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NDT Perspectives

Primary hyperoxaluria Type 1: indications for screening and guidance for diagnosis and treatment

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Abstract

Primary hyperoxaluria Type 1 is a rare autosomal recessive inborn error of glyoxylate metabolism, caused by a deficiency of the liver-specific enzyme alanine:glyoxylate aminotransferase. The disorder results in overproduction and excessive urinary excretion of oxalate, causing recurrent urolithiasis and nephrocalcinosis. As glomerular filtration rate declines due to progressive renal involvement, oxalate accumulates leading to systemic oxalosis. The diagnosis is based on clinical and sonographic findings, urine oxalate assessment, enzymology and/or DNA analysis. Early initiation of conservative treatment (high fluid intake, pyridoxine, inhibitors of calcium oxalate crystallization) aims at maintaining renal function. In chronic kidney disease Stages 4 and 5, the best outcomes to date were achieved with combined liver–kidney transplantation.

Keywords: combined liver–kidney transplantation; nephrocalcinosis; oxalosis; primary hyperoxaluria type 1; urolithiasis

Introduction

The term 'primary hyperoxaluria' (PH) encompasses an indeterminate number of rare autosomal recessive calcium oxalate kidney stone diseases, of which three have been described at the molecular level. PH1 is caused by mutations in the *AGXT* gene, which lead to dysfunction of the vitamin B6-dependent liver-specific peroxisomal enzyme alanine:glyoxylate aminotransferase (AGT) [1, 2]. PH2 arises from mutations in the *GRHPR* gene and subsequent dysfunction of the enzyme glyoxylate/hydroxypyruvate reductase (GRHPR) [3–5]. PH3 is caused by mutations in the *HOGA1* gene, which is thought to encode the mitochondrial enzyme 4-hydroxy-2-oxoglutarate aldolase [6].

This paper focuses on PH Type 1 (PH1, OMIM 259900), the commonest form of PH. The clinical presentation ranges from asymptomatic through to isolated or recurrent renal stones, nephrocalcinosis and renal impairment. The heterogeneous presentation leads to a diagnostic challenge and therefore, specific biochemical and genetic assessment is required to confirm a diagnosis of PH1 and to institute appropriate treatment.

Materials and methods

PH1 is a very rare inherited disease with a limited access to recommendations for diagnosis and management, due to the lack of randomized clinical trials and meta-analyses. An expert group (OxalEurope) has therefore been established to provide diagnostic and therapeutic recommendations for patients with PH. Experts were selected on both their individual commitment and their peer-reviewed publication activity in this field. Number of PubMed papers were (MeSH: hyperoxaluria, October 2011):

Acquaviva 3, Cochat 34, Danpure 64, Daudon 25, De Marchi 3, Fargue 8, Groothof 6, Harambat 7, Hoppe 43, Hulton 7, Jamieson 10, Kemper 20, Mandrile 3, Marangella 45, Picca 1, Rumsby 41, Salido 15, Straub 2 and van Woerden 6. Due to the rarity of the disease and the lack of evidence coming from randomized clinical trials, recommendations are based on ungraded statements.

Demography

PH1 has an estimated prevalence ranging from one to three per million and an estimated incidence rate of ~1:100 000 live births per year in Europe [7–9]. Higher rates are reported in isolated populations [10]. PH accounts for ~1% of paediatric end-stage renal disease (ESRD) in registries from Europe, USA and Japan [11–13]. In contrast, PH is more prevalent in countries where consanguineous marriages are common: ~10% of Kuwaiti and ~13% of Tunisian children with ESRD have been reported to have PH [14, 15].

Presentation

PH1 may present at any age. The presentation varies from infantile nephrocalcinosis and failure to thrive as a result of renal impairment to recurrent or only occasional stone formation [16]. Although patients with presentation in adulthood often have a history of only sporadic stone disease, over 50% of these patients present with ESRD at the time of diagnosis [9, 17]. Some patients may be identified as presymptomatic subjects with a family history of PH1 [16]. As a result of kidney injury, glomerular filtration rate (GFR) always declines leading to chronic kidney disease (CKD) and ultimately to ESRD and further systemic involvement (named 'oxalosis').

Clinical and radiological assessment

(1) We recommend considering a diagnosis of PH in any child with a first kidney stone and in adults with recurrent stone disease.

(2) We recommend considering a diagnosis of PH in any subject with nephrocalcinosis particularly when associated with decreased GFR.

(3) We recommend searching for PH in the presence of oxalate crystals (calcium oxalate monohydrate) in any biological fluid or tissue.

(4) We recommend screening relatives of index cases.

(5) We do not recommend screening in the general population.

Patients should undergo metabolic screening for PH1 at presentation of a first kidney stone (in a child) or recurrent or familial stone disease (at any age) or if nephrocalcinosis is detected. Stone analysis may reveal characteristic morphology and contain >95% calcium oxalate (CaOx) monohydrate (whewellite) often presenting with a particular morphology [18]. PH1 should be considered in any patient with renal failure of unknown cause, particularly in the presence of nephrocalcinosis or severe stone burden.

Preliminary PH1 diagnostic workup should include 24-h urine collection for oxalate, creatinine and glycolate; plasma oxalate (POx) when GFR is <60 mL/min/1.73m^2.

More specific investigations are covered in the biochemical and genetic sections below.

Ultrasonography (US) of the kidneys may elucidate stones and/or medullary or diffuse nephrocalcinosis. Patients with ESRD from PH may have diffuse cortical nephrocalcinosis which can be hard to distinguish from the common picture of an 'end-stage kidney' by US (Table 1).

Table 1. Organ involvement in PH patients with renal failure[a]

Organ	Symptoms	Diagnosis
Kidney[b]	Stones, medullary or diffuse nephrocalcinosis, cortical nephrocalcinosis	US CT (cortical nephrocalcinosis may be missed on US)
Bone[c]	Fractures, bone pain, growth retardation	X-ray: dense or lucent metaphyseal bands at the growth cartilage plate, vertebral condensations, osteopenia, epiphyseal nuclei (target-like) knee epiphyses
Eye[c]	Disturbed vision, specific brown coloured retinal deposits	Fundoscopy
Arteries[d]	Media calcifications	US, CT
Myocardium[d]	Cardiac failure, arrhythmia, heart block, left ventricular hypertrophy, systolic and diastolic dysfunction	ECG, echocardiography CT: calcifications
Thyroid[d]	Hypothyroidism	US Thyroid function tests
Skin[e]	(Painful) skin nodules, skin necrosis, gangrene, calciphylaxis-like skin lesions, pruritus	Skin biopsy
Nerves[e]	Ischaemic neuropathy	Clinical assessment
Muscle[e]	Myopathy by CaOx deposition	Biopsy, CT
Bowel[e]	Prolonged oxalosis: depositions of CaOx in the intestinal wall	CT
Joints[e]	Arthritis (late sign)	X-ray, CT

[a]CT, computed tomography.
[b]Always involved.
[c]Frequently involved.
[d]Often involved.
[e]Less often involved.

PH patients with a GFR <60 mL/min/1.73m^2 should undergo regular measurement of POx and monitoring of eye involvement by fundoscopy (Table 1). In addition, those with a GFR <30 mL/min/1.73m^2 should undergo assessment of cardiac involvement by ECG—echocardiography, and bone by X-ray as appropriate.

US and computed tomography scan of heart and visceral organs can assist in evaluating the level of calcification in patients with systemic oxalosis.

Biochemical and enzymological assessment

(1) We recommend measuring 24-h urine oxalate, creatinine and glycolate in any patient with a possible diagnosis of PH1 and preserved renal function as a first-line evaluation.
(2) We recommend measuring plasma oxalate in CKD patients.
(3) We recommend measurement of AGT enzyme activity if genetic testing is inconclusive.

The usual biochemical indicator of PH1 is a persistently and markedly elevated urine oxalate (UOx) excretion >0.5 mmol/1.73m^2 per day in the absence of secondary causes of hyperoxaluria. There is no clear cut-off for primary disease versus secondary hyperoxaluria: an excretion >0.7 mmol/1.73m^2 per day is more likely to have a metabolic cause but some secondary cases due to Crohn's disease, other chronic intestinal disease, short bowel syndrome and pancreatic insufficiency secondary to cystic fibrosis [19, 20] can have grossly elevated (>1 mmol/1.73m^2 per day) oxalate excretion. Values which fall between 0.5 and 0.7 cannot exclude PH and a strong clinical suspicion e.g. recurrent stones, young age, heavy crystalluria (>200 calcium oxalate monohydrate crystals/mm^3) should lead to more specific investigations. In children, oxalate to creatinine ratio can be determined on random urine specimens, but ratios fall rapidly in early life and are influenced by prematurity and nutrition; thus, interpretation requires an age-related reference range [21, 22]. Molar creatinine ratios from spot urine may give conflicting results so that confirmation of hyperoxaluria from a 24-h urine collection related to body surface area is recommended at all ages. A raised urine glycolate excretion is suggestive of PH1 but has a low diagnostic sensitivity and specificity; indeed, it is elevated in only two-thirds of patients and can rise as a result of dietary intake.

POx is unhelpful for diagnosis if renal function is normal. POx will increase as GFR falls and there is no clear cut-off to distinguish patients with PH from those with renal failure from any other cause, although values >100 μmol/L are more likely to be due to PH. Plasma glycolate may also be helpful in some patients [23].

The presence of oxalate crystals in a renal biopsy brings further support for a metabolic disturbance as the underlying cause.

The gold standard diagnostic test is the measurement of AGT catalytic and immunoreactivity in a liver biopsy specimen [24], which has a sensitivity >95%; false negatives are possible, albeit rarely, in patients with the p.Gly170Arg mutation [25] in which catalytic activity is preserved but the enzyme is non-functional *in vivo* due to intracellular mislocation. The wider availability of genetic testing has increased use of DNA analysis for diagnosis although there are still some cases in whom no mutation is found in the *AGXT* gene; AGT catalytic activity is therefore needed in these patients in order to completely exclude PH1. Additional genetic analysis of the *GRHPR* and *HOGA1* genes can be performed to confirm/exclude PH2 and PH3, which may have a similar presentation.

Whenever the causative mutation(s) are known, DNA analysis is the method of choice for prenatal testing and diagnosis in other family members.

Genetic tests for mutations in the AGXT *gene*

(1) We recommend genetic testing in subjects with phenotypic characteristics of PH1.
(2) We recommend extending mutation analysis to siblings and parents.
(3) We recommend offering prenatal diagnosis using mutation analysis to parents of an affected child.

Over 150 different mutations have been found so far in the *AGXT* gene [26]. Although most mutations are restricted to individual families, some are found at high frequency e.g. p.Gly170Arg (also known as G170R) found in ~30% of mutant PH1 alleles. Many PH1 mutations, including p.Gly170Arg, segregate and functionally interact with the common intragenic polymorphism Pro11Leu [27], which appears to increase their pathogenicity.

Genomic DNA isolated from ethylenediaminetetraacetic acid blood is the sample of choice. Salivary DNA and chorionic villus (for prenatal) are also suitable for diagnosis and carrier testing. All samples should be accompanied by detailed clinical and laboratory data to support the appropriateness of the request as well as documented consent for the analysis.

Targeted sequence analysis of Exons 1, 4 and 7 of *AGXT* has been proposed for first-line testing, with test sensitivity of 70% for a single mutation in a biopsy-proven population [28]. However, additional sequence of the entire coding region and flanking intronic regions will be required in up to 50% of patients and is strongly recommended. While it is not advised to include polymorphic variants in reports, the presence of the p.Pro11Leu (major/minor) variant is of significance and we recommend that this change is included in the report. It is recommended to always extend the analysis to both parents to confirm the segregation of any identified mutation(s). The results should be reported following recognized guidelines for nomenclature (www.hgvs.org) and content (www.ssgm.ch). For novel mutations, the report should include some indication of the likely pathogenicity.

For affected individuals and families in whom no mutation or only a single disease-causing mutation is identified, additional analyses may be indicated. Multiplex ligation-dependent probe amplification analysis can be used to search for gene deletions or duplications. No recommendation can yet be given on its performance with *AGXT* due to

little experience with the available kit. If no diagnosis is achieved, testing for PH2 and PH3 should be considered, even if evidence is limited to few patients studied. In cases with a strong suspicion but no mutation found in the three genes, a liver biopsy should be considered.

Linkage analysis with intragenic (e.g. the variable number tandem repeat in intron 4) and extragenic markers can be helpful particularly for prenatal diagnosis and family studies [29–31]. The accuracy can be as high as 99% but depends on a correct clinical diagnosis of PH1 in the affected relative(s) and on the informativeness of genetic markers in the family.

Any report of genetic test should be given to the patients by a genetic counsellor or specialist/consultant with a good knowledge of PH. However, prediction on the clinical course of the disease cannot be made on the basis of the genetic findings and the clinical follow-up of the index case, hence, prenatal counselling is extremely difficult.

Conservative treatment

(1) We recommend starting conservative therapy as soon as a diagnosis of PH1 has been suggested.

a) We recommend a high fluid intake, at least 3 L/m^2 per 24 h.

b) We recommend using a nasogastric tube or gastrostomy feeding tube to guarantee adequate hydration, mainly in infants.

c) We recommend administering vitamin B6 (pyridoxine) in any patients with proven PH1, starting at a dose of 5 mg/kg per day and not exceeding 20 mg/kg per day, aiming to decrease urine oxalate excretion by <30%.

d) We recommend calcium oxalate crystallization inhibition by use of alkalization with oral potassium citrate at a dose of 0.10–0.15 g/kg body weight per day (0.3–0.5 mmol/kg) as long as GFR is preserved.

(2) We do not recommend special dietary interventions other than for other concurrent diseases in the absence of CKD.

Conservative measures should be initiated, as soon as investigations are completed and while renal function is maintained. Once ESRD is established, pyridoxine is the only specific treatment that should be pursued.

The following measures apply to all types of PH with the exception of pyridoxine, which is specific to PH1.

High fluid intake. High fluid intake in stone formers has been proven to be effective in epidemiological and prospective intervention studies [32]. In PH, the recommended fluid intake is >3 L/m^2 per day, distributed throughout 24 h. In infants and small children, a feeding or gastrostomy tube is often required. Special care should be taken in situations of fluid losses (diarrhoea, vomiting and fever) or limited oral hydration (surgery) and intravenous (i.v.) fluid intake instituted if necessary.

Vitamin B6. Pyridoxal phosphate, one of the vitamin B6 vitaminers, is a cofactor for AGT. Administration of pyridoxine hydrochloride has been shown to be associated with a decrease in UOx in ~30% of patients with PH [33, 34], but the metabolic basis of pyridoxine responsiveness is not clear. All PH1 patients should be tested for pyridoxine responsiveness, and if responsive, treated until liver transplantation is performed, even if undergoing haemodialysis (HD). The recommended starting dose is 5 mg/kg per day, increasing by 5 mg/kg steps to a maximum of 20 mg/kg per day [35]. Responsiveness has been noted at doses inferior to 5 mg/kg per day. Responsiveness is currently defined by a >30% decrease in UOx excretion after a test period of a minimum of 3 months at maximum dose [36, 37]. Absorption of pyridoxine may vary between patients and assessing plasma levels may be useful, although therapeutic levels are not clearly defined. Side effects are rarely seen and sensory neurotoxicity is unusual. A subset of patients carrying one or two copies of p.Gly170Arg or p.Phe152Ile mutation are more likely to respond to pharmacological doses of pyridoxine, with other mutations possibly similarly responsive [38, 39].

Alkalization of the urine. Alkalization of the urine with alkali citrate can reduce urinary CaOx saturation by forming complexes with calcium thus decreasing stone growth or nephrocalcinosis [40]. Potassium citrate at a dose of 0.10–0.15 g/kg body weight per day (0.3–0.5 mmol/kg) is recommended. It may be replaced by sodium citrate appropriate to GFR and plasma potassium.

Other inhibitors of calcium oxalate crystallization. Other inhibitors of calcium oxalate crystallization such as pyrophosphate ions may decrease CaOx crystallization although orthophosphate has never been evaluated independently of other treatments [41]. Moderate doses of phosphate 20–30 mg/kg per day may be administered. There is no evidence that magnesium monotherapy can prevent stone formation [42, 43]. Despite the ability of *Oxalobacter formigenes* to metabolize oxalate, there is as yet no evidence that probiotics can significantly decrease UOx excretion in PH patients [44, 45].

Diet. A restriction in oxalate intake is of limited use as the main source of oxalate is endogenous and intestinal oxalate absorption is lower in PH patients compared to normal subjects [46]; however, relying on precautionary principle, some experts recommend avoiding oxalate-rich foods in the diet. Calcium intake should remain normal as oral calcium binds intestinal oxalate and dietary calcium restriction results in higher oxalate intestinal absorption [47, 48]. Excessive intake of vitamin C and D is to be avoided. Careful vitamin D supplementation in children is recommended. Ascorbic acid i.v. supplementation should be used with caution in dialysis PH patients [49].

Monitoring. The monitoring of urinary pH, volume and oxalate excretion may be useful. When advanced CKD has been reached, oxalosis bone involvement may be responsible for impaired responsiveness to erythropoiesis-stimulating agents and to growth hormone treatment [50–52].

Surgical management of urolithiasis

(1) We do not recommend any kind of surgical intervention in PH1 patients with uncomplicated urinary stone disease, except when there is obstruction, infection or multiple urolithiasis.

(2) We recommend endoscopic procedure as preferential strategy to manage urolithiasis in patients who require intervention.

The management of intraluminal stones by the urological surgeon is complicated by the potential of concomitant presence of nephrocalcinosis. The successful removal of intraluminal stones can only be assessed by endoscopy, as even successfully treated completely stone-free kidneys will reveal 'residual stones' on imaging when nephrocalcinosis is present. Non-endoscopic treatment (i.e. lithotripsy) holds the risk of misinterpretation, which means that shock waves are applied on nephrocalcinosis spots instead of stones [53]. Different minimally invasive methods like extracorporeal shock wave lithotripsy (ESWL), semi-rigid ureterorenoscopy (URS), flexible ureterorenoscopy (RIRS), percutaneous nephrolithotomy (PCNL) and laparoscopic approaches are currently established for interventional stone treatment. Open surgery has become exceptional in this field.

ESWL has been successfully applied to most kidney and ureter stones and has emerged worldwide as a standard tool [54]. It is the preferred treatment for intrarenal calculi <20 mm diameter. Success rates after ESWL, meaning stone-free kidneys, range from 55 to 90%. However, ESWL means *in situ* fragmentation of the stone, leaving the gravel behind for elimination by natural route. As a consequence, stone clearance of the urinary tract can be incomplete. Up to 60% of patients with small residual stone fragments (<3 mm) after ESWL will have increasing accumulation and formation of new stone masses on these residues [55]. PH1 stone formers experience a high risk of prompt stone re-growth on such residues because of ongoing hyperoxaluria.

While guidelines still recommend ESWL [56], in daily practice, this is completely replaced by endoscopy in PH1 patients when multiple stones are present [57]. URS, RIRS and PCNL allow fragmentation and achieve removal of stone material under direct visual control. Stone size and localization determine whether a retrograde, flexible or percutaneous access is the most appropriate technique. By the aid of pneumatic, electrohydraulic, ultrasound or holmium laser probes, stones are crushed into small removable fragments or even dust which can be flushed out. The patient can expect excellent stone-free rates, reaching 80–100% for all techniques [URS, RIRS (kidney stones < 20 mm) and PCNL]. Endoscopy allows a complete clearance of the urinary tract at the end of the procedure, which is different from ESWL.

Dialysis procedures

(1) We recommend avoiding any form of dialysis unless absolutely necessary and to consider pre-emptive transplantation in PH1 patients with progressive CKD.

(2) We recommend using high efficacy dialysis, such as daily HD, nocturnal dialysis, combination of HD and peritoneal dialysis (PD), in patients where pre-emptive transplantation is not an option.

(3) We do not recommend dialysis in the early postoperative transplantation period other than indications described in the transplant guidelines.

(4) We do recommend haemodialysis/filtration for clearance of oxalate during and after organ transplantation in patients with systemic involvement and/or insufficient urine outflow in the early post-transplant period.

Although the molecular mass of oxalic acid is small (90 Da), conventional dialysis is unable to remove sufficient quantities of oxalate proportionate to the continuous daily production. Oxalate is generated at a rate of 4–7 mmol/1.73m^2 per day in contrast to removal via conventional dialysis at a rate of 1–2 mmol/1.73m^2 per day in adults and 3–4 mmol/1.73m^2 per day in children, resulting in an uncontrolled tissue accretion rate [23, 58, 59].

Consequently, conventional dialysis is not considered ideal for patients with systemic oxalosis who have reached ESRD [16, 60]. However, long-term dialysis may be needed while awaiting organ transplantation and achieving adequate body size. PD and HD have been used either alone or in combination in order to maximize oxalate removal [59, 61]. The peculiar distribution of oxalate mass in the body explains the limitations of dialysis treatment even when optimized. In systemic oxalosis, tissue oxalate is in equilibrium with oxalate in body fluids. When plasma CaOx supersaturation (β_{CaOx}) is reached, oxalate precipitation occurs; the threshold of CaOx supersaturation ($\beta_{CaOx} > 1$) ranges between 30 and 45 μmol/L, also depending on serum calcium concentration [62, 63]. Thus, the goal should be to lower POx enough with dialysis to keep it below β_{CaOx} for as long as possible during the interdialytic period.

Oxalate clearance on HD is greater than on PD (~120 mL/min on HD compared to ~7 mL/min on PD) [64]. Standard HD programmes will result in a weekly clearance of oxalate of 6–9 mmol/1.73m^2 per week equivalent to 2–3 days of endogenous production of oxalate [65]. PD is insufficient to clear adequate quantities of oxalate but in some patients, a combination of overnight PD using continuous cycling PD/nocturnal intermittent PD and intermittent daily HD can enhance the overall clearance of oxalate and attempt to reduce the rebound which occurs after HD. The use of combination therapy, high-flux dialysers or long episodes of haemofiltration has been advocated to improve oxalate removal [60, 66].

However, while HD can reduce POx by ~60% following a dialysis session, this will return to 80% of the pre-dialysis levels within 24 h as HD removes only a small fraction of total body oxalate, followed by a rebound from bone turnover [67].

HD and/or continuous renal replacement therapy may be required following isolated liver transplantation where sequential hepatorenal transplantation is being undertaken or following combined transplantation where there has been a delay in improvement of renal graft function. In

these circumstances, the benefit of intra-operative and post-transplantation dialysis is debated. It can be considered in patients with significant systemic involvement where the urine excretion is limited. Dialysis in these circumstances will produce a rapid fall in POx thus protecting the transplanted kidney from tubulotoxic effects and oxalate deposition. In any case, the risk of CaOx supersaturation should be avoided with accurate fluid management [60, 68].

Transplantation strategy

(1) We recommend planning pre-emptive organ transplantation at CKD Stage 3b to avoid the complications of systemic oxalosis.
(2) We do not recommend isolated kidney transplantation, unless there is no other option.
(3) We recommend combined liver–kidney transplantation in most patients, either simultaneously or sequentially according to patient's condition and to local facilities.
(4) We do not recommend pre-emptive isolated liver transplantation unless in very well-defined and selected patients.

Organ transplantation should be planned prior to systemic oxalosis, i.e. before CKD Stage 4.

Kidney transplantation. There is no scientific rationale for isolated kidney transplantation, and it should be considered only for selected adult patients with confirmed evidence of B6 responsiveness [38].

Liver transplantation. As the liver is the only organ responsible for glyoxylate detoxification by AGT, the excessive production of oxalate will continue as long as the native liver is left in place.

The strategy of liver–kidney transplantation is influenced by the stage of the disease (Table 2) [69]. Simultaneous liver–kidney transplantation is logical in patients with CKD Stage 4 because, at this level, oxalate retention increases rapidly. It has been used successfully with excellent outcome even in small infants [70, 71]. A sequential procedure (first liver transplantation, followed by dialysis attempting to reduce oxalate load from the body, with subsequent kidney transplantation) may be proposed in individual ESRD patients. Pre-emptive isolated liver transplantation may be an option in selected patients supervised by a PH specialist [72–74]. Such a strategy has a strong rationale but raises ethical controversies since the transplant procedure of choice needs to be individualized as conservative management has improved long-term outcome in many patients with PH1.

Most publications currently report on the use of deceased donors but a living related donor for split liver or renal donation may be considered under appropriate conditions.

Post-transplantation reversal of renal and extrarenal involvement. After combined liver–kidney transplantation, UOx can remain elevated for many years due to slow resolubilization of systemic CaOx. Therefore, recurrent nephrocalcinosis or renal calculi is still a risk and may jeopardize kidney graft function. The kidney must therefore be protected by forced fluid intake supported by the use of crystallization inhibitors, and calcineurin inhibitors should be used with caution in order to minimize additional nephrotoxicity. The benefit of post-transplantation HD is still debated and should be limited to patients with significant systemic involvement and those with acute tubular necrosis or delayed graft function.

Conclusions

Hyperoxaluria should be considered in any patient with a history of urolithiasis and/or nephrocalcinosis. Such patients should be referred to reference centres with access to appropriate biochemical and genotyping facilities. An early and accurate diagnosis leading to aggressive supportive treatment is a major factor in short- and long-term outcomes. No method of dialysis is ideal; however, intensive extended daily dialysis should be recommended. Early pre-emptive transplantation should be considered in those with impaired renal function at an early stage (CKD Stage 3b); most experience in PH1 is available with combined liver–kidney transplantation.

Table 2. Suggested transplantation options in pyridoxine-resistant PH1 patients according to residual GFR, systemic involvement and local facilities[a]

Tx options	*Simultaneous liver + kidney*	*Sequential liver–kidney*	*Isolated kidney*	*Isolated liver*
HD strategy	Peroperative ± postoperative according to POx and GFR	Standard HD following liver Tx aiming at POx < 20 μmol/L	Preoperative and peroperative	Sometimes peroperative
CKD Stage 3 (30 < GFR < 59)	No	No	No	Option in carefully selected patients
CKD Stage 4 (15 < GFR < 29)	Yes	Option	Option if B6 response but no evidence	No
CKD Stage 5 (GFR < 15)	Yes	Yes	Option if B6 response but no evidence	No
Infantile form (ESRD < 2 years)	Yes	Yes	No	No

[a]POx, plasma oxalate; Tx, transplantation.

New insights into potential therapies, including restoration of defective enzyme activity through chemical chaperones, hepatocyte cell transplantation or recombinant gene therapy for enzyme replacement, provide some hope for a curative approach of PH1 in the future.

Access to information

Several national and international societies provide information on the PHs. The Oxalosis and Hyperoxaluria Foundation (www.ohf.org) has an extended website with open access and provides regular updates for physicians, patients and scientists. It offers an overview of presentation, diagnosis and treatment of the disease. The European Hyperoxaluria Consortium OxalEurope (www.oxaleurope.org) brings together clinicians and scientists throughout Europe; it hosts a website that directs visitors to country and language-specific websites. UpToDate, Inc. (www.uptodate.com) and Medscape (www.medscape.com) provide useful information. Genetic information can be obtained on www.orpha.net and www.genereviews.org.

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