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Primary Hyperoxaluria Type 1

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Summary

Clinical characteristics

Primary hyperoxaluria type 1 (PH1) is caused by deficiency of the liver peroxisomal enzyme alanine-glyoxylate aminotransferase (AGT), which catalyzes the conversion of glyoxylate to glycine. When AGT activity is reduced or absent, glyoxylate is converted to oxalate, which cannot be metabolized and must be excreted by the kidneys. Insoluble calcium oxalate crystals form due to high urinary oxalate concentration. Urinary crystals aggregate, leading to nephrolithiasis (i.e., calcium oxalate kidney stones) in the renal pelvis / urinary tract; often the crystals deposit in kidney parenchyma (nephrocalcinosis). The age at presentation of PH1 ranges from infancy (age <12 months) in 10% of individuals, childhood/adolescence (age 1-17 years) in 70%, and adulthood (age ≥18 years) in 20%.

The natural history of untreated PH1 is (1) progressive decline in kidney function due to complications of nephrolithiasis (e.g., urinary obstruction, infection) and nephrocalcinosis, and (2) in persons with advanced chronic kidney disease (CKD), high plasma oxalate concentrations result in other organ and tissue damage from calcium oxalate deposition (i.e., "oxalosis"), most commonly in the bones, heart, and retina. In the absence of treatment, progression of oxalosis results in death from kidney failure and/or other organ involvement.

Diagnosis/testing

The diagnosis of PH1 is established in a proband with supportive laboratory findings (excess excretion of oxalate in the urine and/or markedly increased plasma oxalate concentration) and biallelic pathogenic variants in *AGXT* identified by molecular genetic testing.

Management

Targeted therapies: (1) Pyridoxine (vitamin B_6) to reduce liver oxalate production in individuals with missense *AGXT* variants known to be pyridoxine responsive; (2) RNA interference (RNAi) therapeutics (lumasiran and nedosiran) that target specific hepatic enzymes to reduce liver overproduction of oxalate; and (3) liver transplantation to restore normal hepatic AGT enzyme activity.

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Supportive care: Goal is to reduce stone formation, reduce frequency of symptomatic stone events, and preserve kidney function. Advanced loss of kidney function may require dialysis and kidney transplantation. Kidney and liver transplantation can be performed simultaneously or sequentially.

Surveillance: Individuals with PH1 require lifelong care including regularly scheduled assessments of (1) kidney function and urinalysis; (2) urine volume and urine oxalate excretion; (3) kidney ultrasound examination; and (4) signs and symptoms of systemic oxalosis (most commonly involving bones, heart, and retina). The frequency of these assessments is based on the individual's kidney function.

Agents/circumstances to avoid: Intravascular volume depletion; high doses of nonsteroidal anti-inflammatory drugs or any pharmacologic agent that can compromise kidney function; intake of vitamin C exceeding the recommended daily allowance; loop diuretics; large intake of foods high in oxalate (e.g., chocolate, rhubarb, starfruit).

Evaluation of relatives at risk: Family screening for PH1, particularly sibs of the proband, is warranted given intrafamilial variability, significant disease risks even in asymptomatic family members, and availability of therapeutic agents highly effective in reducing urine oxalate.

Pregnancy management: Although pregnancy does not appear to be an important risk factor for developing end-stage kidney disease (ESKD) in most women with PH1, close monitoring is warranted by both an obstetrician and nephrologist during pregnancy and the postpartum period. Of note, the recently approved targeted therapies, lumasiran and nedosiran, have not been studied during human pregnancy. While preclinical animal studies have been reassuring, pending more clinical data the authors would advise women to discontinue use of either therapy prior to becoming pregnant and during pregnancy.

Genetic counseling

PH1 is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an *AGXT* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Once the *AGXT* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and prenatal/preimplantation genetic testing are possible.

Diagnosis

Consensus guidelines for the diagnostic approach to individuals with a suspicion of primary hyperoxaluria and management of all types of primary hyperoxaluria have been published [Groothoff et al 2023, Michael et al 2024]. See Figure 1 for a diagnostic algorithm.

Suggestive Findings

Primary hyperoxaluria type 1 (PH1) **should be suspected** in a proband of any age with recurrent calcium oxalate stones or nephrocalcinosis, especially if associated with progressive chronic kidney disease (CKD) or a family history of stones and CKD [Groothoff et al 2023, Michael et al 2024]. Typical clinical findings vary by age at presentation.

Clinical Findings

Infancy (age <12 months)

- Impaired kidney function or poor weight gain and/or poor linear growth of undetermined etiology [Deesker et al 2022]

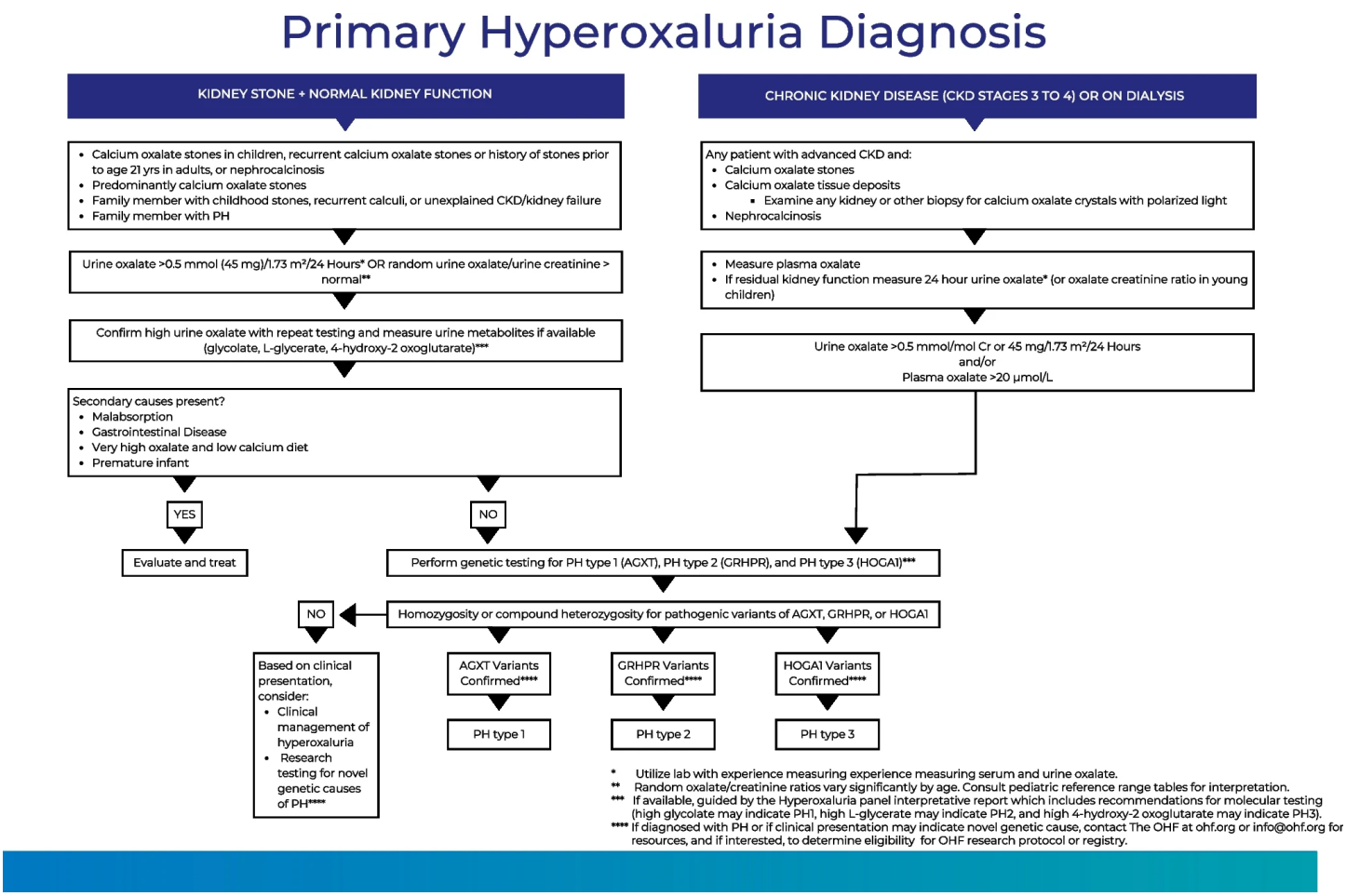

Figure 1. Algorithm for diagnostic evaluation of primary hyperoxaluria

Reproduced with permission from Michael et al [2024]

- Nephrocalcinosis. Renal ultrasound examination most commonly reveals diffuse nephrocalcinosis with few if any observable discrete stones.
- First kidney stone

Childhood/adolescence (ages 1-17 years)

- First kidney stone [Cochat et al 2012]
- Multiple or recurring calcium-containing kidney stones
- Impairment of kidney function associated with stones or nephrocalcinosis. Nephrocalcinosis has been observed at the time of the first imaging study in 30% of individuals with preserved kidney function [Tang et al 2014].

Adulthood (age ≥18 years)

- Recurrent nephrolithiasis in which kidney imaging reveals multiple bilateral radiopaque calculi known or suspected to be calcium oxalate, especially if urinary testing is available and confirms hyperoxaluria [Pszczolinski et al 2024]
- Nephrocalcinosis
- Reduced kidney function or end-stage kidney disease (ESKD) with a history of kidney stones or nephrocalcinosis [Edvardsson et al 2013]

Post kidney transplantation. In approximately 10% of individuals with PH1 the diagnosis is made following kidney transplantation when calcium oxalate crystals are found on allograft biopsy performed for early non-function of the transplanted kidney and/or a subsequent increase in serum creatinine concentration [Cochat & Rumsby 2013].

Supportive Laboratory Findings

Hyperoxaluria resulting from increased hepatic production of oxalate is the central laboratory feature of PH1 (see Table 1). Preferred testing for assessment of oxalate excretion is based on kidney function [Milliner et al 2020].

- CKD stages 1 to 3b (i.e., kidney function is preserved). Because most excess oxalate is excreted in the urine and plasma oxalate concentrations are normal to mildly elevated, measurement of urine oxalate is important.
- CKD stages 4 and 5 (advanced CKD or the individual is on dialysis). Because less oxalate than expected is excreted in the urine and plasma oxalate concentration is markedly increased, assessment of plasma oxalate concentration is preferred.

Table 1. Primary Hyperoxaluria Type 1: Supportive Laboratory Findings

Laboratory Test	Constraints	Findings in PH1	Comments
Urine oxalate, 24-hr collection [1]	All individuals where possible	UOx >0.5 mmol/24 hours	• Must be corrected to BSA 1.73 m^2 in children • At least 2 collections required to confirm abnormality • Less reliable when eGFR <30 mL/min/BSA • Data for normal values for children age <2 yrs are limited.
Urine oxalate:creatinine, spot urine specimen [1]	Young children or others in whom 24-hr collection is difficult	UOx > normal range for age [2]	At least 2 collections to confirm abnormality
Plasma oxalate concentration	When eGFR <30 mL/min/1.73 m^2	• POx >20 is consistent w/ PH1. • POx >50 µmol/L is strongly suggestive of PH1 [Perinpam et al 2017] [3, 4]	• Plasma samples require special handling. • Results vary by method. • Available only in specialty labs
Kidney stone analysis	When stone is available	100% calcium oxalate monohydrate	Suggestive of but not specific for PH1

BSA = body surface area; eGFR = estimated glomerular filtration rate; POx = plasma oxalate; UOx = urine oxalate

1. Accurate measurements rely on acidification of the urine to a urine pH ≤2 either during collection or in the laboratory to dissolve any calcium oxalate crystals that form in the urine in vivo or in vitro after collection.

2. Urine oxalate:creatinine changes rapidly in infancy and childhood [Sas et al 2024]. See Table 2 for normal values by age.

3. Plasma oxalate concentration, increased in individuals with kidney failure of any cause, is much greater in individuals with PH1; thus, plasma oxalate concentration in individuals with suspected PH1 should be compared with that of other individuals with kidney failure rather than healthy individuals [Groothoff et al 2023].

4. Plasma oxalate concentrations are highest in individuals with PH1 on dialysis, often >100 µmol/L [Sas et al 2021, Metry et al 2023].

Table 2. Normal Spot Urine Oxalate:Creatinine Ratio by Age

Age	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

Modified from Edvardsson & Sas [2022] with permission

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of PH1 **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *AGXT* identified by molecular genetic testing (see Table 3).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of biallelic *AGXT* variants of uncertain significance (or of one known *AGXT* pathogenic variant and one *AGXT* variant of uncertain significance (VUS) does not establish or rule out the diagnosis. For information about evaluation of VUSs, see Molecular Genetics, ***AGXT*-specific technical laboratory considerations**.)

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1) whereas genomic testing does not (see Option 2).

Option 1

A nephrology multigene panel that includes *AGXT* and all known monogenic forms of kidney stone disease and/or nephrocalcinosis (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

Comprehensive genomic testing does not require the clinician to determine which group of genes is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. To date, the majority of reported *AGXT* pathogenic variants are within the coding region and are likely to be identified on exome

sequencing. A common approach with exome and genome sequencing is to limit the initial analysis to known genes for monogenic forms of kidney stone disease and/or nephrocalcinosis, to limit identification of variants with a low likelihood of being causative.

Note: If an individual has clinical features of PH1 (see Suggestive Findings) and only one or no pathogenic variant in *AGXT* is identified on multigene panel testing or exome sequencing, genome sequencing may be considered to more thoroughly interrogate *AGXT* (e.g., to detect deep intronic variants or structural variants).

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 3. Molecular Genetic Testing Used in Primary Hyperoxaluria Type 1

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
AGXT	Sequence analysis [3]	>97% [4]
	Gene-targeted deletion/duplication analysis [5]	<3% [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Out of more than 260 known *AGXT* pathogenic variants, approximately ten large deletions have been reported [Nogueira et al 2000, Coulter-Mackie et al 2001, Coulter-Mackie et al 2005, Monico et al 2007, Williams et al 2009, Tammachote et al 2012, Cogal et al 2021, Zhao et al 2022].

Clinical Characteristics

Clinical Description

Primary hyperoxaluria type 1 (PH1) is caused by deficiency of the liver peroxisomal enzyme alanine-glyoxylate aminotransferase (AGT), which catalyzes the conversion of glyoxylate to glycine. When AGT activity is reduced or absent, glyoxylate is converted to oxalate, which cannot be metabolized and must be excreted by the kidneys. Insoluble calcium oxalate crystals form due to high urinary oxalate concentration. Crystal deposition leads to nephrolithiasis (i.e., calcium oxalate kidney stones) in the renal pelvis / urinary tract and often in kidney parenchyma (nephrocalcinosis).

The natural history of untreated PH1 is (1) progressive decline in kidney function because of complications of nephrolithiasis (e.g., urinary obstruction, infection) and nephrocalcinosis, and (2) other organ and tissue damage from calcium oxalate deposition (i.e., "oxalosis"). In the absence of treatment oxalosis progresses leading to death from kidney failure and/or other organ involvement [van der Hoeven et al 2012, Cochat & Groothoff 2013, Metry et al 2023].

Table 4. Primary Hyperoxaluria Type 1: Clinical Presentations

Age at Presentation	% of All PH1	Initial Manifestations			
		Nephrolithiasis	Nephrocalcinosis	Kidney function	Oxalosis
Infantile onset (age <12 mos)	10% [1]	±	+++	Advanced CKD or ESKD	+++
Childhood/ adolescence (ages 1-17 yrs)	70%	+++	+	Normal-to-moderate reduction	Only occurs w/ ESKD
Adulthood (age ≥18 yrs)	20%	+++	++ w/advanced CKD or ESKD	Mild-to-moderate reduction; some w/ ESKD	Only occurs w/ ESKD

± = variably present or not; + = present in some affected individuals; ++ = often present; +++ = present in most affected individuals; CKD = chronic kidney disease; ESKD = end-stage kidney disease

1. In most reports from Europe and the United States, infantile onset accounts for 10% or less of PH1 [Hopp et al 2015, Deesker et al 2022], whereas it can be as high as 35% in other areas, especially where consanguinity is common [Soliman et al 2017].

Infantile Onset (age <12 months)

In severe, early-onset (infantile) disease, the presenting signs and symptoms include nephrocalcinosis (with or without nephrolithiasis) and poor weight gain and/or poor linear growth related to advanced kidney failure.

End-stage kidney disease (ESKD) can appear as early as age four to six months and typically before age 12 months. Infants who do not require dialysis at the time of diagnosis often progress to ESKD over months despite optimal supportive care [Deesker et al 2022]. When ESKD occurs, the intensive kidney dialysis required to remove oxalate is particularly demanding for the infants, their families, and providers [Lawrence & Wattenberg 2020, Gupta et al 2022].

Over time, worsening systemic oxalate deposition results in multiorgan disease including oxalate osteopathy characterized by growth delay and pathologic fractures, retinal deposition with visual impairment, and cardiomyopathy and cardiac arrythmias [Ben-Shalom et al 2021].

Prognosis of infantile-onset PH1. Mortality is high in infantile-onset PH1 but has improved in recent years [Deesker et al 2022]. Earlier diagnosis, advances in supportive care including kidney dialysis, and successful liver transplantation in infants have all played a role. Further improvement may be anticipated due to the recent availability of effective RNA interference agents that reduce hepatic oxalate generation (see Management, Treatment of Manifestations).

Childhood/Adolescent Onset (ages 1-17 years)

In most of the 70% of individuals with PH1 who are first diagnosed in childhood or adolescence, the initial manifestations occur before age ten years, and in 85%-90% by age 20 years [van der Hoeven et al 2012, Mandrile et al 2014]. In one large study, median age at symptom onset was 4.0 years and age at diagnosis was 8.0 years [Metry et al 2023].

Most often individuals with disease onset in this age group have findings related to nephrolithiasis including hematuria, dysuria, pain, urinary tract infection, and/or stone passage [Pszczolinski et al 2024]. New stones and recurring signs and symptoms caused by stones develop over time and may require urologic intervention. However, children and adolescents with PH1 most often have normal growth and development and are well between the symptoms caused by stones.

Occasionally individuals with disease onset in this age group present with moderate-to-severe chronic kidney disease (CKD) and progress to ESKD during childhood or adolescence.

At the time of diagnosis, kidney function may be normal or show mild-to-moderate reduction, which worsens slowly over time [Singh et al 2022a, Pszczolinski et al 2024]. As in individuals of all ages with PH1, rapid decline in kidney function can result from stones that cause bilateral obstruction, stone removal procedures [Carrasco et al 2015], and/or dehydration from any cause.

Prognosis of childhood/adolescent-onset PH1. Although most individuals retain sufficient kidney function to avoid kidney replacement therapy until adulthood, they may progress to kidney failure before age 40 years [Singh et al 2022b]. Higher urine oxalate excretion and nephrocalcinosis are associated with greater risk of subsequent kidney failure [Tang et al 2015, Zhao et al 2016, Metry et al 2023]. Among individuals with onset of kidney failure during childhood, the intensity of kidney dialysis required to remove oxalate is demanding for the affected individuals and their families [Lawrence & Wattenberg 2020].

In 54 individuals with PH1 who developed kidney failure during childhood or adolescence in the years 2000 to 2009 the five-year survival was 83% following initiation of kidney replacement therapy (i.e., dialysis and/or transplantation), an improvement when compared to the outcome of individuals with PH1 treated with kidney replacement therapy prior to 2000 (particularly in children younger than age two years). Nonetheless, outcomes in children with PH1 were less favorable when compared to children with other types of kidney disease who required kidney replacement therapy [Harambat et al 2012].

Adult Onset (age ≥18 years)

The 20% of individuals with PH1 first diagnosed as adults [Metry et al 2023] most often present with kidney stones [van der Hoeven et al 2012, Pszczolinski et al 2024]. Of note, a focused past medical history often reveals that many of these adults have had past stone-related symptoms or stone removal procedures without consideration of PH1 as a potential cause, resulting in delay in establishing the correct diagnosis [Metry et al 2023, Pszczolinski et al 2024].

The finding at initial presentation in adults with PH1 may be acute kidney failure due to bilateral renal obstruction caused by calcium oxalate stones or other illnesses that compromise fluid intake and thus urine volume. Acute kidney failure can also occur following stone removal procedures [Grateau et al 1987, Carrasco et al 2015].

PH1 is not correctly diagnosed in 20%-50% of individuals with adult-onset disease until later stages of CKD or after kidney failure [Zhao et al 2016, Metry et al 2023, Pszczolinski et al 2024]. Indeed, in approximately 10% of these adults the diagnosis of PH1 is only first considered following recurrent disease in a transplanted kidney when an allograft biopsy reveals calcium oxalate crystals, which is often accompanied by graft loss [Cochat & Groothoff 2013, Mandrile et al 2023, Metry et al 2023].

In contrast, some individuals with PH1 remain free of manifestations or have minimal findings into the sixth decade of life [Cochat & Rumsby 2013, Hopp et al 2015].

Prognosis of adult-onset PH1. Of note, mild-to-moderate reduction in kidney function is common at diagnosis. Glomerular filtration rate (GFR) in these adults tends to be lower compared to that in children and adolescents with PH1 at the time of initial diagnosis [Pszczolinski et al 2024]. The rate of decline in estimated GFR (eGFR) over time is variable, though more rapid in more advanced stages of CKD [Singh et al 2022a].

PH1 of Any Age

Oxalosis is a complication of PH1 at any age when GFR is less than 30 mL/min/1.73 m^2, the point at which the daily production of oxalate exceeds renal oxalate clearance, resulting in a rapid rise in plasma oxalate concentration and deposition of calcium oxalate crystals in the kidneys (nephrocalcinosis), with further reduction in kidney function and damage to other tissues/organs including bone, retina, myocardium, blood vessels, bone marrow, subcutaneous tissue, peripheral nerves, and synovia [Cochat & Rumsby 2013, Ben-Shalom

et al 2021, Sas et al 2021]. Progressive oxalosis, observed over time in most individuals with PH1 who are on dialysis, eventually leads to death.

- **Bone.** Involvement of bone, the largest repository for excess oxalate, can result in oxalate osteodystrophy characterized by bone pain and pathologic fractures as well as growth delay. Oxalate osteodystrophy can be especially severe in infants on dialysis [Bacchetta et al 2016, Ben-Shalom et al 2021].
- **Retina.** Retinal oxalate deposition, frequent in infants with PH1 in kidney failure, is associated with retinal fibrosis that can cause visual impairment that may be permanent [Birtel et al 2019, Deesker et al 2022]. Retinal oxalate deposits, less common in adults, typically do not cause visual impairment [Birtel et al 2019].
- **Heart.** Calcium oxalate crystals in the myocardium can cause cardiomyopathy resulting in heart failure; crystals in the conduction system can cause arrythmias and heart block [Sas et al 2021, Deesker et al 2022].

Other less common clinical manifestations of oxalate deposition include:

- Bone marrow involvement resulting in anemia refractory to erythropoietin-stimulating agents (ESA) and splenomegaly [Ben-Shalom et al 2021, Deesker et al 2022];
- Vascular involvement resulting in ischemia, most often manifesting as non-healing cutaneous ulcers;
- Cerebral infarcts resulting from cerebral vessel involvement [Rao et al 2014];
- Refractory hypotension in advanced oxalosis;
- Peripheral neuropathy [Berini et al 2015];
- Dental pain and root resorption [Mitsimponas et al 2012];
- Hypothyroidism [Ben-Shalom et al 2021].

Most manifestations of oxalosis are slowly reversible following successful liver and kidney transplantation (see Management, Targeted Therapies); however, mobilization of oxalate tissue deposits poses risk of oxalate injury to the transplanted kidney.

Note: While infantile oxalosis was observed to be rare in those homozygous for pyridoxine-responsive *AGXT* variants (see Genotype-Phenotype Correlations) and to occur in up to 25% of those homozygous for null *AGXT* variants [Metry et al 2023], no specific *AGXT* pathogenic variants appear to account for such severe manifestations. Factors such as physiologically lower eGFR in infants associated with high oxalate production may play important roles [Sas et al 2024].

Intrafamilial Variability

The age at onset and clinical manifestations can vary widely even among sibs with the same biallelic *AGXT* pathogenic variants. Differences of more than 20 years between age of onset of ESKD have been observed among sibs in some families [Hopp et al 2015]. Likewise, affected sibs often demonstrate widely discordant disease manifestations [Frishberg et al 2005, Cochat & Rumsby 2013, Ben-Shalom et al 2022, Deesker et al 2022].

Genotype-Phenotype Correlations

Genotype-phenotype correlations reported with specific *AGXT* pathogenic variants (see Table 10) and classes of *AGXT* variants are summarized below.

Pyridoxine-responsive variants. Pyridoxine (vitamin B_6), a cofactor for AGT, acts as a chemical chaperone that promotes enzyme function. Individuals homozygous for three pathogenic variants (p.Phe152Ile, p.Gly170Arg, or p.Ile244Thr) who are treated with pharmacologic doses of pyridoxine have reduced oxalate production and thus significantly older age at time of first presentation, diagnosis, and onset of kidney failure compared to other genotypes (see Figure 1 in Metry et al [2023]) (full text).

Although individuals who are compound heterozygotes for p.Phe152Ile, p.Gly170Arg, or p.Ile244Thr and a non-pyridoxine-sensitive pathogenic variant developed kidney failure at a slightly younger age than those homozygous for either variant, it was not significantly different.

- **p.Phe152Ile** (mostly from Western European countries). The median age of symptom onset was 19.6 years (range: 0.4-57.9) and age at diagnosis was 30.9 years (range: 8.4-59.3), the oldest of all other genotypes.
- **p.Gly170Arg** (responsible for approximately 30% of all variants). When compared to all other pathogenic variants, the urine oxalate excretion rates are lower even in the absence of treatment, the decline in eGFR is slower, and the onset of ESKD is later [Mandrile et al 2014, Hopp et al 2015, Singh et al 2022a, Metry et al 2023, Sas et al 2024]. Mean age at symptom onset was 14.0 years (range: 0.2-63.4) and age at diagnosis was 28.1 years (range: 0.2-63.4) [Metry et al 2023].
- **p.Ile244Thr** (primarily found in individuals from the Canary Islands and North Africa). Although data are limited, median age of symptom onset was 3.0 years (range: 0-49.6) and age at diagnosis was 8.0 years (range: 0-52.2) [Metry et al 2023]. Homozygotes for this variant showed kidney survival like that of homozygotes for p.Gly170Arg [Metry et al 2023].
- **p.Gly41Arg.** Anecdotal evidence suggests that this variant may be pyridoxine responsive [Singh et al 2020].

Classes of variants (missense and null variants). For information on classes of *AGXT* pathogenic variants by age of onset of symptoms, age at diagnosis, and age at kidney failure, see Figure 1 in Metry et al [2023] (full text).

Prevalence

Population-based analysis of *AGXT* pathogenic variants identified in the National Heart, Lung, and Blood Institute Exome Sequencing Project suggested that the prevalence of PH1 is 1:149,000 in European Americans and 1:157,000 in African Americans [Hopp et al 2015].

Clinical estimates of prevalence of PH1, primarily from European studies, range from one to three in 1,000,000 and one in 120,000 live births [Cochat & Rumsby 2013].

It is estimated that PH1 accounts for 1%-2% of children with ESKD in Western Europe and North America [Harambat et al 2012] and 10%-17% in Middle Eastern countries [Soliman & Mabrouk 2022].

The increased prevalence of PH1 in the Canary Islands is attributed to the *AGXT* pathogenic variant p.Ile244Thr (see Table 10) [Santana et al 2003].

A higher prevalence of PH1 is reported in Tunisia, Syria, and Druze communities due to high rates of consanguinity and founder variants in these populations [Kalfon et al 2017, Mbarek et al 2017, Murad et al 2021]. PH1 is also reported to be more common in Kuwait and other North African and Middle Eastern countries for similar reasons [Soliman & Mabrouk 2022].

When considering the above data, it is important to remember that PH1 remains underdiagnosed because of wide variability in its age of onset (infancy to adulthood) and clinical presentation (ranging from severe disease in infancy to adults with recurrent stones to advanced disease present in 20%-50% at the time of diagnosis). Additional factors contributing to underdiagnosis are lack of familiarity with PH1 among many physicians and lack of laboratory resources to measure oxalate concentration and perform genetic testing, especially in developing countries.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *AGXT*.

Differential Diagnosis

Differential diagnosis of primary hyperoxaluria type 1 (PH1) needs to take into consideration the three known causes of primary hyperoxaluria (type 1, type 2, and type 3; see Table 5) and other monogenic causes of stone diseases (see Table 6) while also considering calcium oxalate stone disease of unknown cause (also known as idiopathic calcium oxalate stone disease) and secondary hyperoxaluria.

All individuals with hyperoxaluria not attributable to secondary causes or who have CKD with suggestive clinical findings such as nephrolithiasis, nephrocalcinosis, or plasma oxalate concentration higher than expected for the CKD stage should undergo genetic testing for definitive diagnosis.

Primary Hyperoxaluria

Primary hyperoxaluria (PH) should be included in the differential diagnosis of any condition that causes calcium oxalate kidney stone disease and/or nephrocalcinosis or is associated with hyperoxaluria. The three known types of PH are PH1 (due to biallelic *AGXT* pathogenic variants), PH2 (due to biallelic *GRHPR* pathogenic variants), and PH3 (due to biallelic *HOGA1* pathogenic variants). Each gene encodes an enzyme for different metabolic pathways relevant for the metabolism of glyoxylate [Cochat & Rumsby 2013].

Of note, up to 10% of clinically suspected primary hyperoxaluria is genetically unresolved.

The clinical manifestations of the three known types of PH overlap considerably (see Table 5).

- Urinary organic acid metabolites reflect the metabolic pathways and can be useful in differentiating among PH types. Metabolites are typically measured in random urine specimens with correction for creatinine concentration. Urine glycolate is often elevated in PH1, glycerate is increased in PH2, and 4-hydroxy-2-oxoglutarate (HOG) and 2,4-dihydroxyglutarate (DHG) are increased in most individuals with PH3.
- One recent series of predominantly North American populations found urine oxalate to be lower in PH3 than in PH1 and PH2 [Singh et al 2022b], whereas a largely European series observed similar oxalate excretion rates among all three PH types [Martin-Higueras et al 2021].
- In both series urinary citrate and calcium excretion rates were normal in individuals with PH3 [Martin-Higueras et al 2021, Singh et al 2022b]. These observations in individuals with PH3 contrast to those in individuals with PH1, who often manifest lower urinary citrate and calcium excretion rates [Singh et al 2022b].

Table 5. Comparison of Primary Hyperoxaluria Types 1, 2, and 3

Gene (Disorder)	Proportion of PH [1]	Age of 1st Symptoms [2]	Suggestive Organic Acid Findings [3]	NC	eGFR [1] at Diagnosis (mL/min/1.73 m^2)	Plasma Oxalate [2] (µmol/L; nL <1.6)	Urine [2]			ESKD at Age 40 Yrs
							Oxalate (mmol/1.73 m^2/24 hr; nL <0.46)	Calcium (mg/1.73 m^2/24 hr; nL = 100-300)	Citrate (mg/1.73 m^2/24 h; nL = 320-1240)	
AGXT (PH1)	70%-80%	4.9 yrs	↑ glycolate	25.5%	48	12.5	1.6	51	255	~65%
GRHPR (PH2)	10%	5.7 yrs	↑ glycerate	15.7%	83	4.3	1.5	98	717	~35%

Table 5. continued from previous page.

Gene (Disorder)	Proportion of PH [1]	Age of 1st Symptoms [2]	Suggestive Organic Acid Findings [3]	NC	eGFR [1] at Diagnosis (mL/min/ 1.73 m^2)	Plasma Oxalate [2] (µmol/L; nL <1.6)	Urine [2]			ESKD at Age 40 Yrs
							Oxalate (mmol/ 1.73 m^2/24 hr; nL <0.46)	Calcium (mg/1.73 m^2/24 hr; nL = 100-300)	Citrate (mg/1.73 m^2/24 h; nL = 320-1240)	
HOGA1 (PH3)	10%-20%	2.7 yrs	↑ HOG & DHG	6.5%	96	2.1	1.1	112	638	~3%

Adapted from Singh et al [2022b], Table 1

DHG = 2,4-dihydroxyglutarate; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HOG = 4-hydroxy-2-oxoglutarate; NC = nephrocalcinosis; nL = normal limit; PH = primary hyperoxaluria

1. Percentage among currently diagnosed individuals with primary hyperoxaluria [Hopp et al 2015, Cochat & Rumsby 2013, Martin-Higueras et al 2021, Singh et al 2022b]. Since analysis of *AGXT* pathogenic variants in large population-based repositories suggest a prevalence of PH3 that approaches that of PH1, these proportions may shift with increasing awareness of primary hyperoxaluria and more readily available genetic testing [Hopp et al 2015, Zhao et al 2022].

2. Parameters presented are the median.

3. Although increased urinary excretion of these specific organic acids is suggestive of PH type [Woodward et al 2019], definitive diagnosis requires genetic testing.

Phenotypic overlap of PH1 with other monogenic stone diseases can occur [Daga et al 2018, Cogal et al 2021], particularly among those with childhood onset of calcium-containing stones and/or nephrocalcinosis. These monogenic stone diseases can be differentiated from PH by the absence of marked hyperoxaluria and comprehensive genetic testing.

Table 6. Comparison of Primary Hyperoxaluria and Other Monogenic Stone Diseases

Urinary Oxalate Conc	Gene	Diagnosis	MOI	Stones	NC	CKD	Conc						
							UCa	UPhos	UMg	UDHA	SCa	SPhos	SMg
↑↑	*AGXT* *GRHPR* *HOGA1*	PH1 PH2 PH3	AR	+++	++	+++	Normal to ↓	Normal	Normal	--	Normal	Normal	Normal
					+	++	Normal						
					+	+	Normal						

Table 6. continued from previous page.

Urinary Oxalate Conc	Gene	Diagnosis	MOI	Stones	NC	CKD	Conc						
							UCa	UPhos	UMg	UDHA	SCa	SPhos	SMg
Normal / --	*APRT*	Adenine phosphoribosyltransferase deficiency	AR	+++ [1]	+	++	Normal	Normal	Normal	↑	Normal	Normal	Normal
	CLCN5 *OCRL1*	Dent disease	XL	++	++	+++	↑	Variably ↑	--	--	Normal	Variably ↓	--
	CLDN16 *CLDN19*	Familial hypomagnesemia w/hypercalciuria & nephrocalcinosis [2] (OMIM 248250 & 248190)	AR	++	+++	+++	↓	--	↑	--	↓	--	↓
	CYP24A1	Infantile hypercalcemia [3] (OMIM 143880)	AR	++	+++	++	↑	↑	--	--	↑	Normal to slightly ↓	--
	SLC34A1 *SLC34A3*	Hereditary hypophosphatemic rickets w/hypercalciuria [4]	AR	++	+	+	↑	↑	--	--	Normal	↓	--

+ = present in some affected individuals; ++ = often present; +++ = present in most affected individuals; -- not recognized to be abnormal but data are limited; AR = autosomal recessive; CKD = chronic kidney disease; Conc = concentration; MOI = mode of inheritance; NC = nephrocalcinosis; PH = primary hyperoxaluria; SCa = serum total calcium; SMg = serum magnesium; SPhos = serum phosphate; UCa = urine calcium; UDHA = urine dihydroxyadenine; UMg = urine magnesium; UPhos = urine phosphate; XL = X-linked

1. Stones comprised of dihydroxyadenine are radiolucent to intermediate density on radiographs and ultrasonography.

2. Disorder of renal magnesium wasting; presentation in childhood or adolescence with UTIs, nephrolithiasis, nephrocalcinosis, and polydipsia/polyuria is characteristic, as is CKD progressing to ESKD in early to mid-adulthood in many [Godron et al 2012].

3. Resulting hypercalcemia may be severe in infancy and may present as poor weight gain and/or poor linear growth. Hypercalcemia typically abates during early childhood, though serum calcium may be intermittently mildly elevated through adulthood. Many individuals first present with stones or nephrocalcinosis in childhood or as adults. Kidney cysts are often present. CKD is common and some individuals progress to ESKD [Janiec et al 2021].

4. Characterized by renal phosphate wasting, hypophosphatemia, increased 1,25-dihydroxyvitamin D, hypercalciuria, nephrolithiasis, nephrocalcinosis, and bone disease (rickets/osteomalacia) [Dasgupta et al 2014]. Monoallelic *SLC34A3* pathogenic variants may be enriched in the calcium-stone forming population [Nwachukwu et al 2023].

Calcium oxalate stone disease of unknown cause (also called idiopathic calcium oxalate stone disease) can be associated with mild hyperoxaluria. Among individuals who form idiopathic stones, urine oxalate excretion (1) is typically lower (<0.6 mmol/day) compared to individuals with a primary hyperoxaluria, (2) varies from one collection to the next, and (3) is frequently accompanied by hypercalciuria. Since idiopathic stone disease is very common and since calcium oxalate is found in approximately 80% of stones [Worcester & Coe 2010], a high index of clinical suspicion is necessary to identify the small proportion of individuals who form calcium oxalate stones due to a primary hyperoxaluria.

Secondary Hyperoxaluria

Secondary forms of hyperoxaluria – including excessive dietary intake of oxalate or oxalate precursors and enteric hyperoxaluria – should be considered in the differential diagnosis of all individuals who present with hyperoxaluria [Lumlertgul et al 2018].

Dietary or other sources of excessive oxalate or oxalate precursors include:

- Foods high in oxalate (e.g., spinach, beetroot, dark chocolate), especially if dietary calcium intake is low;

- Diets markedly deficient in calcium, which result in a greater proportion of free oxalate in the intestinal lumen, thus enhancing absorption of oxalate and resulting in hyperoxaluria;
- Very high doses of vitamin C [D'Costa et al 2019];
- Toxins, such as ethylene glycol, which can cause marked hyperoxaluria and associated acute kidney failure.

Enteric hyperoxaluria results from fat malabsorption in the small intestine. Undigested fat reaching the colon combines with calcium, thus decreasing the amount of calcium available to bind to oxalate, which is subsequently absorbed. Fatty acids not absorbed in the small intestine can damage the colonic mucosa, leading to further increase in oxalate absorption. Causes to consider include the following:

- Any gastrointestinal disease or surgery that impairs fat absorption [Witting et al 2021]. Note that hyperoxaluria resulting from short bowel syndrome can be quite marked and can overlap the range seen in any of the primary hyperoxalurias. Bariatric surgical procedures such as gastric bypass are a frequent cause of hyperoxaluria and stones.
- Medications that interfere with fat absorption from the gastrointestinal tract (e.g., orlistat)

Zellweger Spectrum Disorder

Generalized loss of peroxisomal function is observed in Zellweger spectrum disorder (ZSD) including cerebrohepatorenal syndrome, neonatal adrenoleukodystrophy, and Refsum disease. Among a Dutch cohort of 31 individuals with ZSD, 19/23 (83%) of those in whom urine testing was performed had hyperoxaluria, often with associated hyperglycolic aciduria [van Woerden et al 2006]. Five of the individuals with ZSD had renal involvement characterized by urolithiasis, three had nephrocalcinosis, and one had kidney failure. The presence of neurodevelopmental impairment, retinopathy, hearing loss, and hepatic dysfunction in ZSD [Braverman et al 2016] facilitates clinical differentiation from primary hyperoxaluria.

Nephrocalcinosis of Prematurity

Nephrocalcinosis of prematurity, which occurs in a significant proportion of infants born prior to 28 weeks' gestation, is also characterized by nephrolithiasis [Habbig et al 2011]. Contributing risk factors in premature infants are thought to include (1) urine oxalate that is higher than that observed in infants born at term [Schell-Feith et al 2010], (2) hypercalciuria, and (3) hypocitraturia.

Management

Clinical practice recommendations for management of primary hyperoxaluria (PH) have been published [Groothoff et al 2023, Michael et al 2024]. The following recommendations are also based on the authors' experience and participation in the Rare Kidney Stone Consortium PH Registry.

Evaluations Following Initial Diagnosis

The following evaluations are recommended to establish the extent of disease and needs in an individual diagnosed with primary hyperoxaluria type 1 (PH1):

- Kidney imaging for assessment of number and location of stones and presence of nephrocalcinosis
- Baseline 24-hour urine collection with measurement of excretion rates of oxalate, calcium, and citrate, pH, urine volume, and other components of a supersaturation profile to identify specific risk factors for stones

  Note: Baseline measurement of 24-hour excretion rates is recommended in nearly all individuals, even those requiring catheter placement for accurate collection. In rare exceptions only a spot urine with concentrations corrected for creatinine content is used (see Table 1).

- Measurement of plasma oxalate concentration (see Table 1)
- Assessment of kidney function (estimated glomerular filtration rate [eGFR]) by serum creatinine concentration, blood urea nitrogen, and/or cystatin C concentration
- When chronic kidney disease (CKD) is stage 3b or higher, evaluate for systemic oxalate deposits (i.e., oxalosis) with:
  - Bone imaging for evidence of sclerosis and/or pathologic fractures due to oxalate osteodystrophy;
  - Ophthalmologic examination including visual acuity and retinal examination for retinal oxalate deposition;
  - Echocardiography for evidence of cardiomyopathy;
  - Electrocardiogram for conduction disturbances;
  - Complete blood count for evidence of anemia, with further studies as needed to determine if erythropoietin resistance is the cause.
- Consultation with a medical geneticist, certified genetic counselor, or certified advanced genetic nurse to obtain a pedigree and inform affected individuals and their families about the nature, mode of inheritance, and implications of PH1 to facilitate medical and personal decision making
- Assessment of need for family support and resources from patient advocacy groups such as Oxalosis and Hyperoxaluria Foundation and Parent to Parent

Treatment of Manifestations

Management options for PH1 include targeted therapies and supportive care [Groothoff et al 2023, Michael et al 2024].

Targeted Therapies

In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure. —ED

Targeted therapy for PH1 includes pyridoxine (for individuals with specific *AGXT* missense variants), RNA interference (RNAi) therapeutics to reduce hepatic overproduction of oxalate, and liver and kidney organ transplantation (either combined or performed sequentially).

Note: Use of RNAi therapeutics to reduce hepatic oxalate production in pre- and post-transplantation management of kidney recipients is complicated; information to date is limited to case reports [Stone et al 2021, Sellier-Leclerc et al 2023, Bacchetta et al 2024]. As clinical experience increases, best practices for management of organ transplantation will evolve rapidly [Devresse et al 2020, Bacchetta et al 2024], making published practice guidelines [Groothoff et al 2023, Michael et al 2024] and centers/clinicians experienced in PH1 management the best sources of information.

Because disease manifestations, including CKD or even kidney failure, are often present at the time of diagnosis, several approaches to targeted therapy are necessary (see Table 7).

Table 7. Primary Hyperoxaluria Type 1: Targeted Therapies

Treatment Class	Treatment	Therapy Candidates	Mechanism	Comment
Small molecule therapy	Pyridoxine (vitamin B_6 analog)	Persons w/missense *AGXT* variants, esp homozygotes for p.Phe152Ile, p.Gly170Arg, & p.Ile244Thr (See Genotype-Phenotype Correlations & Table 10.)	Enhances residual activity of AGT (a pyridoxal 5'-phosphate-dependent enzyme) [1]	• ~30%-50% of individuals w/PH1 are pyridoxine responsive. • Since there are multiple mechanisms of pyridoxine response & only a few pathogenic variants have been tested, a trial of pyridoxine should be considered in all persons w/1 or 2 missense *AGXT* pathogenic variants, incl those w/advanced CKD or kidney failure. [2]
Gene therapy (RNAi)	Lumasiran (Oxlumo®)	Effective in all persons w/PH1, independent of specific *AGXT* pathogenic variants	siRNA therapeutic agent that ↓s glyoxylate substrate available for metabolic conversion to oxalate by targeted reduction of hepatic glycolate oxidase	• FDA & EMA approved for persons of all ages • Experience using lumasiran in persons w/advanced CKD, on dialysis, or following kidney transplantation alone is limited.
	Nedosiran (Rivfloza®)	Effectiveness demonstrated in PH1 independent of specific *AGXT* pathogenic variants	siRNA therapeutic agent that ↓s conversion of glyoxylate to oxalate by targeted reduction of hepatic LDHA	FDA approved in persons w/PH1 age >9 yrs w/eGFR >30 mL/min/1.73 m^2
Organ transplantation	Liver transplant	Persons w/GFR <25-30 mL/min/1.73 m^2	Liver transplantation restores normal AGT activity.	When kidney replacement therapy is needed, the decision needs to be made between kidney transplant alone or liver & kidney transplant simultaneously. [3]

AGT = alanine-glyoxylate aminotransferase; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; EMA = European Medicines Agency; FDA = US Food and Drug Administration; GFR = glomerular filtration rate; LDHA = lactate dehydrogenase A; RNAi = RNA interference; siRNA = small interfering RNA

1. Cochat & Rumsby [2013], Fargue et al [2013]

2. Groothoff et al [2023], Michael et al [2024]

3. Liver transplant is considered "targeted therapy" because it restores normal hepatic AGT function. Kidney transplant replaces kidney function but does not address the underlying cause of the disorder, and thus is considered supportive care.

Pyridoxine (vitamin B_6). Pyridoxine, available for oral administration as pyridoxine hydrochloride, can reduce oxalate production in some individuals with PH1 by enhancing residual activity of alanine-glyoxylate aminotransferase (AGT), a pyridoxal 5'-phosphate-dependent enzyme [Cochat & Rumsby 2013, Garrelfs et al 2021b, Fargue & Acquaviva Bourdain 2022].

Pyridoxine response is assessed by comparing the 24-hour urine oxalate excretion rate before treatment and after at least three months of pyridoxine treatment at a minimum dose of 5 mg/kg/day. Reduction of ≥30% or normalization of urinary oxalate excretion while receiving pyridoxine indicates responsiveness [Cochat et al 2012]. Note: Due to the difficulty of accurate 24-hour urine collections in infants and small children, comparison of random urine oxalate:creatinine measurements before and after treatment may be used.

Most individuals who are pyridoxine responsive show maximum benefit at a dose of 5-8 mg/kg/day [Monico et al 2005, Hoyer-Kuhn et al 2014]. Several authors have observed little additional benefit with pyridoxine doses >10 mg/kg/day and thus recommend close monitoring for adverse effects with use of higher doses [Groothoff et al 2023].

- A starting pyridoxine dose of 5 mg/kg/day is recommended. Stepwise increases in pyridoxine dose to a maximum of 10-20 mg/kg/day with assessments of response by measurement of urine oxalate excretion at each step determines the minimum effective dose.
- Pyridoxine responsiveness can be difficult to determine in individuals with advanced CKD or end-stage kidney disease (ESKD), whose urinary oxalate excretion rates may be influenced by the low glomerular filtration rate (GFR). When the GFR is <30 mL/min/1.73 m^2, assessing changes in plasma oxalate concentration may be more effective.

Certain *AGXT* pathogenic variants are known to be pyridoxine responsive (see Genotype-Phenotype Correlations).

Because 30%-50% of individuals with PH1 are pyridoxine responsive (and only a few *AGXT* variants have been tested), assessment of pyridoxine responsiveness should be considered in all individuals who have one or two missense *AGXT* variants, including those with advanced CKD or kidney failure. Following treatment with pyridoxine, p.Gly170Arg homozygotes may have improved kidney function with recovery from dialysis dependence [Lorenz et al 2021] and good outcomes following kidney transplantation without liver transplantation [Lorenz et al 2014].

Individuals responsive to pyridoxine should continue this therapy indefinitely or until successful orthotopic liver transplantation (when a liver with normal AGT enzyme activity replaces the liver with deficient AGT enzyme activity). Additionally, the recent availability of lumasiran and nedosiran requires comparing pyridoxine and siRNA therapeutic agents regarding efficacy, durability of effect, long-term tolerability, safety, and use under special circumstances such as pregnancy (see Pregnancy Management).

Pyridoxine has an excellent safety profile in individuals with PH1, even after decades of use. In contrast, peripheral neuropathy (including paresthesias) has been reported in individuals who do not have PH1 who were receiving very large doses of pyridoxine (typically, adults receiving 1-2 g/day) [Toussaint 1998]. Of note, paresthesias reported in one individual with PH1 on a dose of pyridoxine of 2.1 mg/kg/day resolved following its discontinuation.

RNA interference (RNAi) therapy. Early experience with lumasiran, a small interfering RNA (siRNA) therapeutic agent that targets glycolate oxidase approved in late 2020 by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA), demonstrates that it significantly reduces hepatic oxalate production and urinary oxalate excretion in individuals with PH1 [Scott & Keam 2021, Garrelfs et al 2023].

Nedosiran, a second siRNA therapeutic agent approved for PH1 in late 2023, targets a separate hepatic enzyme, lactate dehydrogenase A (LDHA) [Baum et al 2023]. However, preliminary data regarding efficacy of lumasiran and nedosiran suggest individual variability in response; thus, complete normalization of oxalate production does not occur in all treated individuals [Baum et al 2023, Gang et al 2023, Garrelfs et al 2023].

Additional data are needed to confirm long-term safety and efficacy of lumasiran and nedosiran in reversing the kidney-related effects of hepatic overproduction of oxalate.

- **Lumasiran (Oxlumo®)** reduces the amount of glyoxylate substrate available for metabolic conversion to oxalate by targeted reduction of hepatic glycolate oxidase [Scott & Keam 2021]. Since lumasiran targets an enzyme that is in the same metabolic pathway as AGT, but distinct from AGT, lumasiran is expected to be

effective in all individuals with PH1, independent of specific *AGXT* pathogenic variants, a limiting factor in pyridoxine responsiveness.

In double-blind, placebo-controlled trials of 39 individuals with PH1 (lumasiran-treated n=26, placebo n=13), lumasiran was highly effective in reducing urine and plasma oxalate concentrations [Garrelfs et al 2021a]. After six months of treatment, 84% of individuals treated with lumasiran had 24-hour urinary oxalate concentrations ≤1.5 times the upper limit of the normal range, as compared with none of the individuals who received placebo (P <0.001). About half of individuals treated with lumasiran had 24-hour urinary oxalate concentrations within the normal range [Garrelfs et al 2021a].

Lumasiran has been effective in infants and young children [Sas et al 2022] and in individuals with PH1 whose eGFR was less than 45 mL/min/1.73 m^2, including those on dialysis [Michael et al 2023]. To date, experience with lumasiran after kidney-only transplantation is limited to case reports [Stone et al 2021, Sellier-Leclerc et al 2023, Bacchetta et al 2024].

Although early clinical trials demonstrated promising reductions in plasma and urine oxalate concentrations with lumasiran treatment [Garrelfs et al 2021a, Sas et al 2022, Gang et al 2023], more data are needed to assess possible improved clinical outcomes such as reduced number of symptomatic kidney stone events and stabilization of kidney function.

Because the currently approved lumasiran dose is administered subcutaneously on a monthly or quarterly basis (see Table 8 for loading and maintenance dose schedule), it has the advantage of less medication burden than other agents used historically to manage PH1. With more clinical experience the recommended dose schedule may be modified. Except for mild and transient injection site reactions observed in early clinical trials, lumasiran appears to be well tolerated; to date no serious adverse effects have been identified.

Table 8. Schedule for Weight-Based Subcutaneous Administration of Lumasiran

Weight	Dose Schedule	
	First 3 mos of treatment (loading dosage)	Subsequent mos of treatment (maintenance dosage)
20 kg	3 mg/kg 1x/mo	3 mg/kg every 3 mos
10 to <20 kg	6 mg/kg 1x/mo	6 mg/kg every 3 mos
<10 kg	6 mg/kg 1x/mo	3 mg/kg 1x/mo

- **Nedosiran (Rivfloza®)** is an siRNA therapeutic agent targeted to reduce hepatic lactate dehydrogenase A (LDHA), believed to be the terminal step for synthesis of oxalate from glyoxylate in PH1 [Ariceta et al 2021]. Nedosiran was approved by the FDA in 2023 for treatment of PH1 in adults and children age >9 years whose eGFR is >30 mL/min/1.73 m^2.

  A double-blind, placebo-controlled clinical trial that included 29 individuals with PH1 older than age six years and an eGFR >30 ml/in/1.73m^2 showed that once monthly subcutaneous administration of nedosiran resulted in sustained reduction in urinary and plasma oxalate concentration compared with placebo. Of these, half achieved normal or near-normal urine oxalate excretion [Baum et al 2023]. (Note: This effect was not observed in any of the six individuals with PH2 included in the study.) Interim analysis of individuals who participated in open label continuation of the study demonstrated sustained substantial reduction in urine oxalate excretion for up to 30 months of treatment [Groothoff et al 2024].

  Nedosiran was well tolerated without serious adverse effects.

  Nedosiran clinical trials are under way for individuals with PH1 and advanced CKD who are on dialysis (see Therapies Under Investigation). Longer-term studies of nedosiran are needed to confirm safety as well

as benefit for PH1 clinical outcome measures such as reduction in symptomatic kidney stone events and stabilization of kidney function.

Organ transplantation. Prior to targeted therapy, organ transplantation was the only option to prevent systemic oxalosis once GFR was lower than 25-30 mL/min/1.73 m^2.

Until 2020 whole liver transplantation was – despite limited organ availability, high cost, and significant morbidity and mortality – the only intervention capable of restoring normal hepatic AGT enzyme activity and thus normalizing oxalate production. Liver and kidney transplantation were often performed either as a single combined procedure or sequential procedures, with similar outcomes achieved using either approach [Metry et al 2021].

With recent availability of RNAi therapeutic agents capable of reducing hepatic oxalate production, some have suggested that liver transplantation may no longer be needed [Devresse et al 2020]. However, RNAi agents are costly and not universally available. Early data regarding outcomes of treatment with lumasiran and nedosiran suggest individual variability in response; thus, complete normalization of oxalate production does not occur in all [Baum et al 2023, Gang et al 2023, Garrelfs et al 2023]. Pending long-term data on sustained efficacy and safety of these agents, recommendations regarding liver transplantation in PH1 may change over time.

Points to consider regarding transplantation include the following:

- Kidney transplantation will continue to be the option for individuals who either have progressed to advanced CKD or ESKD before being diagnosed with PH1 or have not had the benefit of RNAi agents. Pre- and post-transplant management of kidney recipients with PH1 has been challenging and will be profoundly influenced by the ability to reduce hepatic oxalate production using siRNA therapeutics. Experience with use of such agents after kidney transplantation is thus far limited to case reports [Stone et al 2021, Breeggemann et al 2023, Sellier-Leclerc et al 2023, Bacchetta et al 2024]. Best practices for management of kidney transplant recipients are evolving rapidly as clinical experience increases [Devresse et al 2020, Groothoff et al 2023, Bacchetta et al 2024, Michael et al 2024].
- When systemic oxalosis is present prior to transplantation, mobilization of systemic oxalate places the kidney allograft at risk until tissue oxalate stores are completely cleared [Bacchetta et al 2024]; thus, transplant recipients must be monitored closely to assure maintenance of high urine volumes and use of crystal inhibitor medication. Dialysis may be required if plasma oxalate concentrations are high due to delay or compromise of kidney allograft function [Michael et al 2024].
- Clearance of tissue oxalate stores by a well-functioning kidney allograft requires months to more than five years following liver transplantation or RNAi reduction of oxalate production [Bergstralh et al 2010, Tang et al 2015, Bacchetta et al 2024].
- Liver transplantation for PH1 should always be performed with complete removal of the native liver.
- Pyridoxine supplementation in individuals who have been pyridoxine responsive can be discontinued at the time of liver transplantation, since normal AGT enzyme activity will have been restored.
- Although most publications report transplantation of organs from deceased donors, living donor kidney or liver allografts are viable alternatives in some situations. It is important to note that the appropriateness of using a parent or sib who is heterozygous for an *AGXT* pathogenic variant as a donor remains unclear. Although heterozygotes can have reduced AGT enzyme activity in the liver, they typically have normal urine oxalate excretion and remain free of stones or oxalate-related CKD.

Supportive Care

Early diagnosis of PH1 with initiation of supportive care (also referred to as conservative treatment) aims to prevent crystal injury to kidneys, reduce stone formation and stone-related kidney damage, preserve kidney function, and prevent systemic oxalosis (see Table 9).

Table 9. Primary Hyperoxaluria Type 1: Supportive Care

Objective	Treatment	Consideration/Other
Prevent crystal injury to kidneys by ↓ crystal formation	• Maintain high oral fluid intake to assure good urine volume. • Use oral citrate or pyrophosphate to inhibit calcium oxalate crystal formation.	Infants or small children may need gastrostomy tube placement.
Reduce stone formation	• Maintain high urine volume. • Minimize urine oxalate concentration. • Optimize urine citrate.	Use imaging studies at regular intervals to guide mgmt.
Reduce stone-related kidney damage	• Consult w/urologist experienced in mgmt of PH. • Ureteroscopic mgmt of symptomatic stones preferred when appropriate.	• Prompt attention to pain or other symptoms suggesting infection or possible urinary obstruction. • Use imaging studies at regular intervals to guide mgmt.
Preserve kidney function	• Avoid dehydration. • Avoid nephrotoxins that can cause kidney injury (e.g., NSAIDs).	Use IV fluid if needed to assure high urine volume (e.g., during vomiting or diarrhea).
Prevent systemic oxalosis	• Monitor plasma oxalate concentration during transient or permanent periods of low GFR. • Initiate dialysis promptly to ↓ oxalate concentration. [1, 2]	Dialysis, most often used as a bridge to kidney recovery or transplantation, often requires ≥4 dialysis sessions per week to maintain plasma oxalate concentrations that minimize risk of oxalosis. [2, 3]

GFR = glomerular filtration rate; NSAID = nonsteroidal anti-inflammatory drug; PH = primary hyperoxaluria

1. Michael et al [2024]

2. Groothoff et al [2023]

3. Tang et al [2015]

Reduce calcium oxalate crystallization in the urine. Reduction of calcium oxalate crystals helps to minimize crystal injury to kidney tissue and reduces stone formation [Groothoff et al 2023, Michael et al 2024]. Recommendations include the following:

- High oral fluid intake. Drinking large volumes of fluid (2-3 L/m^2/24 hours) at regular intervals over the entire day/night minimizes calcium oxalate crystal formation through urinary dilution.
  - Small children may require gastrostomy tube placement or nasogastric tube for feeding and fluid supplementation.
  - Extreme care should be taken during any illness that could lead to hypovolemia or decreased oral fluid intake; individuals should be advised to seek early medical attention to initiate intravenous fluids if needed to maintain urine volume.
- Inhibition of calcium oxalate crystallization. If the GFR is preserved, increase urine citrate excretion using oral potassium citrate at a dose of 0.1-0.15 mg/kg or 0.3-0.5 mmol/kg/day in three to four divided doses. If the GFR is reduced or blood potassium concentration is elevated, sodium citrate can be used.
- In individuals with good kidney function (eGFR >30 mL/min/1.73 m^2), oral pyrophosphate-containing solutions (at 20-30 mg/kg/day of phosphate in divided doses) can be used to inhibit crystal formation.
- In PH1 excess oxalate results from endogenous metabolism, not dietary intake of oxalate, and dietary restriction of oxalate intake is of little benefit. Thus, avoiding specific foods or beverages with very high oxalate content, without strict limits, is appropriate.

Reduce stone formation and stone-related kidney damage. Monitoring new stone formation and stone size at regular intervals helps clinicians adjust fluids and medications and allows early identification of stones at risk of causing urinary obstruction.

Since recurring symptomatic stone events requiring urologic interventions are common, consultation with a urologist experienced in the care of individuals with PH1 helps individualize care and improve outcomes, particularly when specialized equipment and techniques may be required for infants and small children [Pais & Assimos 2005, Carrasco et al 2015].

Calcium oxalate stones can be resistant to shock wave lithotripsy (SWL); nephrocalcinosis can also complicate stone management. Because stone removal can result in acute kidney failure, interventions least likely to cause kidney injury are preferred [Carrasco et al 2015, Kohli & Kurtz 2022].

Surgical modalities used for stone management include the following:

- **Ureteroscopy,** which effectively removes stones with minimal complications, is least likely to be associated with kidney injury.
- **Shockwave lithotripsy (SWL).** Although a reasonable option, SWL has a lower success rate than endoscopic lithotripsy or endoscopic stone removal, thus increasing the need for repeated procedures [Kohli & Kurtz 2022]. Calcium oxalate monohydrate stones, typical of PH1, are among the hardest stones, making them more likely to be resistant to SWL [Kohli & Kurtz 2022]. Particularly stones in the lower pole of the kidney or parenchyma do not respond as well to SWL as stones in other locations [Al-Abadi & Hulton 2013]. Multiple treatments are often needed; incomplete stone clearance may lead to their rapid enlargement [Kohli & Kurtz 2022].
- **Percutaneous nephrolithotomy** may be needed for larger, bulky stone burden.

Prevent systemic oxalosis by reducing the plasma oxalate concentration. This can be accomplished by dialysis to remove oxalate and/or reduction in oxalate production. Hemodialysis, which is more effective at oxalate removal than peritoneal dialysis, is most often used as a bridge to transplantation in individuals with PH1; however, it may also be an adjunct therapy when kidney allograft function following kidney transplantation is delayed or poor. In countries without access to organ transplantation, hemodialysis may be used for long-term management.

Hemodialysis is the primary dialysis modality used in persons with PH1 with kidney failure to reduce plasma oxalate concentration to prevent or treat oxalosis; however, absent targeted therapy to reduce hepatic oxalate production, the high rate of oxalate production (often 2-7 mmol/1.73 m^2/day) exceeds the ability of hemodialysis to prevent or treat oxalosis. In some individuals both hemodialysis and peritoneal dialysis are required.

Current guidelines suggest reducing and maintaining plasma oxalate concentration below 30-45 µmol/L (the calcium oxalate supersaturation threshold at which tissue deposition occurs) as long as possible between dialysis sessions. Although most individuals with PH1 require four or more dialysis sessions per week to maintain acceptable plasma oxalate concentrations, significant individual variation in oxalate production requires individualization of dialysis prescriptions [Tang et al 2014]. Detailed kidney dialysis recommendations can be found in published practice guidelines [Groothoff et al 2023, Michael et al 2024]. It has been noted that such intensive dialysis regimens are difficult for patients, their families, and nephrology providers [Lawrence & Wattenberg 2020].

Following increasing clinical experience with RNAi therapeutics effective in reducing hepatic oxalate production in individuals with PH1, it is expected that guidelines for PH1 [Groothoff et al 2023, Michael et al 2024] will continue to evolve.

Surveillance

Individuals with PH1 require lifelong care, the frequency of which is related to kidney function [Cochat & Rumsby 2013, Groothoff et al 2023, Michael et al 2024].

CKD stages 1 and 2 (measured GFR or estimated GFR [eGFR] >60 mL/min/1.73 m^2). The following are required to evaluate/ensure treatment efficacy:

- Regular monitoring of kidney function. Serum creatinine and/or cystatin C for determination of eGFR should be performed at least annually and more frequently in children and adolescents and in individuals with changing kidney function or clinically active stone disease.
- Regular kidney ultrasound examinations at least annually, or more often as needed to monitor and manage stone-forming activity
- Urinalysis and measurements of urine oxalate excretion, urine volume, and calcium oxalate saturation (spot and 24-hour collections) at least annually, more often in individuals with active stones or changes in kidney function

CKD stages 3a and 3b (GFR <60 and >30 mL/min/1.73 m^2). Monitor the following at least every six months or more often with any change in clinical status:

- Kidney function
- Kidney ultrasound for stones and incipient nephrocalcinosis
- Urine oxalate and plasma oxalate concentrations

CKD stages 4 and 5 (GFR <30 mL/min/1.73 m^2) or a rapid deterioration in function. The following should be performed at regular intervals, including prior to initiation of dialysis and during ongoing dialysis care:

- History and physical examination at least every three months for signs and symptoms of systemic oxalosis with assessment of growth and development (in children), bone or joint involvement, evidence of cardiomyopathy, signs of arterial insufficiency or ischemia, and skin examination for livedo reticularis, subcutaneous oxalate deposits, and/or ischemic ulcers
- Serum creatinine and plasma oxalate concentrations, typically monthly or more often depending on clinical circumstances
- Radiographs of the long bones to evaluate for radiodense metaphyseal bands and diffuse demineralization. Obtain initially, then repeat for bone symptoms and/or pathologic fractures; more frequent bone evaluation is needed in infants and young children.
- Ophthalmologic examination for visual acuity testing, evidence of retinal oxalate deposits, and optical coherence tomography (OCT) if available. Retinal photographs can be valuable to monitor changes over time.
- Electrocardiogram to evaluate for associated atrioventricular block or other oxalate-related conduction abnormalities, repeated every six to 12 months
- Echocardiogram for evidence of oxalate cardiomyopathy, repeated every 6-12 months.
- Hemoglobin to evaluate for anemia associated with either renal dysfunction or marrow deposition of oxalate, repeated every three months
- Thyroid function testing once a year
- Regular dental examinations/care

Note: Evaluations should occur more often in newly diagnosed symptomatic individuals or in children younger than ages two to three years.

Agents/Circumstances to Avoid

Avoid the following:

- Intravascular volume depletion. The importance of maintaining dilute urine cannot be overemphasized.
- Intake of vitamin C that exceeds the recommended daily allowance

- Loop diuretics to maintain dilute urine, as they can lead to hypercalciuria and increase calcium oxalate stone production
- High doses of nonsteroidal anti-inflammatory drugs (NSAIDs) or any pharmacologic agent that can compromise kidney function
- Large intake of foods high in oxalate (e.g., chocolate, rhubarb, starfruit)

Evaluation of Relatives at Risk

For early diagnosis and treatment. Family screening for PH1, particularly of sibs of the proband, is warranted given intrafamilial variability, significant disease risks even in asymptomatic individuals, and availability of therapeutic agents highly effective in reducing urine oxalate (see Targeted Therapies) [Cochat et al 2012]. Asymptomatic individuals found to have biallelic *AGXT* pathogenic variants are at increased risk for kidney stones and kidney damage [Sas et al 2020] and thus require the same management as those who have manifestations of PH1.

For kidney or liver organ donation. Molecular genetic testing to clarify the genetic status is recommended for relatives who are potential donors to inform decisions regarding living donor selection. It is unclear if a parent or sib who is heterozygous for an *AGXT* pathogenic variant is an appropriate donor. Although heterozygotes can have reduced liver AGT enzyme activity, they typically have normal urine oxalate excretion and remain free of stones or oxalate-related CKD.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Of note, women with PH1 warrant close monitoring by both an obstetrician and nephrologist during pregnancy and the postpartum period.

Although pregnancy does not appear to be an important risk factor for the development of ESKD in most women with PH1 [Miao et al 2022], women have been reported whose kidney function has deteriorated during the pregnancy and has remained abnormal post delivery [Cimino et al 2005]. Maintenance of adequate fluid intake throughout pregnancy can be challenging, especially during the first trimester and in women with hyperemesis gravidarum, when intravenous fluid administration may be required. Recommendations include continuation of pyridoxine throughout pregnancy for women known to be pyridoxine responsive and monitoring kidney function and possible stone formation throughout pregnancy and the early postpartum period.

Women with PH1 have had successful pregnancies following kidney transplantation alone and combined liver and kidney transplantation [Miao et al 2022]. In one woman liver function was apparently preserved, but kidney graft function declined transiently after the birth of her first child and permanently after the birth of her second child [Pruvot et al 1997].

Lumasiran and nedosiran, recently approved for use in individuals with PH1 (see Targeted Therapies), have not been studied during human pregnancy. Although preclinical animal studies were reassuring, pending more clinical experience the authors would advise women taking lumasiran or nedosiran to discontinue it prior to becoming pregnant and to consult with their nephrologist throughout the pregnancy regarding supportive care.

To date, no information is available regarding lumasiran or nedosiran transmission in breast milk; thus, risk to breast-feeding infants cannot be ruled out.

Therapies Under Investigation

Several novel therapies are under investigation.

Gene modification. Now that effectiveness of RNAi therapeutic agents lumasiran and nedosiran, which reduce the activity of the hepatic enzymes glycolate oxidase and lactate dehydrogenase A (LDHA), has been confirmed in individuals with PH1, the use of CRISPR/Cas9 for gene editing holds promise of a durable effect following a single treatment [Zheng et al 2020, Martinez-Turrillas at al 2022]. While such agents could avoid the inconvenience and risk of non-adherence associated with repeated dosing required with RNAi therapeutics, there is limited clinical experience to date with this technology and investigations in its use in PH1 are at the preclinical stage.

Small molecule therapies. Chemical chaperones may have general stabilizing functions, or they may be designed to target proteins with specific pathogenic variants. Missense pathogenic variants that do not cause loss of protein stability are not suitable candidates for this pharmacogenetic approach; nor are insertions, deletions, nonsense variants, or splice junction changes, which usually do not produce a protein product.

Small molecule inhibitors of LDHA for treatment of PH1 are in early clinical studies. Stiripentol, administered orally, inhibits activity of LDHA and is approved by the FDA for clinical use as an anti-seizure medication in Dravet syndrome. A few case reports have suggested a possible urine oxalate-reducing effect of stiripentol in PH1. However, to date, anecdotal evidence has been scattered, with effects in one report indistinguishable from those of concomitantly administered pyridoxine, and in individuals with PH1 with CKD or kidney failure, neither plasma oxalate concentration nor urine oxalate declined significantly [Kempf et al 2020, Martin-Higueras et al 2021, Violier et al 2022]. A clinical trial is currently ongoing.

Oxalate-degrading bacteria. Oral administration of bacteria such as *Oxalobacter formigenes* (*O formigenes*) or lactic acid bacteria to degrade oxalate and reduce the amount of oxalate available for intestinal absorption [Ivanovski & Drüeke 2013] is being investigated. *O formigenes* is also thought to stimulate secretion of endogenous oxalate into the intestine [Arvans et al 2017]. A human strain of *O formigenes* (HC-1) has been shown to promote oxalate secretion into the intestine of a mouse model of primary hyperoxaluria [Hatch et al 2011] and in this model reduced the amount of oxalate excreted via the kidney. Despite these findings in animal studies, and promising early findings in pilot studies in individuals with PH [Hoppe et al 2006], four double-blind, placebo-controlled trials of *O formigenes* administered orally to individuals with PH with preserved kidney function have failed to show benefit [Hoppe et al 2011, Hoppe et al 2017, Milliner et al 2018, Ariceta et al 2023], and a study of individuals with PH1 on dialysis also failed end points for efficacy [Hoppe et al 2021].

Other efforts to insert oxalate-degrading enzymes into bacteria that inhabit normal intestinal flora [Lubkowicz et al 2022] and to bind intestinal oxalate with compounds such as lanthanum [Pozdzik et al 2021] are in early stages of development.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Primary hyperoxaluria type 1 (PH1) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are presumed to be heterozygous for an *AGXT* pathogenic variant.
- Targeted molecular genetic testing for the *AGXT* pathogenic variants identified in the proband is recommended for the parents of the proband to confirm that both parents are heterozygous for an *AGXT* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
    - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
    - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.

      One individual with PH1 caused by maternal chromosome 2 telomeric isodisomy has been reported. The affected individual was homozygous for the common p.Lys12GlnfsTer156 pathogenic variant. The mother was heterozygous for the variant; the variant was absent in the father [Chevalier-Porst et al 2005].
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for an *AGXT* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- The age at onset and clinical manifestations can vary widely among sibs with the same biallelic *AGXT* pathogenic variants. Affected sibs often demonstrate significantly discordant disease expression [Frishberg et al 2005, Cochat & Rumsby 2013, Ben-Shalom et al 2022, Deesker et al 2022], with differences of more than 20 years between timing of end-stage kidney disease onset among sibs in some families [Hopp et al 2015].
- Given the variability in clinical expression, significant disease risk in asymptomatic individuals [Sas et al 2020], and the availability of therapeutic agents highly effective in reducing urinary oxalate, family screening, particularly of sibs, is strongly recommended.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband

- Unless an affected individual's reproductive partner also has PH1 or is a carrier of an *AGXT* pathogenic variant, offspring will be obligate heterozygotes (carriers) for an *AGXT* pathogenic variant.
- One family with pseudodominant inheritance (i.e., an autosomal recessive condition present in individuals in two or more generations) has been reported: offspring of an affected individual and a carrier were affected [Hoppe et al 1997].

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *AGXT* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *AGXT* pathogenic variants in an affected family member.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the *AGXT* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal and preimplantation genetic testing. While most health care professionals would consider use of prenatal and preimplantation genetic testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **MedlinePlus**
  Primary hyperoxaluria
- **Oxalosis & Hyperoxaluria Foundation**
  Phone: 212-777-0470
  Email: info@ohf.org
  ohf.org
- **Kidney Health Initiative Patient and Family Partnership Council (KHI PFPC)**
  Engaging the Patient Voice
- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  metabolicsupportuk.org
- **National Kidney Foundation**
  Phone: 855-NKF-CARES; 855-653-2273
  Email: nkfcares@kidney.org
  kidney.org
- **OxalEurope Registry (OER)**

oxaleurope.org/registry

- **Rare Kidney Stone Consortium Registry**
  Phone: 800-270-4637 (toll-free)
  Email: hyperoxaluriacenter@mayo.edu
  Rare Kidney Stone Consortium Registry

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Primary Hyperoxaluria Type 1: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
AGXT	2q37.3	Alanine-glyoxylate transaminase	AGXT database	AGXT	AGXT

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Primary Hyperoxaluria Type 1 (View All in OMIM)

259900	HYPEROXALURIA, PRIMARY, TYPE I; HP1
604285	ALANINE-GLYOXYLATE AMINOTRANSFERASE; AGXT

Molecular Pathogenesis

AGXT encodes alanine-glyoxylate aminotransferase (AGT), a key enzyme in the detoxification of glyoxylate, which converts glyoxylate to glycine (see Figure 1a in Groothoff et al [2023]). AGT, synthesized mainly in the liver, is translated in the cytosol and then guided into peroxisomes by a C-terminal peroxisomal targeting signal. Pyridoxine (vitamin B_6) is an essential cofactor for AGT activity.

Mechanism of disease causation. Loss of AGT function results in accumulation of its substrate, glyoxylate, and the conversion of glyoxylate into oxalate, which forms insoluble calcium oxalate salts that the body cannot readily eliminate, resulting in nephrolithiasis and nephrocalcinosis. Loss of protein function is caused by typical mechanisms such as frameshifting variants and nonsense-mediated mRNA decay.

Abnormal AGT function can also result from:

- **Misfolding of AGT,** which affects binding of the essential cofactor, pyridoxine (vitamin B_6) [Fargue et al 2013, Fargue & Acquaviva Bourdain 2022].
- **"Mistargeting" of AGT,** whereby the genetic change affects the AGT peroxisomal targeting sequence, causing the enzyme to be mislocated to mitochondria, where it is unable to detoxify glyoxylate, which in turn is metabolized to oxalate. Note: The variant p.Pro11Leu (the so-called minor allele) creates a cryptic N-terminal mitochondrial targeting sequence with no functional effect on the protein and, therefore, does not cause PH1 by itself. However, when in *cis* with one of four other pathogenic variants, p.Pro11Leu mistargets the enzyme to mitochondria, where it is unable to detoxify glyoxylate, which is then metabolized to oxalate. The four mistargeting variants are c.121G>A (p.Gly41Arg), c.454T>A (p.Phe152Ile), c.508G>A (p.Gly170Arg), and c.731T>C (p.Ile244Thr) [Oppici et al 2015, Fargue & Acquaviva Bourdain 2022] (see Table 10).

- **The "minor allele" variant** differs from the major (wild type) allele by a c.32C>T (p.Pro11Leu) substitution, c.1020A>G (p.Ile340Met), and a 74-base pair insertion in intron 1 [Oppici et al 2015, Fargue & Acquaviva Bourdain 2022].

***AGXT*-specific laboratory technical considerations.** For individuals who have clinical findings of PH1 but only one or no *AGXT* pathogenic variant identified by multigene panel testing or exome sequencing, genome sequencing may be considered to more thoroughly interrogate *AGXT* (e.g., to detect deep intronic variants or structural variants).

Evaluation of *AGXT* variants of uncertain significance (VUSs)

- Family segregation studies can sometimes be helpful to classify a VUS as pathogenic or benign.
- Enzyme analysis can be used to identify alanine-glyoxylate aminotransferase (AGT) enzyme deficiency. Note that such testing requires use of liver tissue obtained by liver biopsy.

Table 10. *AGXT* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000030.3 NP_000021.1	c.32C>T	p.Pro11Leu	Acts synergistically, thus exacerbating the deleterious effects of certain pathogenic variants in *cis*. Is not pathogenic alone.
	c.121G>A	p.Gly41Arg	Common pathogenic variant that may be vitamin B_6 responsive [Danpure et al 1993]
	c.454T>A	p.Phe152Ile	Pathogenic variant assoc w/vitamin B_6 responsiveness [Demoulin et al 2022]
	c.508G>A	p.Gly170Arg	Common pathogenic variant assoc w/vitamin B_6 responsiveness [Demoulin et al 2022]
	c.731T>C	p.Ile244Thr	Common variant in the Canary Islands w/homozygotes showing kidney survival like that of homozygotes for p.Gly170Arg [Metry et al 2023]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

Author Notes

The Oxalosis and Hyperoxaluria Foundation (OHF; info@ohf.org) and Rare Kidney Stone Consortium (RKSC; rarekidneystones@mayo.edu) are actively involved in clinical research regarding individuals with primary hyperoxaluria type 1 (PH1). They would be happy to communicate with persons who have any questions regarding diagnosis of primary hyperoxaluria type 1 (PH1) or other considerations.

The OHF and RKSC are also interested in hearing from clinicians treating families affected by frequent kidney stones, nephrocalcinosis, and/or kidney failure in whom no causative variant has been identified through molecular genetic testing of the genes known to be involved in this group of disorders.

Contact Dr Peter C Harris (harris.peter@mayo.edu) to inquire about review of *AGXT* variants of uncertain significance.

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References

Literature Cited

Al-Abadi E, Hulton SA. Extracorporal shock wave lithotripsy in the management of stones in children with oxalosis--still the first choice? Pediatr Nephrol. 2013;28:1085–9. PubMed PMID: 23397522.

Ariceta G, Barrios K, Brown BD, Hoppe B, Rosskamp R, Langman CB. Hepatic Lactate Dehydrogenase A: An RNA Interference Target for the Treatment of All Known Types of Primary Hyperoxaluria. Kidney Int Rep. 2021;6:1088-98. PubMed PMID: 33912759.

Ariceta G, Collard L, Abroug S, Moochhala SH, Gould E, Boussetta A, Ben Hmida M, De S, Hunley TE, Jarraya F, Fraga G, Banos A, Lindner E, Dehmel B, Schalk G. ePHex: a phase 3, double-blind, placebo-controlled, randomized study to evaluate long-term efficacy and safety of Oxalobacter formigenes in patients with primary hyperoxaluria. Pediatr Nephrol. 2023;38:403-15. PubMed PMID: 35552824.

Arvans D, Jung YC, Antonopoulos D, Koval J, Granja I, Bashir M, Karrar E, Roy-Chowdhury J, Musch M, Asplin J, Chang E, Hassan H. Oxalobacter formigenes-derived bioactive factors stimulate oxalate transport by intestinal epithelial cells. J Am Soc Nephrol. 2017;28:876–87. PubMed PMID: 27738124.

Bacchetta J, Boivin G, Cochat P. Bone impairment in primary hyperoxaluria: a review. Pediatr Nephrol. 2016;31:1-6. PubMed PMID: 25631241.

Bacchetta J, Clavé S, Perrin P, Lemoine S, Sellier-Leclerc AL, Deesker LJ. Lumasiran, Isolated Kidney Transplantation, and Continued Vigilance. N Engl J Med. 2024;390:1052-54. PubMed PMID: 38477995.

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. PHYOX2: a pivotal randomized study of nedosiran in primary hyperoxaluria type 1 or 2. Kidney Int. 2023;103:207-17. PubMed PMID: 36007597.

Ben-Shalom E, Cytter-Kuint R, Rinat C, Becker-Cohen R, Tzvi-Behr S, Goichberg J, Peles V, Frishberg Y. Long-term complications of systemic oxalosis in children-a retrospective single-center cohort study. Pediatr Nephrol. 2021;36:3123-32. PubMed PMID: 33651179.

Ben-Shalom E, Garrelfs SF, Groothoff JW. Primary hyperoxaluria: the pediatric nephrologist's point of view. Clin Kidney J. 2022;15:i23-i28. PubMed PMID: 35592624.

Bergstralh EJ, Monico CG, Lieske JC, Herges RM, Langman CB, Hoppe B, Milliner DS. IPHR Investigators. Transplantation outcomes in primary hyperoxaluria. Am J Transplant. 2010;10:2493–501. PubMed PMID: 20849551.

Berini SE, Tracy JA, Engelstad JK, Lorenz EC, Milliner DS, Dyck PJ. Progressive polyradiculoneuropathy due to intraneural oxalate deposition in type 1 primary hyperoxaluria. Muscle Nerve. 2015;51:449–54. PubMed PMID: 25363903.

Birtel J, Herrmann P, Garrelfs SF, Dulz S, Atiskova Y, Diederen RM, Gliem M, Brinkert F, Holz FG, Boon CJF, Hoppe B, Charbel Issa P. The ocular phenotype in primary hyperoxaluria type 1. Am J Ophthalmol. 2019;206:184-91. PubMed PMID: 31078535.

Braverman NE, Raymond GV, Rizzo WB, Moser AB, Wilkinson ME, Stone EM, Steinberg SJ, Wangler MF, Rush ET, Hacia JG, Bose M. Peroxisome biogenesis disorders in the Zellweger spectrum: An overview of current diagnosis, clinical manifestations, and treatment guidelines. Mol Genet Metab. 2016;117:313-21. PubMed PMID: 26750748.

Breeggemann MC, Gluck SL, Stoller ML, Lee MM. A case report of kidney-only transplantation in primary hyperoxaluria type 1: a novel approach with the use of nedosiran. Case Rep Nephrol Dial. 2023;13:63-9. PubMed PMID: 37497389.

Carrasco A Jr, Granberg CF, Gettman MT, Milliner DS, Krambeck AE. Surgical management of stone disease in patients with primary hyperoxaluria. Urology. 2015;85:522–6. PubMed PMID: 25733260.

Chevalier-Porst F, Rolland MO, Cochat P, Bozon D. Maternal isodisomy of the telomeric end of chromosome 2 is responsible for a case of primary hyperoxaluria type 1. Am J Med Genet A. 2005;132A:80–3. PubMed PMID: 15580638.

Cimino S, Ranno S, Garozzo M, Reggio M, Battaglia G, Maugeri O, Ventimiglia B. Minerva Urol Nefrol. 2005;57:341–3. [Primary hyperoxaluria and pregnancy] PubMed PMID: 16247357.

Cochat P, Groothoff J. Primary hyperoxaluria type 1: practical and ethical issues. Pediatr Nephrol. 2013;28:2273. PubMed PMID: 23494551.

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. Primary hyerpoxaluria type 1: indications for screening and guidance for diagnosis and treatment. Nephrol Dial Transplant. 2012;27:1729–36. PubMed PMID: 22547750.

Cochat P, Rumsby G. Primary hyperoxaluria. New Engl J Med. 2013;369:649–58. PubMed PMID: 23944302.

Cogal AG, Arroyo J, Shah RJ, Reese KJ, Walton BN, Reynolds LM, Kennedy GN, Seide BM, Senum SR, Baum M. erickson SB, Jagadeesh S, Soliman NA, Goldfarb DS, Beara-Lasic L, Edvardsson VO, Pallson R, Milliner DS, Sas DJ, Lieske JC, Harris PC. Comprehensive genetic analysis reveals complexity of monogenic urinary stone disease. Kidney Int Rep. 2021;6:2862–84. PubMed PMID: 34805638.

Coulter-Mackie MB, Lian Q, Applegarth D, Toone J. The major allele of the alanine:glyoxylate aminotransferase gene: nine novel mutations and polymorphisms associated with primary hyperoxaluria type 1. Mol Genet Metab. 2005;86:172–8. PubMed PMID: 15963748.

Coulter-Mackie MB, Rumsby G, Applegarth DA, Toone JR. Three novel deletions in the alanine:glyoxylate aminotransferase gene of three patients with type 1 hyperoxaluria. Mol Genet Metab. 2001;74:314–21. PubMed PMID: 11708860.

Daga A, Majmundar AJ, Braun DA, Gee HY, Lawson JA, Shril S, Jobst-Schwan T, Vivante A, Schapiro D, Tan W, Warejko JK, Widmeier E, Nelson CP, Fathy HM, Gucev Z, Soliman NA, Hashmi S, Halbritter J, Halty M, Kari JA, El-Desoky S, Ferguson MA, Somers MJG, Traum AZ, Stein DR, Daouk GH, Rodig NM, Katz A, Hanna C, Schwaderer AL, Sayer JA, Wassner AJ, Mane S, Lifton RP, Milosevic D, Tasic V, Baum MA, Hildebrandt F. Whole exome sequencing frequently detects a monogenic cause in early onset nephrolithiasis and nephrocalcinosis. Kidney Int. 2018;93:204-13. PubMed PMID: 28893421.

Danpure CJ, Purdue PE, Fryer P, Griffiths S, Allsop J, Lumb MJ, Guttridge KM, Jennings PR, Scheinman JI, Mauer SM, et al. Enzymological and mutational analysis of a complex primary hyperoxaluria type 1 phenotype involving alanine:glyoxylate aminotransferase peroxisome-to-mitochondrion mistargeting and intraperoxisomal aggregation. Am J Hum Genet. 1993;53:417-32. PubMed PMID: 8101040.

Dasgupta D, Wee MJ, Reyes M, Li Y, Simm PJ, Sharma A, Schlingmann KP, Janner M, Biggin A, Lazier J, Gessner M, Chrysis D, Tuchman S, Baluarte HJ, Levine MA, Tiosano D, Insogna K, Hanley DA, Carpenter TO, Ichikawa S, Hoppe B, Konrad M, Sävendahl L, Munns CF, Lee H, Jüppner H, Bergwitz C. Mutations in SLC34A3/NPT2c are associated with kidney stones and nephrocalcinosis. J Am Soc Nephrol. 2014;25:2366-75. PubMed PMID: 24700880.

D'Costa MR, Winkler NS, Milliner DS, Norby SM, Hickson LJ, Lieske JC. Oxalosis associated with high-dose vitamin C ingestion in a peritoneal dialysis patient. Am J Kidney Dis. 2019;74:417-20. PubMed PMID: 30910370.

Deesker LJ, Garrelfs SF, Mandrile G, Oosterveld MJS, Cochat P, Deschênes G, Harambat J, Hulton SA, Gupta A, Hoppe B, Beck BB, Collard L, Topaloglu R, Prikhodina L, Salido E, Neuhaus T, Groothoff JW, Bacchetta J. Improved Outcome of Infantile Oxalosis Over Time in Europe: Data From the OxalEurope Registry. Kidney Int Rep. 2022;7:1608-18. PubMed PMID: 35812297.

Demoulin N, Aydin S, Gillion V, Morelle J, Jadoul M. Pathophysiology and management of hyperoxaluria and oxalate nephropathy: a review. Am J Kidney Dis. 2022;79:717-27. PubMed PMID: 34508834.

Devresse A, Cochat P, Godefroid N, Kanaan N. Transplantation for primary hyperoxaluria type 1: designing new strategies in the era of promising therapeutic perspectives. Kidney Int Rep. 2020;5:2136-45. PubMed PMID: 33305106.

Edvardsson VO, Goldfarb DS, Lieske JC, Beara-Lasic L, Auglani F, Milliner DS, Palsson R. Hereditary causes of kidney stones and chronic kidney disease. Pediatr Nephrol. 2013;28:1923–42. PubMed PMID: 23334384.

Edvardsson VO, Sas DJ. Urinary Stone Disease and Nephrocalcinosis. In: Emma F, Goldstein SL, Bagga A, Bates CM, Shroff R, editors. Pediatric Nephrology. Cham: Springer International Publishing; 2022. p. 1295-322.

Fargue S, Acquaviva Bourdain C. Primary hyperoxaluria type 1: pathophysiology and genetics. Clin Kidney J. 2022;15(Suppl 1):i4-i8. PubMed PMID: 35592619.

Fargue S, Rumsby G, Danpure CJ. Multiple mechanisms of action of pyridoxine in primary hyperoxaluria type 1. Biochim Biophys Acta. 2013;1832:1776–83. PubMed PMID: 23597595.

Frishberg Y, Rinat C, Shalata A, Khatib I, Feinstein S, Becker-Cohen R, Weismann I, Wanders RJ, Rumsby G, Roels F, Mandel H. Intra-familial clinical heterogeneity: absence of genotype-phenotype correlation in primary hyperoxaluria type 1 in Israel. Am J Nephrol. 2005;25:269–75. PubMed PMID: 15961946.

Gang X, Liu F, Mao J. Lumasiran for primary hyperoxaluria type 1: What we have learned? Front Pediatr. 2023;10:1052625. PubMed PMID: 36704142.

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, et al. Lumasiran, an RNAi therapeutic for primary hyperoxaluria type 1. N Engl J Med. 2021a;384:1216–26. PubMed PMID: 33789010.

Garrelfs SF, Metry EL, van Harskamp D, Vaz FM, van den Akker CHP, Schierbeek H, Groothoff JW, Oosterveld MJS. Glycolate oxidase inhibition by lumasiran varies between patients with primary hyperoxaluria type 1. Kidney Int. 2023;103:990-3. PubMed PMID: 36871948.

Garrelfs SF, van Harskamp D, Peters-Sengers H, van den Akker CHP, Wanders RJA, Wijburg FA, van Goudoever JB, Groothoff JW, Schierbeek H, Oosterveld MJS. Endogenous oxalate production in primary hyperoxaluria type 1 patients. J Am Soc Nephrol. 2021b;32:3175-86. PubMed PMID: 34686543.

Godron A, Harambat J, Boccio V, Mensire A, May A, Rigothier C, Couzi L, Barrou B, Godin M, Chauveau D, Faguer S, Vallet M, Cochat P, Eckart P, Guest G, Guigonis V, Houillier P, Blanchard A, Jeunemaitre X, Vargas-Poussou R. Familial hypomagnesemia with hypercalciuria and nephrocalcinosis: phenotype-genotype correlation and outcome in 32 patients with CLDN16 or CLDN19 mutations. Clin J Am Soc Nephrol. 2012;7:801-9. PubMed PMID: 22422540.

Grateau G, Grünfeld JP, Beurton D, Hannedouche T, Crosnier J. Post-surgical deterioration of renal function in primary hyperoxaluria. Nephrol Dial Transplant. 1987;1:261-4. PubMed PMID: 3110687.

Groothoff J, Sellier-Leclerc AL, Deesker L, Bacchetta J, Schalk G, Tönshoff B, Lipkin G, Lemoine S, Bowman T, Zhou J, Hoppe B. Nedosiran Safety and Efficacy in PH1: Interim Analysis of PHYOX3. Kidney Int Rep. 2024;9:1387-96. PubMed PMID: 38707801.

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. Clinical practice recommendations for primary hyperoxaluria: an expert consensus statement from ERKNet and OxalEurope. Nat Rev Nephrol. 2023;19:194-211. PubMed PMID: 36604599.

Gupta A, Somers MJG, Baum MA. Treatment of primary hyperoxaluria type 1. Clin Kidney J. 2022;15:i9-i13. PubMed PMID: 35592620.

Habbig S, Beck BB, Hoppe B. Nephrocalcinosis and urolithiasis in children. Kidney Int. 2011;80:1278–91. PubMed PMID: 21956187.

Harambat J, van Stralen KJ, Espinosa L, Groothoff JQ, Hulton SA, Cerkausiene R, Schaefer F, Verrina E, Jager KJ, Cochat P. Characteristics and outcomes of children with primary oxalosis requiring renal replacement therapy. Clin J Am Soc Nephrol. 2012;7:458–65. PubMed PMID: 22223608.

Hatch M, Gjymishka A, Salido EC, Allison MJ, Freel RW. Enteric oxalate elimination is induced and oxalate is normalized in a mouse model of primary hyperoxaluria following intestinal colonization with Oxalobacter. Am J Physiol Gastrointest Liver Physiol. 2011;300:G461-9. PubMed PMID: 21163900.

Hopp K, Cogal AG, Bergstralh EJ, Seide BM, Olson JB, Meek AM, Lieske JC, Milliner DS, Harris PC., Rare Kidney Stone Consortium. Phenotype-genotype correlations and estimated carrier frequencies of primary hyperoxaluria. J Am Soc Nephrol. 2015;26:2559–70. PubMed PMID: 25644115.

Hoppe B, Beck B, Gatter N, von Unruh G, Tischer A, Hesse A, Laube N, Kaul P, Sidhu H. Oxalobacter formingenes: a potential tool for the treatment of primary hyperoxaluria type 1. Kidney Int. 2006;70:1305–11. PubMed PMID: 16850020.

Hoppe B, Danpure CJ, Rumsby G, Fryer P, Jennings PR, Blau N, Schubiger G, Neuhaus T, Leumann E. A vertical (pseudodominant) pattern of inheritance in the autosomal recessive disease primary hyperoxaluria type 1: lack of relationship between genotype, enzymic phenotype, and disease severity. Am J Kidney Dis. 1997;29:36–44. PubMed PMID: 9002528.

Hoppe B, Groothoff JW, Hulton SA, Cochat P, Niaudet P, Kemper MJ, Deschenes G, Unwin R, Milliner D. Efficacy and safety of Oxalobacter formigenes to reduce urinary oxalate in primary hyperoxaluria. Nephrol Dial Transplant. 2011;26:3609–15. PubMed PMID: 21460356.

Hoppe B, Niaudet P, Salomon R, Harambat J, Hulton SA, Van't Hoff W, Moochhal SH, Deschênes G, Lindner E, Sjögren A, Cochat P. A randomised Phase I/II trial to evaluate the efficacy and safety of orally administered Oxalobacter formigenes to treat primary hyperoxaluria. Pediatr Nephrol. 2017;32:781–90. PubMed PMID: 27924398.

Hoppe B, Pellikka PA, Dehmel B, Banos A, Lindner E, Herberg U. Effects of Oxalobacter formigenes in subjects with primary hyperoxaluria Type 1 and end-stage renal disease: a Phase II study. Nephrol Dial Transplant. 2021;36:1464-73. PubMed PMID: 32810261.

Hoyer-Kuhn H, Kohbrok S, Volland R, Franklin J, Beck BB, Hoppe B. Vitamin B6 in primary hyperoxaluria 1: first prospective trial after 40 years of practice. Clin J Am Soc Nephrol. 2014;9:468–77. PubMed PMID: 24385516.

Ivanovski O, Drüeke TB. A new era in the treatment of calcium oxalate stones? Kidney Int. 2013;83:998–1000. PubMed PMID: 23728004.

Janiec A, Halat-Wolska P, Obrycki Ł, Ciara E, Wójcik M, Płudowski P, Wierzbicka A, Kowalska E, Książyk JB, Kułaga Z, Pronicka E, Litwin M. Long-term outcome of the survivors of infantile hypercalcaemia with CYP24A1 and SLC34A1 mutations. Nephrol Dial Transplant. 2021;36:1484-92. PubMed PMID: 33099630.

Jónsson H, Sulem P, Kehr B, Kristmundsdottir S, Zink F, Hjartarson E, Hardarson MT, Hjorleifsson KE, Eggertsson HP, Gudjonsson SA, Ward LD, Arnadottir GA, Helgason EA, Helgason H, Gylfason A, Jonasdottir A, Jonasdottir A, Rafnar T, Frigge M, Stacey SN, Th Magnusson O, Thorsteinsdottir U, Masson G, Kong A, Halldorsson BV, Helgason A, Gudbjartsson DF, Stefansson K. Parental influence on human germline de novo mutations in 1,548 trios from Iceland. Nature. 2017;549:519-22. PubMed PMID: 28959963.

Kalfon L, Weissman I, Hershkovits M, Nasser Samra N, Edri N, Khayat M, Tanus M, Shihab S, Mandel H, Falik-Zaccai T. [Oxalate stones are prevalent among Druze and Muslim Arabs in the Galilee]. Harefuah. 2017;156:156-62. PubMed PMID: 28551940.

Kempf C, Pfau A, Holle J, Müller-Schlüter K, Bufler P, Knauf F, Müller D. Stiripentol fails to lower plasma oxalate in a dialysis-dependent PH1 patient. Pediatr Nephrol. 2020;35:1787-9. PubMed PMID: 32418144.

Kohli H, Kurtz MP. Primary hyperoxaluria type 1: urologic and therapeutic management. Clin Kidney J. 2022;15:i14-i16. PubMed PMID: 35592623.

Lubkowicz D, Horvath NG, James MJ, Cantarella P, Renaud L, Bergeron CG, Shmueli RB, Anderson C, Gao JR, Kurtz CB, Perreault M, Charbonneau MR, Isabella VM, Hava DL. An engineered bacterial therapeutic lowers urinary oxalate in preclinical models and in silico simulations of enteric hyperoxaluria. Mol Syst Biol. 2022;18:e10539. PubMed PMID: 35253995.

Lawrence JE, Wattenberg DJ. Primary Hyperoxaluria: The Patient and Caregiver Perspective. Clin J Am Soc Nephrol. 2020;15:909-11. PubMed PMID: 32165441.

Lorenz EC, Lieske JC, Seide BM, Meek AM, Olson JB, Bergstralh EJ, Milliner DS. Sustained pyridoxine response in primary hyperoxaluria type 1 recipients of kidney alone transplant. Am J Transplant. 2014;14:1433-8. PubMed PMID: 24797341.

Lorenz EC, Lieske JC, Seide BM, Olson JB, Mehta R, Milliner DS. Recovery From Dialysis in Patients With Primary Hyperoxaluria Type 1 Treated With Pyridoxine: A Report of 3 Cases. Am J Kidney Dis. 2021;77:816-9. PubMed PMID: 32891627.

Lumlertgul N, Siribamrungwong M, Jaber BL, Susantitaphong P. Secondary oxalate nephropathy: a systematic review. Kidney Int Rep. 2018;3:1363–72. PubMed PMID: 30450463.

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. Genetic assessment in primary hyperoxaluria: why it matters. Pediatr Nephrol. 2023;38:625-34. PubMed PMID: 35695965.

Mandrile G, van Woerden CS, Berchialla P, Beck BB, Acquaviva Bourdain C, Hulton SA, Rumsby G. OxalEurope Consortium. Data from a large European study indicate that the outcome of primary hyperoxaluria type 1 correlates with the AGXT mutation type. Kidney Int. 2014;86:1197–204. PubMed PMID: 24988064.

Martin-Higueras C, Garrelfs SF, Groothoff JW, Jacob DE, Moochhala SH, Bacchetta J, Acquaviva C, Zaniew M, Sikora P, Beck BB, Hoppe B. A report from the European Hyperoxaluria Consortium (OxalEurope) Registry on a large cohort of patients with primary hyperoxaluria type 3. Kidney Int. 2021;100:621–35. PubMed PMID: 33865885.

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. In vivo CRISPR-Cas9 inhibition of hepatic LDH as treatment of primary hyperoxaluria. Mol Ther Methods Clin Dev. 2022;25:137-46. PubMed PMID: 35402636.

Mbarek IB, Mdimeg S, Moussa A, Zellama D, Kaarout H, Abdelmoula J, Achour A, Abroug S, Omezzine A, Bouslama A. Unusual clinical outcome of primary hyperoxaluria type 1 in Tunisian patients carrying 33_34InsC mutation. BMC Nephrol. 2017;18:195. PubMed PMID: 28619084.

Metry EL, Garrelfs SF, Deesker LJ, Acquaviva C, D'Ambrosio V, Bacchetta J, Beck BB, Cochat P, Collard L, Hogan J, Ferraro PM, Franssen CFM, Harambat J, Hulton SA, Lipkin GW, Mandrile G, Martin-Higueras C, Mohebbi N, Moochhala SH, Neuhaus TJ, Prikhodina L, Salido E, Topaloglu R, Oosterveld MJS, Groothoff JW, Peters-Sengers H. Determinants of Kidney Failure in Primary Hyperoxaluria Type 1: Findings of the European Hyperoxaluria Consortium. Kidney Int Rep. 2023;8:2029-42. PubMed PMID: 37849991.

Metry EL, van Dijk LMM, Peters-Sengers H, Oosterveld MJS, Groothoff JW, Ploeg RJ, Stel VS, Garrelfs SF. Transplantation outcomes in patients with primary hyperoxaluria: a systematic review. Pediatr Nephrol. 2021;36:2217-26. PubMed PMID: 33830344.

Miao J, Mehta RA, Norby S, Seide B, Milliner DS, Lieske J, Kattah A. Comparison of clinical features of pregnant and non-pregnant females with primary hyperoxaluria. J Nephrol. 2022;35:1771-4. PubMed PMID: 35041195.

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. Lumasiran for Advanced Primary Hyperoxaluria Type 1: Phase 3 ILLUMINATE-C Trial. Am J Kidney Dis. 2023;81:145-55.e1. PubMed PMID: 35843439.

Michael M, Harvey L, Milliner DS, Frishberg Y, Sas DJ, Calle J, Copelovitch L, Penniston K, Saland J, Somers MJG, Baum MA. Diagnosis and management of primary hyperoxaluria: best practices. Ped Neph. 2024.

Milliner D, Hoppe B, Groothoff J. A randomised Phase II/III study to evaluate the efficacy and safety of orally administered Oxalobacter formigenes to treat primary hyperoxaluria. Urolithiasis. 2018;46:313–23. PubMed PMID: 28718073.

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. End Points for Clinical Trials in Primary Hyperoxaluria. Clin J Am Soc Nephrol. 2020;15:1056-65. PubMed PMID: 32165440.

Mitsimponas KT, Wehrhan T, Falk S, Wehrhan R, Neukam FW, Schlegel KA. Oral findings associated with primary hyperoxaluria type 1. J Craniomaxillofac Surg. 2012;40:e301–6. PubMed PMID: 22417769.

Monico CG, Olson JB, Milliner DS. Implications of genotype and enzyme phenotype in pyridoxine response of patients with type I primary hyperoxaluria. Am J Nephrol. 2005;25:183–8. PubMed PMID: 15849466.

Monico CG, Rossetti S, Schwanz HA, Olson J, Lundquist P, Dawson D, Harris P, Milliner DS. Comprehensive mutation screening in 55 probands with type 1 primary hyperoxaluria shows feasibiity of a gene-based diagnosis. J Am Soc Nephrol. 2007;18:1905–14. PubMed PMID: 17460142.

Murad H, Alhalabi MB, Dabboul A, Alfakseh N, Nweder MS, Zghib Y, Wannous H. Molecular analysis of the AGXT gene in Syrian patients suspected with primary hyperoxaluria type 1. BMC Med Genomics. 2021;14:146. PubMed PMID: 34082749.

Nogueira PK, Vuong TS, Bouton O, Maillard A, Marchand M, Rolland MO, Cochat P, Bozon D. Partial deletion of the AGXT gene (EX1_EX7del): a new genotype in hyperoxaluria type 1. Hum Mutat. 2000;15:384–5. PubMed PMID: 10737993.

Nwachukwu C, Singh G, Moore B, Strande NT, Bucaloiu ID, Chang AR. Risk of Nephrolithiasis in Adults Heterozygous for SLC34A3 Ser192Leu in an Unselected Health System Cohort. J Am Soc Nephrol. 2023;34:1819-21. PubMed PMID: 37639356.

Oppici E, Montioli R, Cellini B. Liver peroxisomal alanine:glyoxylate aminotransferase and the effects of mutations associated with Primary Hyperoxaluria Type I: An overview. Biochim Biophys Acta. 2015;1854:1212-9. PubMed PMID: 25620715.

Pais VM Jr, Assimos DG. Pitfalls in the management of patients with primary hyperoxaluria: a urologist's perspective. Urol Res. 2005;33:390-3. PubMed PMID: 16284885.

Perinpam M, Enders FT, Mara KC, Vaughan LE, Mehta RA, Voskoboev N, Milliner DS, Lieske JC. Plasma oxalate in relation to eGFR in patients with primary hyperoxaluria, enteric hyperoxaluria and urinary stone disease. Clin Biochem. 2017;50:1014–9. PubMed PMID: 28764885.

Pozdzik A, David C, Vekeman J, Tielens F, Daudon M. Lanthanum carbonate to control plasma and urinary oxalate level in type 1 primary hyperoxaluria? IJU Case Rep. 2021;4:235-8. PubMed PMID: 34258537.

Pruvot FR, Noel C, Declerck N, Valat-Rigot AS, Roumilhac D, Hazzan M, Puech F, Lelievre G. Consecutive successful pregnancies in a combined liver and kidney transplant recipient with type 1 primary hyperoxaluria. Transplantation. 1997;63:615–6. PubMed PMID: 9047162.

Pszczolinski R, Acquaviva C, Berrahal I, Biebuyck N, Burtey S, Clabault K, Dossier C, Guillet M, Hemery F, Letavernier E, Rousset-Rouvière C, Bacchetta J, Moulin B. Primary hyperoxaluria in adults and children: a nationwide cohort highlights a persistent diagnostic delay. Clin Kidney J. 2024;17:sfae099. PubMed PMID: 38737343.

Rao NM, Yallapragada A, Winden KD, Saver J, Liebeskind DS. Stroke in primary hyperoxaluria type I. J Neuroimaging. 2014;24:411–3. PubMed PMID: 23551880.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405-24. PubMed PMID: 25741868.

Santana A, Salido E, Torres A, Shapiro LJ. Primary hyperoxaluria type 1 in the Canary Islands: a conformational disease due to I244T mutation in the P11L-containing alanine:glyoxylate aminotransferase. Proc Natl Acad Sci U S A. 2003;100:7277–82. PubMed PMID: 12777626.

Sas DJ, Enders FT, Gunderson TM, Mehta RA, Olson JB, Seide BM, Banks CJ, Dehmel B, Pellikka PA, Lieske JC, Milliner DS. Natural History of Clinical, Laboratory, and Echocardiographic Parameters of a Primary

Hyperoxaluria Cohort on Long Term Hemodialysis. Front Med (Lausanne). 2021;8:592357. PubMed PMID: 33898474.

Sas DJ, Enders FT, Mehta RA, Tang X, Zhao F, Seide BM, Milliner DS, Lieske JC. Clinical features of genetically confirmed patients with primary hyperoxaluria identified by clinical indication versus familial screening. Kidney Int. 2020;97:786-92. PubMed PMID: 32093915.

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. Phase 3 trial of lumasiran for primary hyperoxaluria type 1: a new RNAi therapeutic in infants and young children. Genet Med. 2022;24:654-62. PubMed PMID: 34906487.

Sas DJ, Mara K, Mehta RA, Seide BM, Banks CJ, Danese DS, McGregor TL, Lieske JC, Milliner DS. Natural history of urine and plasma oxalate in children with primary hyperoxaluria type 1. Pediatr Nephrol. 2024;39:141-8. PubMed PMID: 37458799.

Schell-Feith EA, Kist-van Holthe JE, van der Heijden AJ. Nephrocalcinosis in preterm neonates. Pediatr Nephrol. 2010;25:221-30. PubMed PMID: 18797936.

Scott LJ, Keam SJ. Lumasiran: first approval. Drugs. 2021;81:277–82. PubMed PMID: 33405070.

Sellier-Leclerc AL, Metry E, Clave S, Perrin P, Acquaviva-Bourdain C, Levi C, Crop M, Caillard S, Moulin B, Groothoff J, Bacchetta J. Isolated kidney transplantation under lumasiran therapy in primary hyperoxaluria type 1: a report of five cases. Nephrol Dial Transplant. 2023;38:517-21. PubMed PMID: 36307929.

Singh P, Chebib FT, Cogal AG, Gavrilov DK, Harris PC, Lieske JC. Pyridoxine responsiveness in a type 1 primary hyperoxaluria patient with a rare (atypical) AGXT gene mutation. Kidney Int Rep. 2020;5:955-8. PubMed PMID: 32518881.

Singh P, Vaughan LE, Schulte PJ, Sas DJ, Milliner DS, Lieske JC. Estimated GFR Slope Across CKD Stages in Primary Hyperoxaluria Type 1. Am J Kidney Dis. 2022a;80:373-82. PubMed PMID: 35306035.

Singh P, Viehman JK, Mehta RA, Cogal AG, Hasadsri L, Oglesbee D, Olson JB, Seide BM, Sas DJ, Harris PC, Lieske JC, Milliner DS. Clinical characterization of primary hyperoxaluria type 3 in comparison with types 1 and 2. Nephrol Dial Transplant. 2022b;37:869–75. PubMed PMID: 33543760.

Soliman NA, Mabrouk S. Primary hyperoxaluria type 1 in developing countries: novel challenges in a new therapeutic era. Clin Kidney J. 2022;15:i33-i36. PubMed PMID: 35592622.

Soliman NA, Nabhan MM, Abdelrahman SM, Abdelaziz H, Helmy R, Ghanim K, Bazaraa HM, Badr AM, Tolba OA, Kotb MA, Eweeda KM, Fayez A. Clinical spectrum of primary hyperoxaluria type 1: Experience of a tertiary center. Nephrol Ther. 2017;13:176-82. PubMed PMID: 28161266.

Stenson PD, Mort M, Ball EV, Chapman M, Evans K, Azevedo L, Hayden M, Heywood S, Millar DS, Phillips AD, Cooper DN. The Human Gene Mutation Database (HGMD®): optimizing its use in a clinical diagnostic or research setting. Hum Genet. 2020;139:1197-207. PubMed PMID: 32596782.

Stone HK, VandenHeuvel K, Bondoc A, Flores FX, Hooper DK, Varnell CD Jr. Primary hyperoxaluria diagnosed after kidney transplant: A review of the literature and case report of aggressive renal replacement therapy and lumasiran to prevent allograft loss. Am J Transplant. 2021;21:4061-7. PubMed PMID: 34254430.

Tammachote R, Kingsuwannapong N, Tongkobpetch S, Srichomthong C, Yeetong P, Kingwatanakul P, Monico CG, Suphapeetiporn K, Shotelersuk V. Primary hyperoxaluria type 1 and brachydactyly mental retardation syndrome caused by a novel mutation in AGXT and a terminal deletion of chromosome 2. Am J Med Genet A. 2012;158A:2124–30. PubMed PMID: 22821680.

Tang X, Bergstralh EJ, Mehta RA, Vrtiska TJ, Milliner DS, Lieske JC. Nephrocalcinosis is a risk factor for kidney failure in primary hyperoxaluria. Kidney Int. 2015;87:623-31. PubMed PMID: 25229337.

Tang X, Voskoboev NV, Wannarka SL, Olson JB, Milliner DS, Lieske JC. Oxalate quantification in hemodialysate to assess dialysis adequacy for primary hyperoxaluria. Am J Nephrol. 2014;39:376–82. PubMed PMID: 24776840.

Toussaint C. Pyridoxine-responsive PH1: treatment. J Nephrol. 1998;11 Suppl 1 :49–50. PubMed PMID: 9604811.

van der Hoeven SM, van Woerden CS, Groothoff JW. Primary hyperoxaluria type 1, a too often missed diagnosis and potentially treatable cause of end-stage renal disease in adults: results of the Dutch cohort. Nephrol Dial Transplant. 2012;27:3855–62. PubMed PMID: 22844106.

van Woerden CS, Groothoff JW, Wijburg FA, Duran M, Wanders RJA, Barth PG, Poll-The BT. High incidence of hyperoxaluria in generalized peroxisomal disorders. Mol Genet Metab. 2006;88:346–50. PubMed PMID: 16621644.

Violier P, Boyer O, Berthaud R, Dorval G. Treatment with stiripentol in a patient with primary hyperoxaluria type 1: lesson for the clinical nephrologist. J Nephrol. 2022;35:1049-51. PubMed PMID: 34283403.

Williams EL, Acquaviva A, Chevalier F, Coulter-Mackie B, Monico C, Giachino D, Robbiano A, Salido E, Waterham H, Rumsby G. Primary hyperoxaluria type 1: Update and additional mutation analysis of the AGXT gene. Hum Mut. 2009;30:910–7. PubMed PMID: 19479957.

Witting C, Langman CB, Assimos D, Baum MA, Kausz A, Milliner D, Tasian G, Worcester E, Allain M, West M, Knauf F, Lieske JC. Pathophysiology and treatment of enteric hyperoxaluria. Clin J Am Soc Nephrol. 2021;16:487–95. PubMed PMID: 32900691.

Woodward G, Pryke R, Hoppe B, Rumsby G. Rapid liquid chromatography tandem mass-spectrometry screening method for urinary metabolites of primary hyperoxaluria. Ann Clin Biochem. 2019;56:232–9. PubMed PMID: 30373392.

Worcester EM, Coe FL. Calcium kidney stones. N Engl J Med. 2010;363:954–63. PubMed PMID: 20818905.

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. Predictors of incident ESRD among patients with primary hyperoxaluria presenting prior to kidney failure. Clin J Am Soc Nephrol. 2016;11:119–26. PubMed PMID: 26656319.

Zhao Y, Li Y, Fang X, He L, Fan Y, Geng H, Wu J. Extended genetic analysis of exome sequencing for primary hyperoxaluria in pediatric urolithiasis patients with hyperoxaluria. Gene. 2022;815:146155. PubMed PMID: 34995728.

Zheng R, Fang X, Chen X, Huang Y, Xu G, He L, Li Y, Niu X, Yang L, Wang L, Li D, Geng H. Knockdown of lactate dehydrogenase by adeno-associated virus-delivered CRISPR/Cas9 system alleviates primary hyperoxaluria type 1. Clin Transl Med. 2020;10:e261. PubMed PMID: 33377632.

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