoxaluria type 1 recipients of kidney alone transplant. Am J Transplant 14:1433–1438
51. Hopp K, Cogal AG, Bergstralh EJ, Seide BM, Olson JB, Meek AM, Lieske JC, Milliner DS, Harris PC; Rare Kidney Stone Consortium (2015) Phenotype-genotype correlations and estimated carrier frequencies of primary hyperoxaluria. J Am Soc Nephrol 26:2559–2570
52. Mandrile G, Beck B, Acquaviva C, Rumsby G, Deesker L, Garrelfs S, Gupta A, Bacchetta J, Groothoff J; OxalEurope Consortium/Erknet Guideline Workgroup On Hyperoxaluria (2022) Genetic assessment in primary hyperoxaluria: why it matters. Pediatr Nephrol 38:625-634
53. Milliner DS, Eickholt JT, Bergstralh EJ, Wilson DM, Smith LH (1994) Results of long-term treatment with orthophosphate and pyridoxine in patients with primary hyperoxaluria. N Engl J Med 331:1553–1558
54. Berini SE, Tracy JA, Engelstad JK, Lorenz EC, Milliner DS, Dyck PJ (2015) Progressive polyradiculoneuropathy due to intraneural oxalate deposition in type 1 primary hyperoxaluria. Muscle Nerve 51:449–454
55. Biebuyck N, Destombes C, Prakash R, Boyer O (2023) Is withdrawal of nocturnal hyperhydration possible in children with primary hyperoxaluria treated with RNAi? J Nephrol 36:1473–1476
56. Baum MA, Langman C, Cochat P, Lieske JC, Moochhala SH, Hamamoto S, Satoh H, Mourani C, Ariceta G, Torres A, Wolley M, Belostotsky V, Forbes TA, Groothoff J, Hayes W, Tönshoff B, Takayama T, Rosskamp R, Russell K, Zhou J, Amrite A, Hoppe B; PHYOX2 study investigators (2023) PHYOX2: a pivotal randomized study of nedosiran in primary hyperoxaluria type 1 or 2. Kidney Int 103:207–217
57. Martin-Higueras C, Feldkötter M, Hoppe B (2021) Is stiripentol truly effective for treating primary hyperoxaluria? Clin Kidney J 14:442–444
58. Martinez-Turrillas R, Martin-Mallo A, Rodriguez-Diaz S, Zapata-Linares N, Rodriguez-Marquez P, San Martin-Uriz P, Vilas-Zornoza A, Calleja-Cervantes ME, Salido E, Prosper F, Rodriguez-Madoz JR (2022) CRISPR-Cas9 inhibition of hepatic LDH as treatment of primary hyperoxaluria. Mol Ther Methods Clin Dev 25:137–146
59. Sellier-Leclerc AL, Metry E, Clave S, Perrin P, Acquaviva-Bourdain C, Levi C, Crop M, Caillard S, Moulin B, Groothoff J, Bacchetta J (2023) Isolated kidney transplantation under lumasiran therapy in primary hyperoxaluria type 1: a report of five cases. Nephrol Dial Transplant 38:517–521
60. Breeggemann MC, Gluck SL, Stoller ML, Lee MM (2023) A case report of kidney-only transplantation in primary hyperoxaluria type 1: a novel approach with the use of nedosiran. Case Rep Nephrol Dial 13:63–69
61. Zhao F, Bergstralh EJ, Mehta RA, Vaughan LE, Olson JB, Seide BM, Meek AM, Cogal AG, Lieske JC, Milliner DS; Investigators of Rare Kidney Stone Consortium (2016) Predictors of incident ESRD among patients with primary hyperoxaluria presenting prior to kidney failure. Clin J Am Soc Nephrol 11:119–126
62. Shah RJ, Vaughan LE, Enders FT, Milliner DS, Lieske JC (2020) Plasma oxalate as a predictor of kidney function decline in a primary hyperoxaluria cohort. Int J Mol Sci 21:3608
63. Watts RW, Veall N, Purkiss P (1984) Oxalate dynamics and removal rates during haemodialysis and peritoneal dialysis in patients with primary hyperoxaluria and severe renal failure. Clin Sci (Lond) 66:591–597
64. Marangella M, Cosseddu D, Petrarulo M, Vitale C, Linari F (1993) Thresholds of serum calcium oxalate supersaturation in relation to renal function in patients with or without primary hyperoxaluria. Nephrol Dial Transplant 8:1333–1337
65. Marangella M, Petrarulo M, Cosseddu D, Vitale C, Linari F (1992) Oxalate balance studies in patients on hemodialysis for type I primary hyperoxaluria. Am J Kidney Dis 19:546–553
66. Illies F, Bonzel KE, Wingen AM, Latta K, Hoyer PF (2006) Clearance and removal of oxalate in children on intensified dialysis for primary hyperoxaluria type 1. Kidney Int 70:1642–1648
67. Ermer T, Kopp C, Asplin JR, Granja I, Perazella MA, Reichel M, Nolin TD, Eckardt KU, Aronson PS, Finkelstein FO, Knauf F (2017) Impact of regular or extended hemodialysis and hemodialfiltration on plasma oxalate concentrations in patients with end-stage renal disease. Kidney Int Rep 2:1050–1058
68. Franssen CF (2005) Oxalate clearance by haemodialysis–a comparison of seven dialysers. Nephrol Dial Transplant 20:1916–1921
69. Tang X, Bergstralh EJ, Mehta RA, Vrtiska TJ, Milliner DS, Lieske JC (2015) Nephrocalcinosis is a risk factor for kidney failure in primary hyperoxaluria. Kidney Int 87:623–631
70. Díaz C, Catalinas FG, de Alvaro F, Torre A, Sánchez C, Costero O (2004) Long daily hemodialysis sessions correct systemic complications of oxalosis prior to combined liver-kidney transplantation: case report. Ther Apher Dial 8:52–55
71. Plumb TJ, Swee ML, Fillaus JA (2013) Nocturnal home hemodialysis for a patient with type 1 hyperoxaluria. Am J Kidney Dis 62:1155–1159
72. Yamauchi T, Quillard M, Takahashi S, Nguyen-Khoa M (2001) Oxalate removal by daily dialysis in a patient with primary hyperoxaluria type 1. Nephrol Dial Transplant 16:2407–2411
73. Tang X, Voskoboev NV, Wannarka SL, Olson JB, Milliner DS, Lieske JC (2014) Oxalate quantification in hemodialysate to assess dialysis adequacy for primary hyperoxaluria. Am J Nephrol 39:376–382
74. Cochat P, Fargue S, Harambat J (2010) Primary hyperoxaluria type 1: strategy for organ transplantation. Curr Opin Organ Transplant 15:590–593
75. Cornell LD, Amer H, Viehman JK, Mehta RA, Lieske JC, Lorenz EC, Heimbach JK, Stegall MD, Milliner DS; Rare Kidney Stone Consortium Primary Hyperoxaluria (RKSC PH) investigators (2022) Posttransplant recurrence of calcium oxalate crystals in patients with primary hyperoxaluria: incidence, risk factors, and effect on renal allograft function. Am J Transplant 22:85–95
76. Villani V, Gupta N, Elias N, Vagefi PA, Markmann JF, Paul E, Traum AZ, Yeh H (2017) Bilateral native nephrectomy reduces systemic oxalate level after combined liver-kidney transplant: a case report. Pediatr Transplant 21(3).
77. Mor E, Nesher E, Ben-Ari Z, Weissman I, Shaharabani E, Eizner S, Solomonov E, Rahamimov R, Braun M (2013) Sequential liver and kidney transplantation from a single living donor in two young adults with primary hyperoxaluria type 1. Liver Transpl 19:646–648
78. Metry EL, van Dijk LMM, Peters-Sengers H, Oosterveld MJS, Groothoff JW, Ploeg RJ, Stel VS, Garrelfs SF (2021) Transplantation outcomes in patients with primary hyperoxaluria: a systematic review. Pediatr Nephrol 36:2217–2226
79. Xiang J, Chen Z, Xu F, Mei S, Li Z, Zhou J, Dong Y, Gu Y, Huang Z, Hu Z (2020) Outcomes of liver-kidney transplantation in patients with

primary hyperoxaluria: an analysis of the scientific registry of transplant recipients database. BMC Gastroenterol 20:208
80. Dhondup T, Lorenz EC, Milliner DS, Lieske JC. (2018) Combined liver-kidney transplantation for primary hyperoxaluria type 2: a case report. Am J Transplant 18:253–257
81. Bergstralh EJ, Monico CG, Lieske JC, Herges RM, Langman CB, Hoppe B, Milliner DS; IPHR Investigators (2010) Transplantation outcomes in primary hyperoxaluria. Am J Transplant 10:2493–2501
82. Devresse A, Cochat P, Godefroid N, Kanaan N (2020) Transplantation for primary hyperoxaluria type 1: designing new strategies in the era of promising therapeutic perspectives. Kidney Int Rep 5:2136–2145
83. Lee E, Ramos-Gonzalez G, Rodig N, Elisofon S, Vakili K, Kim HB (2018) Bilateral native nephrectomy to reduce oxalate stores in children at the time of combined liver–kidney transplantation for primary hyperoxaluria type 1. Pediatr Nephrol 33:881–887