


## CKJ REVIEW

# Primary hyperoxaluria type 1 in developing countries: novel challenges in a new therapeutic era

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## ABSTRACT

Primary hyperoxaluria type 1 (PH1) is an autosomal recessive inborn error of metabolism characterized by marked hepatic overproduction of oxalate due to deficiency of hepatic peroxisomal alanine-glyoxylate aminotransferase caused by AGXT gene mutation. One major hallmark of PH1 in developed as well as developing countries (DC) is the diagnostic delay. Notably in DC, where the disease is most prevalent and probably underdiagnosed, there are many challenges in PH1 diagnosis and management, with economic constraints and ethical concerns. This has led to the existing gap in the management of PH1 between developed and DC, which is expected to further deepen with the advent of novel therapeutic agents unless appropriate actions are taken. Until recently, treatment possibilities were limited to supportive measures. Thanks to a better understanding of the molecular basis of the disease a number of new therapies are developed, or being developed, leading to profound changes in management strategies. In this review we discuss the current situation of PH1 in DC as well as the accessibility challenges and the advantages of using promising novel therapeutics to bridge the currently existing gap. We also provide an overview of an integrated approach to ensure equitable access of sustainable therapeutics to PH1 patients in DC. This is expected to reduce global PH1 healthcare disparities, improve its standard of care and reduce disability linked to extrarenal complications of PH1 by implementing personalized medicine.

**Keywords:** combined liver and kidney transplantation, developing countries, diagnosis, ethical concerns, equitable access, novel therapeutics, precision medicine, primary hyperoxaluria type 1

## INTRODUCTION

Primary hyperoxaluria type 1 (PH1) is the most frequent and severe form of primary hyperoxalurias, leading to end-stage renal disease (ESRD) and systemic organ damage [1–4]. The estimated disease prevalence ranges from 1–3 per million population [1, 5]. This prevalence is probably higher in inbred populations [1, 5, 6]. Scientific research has led, during the last few years, to major advances in the understanding as well as the management

of the disease, with some promising options [7–12]. However, in developing countries (DC), where the disease is most prevalent, and probably underdiagnosed [6, 13–15], physicians as well as patients are still facing lots of challenges in terms of diagnosis, management, and economic and ethical aspects [13–19]. In this article we discuss the current situation in DC highlighting the paradox of the increasing difficulty of management while knowledge is progressing and therapeutic tools are improving.

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The challenges and opportunities associated with the use of novel therapeutics are also discussed.

## EPIDEMIOLOGICAL PERSPECTIVE

The real burden of PH1 is still unknown; it has an estimated prevalence ranging from 1–3 per million population and an estimated incidence rate of 1:120 000 live births in Europe [1, 5]. In countries with high consanguinity rates, such as North African and Middle Eastern populations, the prevalence of the disease is clearly higher than Europe, the USA and Japan, and its real extent and burden remain largely unknown [13, 15, 20, 21]. The only available data emanate from isolated referral center reports and case series, with small numbers of patients [6, 13, 16, 22–25]. To get a better understanding of genotype–phenotype correlations in such populations, precise epidemiological data are needed. Creating national registries has been extremely useful to this end, and an invaluable tool in monitoring clinical course and outcome of PH1 patients while effectively managing the resources to improve patients' outcome.

## DIAGNOSTIC CHALLENGES

One major hallmark of PH1 in developed countries as well as DC is the diagnosis delay [3, 14, 26], with an average 5-year time interval from initial symptoms to diagnosis of PH1 [26]. In DC, PH1 is a real public health burden due to diagnosis delay and high rate of ESRD at diagnosis ranging from 27% to 65.4% [6, 22, 23]. Several factors, including the large phenotypic spectrum, the lack of awareness among physicians about the disease and the paucity of diagnostic tools, can explain this diagnosis delay. As a matter of fact, the medical curriculum does not include hyperoxaluria, which remains an unknown disease for many physicians, including pediatricians. Besides, molecular analysis, blood oxalate, urine oxalate, urine glycolate or even urine crystal examination are not easily accessible to all practitioners, as they may be available only in reference centers. To overcome the above hurdles, much effort is deployed to promote a high index of clinical suspicion among pediatricians, urologists, nephrologists and general practitioners. Patients should be screened for PH1: (i) at presentation of a first kidney stone in children, (ii) recurrent or familial stone disease at any age, (iii) nephrocalcinosis and (iv) renal failure of unknown cause, particularly in the presence of nephrocalcinosis and/or urolithiasis burden [2], and subsequently get timely referral to expert centers. Diagnostic strategies should be adapted according to local possibilities, and disease stage and characteristics [8, 24–26] with focus on simple tools such as urine crystal examination and urine oxalate. Also with the technological revolution in next generation sequencing (NGS), cheap and affordable genetic diagnosis and/or screening of PH1 in prevalent communities is now possible.

## THERAPEUTIC RESOURCES

Given the devastating nature of the disease when left untreated or improperly managed, DC are encouraged to act at two main levels to face the medical and societal burden of the disease:

- (i) Invest in awareness programs for early diagnosis of PH1 patients before renal and extrarenal complications ensue, thereby widening the therapeutic window for PH1 patients with preserved kidney function or moderate chronic kidney disease (CKD) stage while allowing identification of high-risk patients.

- (ii) Explore the therapeutic options for PH1 patients who are diagnosed in an advanced CKD stage.

To date, only very few supportive measures are available for patients suffering from PH1, which, together with the severity of the disorder, renders disease management very challenging [7]. Conservative measures are the cornerstone of PH1 management that can prevent further stone formation and renal function loss [1, 2, 25]. These measures should be initiated as soon as the diagnosis is suspected [1, 2]. Patients should increase their daily water intake, which can be challenging in hot settings, as it requires huge quantities of water, up to 3–5 L/day, including overnight intake. This situation is particularly difficult among infants, which may require the use of nasogastric tube or gastrostomy, and is not easily accepted by the parents. In addition, pyridoxin and crystallization inhibitors may not be available in some countries or medical settings, which limits patients' access to these therapies. In that case, patients should be advised to resort to citrate- and pyridoxine-rich food. Health systems should consider focusing on such therapies, making them accessible to all patients, to prevent the progression to ESRD with subsequent additional costs, morbidity including disability and mortality risk [4].

PH1 accounts for 1–2% cases of pediatric ESRD according to registries from Europe, the USA and Japan [1, 4], however its prevalence is much higher in DC. PH1 is reported to cause 13–15% of pediatric ESRD in Tunisia [13, 27], 10.4% in Kuwait [19] and 16.7% in Jordan [21]. Intensive dialysis regimens with daily hemodialysis associated to peritoneal dialysis, are needed to remove calcium oxalate loads [1, 2, 4, 14]. Dialysis is not available in all resource-limited settings, and intensive strategies are often not possible in DC [28].

Until recently, simultaneous or sequential combined liver and kidney transplantation was considered as the sole therapeutic possibility for PH1 patients having reached advanced stages of CKD [1, 2, 27]. Access to organ transplantation, particularly liver transplantation, depends on the country's possibilities and is often difficult in DC [13, 17, 29, 30].

Interestingly, and despite the fact that PH1 is a rare disease, there has been a growing interest among researchers to develop new therapeutics to treat the devastating metabolic consequences of the disease. Novel treatment options are being developed and tested, including substrate-reduction therapies based on small-molecule inhibitors or the RNA interference (RNAi) technology, gene therapy, enzyme administration approaches, colonization with oxalate-degrading intestinal microorganisms and, in PH1, design of pharmacological chaperones [7, 8, 10, 11, 31]. In addition, some inexpensive molecules such as stiripentol, which targets hepatic lactate dehydrogenase (LDH), is another possibility of extending the PH1 therapeutic arsenal [32–34].

The growing body of novel results has led to the reconsideration of the transplantation strategies, particularly with the recent Food and Drug Administration approval of the first RNAi therapeutic agent for PH1 [12, 35]. With novel therapeutics using RNAi, liver transplantation will no longer be necessary. However, some patients with progressing renal disease or those who will be diagnosed with PH1 at an advanced CKD stage will ultimately need kidney transplantation [12]. Hopefully these therapies, if made available, will profoundly change the outcome of PH1 in DC where both intensive dialysis and complex transplantation procedures may not be possible. Thus, it is of prime importance to focus on early diagnosis and early supportive therapy to prevent ESRD occurrence.

Novel PH1 Therapeutics in Developing Countries	
Challenges	Opportunities
<ul style="list-style-type: none"> <li>High cost limiting accessibility in resource constrained health systems</li> </ul>	<ul style="list-style-type: none"> <li>Targeted therapy reducing hepatic overproduction of oxalate</li> <li>Prevalent PH1 allowing more patients to be treated</li> <li>Ease of usage</li> <li>Obviate the need for complex liver transplantation</li> <li>Improved standard of care with reduction of disability and extrarenal complications of PH1</li> </ul>

FIGURE 1: Challenges and opportunities of using novel therapeutics in DC.

## CHALLENGES IN LIMITED RESOURCE COUNTRIES

There is an existing gap in the management of PH1 between developed and developing nations, particularly in infants [6, 36]. It is therefore crucial to improve academic knowledge on PH1 and enhance public and medical awareness to identify index PH1 patients. Subsequently, screening of siblings and at-risk families and antenatal screening will aid in early diagnosis of asymptomatic cases.

The last decade witnessed a therapeutic revolution as some promising, innovative therapeutic agents are in clinical development with preliminary data of significant efficacy in reducing the hepatic overproduction of oxalate, the real culprit behind the disease. Therefore, DC are experiencing novel challenges sailing into this uncharted territory. Notably, novel therapeutics are less complex than liver or combined liver and kidney transplantation, yet questions regarding accessibility and affordability remain to be answered. It is anticipated that the cost of PH1 novel medications will be unaffordable for resource-constrained health systems in DC, where PH1 is more prevalent (>10% in some North African and Middle Eastern nations). The high cost is expected to constitute a major barrier to access PH1 innovative therapeutic agents and to further deepen the existing management gap unless action is taken. Therefore, an integrated approach including, but not limited to, differential pricing and greater affordability is needed to overcome the key challenge of providing novel therapeutics to PH1 patients in DC. This approach will ensure access to game-changer novel therapeutics in DC, thereby reducing global PH1 healthcare disparities and disability. On the other hand, relatively affordable possible therapeutic options have been reported recently. The use of oral inhibitors to LDH as a potential therapeutic in PH1-afflicted patients remains to be confirmed [32–34]. The challenges and opportunities of using PH1 novel therapeutics in DC are illustrated in Figure 1.

## ETHICAL CONCERNS

Ethical concerns are a major issue related to PH1 in DC. As a matter of fact, infantile PH1 is particularly frequent in some DC, and infants often have ESRD at presentation [6, 30, 37]. The burden of the disease varies among different DC and consequently management plans and clinical outcome. This is mainly determined by the level of index of clinical suspicion of PH1 among health professionals, availability of affordable diagnostic tools

as well as access to therapeutic resources including intensive dialysis regimens and transplantation strategies. This situation raises the issue of therapeutic withdrawal in the absence of curative treatment [14, 15]. However, given the new therapeutic advances, this option becomes questionable.

Antenatal diagnosis is another challenging ethical issue, mainly related to cultural convictions. Parental beliefs can be against pregnancy termination in case of a PH1-afflicted fetus [14, 15]. Hopefully, this evolving new era will dramatically change the perspective of PH1 from both the professional and patient/family point of view. The novel NGS technologies allowing cheap and easy genetic screening and antenatal diagnosis would be helpful in diagnosing index cases, at-risk screening and family planning. Moreover the expanding spectrum of potentially effective targeted therapeutics is expected to change the standard of care not only globally, but also in DC, where PH1 is more prevalent.

## CONCLUSION

PH1 is an autosomal recessive inborn error of metabolism characterized by marked hepatic overproduction of oxalate. The novel therapeutic era has led to some promising, innovative therapeutic agents capable of reducing the hepatic overproduction of oxalate, the real culprit behind PH1. Therefore, DC are experiencing novel challenges sailing into the uncharted territory of novel therapeutics. Even though novel therapeutics are less complex than liver or combined liver and kidney transplantation, questions regarding accessibility and affordability remain to be answered. The high cost of PH1 novel medications is a major barrier to access these innovative therapeutics in DC. Nevertheless an integrated approach including, but not limited to, differential pricing and greater affordability is greatly needed to overcome this key challenge, thereby reducing global PH1 healthcare disparities. Equitable access to sustainable targeted therapeutics in the current precision medicine era is the cornerstone to favorably change the standard of care for PH1 in DC and to implementing personalized medicine.

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## REFERENCES

- Cochat P, Rumsby G. Primary hyperoxaluria. *N Engl J Med* 2013; 369: 649–658
- Hoppe B. An update on primary hyperoxaluria. *Nat Rev Nephrol* 2012; 8: 468–475
- Harambat J, Fargue S, Acquaviva C et al. Genotype-phenotype correlation in primary hyperoxaluria type 1: the p.Gly170Arg AGXT mutation is associated with a better outcome. *Kidney Int* 2010; 77: 443–449

4. Harambat J, van Stralen KJ, Espinosa L et al. Characteristics and outcomes of children with primary oxalosis requiring renal replacement therap. *Clin J Am Soc Nephrol* 2012; 7: 458–465
5. Harambat J, Fargue S, Bacchetta J et al. Primary hyperoxaluria. *Int J Nephrol* 2011; 2011: 864580
6. Soliman NA, Nabhan MM, Abdelrahman SM et al. Clinical spectrum of primary hyperoxaluria type 1: experience of a tertiary center. *Nephrol Ther* 2017; 13: 176–182
7. Kletzmayer A, Ivarsson ME, Leroux JC. Investigational therapies for primary hyperoxaluria. *Bioconjug Chem* 2020; 31: 1696–1707
8. Garrelfs SF, Frishberg Y, Hulton SA et al. Lumasiran, an RNAi therapeutic for primary hyperoxaluria type 1. *N Engl J Med* 2021; 384: 1216–1226
9. Danpure CJ. Molecular etiology of primary hyperoxaluria type 1: new directions for treatment. *Am J Nephrol* 2005; 25: 303–310
10. Dindo M, Conter C, Oppici E et al. Molecular basis of primary hyperoxaluria: clues to innovative treatments. *Urolithiasis* 2019; 47: 67–78
11. Martin-Higueras C, Torres A, Salido E. Molecular therapy of primary hyperoxaluria. *J Inherit Metab Dis* 2017; 40: 481–489
12. Devresse A, Cochat P, Godefroid N et al. Transplantation for primary hyperoxaluria type 1: designing new strategies in the era of promising therapeutic perspectives. *Kidney Int Rep* 2020; 5: 2136–2145
13. Chemli J, Abdennabi H, Zorgati M et al. primary hyperoxaluria in children in central Tunisia. *Tunis Médicale* 2007; 85: 513–518
14. Cochat P, Groothoff J. Primary hyperoxaluria type 1: practical and ethical issues. *Pediatr Nephrol* 2013; 28: 2273–2281
15. Cochat P, Koch Nogueira PC, Mahmoud MA et al. Primary hyperoxaluria in infants: medical, ethical and economic issues. *J Pediatr* 1999; 135: 746–750
16. Soliman NA, Bazarara HM, Abdel Hamid RH et al. Nephropathic cystinosis in a developing country: the Egyptian experience. *Saudi J Kidney Dis Transplant* 2013; 24: 147
17. Naderi G, Tabassomi F, Latif A et al. The first experience of sequential liver-kidney transplantation for the treatment of primary hyperoxaluria type-1 in Iran as a developing country. *Saudi J Kidney Dis Transplant* 2016; 27: 791
18. Boualla L, Tajir M, Oulahiane N et al. AGXT gene mutations and prevalence of primary hyperoxaluria type 1 in Moroccan population. *Genet Test Mol Biomark* 2015; 19: 623–628
19. Al-Eisa A, Naseef M, Al-Hamad N et al. chronic renal failure in Kuwaiti children: an eight year-experience. *Pediatr Nephrol* 2005; 10: 1781–1785
20. Al Riyami MS, Al Ghaithi B, Al Hashmi N et al. Primary hyperoxaluria type 1 in 18 children: genotyping and outcome. *Int J Nephrol* 2015; 2015: 634175
21. Almardini RI, Alfarah MG, Salaita GM. The clinical pattern of primary hyperoxaluria in pediatric patient at Queen Rania Abdulla Children Hospital. *Arab J Nephrol Transplant* 2014; 7: 119–123
22. Gargah T, Khelil N, Youssef G et al. Primary hyperoxaluria type 1 in Tunisian children. *Saudi J Kidney Dis Transpl* 2012; 23: 385–390
23. Kamoun A, Daudon M, Zghal A et al. Hyperoxalurie primitive: l'expérience tunisienne à propos de 24 cas pédiatriques [Primary hyperoxaluria: Tunisian experience apropos of 24 pediatric cases]. *Nephrologie* 1997; 18: 59–64
24. Nagara M, Tiar A, Ben Halim N et al. Mutation spectrum of primary hyperoxaluria type 1 in Tunisia: implication for diagnosis in North Africa. *Gene* 2013; 527: 316–320
25. M'dimegh S, Omezzine A, M'barek I et al. Mutational analysis of AGXT in Tunisian population with primary hyperoxaluria type 1. *Ann Hum Genet* 2017; 81: 1–10
26. Cochat P, Liutkus A, Fargue S et al. Primary hyperoxaluria type 1: still challenging! *Pediatr Nephrol* 2006; 21: 1075–1081
27. Kamoun A, Lakhoua R. End stage renal disease of the Tunisian child: epidemiology, etiologies and outcome. *Pediatr Nephrol* 1996; 10: 479–482
28. Niang A, Iyengar A, Luyckx VA. Hemodialysis versus peritoneal dialysis in resource-limited settings: *Curr Opin Nephrol Hypertens* 2018; 27: 463–471
29. El Matri A, Abdallah TB. Organ transplantation in Tunisia. *Exp Clin Transpl* 2015; 13 (Suppl 1): 33–36
30. Kotb MA, Hamza AF, Abd El Kader H et al. Combined liver-kidney transplantation for primary hyperoxaluria type I in children: single center experience. *Pediatr Transplant* 2019; 23: e13313
31. 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: 313–323
32. Letavernier E, Daudon M. Stiripentol identifies a therapeutic target to reduce oxaluria. *Curr Opin Nephrol Hypertens* 2020; 29: 394–399
33. Martin-Higueras C, Feldkötter M, Hoppe B. Is stiripentol truly effective for treating primary hyperoxaluria? *Clin Kidney J* 2020; 14: 442–444
34. Wyatt CM, Drüeke TB. Stiripentol for the treatment of primary hyperoxaluria and calcium oxalate nephropathy. *Kidney Int* 2020; 97: 17–19
35. Belostotsky R, Frishberg Y. Novel therapeutic approaches for the primary hyperoxalurias. *Pediatr Nephrol* 2021; 36: 2593–2606
36. Guillaume A, Chiodini B, Adams B et al. The struggling odyssey of infantile primary hyperoxaluria. *Front Pediatr* 2021; 9: 615183
37. Jellouli M, Ferjani M, Abidi K et al. Primary hyperoxaluria in infants. *Saudi J Kidney Dis Transpl* 2016; 27: 526–532