

**The primary hyperoxalurias are a group of autosomal recessive disorders of endogenous oxalate overproduction.**

**We will discuss the major biochemical, genetic, and therapeutic advances that have led to a better understanding of the disease.**

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**Genetic diseases of man cannot be cured in the host. They can be "cured" in the species by eugenics. Perhaps some day this happy state of affairs can be approached through better recognition of hetero-zygosity and genetic counseling. Few would predict ...**

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**Although the initial recognition of the disease is attributed to Lepoutre, who reported it in 1925, the elucidation of the underlying biochemical abnormalities occurred many years later. This review discusses the major biochemical, genetic, and therapeutic advances that have led to a better understanding of primary hyperoxaluria.**

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**Oxalate, in the form of its calcium salt, is a highly insoluble end product of metabolism in humans. It is excreted almost entirely by the kidney, particularly in the form of its calcium salt, and has a tendency to crystallize in the renal tubules. The main defect of inherited hyperoxaluria is the overproduction of oxalate, primarily by the liver, which results in increased excretion by the kidney. The earliest symptoms among those affected are urolithiasis and nephrocalcinosis, which lead to progressive renal involvement and chronic kidney disease.**

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**Renal damage is ultimately caused by a combination of tubular toxicity from oxalate, nephrocalcinosis (with both intratubular and interstitial deposits of calcium oxalate), and renal obstruction by stones, often with superimposed infection. Inflammation has recently been shown to contribute to the progression of chronic kidney disease in animal models of nephrocalcinosis induced by calcium oxalate. A second phase of damage that is the result of primary hyperoxaluria occurs when the glomerular filtration rate (GFR) drops to 30 to 45 ml per minute per 1.73 m<sup>2</sup> of body-surface area and the kidney is unable to effectively excrete the oxalate load it receives. At this point, plasma levels of oxalate rise and exceed saturation, and oxalate is subsequently deposited in all tissues (systemic oxalosis), particularly in the skeleton.**

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**Secondary hyperoxaluria may occur as a result of excess dietary intake or poisoning with oxalate precursors or may be the result of enteric hyperoxaluria. The latter can occur after bowel resection, which can lead to sequestration of calcium in the gut, leaving oxalate in its more soluble sodium form, which is then taken up by the colon. Secondary hyperoxaluria must be ruled out before an investigation for primary hyperoxaluria begins.**

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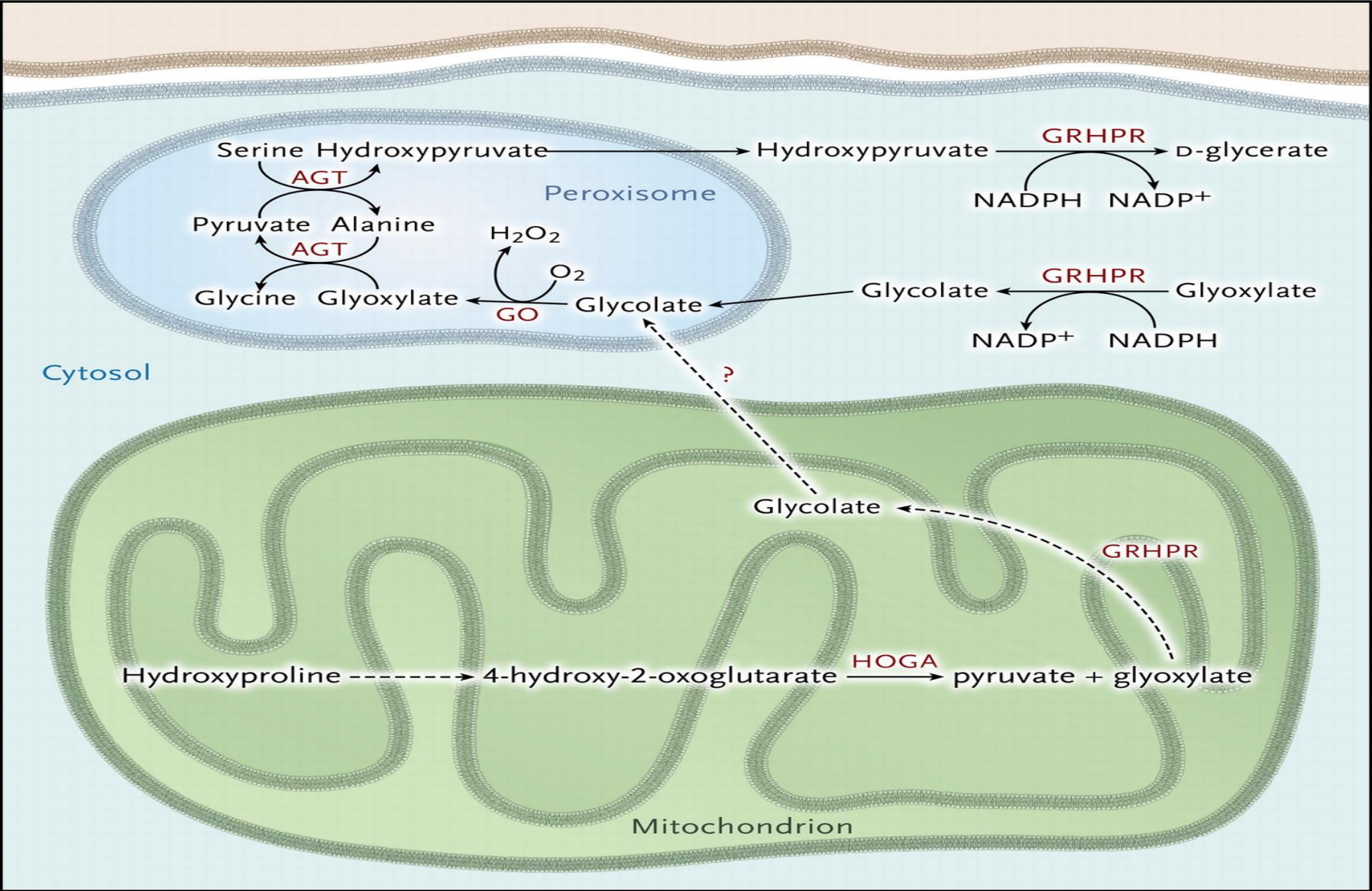
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## **EPIDEMIOLOGY:**

**The true prevalence of primary hyperoxaluria is unknown. Primary hyperoxaluria type 1, the most common form, has an estimated prevalence of 1 to 3 cases per 1 million population and an incidence rate of approximately 1 case per 120,000 live births per year in Europe.**

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**There are three forms of primary hyperoxaluria in which the underlying defects have been identified; they are designated as primary hyperoxaluria types 1, 2, and 3. Each is caused by an enzyme deficiency, and each affects a different intracellular organelle.**

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**Primary hyperoxaluria type 1 (number 259900 in the Online Mendelian Inheritance of Man [OMIM] database) is caused by a deficiency of the liver-specific peroxisomal enzyme alanine-glyoxylate aminotransferase (AGT), a pyridoxal 5'-phosphate–dependent enzyme that catalyzes the transamination of glyoxylate to glycine. This deficiency results in the accumulation of glyoxylate and excessive production of both oxalate and glycolate. AGT is a stable homodimer, with its N-terminal amino acids wrapped around the adjacent monomer.**

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**Primary hyperoxaluria type 2 (OMIM number, 260000) is caused by a lack of glyoxylate reductase–hydroxypyruvate reductase (GRHPR), which catalyzes the reduction of glyoxylate to glycolate and hydroxypyruvate to D-glycerate. GRHPR has a wide tissue distribution, but it is primarily intrahepatic.**

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**Primary hyperoxaluria type 3 (OMIM number, 613616) results from defects in the liver-specific mitochondrial enzyme 4-hydroxy-2-oxoglutarate aldolase (HOGA). This enzyme plays a key role in the metabolism of hydroxyproline, and kinetic studies suggest that the forward reaction, in which 4-hydroxy-2-oxoglutarate (HOG) is converted to pyruvate and glyoxylate, is favored.**

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## **GENETIC FEATURES:**

**Mutations in *AGXT*, the gene encoding AGT, result in primary hyperoxaluria type 1. One mutation, Gly170Arg, can lead to significant catalytic activity in vitro, but in some cases remains at the low end of the normal reference range. This mutation and three others (Ile244Thr, Phe152Ile, and Gly41Arg) unmask the N-terminal mitochondrial targeting sequence of AGT (encoded by Pro11Leu), leading to peroxisome-to-mitochondrion mistargeting (in which AGT, which normally targets peroxisomes, instead targets mitochondria). At least 178 mutations have been described; of these, Gly170Arg and c.33dupC occur across populations at a frequency of 30% and 11%, respectively.**

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## **CLINICAL SPECTRUM:**

**Primary hyperoxaluria may occur at almost any age — from birth to the sixth decade of life — with a median age at onset of 5.5 years.**

**The clinical presentation varies from infantile nephrocalcinosis and failure to thrive as a result of renal impairment to recurrent or only occasional stone formation in adulthood. However, 20 to 50% of patients have advanced chronic kidney disease or even ESRD at the time of diagnosis.**

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**Roughly 10% of patients receive a diagnosis of primary hyperoxaluria only when the disease recurs after kidney transplantation. In other cases, the disease is identified before symptoms appear in the course of family evaluations. Kidney injury, leading to a decrease in the GFR, results in chronic kidney failure and ultimately in ESRD, together with progressive systemic involvement.**

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**The major sites of crystal deposition are the kidneys, the blood-vessel walls, and the bones, with crystal deposits often leading to fractures. Oxalosis can also affect the joints, retina, skin, bone marrow, heart, and central nervous system, leading to severe illness and death. Data from the Rare Kidney Stone Consortium indicate that the median age at diagnosis of ESRD is 24 years. According to the European pediatric registry, the median age at the initiation of renal-replacement therapy is 1.5 years, and the patient survival rate 5 years after the initiation of renal-replacement therapy is 76%, as compared with 92% among children with ESRD resulting from other conditions. These figures translate into a risk of death for patients with primary hyperoxaluria that is three times as high as the risk for those without the disease.**



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**Primary hyperoxaluria type 1 is the most devastating subtype, particularly when it occurs in infancy, but patients who have the Gly170Arg or Phe152Ile mutation have a better overall outcome than other patients with type 1 disease, partly because of their sensitivity to pyridoxine. Patients with primary hyperoxaluria type 2 appear to have a less severe course, although the two disorders cannot be distinguished according to age at onset, and in some instances, primary hyperoxaluria type 2 is initially assumed to be type 1. Primary hyperoxaluria type 3 has the least severe course and may be silent or limited to stone formation, sometimes even improving over time. Whereas hyperoxaluria persists in primary hyperoxaluria type 3, nephrocalcinosis and chronic kidney failure are uncommon, and systemic involvement has not been reported thus far. Other factors, including environmental factors and modifier genes, may contribute to the clinical heterogeneity of primary hyperoxaluria.**

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## **DIAGNOSIS:**

**Given its rarity, primary hyperoxaluria may go unrecognized for several years after the onset of symptoms. Considering the possibility of primary hyperoxaluria and pursuing an evaluation that is in accordance with published algorithms may facilitate earlier recognition.**

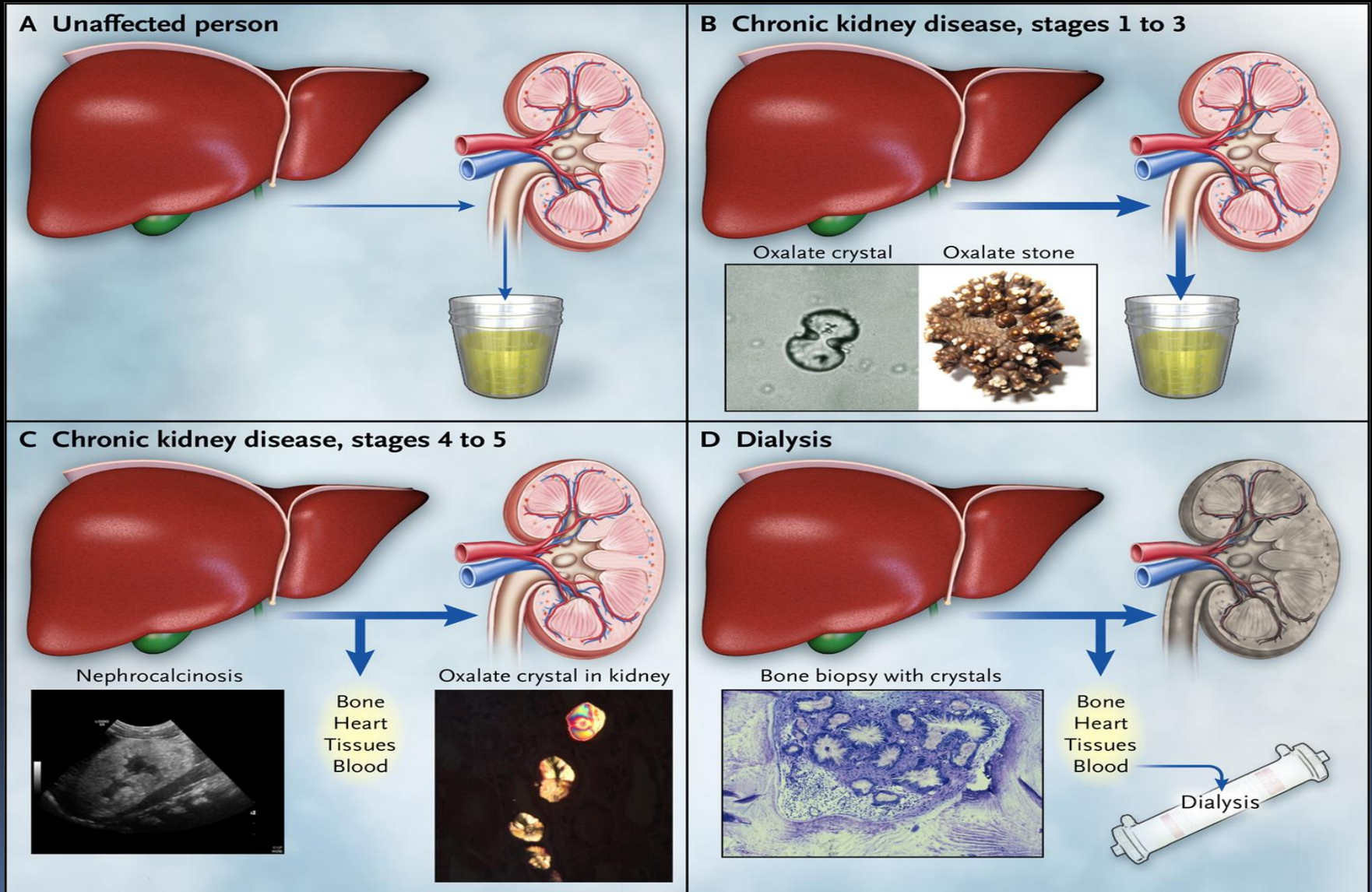
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**Because a majority of patients with primary hyperoxaluria present with symptoms related to urolithiasis, assessment of the risk of kidney stones, based on measurements of urinary levels of oxalate, calcium, citrate, sodium, magnesium, and urate, as well as urinary pH and volume, is central to a good evaluation. In patients with primary hyperoxaluria, kidney stones usually consist of more than 95% calcium oxalate monohydrate (whewellite), and they are unusually pale in color and nonhomogeneous in appearance. A finding of oxalate crystals in a kidney-biopsy specimen is also suggestive of primary hyperoxaluria (Refer Figure D in the next slide). In infancy, the chief presenting feature is metabolic acidosis, along with acute renal failure.**

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**The excretion of urinary oxalate is variable, particularly in the first year of life (According to Age-Related Reference Ranges of Metabolites in Patients with Primary Hyperoxaluria.), but persistently elevated excretion ( $>0.7$  mmol per  $1.73$  m<sup>2</sup> per day, or a urinary oxalate:creatinine ratio greater than the reference range for age), in addition to suggestive clinical symptoms and the absence of secondary hyperoxaluria, indicates the need for further evaluation. Not all patients with primary hyperoxaluria have markedly elevated levels of urinary oxalate, but if symptoms are suggestive, an additional evaluation for primary hyperoxaluria should be considered.**

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**For persons with a family history of primary hyperoxaluria, particularly type 1, genetic screening can be performed, and testing during the first trimester of pregnancy can establish a prenatal diagnosis. Preimplantation diagnosis may be possible, depending on local facilities.**

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## **MANAGEMENT:**

### **Supportive Measures:**

**Once a diagnosis of primary hyperoxaluria is being considered, supportive measures should be initiated, since long-term adherence to such treatment can dramatically improve the prognosis and slow the progression to ESRD. Fluid intake of more than 2 to 3 liters per square meter of body-surface area per day is essential for stone prevention, but in infants tube or gastrostomy feeding may be required to obtain appropriately dilute urine around the clock. Oral potassium citrate (0.10 to 0.15 mg per kilogram of body weight per day) is used to alkalinize urine (ideal pH, 6.2 to 6.8) and, more important, to inhibit crystallization; if renal function is impaired, sodium citrate should be used to avoid an increase in the potassium load.**

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**Extracorporeal shock-wave lithotripsy (ESWL) is not recommended in patients with primary hyperoxaluria who have a heavy stone burden, both because calcium oxalate stones do not easily fragment and because the risk of parenchymal damage, particularly in small kidneys, is high (a problem that has been reported in studies of primary hyperoxaluria in animals). For affected patients with a high stone burden, minimally invasive methods (e.g., ureteroscopic laser lithotripsy with percutaneous stone removal) are preferable to ESWL.**



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## Dialysis:

Conventional hemodialysis and peritoneal dialysis do not eliminate sufficient levels of oxalate to avert a continuous positive balance (Refer Figure D). Thus, more intensive strategies must be used to clear plasma oxalate levels and to limit systemic involvement. If pre-emptive transplantation is not feasible, therapeutic strategies that include short daily sessions of high-flux dialysis, nocturnal dialysis, or combinations of hemodialysis and nocturnal peritoneal dialysis are needed to keep predialysis levels of plasma oxalate below 30 to 45  $\mu\text{mol}$  per liter.

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## **Transplantation:**

**Since the liver is the sole organ responsible for glyoxylate detoxification, the excessive production of oxalate will continue as long as the native liver is present in patients with primary hyperoxaluria type 1. Thus, pre-emptive liver transplantation to avoid the complications of systemic oxalosis would appear to be a logical approach, with the surgery planned before the occurrence of stage 4 chronic kidney disease (estimated GFR, 15 to 30 ml per minute per 1.73 m<sup>2</sup>); this approach does raise ethical issues, given the risk of death associated with the procedure. Kidney transplantation without liver transplantation confers a very high risk of recurrence.**

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**Combined liver and kidney transplantation is therefore the treatment of choice for these patients. Kidney transplantation alone may be considered on an individual basis, such as in adults with confirmed responsiveness to pyridoxine. Dual transplantation is a reasonable choice for patients with stage 4 chronic kidney disease, since oxalate retention increases rapidly at this stage of renal dysfunction. In patients with stage 5 chronic kidney disease (estimated GFR, less than 15 ml per minute per 1.73 m<sup>2</sup>), sequential transplantation, starting with the liver, makes sense because the presence of a new, unaffected liver may permit the use of aggressive dialysis before renal transplantation, which may mobilize some of the systemic oxalate burden.**

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## **Future Therapeutic Developments:**

**Animal models have been developed for primary hyperoxaluria types 1, 2, and 3 (Salido E, Universidad La Laguna, Tenerife, Spain: personal communication). These models do not have the same phenotype as affected humans but are useful in the evaluation of treatments. The underlying problem in primary hyperoxaluria is not the enzyme deficiency itself but the accumulation of precursors, requiring replacement of liver tissue that is sufficient to overcome residual enzyme inactivity.**

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**Cell therapy, in which the liver is repopulated with normal hepatocytes, has been shown to be effective in *Agxt* knockout mice. However, there are still considerable difficulties in clinical applications of this approach to reduce the proliferation of host hepatocytes while boosting that of the transplanted cells. Hepatocyte transplantation has recently been suggested as a potential bridge to orthotopic liver transplantation in patients with primary hyperoxaluria type 1, but this procedure requires standard immunosuppressive therapy and does not fully correct the enzyme deficit.**

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**Gene transfer with the use of adeno-associated virus may be an attractive therapeutic option, but the problem of inducing adequate expression in addition to neutralizing antibodies must be overcome. Although the inhibition of glycolate oxidase could lead to substrate reduction, no suitable inhibitor has been identified as yet. Finally, the identification of pharmacologic chaperones to restore correct protein folding may be applicable to some genotypes. Recognition of such molecules depends on the use of high-throughput screens.**

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**Thank You**