Primary Hyperoxaluria Type 1

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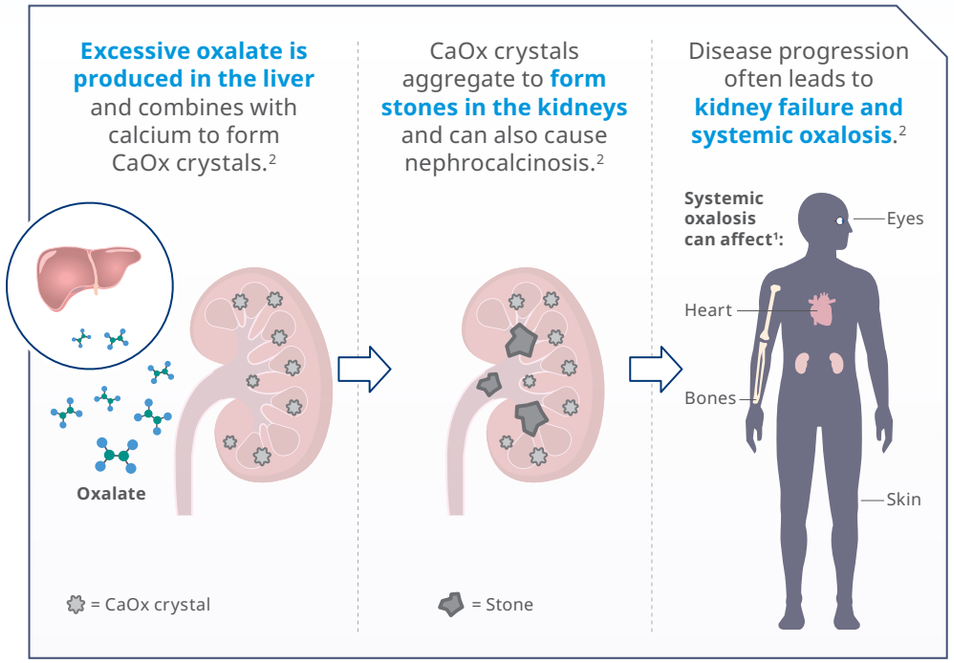
Understanding primary hyperoxaluria type 1 (PH1)

PH1 is a **rare autosomal recessive genetic disorder** in which hepatic oxalate overproduction results in progressive kidney damage.[1,2]



Patients with PH1 can experience acute kidney injury and irreversible kidney damage following **a single episode of dehydration, infection, or obstructive stones**[3]

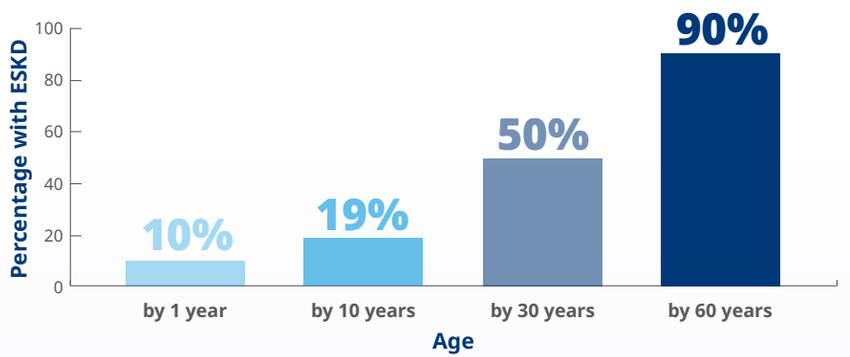
CaOx=calcium oxalate.

The vast majority of patients with PH1 experience kidney stones and many will eventually progress to end-stage kidney disease (ESKD)[4,5]

% of patients with stones	• **73% - 100%**[5,6]
Stone burden	• >50% of patients have multiple stones[6,7] • One study showed an average of 2.7 stones per lifetime[8]
Stone removal	• One study demonstrates 78% of patients require stone removal procedures[7]* • Multiple procedures per patient were required[5]

*Invasive stone removal posed a great burden to patients, including potential adverse effects such as bleeding, scarring, infections, and internal organ damage, as well as days in inpatient care.[7]

Rates of End-Stage Kidney Disease in Patients with PH1[9,10]



1-year and 10-year data are based on retrospective study of 155 patients primarily from western Europe, North Africa, or the Middle East.

30-year and 60-year data are based on 412 patients with PH1 enrolled in the Oxalosis and Hyperoxaluria Rare Kidney Stone Consortium PH registry.

Majority of patients with PH1 remain undiagnosed[4]

PH1 affects ~2700 people in the US based on genetic studies[4,11]*

Approximately 800 are diagnosed based on clinical studies[4,11]

Many patients with PH experience a delay in diagnosis from initial symptom onset[12-14]

In a study, 42% of patients with PH experienced a significant delay in diagnosis[12]

Patients experienced 3.4 ± 5.4 years between first symptom presentation and diagnosis[12]

One study reported that 27% of patients were diagnosed at ESRD with delay of 3.5 years after symptom onset[13]

A separate study found that ~5% were diagnosed after kidney transplant[14]

19% diagnosed after transplant were not diagnosed until after first transplant failure[14]

*Estimated US prevalence from genetic studies[4,11]
CKD=chronic kidney disease; ESRD=end-stage renal disease.

PH1 can be challenging to diagnose[6]

Screening for primary hyperoxaluria should be undertaken if patients are presenting one or a combination of the symptoms listed below[4,9,15-18]

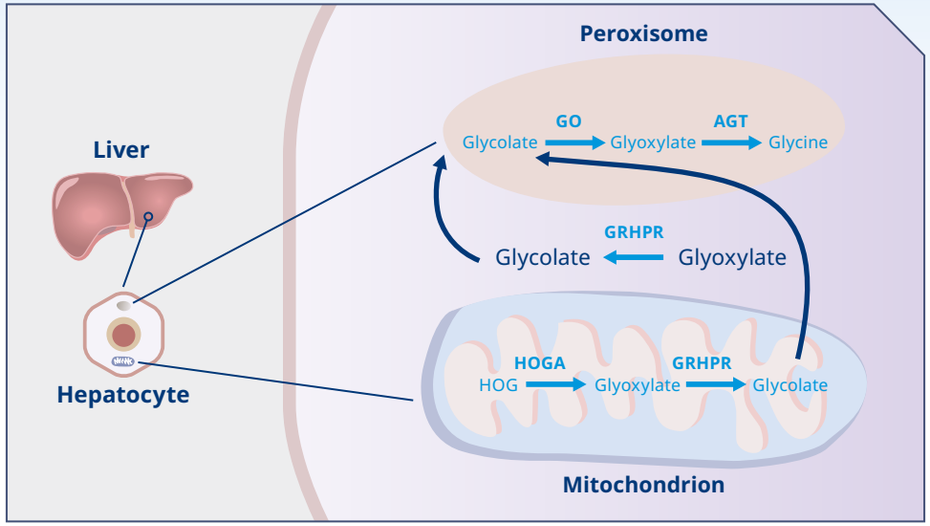
- A single kidney stone in an infant or child <18 years old
- Recurrent kidney stones (RKS) in adults 18 years or older
- Nephrocalcinosis
- Family history of kidney stones
- Elevated urinary oxalate (UOx) levels
- Advanced CKD with unknown cause
- Failure to thrive and ESKD in infants
- Signs of systemic oxalosis

PH1 can present at
any age and affects children and adults[1,15]

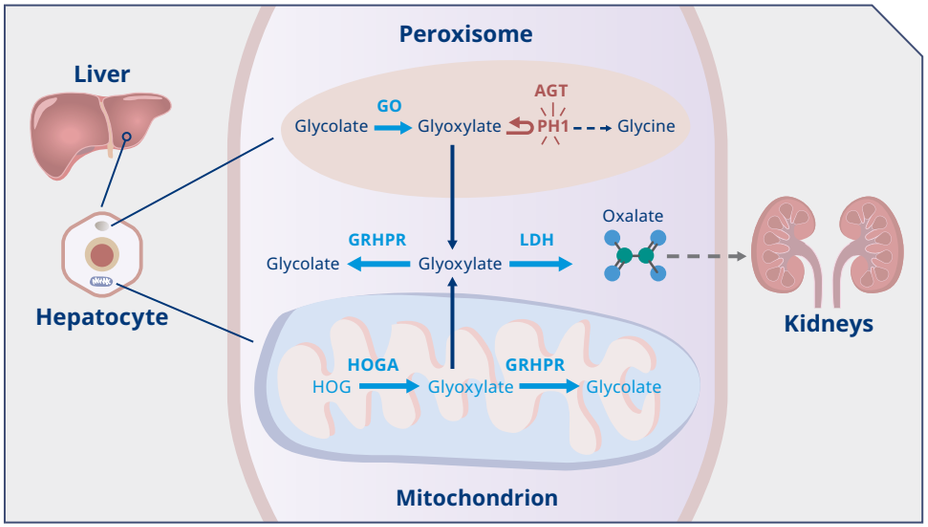
Genetic testing for PH1

Analyzing specific genes is crucial for an accurate diagnosis in patients with kidney-stone diseases with clinical overlap in symptoms, as it helps identify disease-causing mutations. This can allow for patient management that may reduce recurrent symptoms or progression to ESKD.[19-21]

Normal glyoxylate metabolic pathway[1,22]



Dysregulated pathway in PH1[22]



- PH1 is a rare autosomal recessive genetic disorder **caused by mutations in the *AGXT* gene**, resulting in deficiency of the AGT enzyme and buildup of glyoxylate.[1,2,22]
- In PH1, **hepatic LDH catalyzes the final step in this pathway**, converting abnormally high glyoxylate into excessive oxalate[23]

GRHPR=glyoxylate reductase/hydroxypyruvate reductase; GO=glycolate oxidase; LDH=lactate dehydrogenase.

Standard of care

Most current standard of care approaches do not address the underlying cause of oxalate overproduction in PH1.[2] PH1 progression is unpredictable; therefore, it should be treated early and monitored continuously.[2,19]

Hyperhydration can be intense, uncomfortable, and difficult to maintain.[2]

- Adults/older adolescents: 4 liters water/day[24]
- School-age children: 2-3 liters water/day[24]
- Infants/small children: 1-1.5 liters water/day[24]
- Gastrostomy tube for infants or adults struggling with water intake[24]

Pyridoxine (vitamin B6) supplementation is only effective in reducing UOx levels in a subset of PH1 patients.[2]

- One study showed two-thirds of patients with PH1 are completely unresponsive to pyridoxine[4,7-9,24,25]

Stone removal surgeries can cause unintended consequences.[26] They often are only a temporary solution to a chronic problem and do not address the underlying cause of oxalate overproduction.[2,15]

Conventional dialysis often cannot remove enough oxalate to prevent PH1 disease progression, requiring increased treatment time and frequency.[2]

- Often serves as a temporary therapy; the goal is to keep plasma oxalate levels below plasma calcium oxalate supersaturation (30-45 µmol/L) to prevent systemic oxalosis in patients awaiting organ transplant[17,24,27]

Dual liver-kidney transplant may eventually be required for patients with advanced CKD.[2]

- 23% to 36% of transplanted organs may fail within 5 years of transplant[14]
- Kidney and liver transplant recipients require lifelong immunosuppression[28]

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