Primary hyperoxaluria in children in 2023

New guidelines, and new therapeutic strategies

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Primary hyperoxaluria(s)

Table 2. Features and Treatment of the Inherited Primary Hyperoxalurias.

Feature	Type 1	Type 2	Type 3
Chromosomal location	2q37.3	9p13.2	10q24.2
Age at onset	All ages, although mostly in childhood	All ages	All ages
Presentation	Calcium oxalate renal stones, nephrocalcinosis, renal failure	Calcium oxalate renal stones	Calcium oxalate renal stones
Treatment			
Supportive treatment	Hydration, citrate, pyridoxine	Hydration, citrate	Hydration, citrate
Transplantation	Liver and kidney	Kidney	Not required — no reported cases of renal failure to date

- **Clinical presentations can be very different, especially in the PH1 sub-group**
- From the neonatal onset with ESRD within the first months of life
- To the form with nephrolithiasis occuring during teenage or adulthood
- But also « relapse » on a renal graft in a patient with kidney failure of « unknown » origin

Cochat, NEJM 2013

Primary hyperoxaluria(s): symptoms

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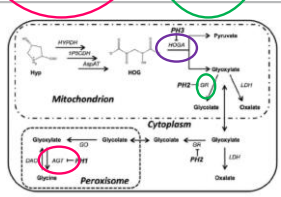
Type 1
Risk KF: almost 100%
Increased Oxalate and glycolate
The most severe form
Combined or Sequential LKT



Type 2
Risque KF 25%, 50% CKD
Increased oxalate and glycerate
Usually isolated KTx

Type 3
The less severe form, 50% CKD, exceptionnally KF
Increased Oxalate and HOG/DHG
Increased Ox and glycolate

Cochat, NEJM 2013; Hoppe 2012

PH1: a severe renal and systemic disease with a significant mortality

- **ESPN-ERA-EDTA Registry**
- 9247 patients < 19 years
- ESRD 1979 - 2009
- 31 countries
- 100 PH1

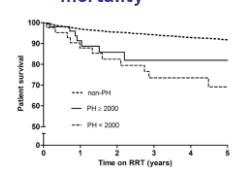
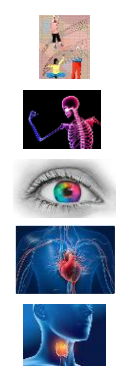


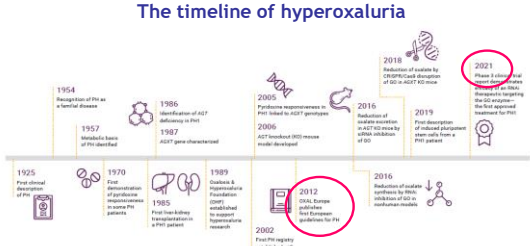
Table 3. Causes of death in 22 patients with primary hyperoxaluria on renal replacement therapy

Cause of Death	n (%)
Acute complications of dialysis (fluid overload, hyperkalemia)	4 (18)
Cardiovascular disease	3 (14)
ESRD treatment refused by patient or withdrawn for medical reasons	3 (14)
Complications of liver transplantation	3 (14)
Infections (pneumonia, bacterial sepsis)	2 (9)
Malignancy	1 (4)
Cachexia	1 (4)
Other/unknown	4 (18)



Harambat cJASN 2012; Groothoff Nature Reviews Nephrology 2023

The timeline of hyperoxaluria



Clinical practice recommendations for primary hyperoxaluria: an expert consensus statement from ERKNet and OxalEurope

Jaap Groothoff[1], Ella Metry[2], Lisa Deesker[3], Sander Garrelfs[3], Cecile Acquaviva[2], Reham Almardini[2], Bodo Beck[4], Olivia Boyer[5], Rimante Cerkauskiene[6], Pietro Manuel Ferraro[7], Luitzen Groen[8], Asheeta Gupta[9], Bertrand Knebelmann[10], Giorgia Mandrile[11], Shabbir Moochhala[12], Agnieszka Prytula[13], Jovana Putnik[14], Gill Rumsby[15], Neveen Soliman[16], Bhaskar Somani[17] and Justine Bacchetta[18]

Bacchetta, CKJ 2022; Groothoff Nature Reviews Nephrology 2023

Statements for genetics

	Statements	Grading
Genetics		
1	We recommend genetic testing of each patient with high clinical and/or biochemical suspicion.	A (strong recommendation)
2	We recommend offering genetic counselling to PH patients and their families.	A (strong recommendation)

Pediatric Nephrology
https://doi.org/10.1007/s00467-022-05615-2

REVIEW

Genetic assessment in primary hyperoxaluria: why it matters

Giorgia Mandrile[1] · Bodo Beck[2] · Cecile Acquaviva[3] · Gill Rumsby[4] · Lisa Deesker[5] · Sander Garrelfs[5] · Asheeta Gupta[6] · Justine Bacchetta[7] · Jaap Groothoff[8] on behalf of the OxalEurope Consortium/Erknet Guideline Workgroup On Hyperoxaluria

Received: 29 March 2022 / Revised: 23 April 2022 / Accepted: 26 April 2022

Table 1 Overview of most frequent PH1, PH2, and PH3 mutations

Frequent mutations of Primary hyperoxaluria

PH type	Gene	Mutation	Protein	Pyridoxine sensitive	Predominant region or ethnicity
1	*AGXT*	c.508G>A	p.G170R	+	Caucasian
		c.33dupC	p.K12fs	-	N/A
		c.731 T>C	p.I244T	±	Northern Africa and Canary Islands
2	*GRHPR*	c.103delG	p.D35TfsTer11	N/A	Caucasian
		c.484 + 2_484 + 6del	Missplicing, p.?	N/A	Asian
		c.494G>A	p.G165D	N/A	Asian
3	*HOGA1*	c.700 + 5G>T	Missplicing, p.?	N/A	European
		c.834_834 + 1GG>TT	Missplicing, p.?	N/A	Chinese
		c.944_946delAGG	p.E315del	N/A	Ashkenazi Jewish

Corresponding literature and references can be found in main text. *N/A* not applicable

Groothoff Nature Reviews Nephrology 2023

Statements for diagnosis

	Statements	Grading
Diagnostics		
3	We recommend assessing urinary oxalate excretion, along with creatinine, by 24h urine collection.	A (strong recommendation)
4	We suggest that spot urine collections may be used in place of 24h urine collections where clinically necessary provided the calculation of oxalate/creatinine ratio	C (moderate recommendation)
5	We recommend at least 2 positive urine assessments (Uox > URL) in order to establish hyperoxaluria.	B (strong recommendation)
6	Acidification of urine samples for oxalate assessment can be done at the laboratory within 24 hours, provided the sample is kept at 4°C after collection.	B (moderate recommendation)
7	We recommend using age-related reference values in interpreting urinary oxalate/creatinine ratios.	B (strong recommendation)
8	We suggest including urinary calcium oxalate crystal volume measurements, if available, in the diagnostic work-up of PH¹	D (weak recommendation)
9	We suggest measuring PH urine metabolites (Glycolate, L-glycerate, HOG, DHG) in the presence of hyperoxaluria.	B (moderate recommendation)
10	We recommend confirmation of PH1 by genetic testing where increased urinary glycolate is found in the presence of hyperoxaluria, noting that normal values of urinary glycolate do not exclude PH1.	A (strong recommendation)
11	We recommend confirmation of PH2 by genetic testing where increased urinary L-glycerate is found in the presence of hyperoxaluria.	A (strong recommendation)
12	We recommend confirmation of PH3 by genetic testing where increased HOG and DHG is found in the presence of hyperoxaluria, noting that normal values of urinary HOG do not exclude PH3 .	A (strong recommendation)
13	We recommend measuring plasma oxalate levels only in patients with CKD 4, CKD 5 or 5D.	A (strong recommendation)
14	We recommend interpreting plasma oxalate levels based on reference values taking the impact of kidney failure into account	B (strong recommendation)

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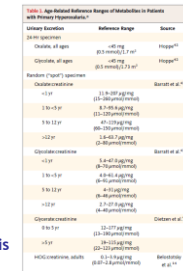
Urine or plasma oxalate?

Urine

- **Oxalate +++**
- **Creatinine +++**
- **Threshold > 500µmol/day**

When renal function is normal



Plasma

- **Oxalate +++**
- **Creatinine +++**

When renal function is impaired:
when eGFR is below 30 mL/min/1,73 m²

Cristalluria as a potential help for diagnosis
Genetic analysis as second-line diagnostic tool to confirm the diagnosis

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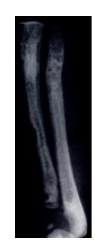
Statements for conservative management

	Statements	Grading
Conservative treatment		
15	We recommend promptly starting conservative therapy in all patients with suspected PH	B (strong recommendation)
16	We recommend starting hyperhydration (3.5-4 L/day in adults, 2-3 L/m² in children, to be consumed throughout 24 hours), in all patients with suspected PH and preserved renal function.	A-B (strong recommendation)
17	We recommend monitoring hyperhydration based on urinary markers, the frequency depending on disease severity.	B (moderate recommendation)
18	We recommend oral administration of potassium citrate (0.1-0.15 g/kg) in patients with preserved renal function	C (moderate recommendation)
19	We recommend a balanced diet to PH patients, avoiding only few extreme high-oxalate containing products.	D (weak recommendation)
20	**We recommend testing pyridoxine responsiveness in all PH1 patients and titrating its dosage on urinary oxalate excretion** ***Maximum dose of 5 mg/kg/day***	**A (strong recommendation)**

Groothoff Nature Reviews Nephrology 2023

1 lemon => citrate content = 2.5-3 grams

Primary hyperoxaluria 1 and bone: oxalate osteopathy as the hallmark of systemic oxalosis



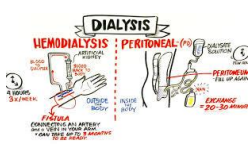
Patients often present with recurrent low-trauma fractures, bone deformities, and severe bone pain

Bacchetta, Pediatr Nephrol 2010; Bacchetta, Bone 2015; Bacchetta, Pediatr Nephrol 2015; Mallik TJH 2020

A vicious circle in hemodialysis

At least before RNAi therapies?

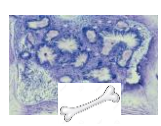
ENDOGENOUS LIVER PRODUCTION
4-7 mmol/1.73 m² per day



DIALYSIS REMOVAL
HD= 1-2 mmol/1.73 m² per day in adults and 3-4 in children
PD = less clearance
But potential interest if combined with HD?

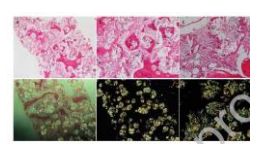
OVERALL
Standard HD (12 hrs/week)
Weekly clearance = 2-3 days of endogenous oxalate production
Accumulation of oxalate in target organs
Bone, vessels, eyes, etc...

Systemic oxalosis worsens in dialysis!
RNAi therapies will have no effect on oxalate release from bone...

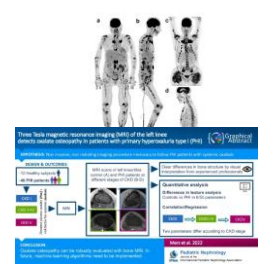


Practical consequences for the management

- **Increased risk of cytopenias because of the bone marrow invasion**
  - Resistance to EPO
  - Sometimes blood transfusions required, with the risk of anti HLA antibodies
  - In adults severe anemia in a context of unexplained ESRD may lead to the diagnosis on a bone marrow aspiration...



- **How to evaluate systemic bone storage?**
  - No gold standard
  - No interest of DXA (increased BMD)
  - Bone biopsy: not doable in routine, heterogeneity
  - Bone MRI?
  - 18F-FDG PET/CT and 99mTc-HMDP Bone Scan ?



Mallik TJH 2020 *Perrin KIR 2022; Merz Pediatr Nephrol 2022*

Statements for dialysis

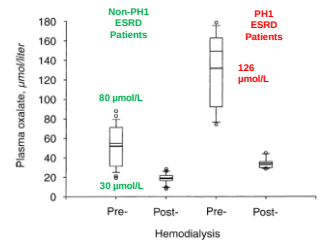
	Statements	Grading
Dialysis treatment		
21	We suggest considering kidney replacement therapy before kidney failure has developed in those PH1 patients with a high risk for systemic oxalosis due to high plasma oxalate values or those already suffering from comorbidity	X (moderate recommendation)
22	In case of no access or response to oxalate lowering therapies, we recommend intensified hemodialysis, dose titrated to clinical condition, plasma oxalate levels and according to what the patient and family can tolerate.	X (strong recommendation)
23	We recommend a high flux hemodialyzer (>1m² capillary surface per 1m² BSA) with maximal blood flow (>150-200 cm³/min/m² BSA) when performing haemodialysis.	C (moderate recommendation)
24	We recommend personalising the dialysis regimen based on clinical observations of oxalosis and plasma oxalate values, aiming to keep plasma oxalate values in the range of non PH patients with kidney failure.	X (strong recommendation)

Groothoff Nature Reviews Nephrology 2023

Specificities of plasma oxalate (Pox) measurements

- **All labs do not have the same reference values +++**
- Most frequent normal level: < 5 µmol/L
- There may be some discrepancies between labs…

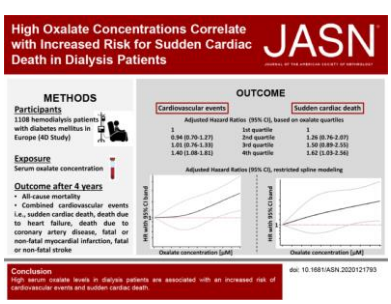
- **The follow-up of POx should be performed at the beginning of the dialysis session whatever the type of management**
- **A non-PH patient in dialysis has Pox levels well above the upper normal limit +++**



Publication	POx
POx in 1108 non PH dialysis patients (4D study), *Pfau 2021 JASN*	42 µmol/L (median)
POx in 135 non PH hemodialysis patients, *Metry NDT Epub 2023*	47 µmol/L (mean)
POx in 23 non PH hemodialysis patients, *Marangella et al, Clinical Science, 1991*	50 µmol/L (mean)

Groothoff Nature Reviews Nephrology 2023; Hoppe 1999

P-Ox and cardiovascular outcomes in non PH patients…

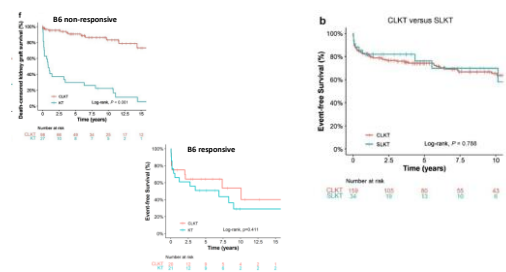


Median oxalate concentration of 42.4 µmol/L
4th quartile: P-Ox > 59.7 µmol/L

Pfau JASN 2021

HP1 et transplantation: données récentes Oxaleurope

- **Données OxalEurope**
- 267 Tx entre 1978 et 2019
- 244 patients: 159 CLKT, 48 Tx rénales isolées, 37 SLKT
- B6 responsive: Tx rénale isolée peut être une option
- B6 non responsive: foie/rein, pas de différence combiné / séquentiel



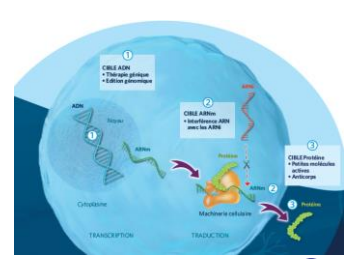
Metry, Kidney Int Reports 2022

Statements for transplantation

	Statements	Grading
Transplantation		
25	Liver transplantation for PH should always be performed with complete removal of the native liver	A (strong recommendation)
26	The strategy for either sequentially or simultaneously performed liver and kidney transplantation should be decided based on the clinical situation and the preference of the local surgeon	B (moderate recommendation)
27	**We recommend to perform liver transplantation ideally combined with kidney transplantation in PH1 patients with advanced disease (eGFR<30) who do not respond to pyridoxine and have no access to RNAi therapy**	**X (strong recommendation)**
28	Liver transplantation may be suggested in PH2 patients with advanced disease (eGFR<30)	C (moderate recommendation)
29	**Isolated kidney transplantation should be considered in PH1 patients with CKD stage 5D who are homozygous for B6 pyridoxine responsive mutations.**	**B (strong recommendation)**
30	We recommend monitoring urinary oxalate and plasma oxalate at least every 6 months after liver transplantation until normalization (below upper limit) has been established on at least 3 occasions.	C (moderate recommendation)
31	We recommend monitoring urinary oxalate and plasma oxalate at least every 6 months after kidney transplantation under B6 therapy or/and RNAi until normalization; thereafter at least once per year.	C (weak recommendation)

Groothoff Nature Reviews Nephrology 2023

RNAi therapies: a novel therapeutic group targeting mRNAs

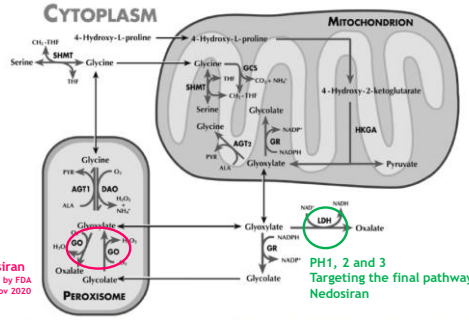


1 **TECHNOLOGY**
To synthesize RNAi complementary to the mRNA to destroy

2 **VECTORS**
To specifically bring RNAi to the target cells using IV or SC injections

3 **CHEMISTRY**
To increase the time between injections

Two possible targets for RNAi therapies in PH



PH1
Lumasiran
Approval by FDA & EMA Nov 2020

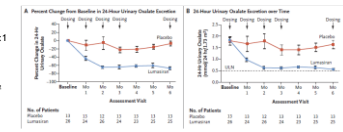
PH1, 2 and 3
Targeting the final pathway
Nedosiran

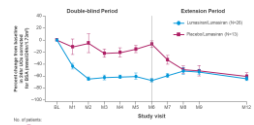
Figure 1. Hepatic oxalate synthesis pathway. ALN-GO1 targets hepatic GO.[27] Copyright clearance center license number 3863190482947.

Liebow J Am Soc Nephrol. 2017 ; Garrelfs, NEJM 2021; Shee Urology 2021; Hoppe Kidney Int 2021; Baum Kidney Int 2022

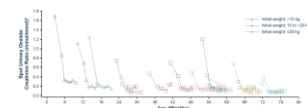
Lumasiran: the Illuminate A-B-C studies

- **ILLU-A**
- Randomized placebo controlled trial 2:1
- 26 lumasiran / 13 placebo
- Age > 6 years
- eGFR > 30 mL/min per 1.73 m²
- Uox 24hr > 0.70 mmol/day per 1.73 m²
- Primary endpoint: % reduction of Uox





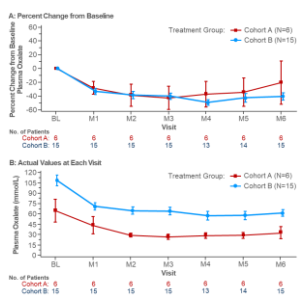
- **ILLU-B**
- Phase 3 Single-Arm Open-Label Study
- In Young Children < 6 years
- eGFR > 45



Garrelfs, NEJM 2021; Hulton Kidney Int Report 2021; Sas DJ, Genetics in Medicine 2022

Lumasiran: the Illuminate A-B-C studies

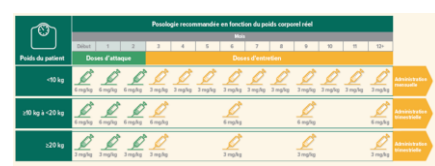
- **ILLU-C**
- Single-Arm, Phase 3 Study of Lumasiran
- CKD3b-5, including hemodialysis
- Full-term infants to adults
- Cohort A: no HD
- Cohort B: HD



Michael AJKD 2022

Modalités pratiques et indications actuelles en France

- Lumasiran
- HP1 avant dialyse ou en dialyse
- Programme d'accompagnement des patients: FreeOse

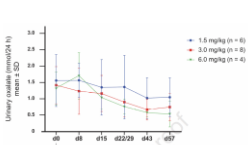


- Si la dose est supérieure à 0,5 mL (94,5 mg), plusieurs flacons seront nécessaires
- Le volume maximal acceptable pour une injection unique est de 1,5 mL
- Les doses nécessitant plus de 1,5 mL doivent être administrées par injections multiples sous-cutanées

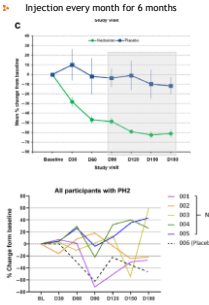
EMA EPAR information lumasiran update 25/11/2020; Figure provided by Alnylam

Nedosiran: the PHYOX studies

- **PHYOX 1**
- Randomized, single-ascending-dose, phase 1 study: PHYOX1
- Safety, pharmacokinetics, pharmacodynamics, and exposure-response of subcutaneous nedosiran
- 25 healthy participants (Group A)
- 18 patients with PH1 or PH2 (Group B)
- Model: fixed monthly dose of 160 mg in adults
- Mean maxiumum reduction in 24-hr-UOx: 55%, day 57
- 67% of patients reached normal or near normal 24-hr-UOx



- **PHYOX 2**
- Randomized, nedosiran versus placebo, 2/1
- 29 HP1 and 6 HP2
- eGFR > 30
- Injection every month for 6 months



Happe Kidney Int 2021; Baum Kidney Int 2022

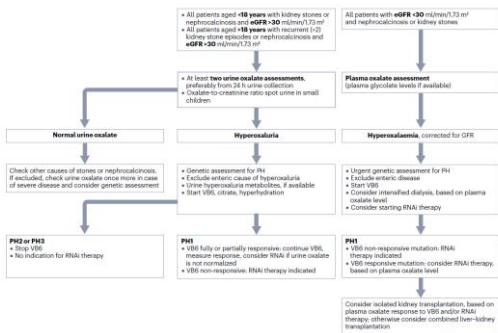
RNAi for all patients with HP1?

Table 2 | Recommended management and monitoring of patients with PH1 on RNAi therapy

Group[a]	Start	Cessation criteria after 6 months of therapy	Six-monthly analyses for 5 years and cessation criteria
Group A (VB6⁻, eGFR >30)	We recommend starting therapy	Uox >1.5 UL or less than a 30% reduction in Uox[b] or a deterioration of the clinical condition or evidence of a SAE[c]	SAE or deterioration in clinical condition related to RNAi therapy[c]
Group B (VB6⁺, eGFR >30)	We suggest starting therapy, based on patient characteristics (not fully VB6 responsive, severe disease)	Uox >1.5 UL or <30% reduction Uox[b]; or deterioration of clinical condition or evidence of a SAE[c]	SAE or deterioration in clinical condition related to RNAi therapy[c]
Group C (VB6⁻, eGFR <30)	We recommend starting therapy	Decrease in Pox <20% from baseline or deterioration of clinical condition or evidence of a SAE[c]	Stop if decrease in Pox is <20%[d,e] from baseline; discuss options if the decrease in Pox is <30% from baseline[e,f]. Also stop treatment if there is evidence of an SAE OR deterioration in clinical condition related to RNAi therapy[c]
Group D (VB6⁺, eGFR <30)	We suggest starting therapy based on patient characteristics (not fully VB6 sensitive, rapidly deteriorating kidney function in case of eGFR 20–30)	Decrease in Pox <20% from baseline[d] or deterioration of clinical condition as assessed by a committee; or evidence of a SAE[c]	Stop therapy if the decrease in Pox is <20%[d,e]; discuss options if the decrease in Pox is <30%[d]. Also stop treatment if there is evidence of a SAE or deterioration in clinical condition related to RNAi therapy[c]
Group E (no genetic diagnosis, eGFR <30)	We recommend starting therapy with monthly monitoring of Pox levels	Decrease Pox <20% of baseline or deterioration of clinical condition as assessed by a committee; or evidence of a SAE[c]. Also stop therapy if the suspected PH diagnosis is not confirmed genetically	Not applicable
Group F (no ongoing clinical disease)	We suggest starting therapy in adults and recommend starting therapy in children	Uox >1.5 UL or <30% reduction Uox of baseline; or deterioration of clinical condition as assessed by a committee; or evidence of a SAE[c]	SAE or deterioration in clinical condition related to RNAi therapy[c]
Group G (full VB6⁺)	We do not recommend starting therapy	Not applicable	Not applicable

Groothoff Nature Reviews Nephrology 2023

Proposed algorithm: management in case of PH suspicion



Groothoff Nature Reviews Nephrology 2023

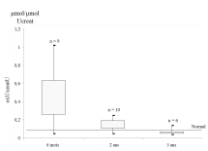
Real-life data: isolated renal transplant and lumasiran

- N=5 patients, genetically confirmed PH1, isolated renal transplantation
- Median age 26 (3-45 years)
- After 13 (5-17) months on lumasiran while on intensive HD
- Isolated kidney transplant, 3 living donors
- Postoperative management: hyperhydration (3 L/m²/day), potassium citrate if tolerated (250 mg/kg/day), and lumasiran (± pyridoxine)
- Delayed graft function: N=0/5
- Dialysis after KTx: N=3/5
- POx: 110 (20-150) µmol/L at lumasiran initiation
- POx: 53 (10-72) µmol/L at KTx
- At 3 months post KTx
  - Pox: 7 (5-26) µmol/L
  - eGFR : 60 (38-125) mL/min.1,73 m²
  - Uox/creat on spot : 103(67-830) µmol/mmol
- **In all patients isolated KTx was successful with at least 6 months of follow-up (in 2 patients more than 1 year of FU)**

Leclerc and al, NDT 2022, collaboration between Lyon, Marseille, Strasbourg and Amsterdam

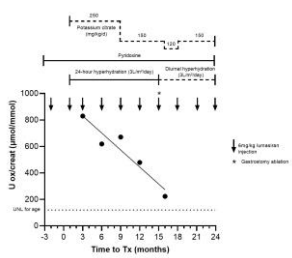
Isolated kidney Tx under lumasiran: keep being proactive after transplantation +++

Combined kidney liver Tx



14 children
Pox at Tx 89 (18-121) µmol/L
Pox at M6 at 5(0-21) µmol/L
4.0(0.5-6.0) years of hyperhydration post Tx
A least 2 years to reach near-normalization of Uox
Normalization in 6 patients within 3 years
One patient still presented high Uox at Y3
Citrate withdrawal in 5 patients 8(3-9) years post Tx

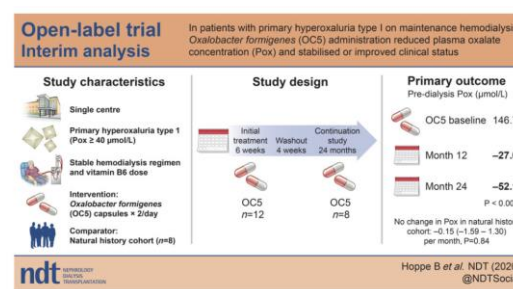
Isolated kidney Tx + RNAi



Infantile oxalosis
10 months on intensive dialysis before Tx at 3 years of age
Pox at Tx 53 µmol/L
18 months to reach near-normalization of UOx

Duclaux-Loras Pediatr Nephrol 2016; Sellier-Leclerc NDT 2022; Unpublished data from Lyon & Marseille

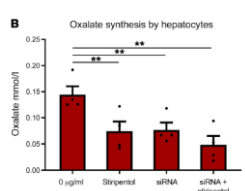
Other therapeutic possibilities: Oxalobacter formigenes

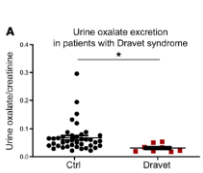


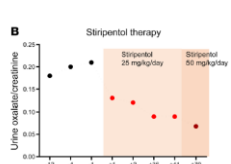
Hoppe NDT 2020

Other therapeutic possibilities: stiripentol

- Stiripentol
- Inhibitor of LDH
- Approved for Dravet syndrome







Le Dudal JCI 2019

Stiripentol and ethylene glycol intoxication

- Ethylene glycol intoxication in children with « anti-freeze » agents
- Colorless, odorless, sweet taste and syrupy consistency
- Ethylene glycol intoxication = acute oxalosis
- A pediatric concern +++
- Multisystemic injury: heart, brain, lung, kidney
- Metabolic acidosis
- Tubular precipitation of oxalate crystals => AKI within 2 to 72 hours
- Measurement of EG in blood or glycol in serum

- Citrate alkalinization
- Renal replacement therapy
- Inhibitors of alcohol dehydrogenase: fomepizole
- Stiripentol in rats

Table 1. Serum parameters after ethylene glycol intoxication

	Serum parameters		
	EG	EG + stiripentol	*P* value
Creatinine, µmol/l	297.1 ± 166.3	78.1 ± 21.4	0.009
Bicarbonate, mmol/l	17.7 ± 4.15	20.8 ± 5.6	0.15
Potassium, mmol/l	6.5 ± 2.4	4.8 ± 1.3	0.07
Sodium, mmol/l	137.6 ± 4.7	147.4 ± 3.7	<0.001
Chloride, mmol/l	93 ± 7.9	107.6 ± 9.3	<0.001
Serum anion Gap, mmol/l	33.5 ± 11.1	23.7 ± 12.2	0.04

Serum parameters at day 2 after ethylene glycol intoxication ($n = 6$ animals/group). Data are mean ± SD. Student bilateral *t* tests (assuming Gaussian distribution of biological values) were performed. EG, ethylene glycol.

Schwerk Acta Paediatr 2007 / Barceloux J Toxicol Clin Toxicol 1999 / Levaternier 2018 / Bacchetta Pediatr Nephrol 2009 / Le Dudal JCI 2019

Pediatric Nephrology
https://doi.org/10.1007/s00467-023-06179-3

ORIGINAL ARTICLE

Worldwide disparities in access to treatment and investigations for nephropathic cystinosis: a 2023 perspective

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Abstract

Background Nephropathic cystinosis (NC) is a rare lysosomal disease, leading to early kidney failure and extra-renal comorbidities. Its prognosis strongly relies on early diagnosis and treatment by cysteamine. Developing economies (DEing) face many challenges when treating patients for rare and chronic diseases. The aim here is to evaluate the access to investigations and treatment in DEing, and to assess for potential inequalities with Developed Economies (DEed).

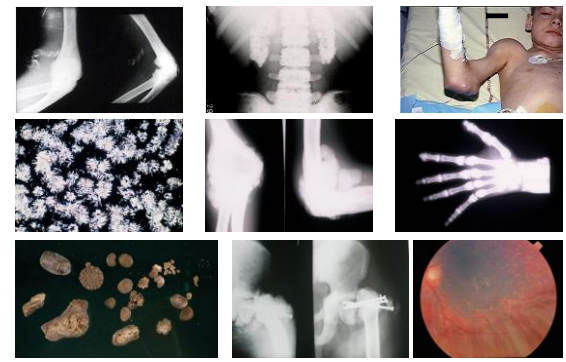
Methods In this international cross-sectional study, a questionnaire on access, price and reimbursement of genetic, biological analyses, and treatment was sent to nephrology centers worldwide during 2022.

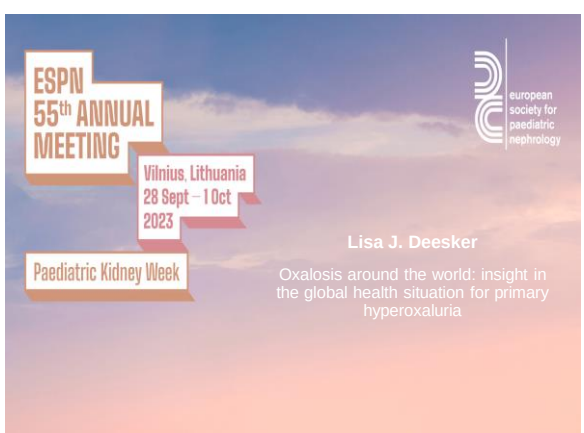
Results A total of 109 centers responded, coming from 49 countries and managing 741 patients: 43 centers from 30 DEing and Economies in transition (TrE), and 66 from 19 DEed. In 2022, genetics availability was 63% in DEing and 100% in DEed, whereas intra leukocytes cystine levels (IL-CL) were available for 30% of DEing patients, and 94% of DEed patients, both increasing over the last decade, as has access to immediate release cysteamine and to cysteamine eye drops in DEing. However, delayed released cysteamine can be delivered to only 7% vs. 74% of patients from DEing and DEed, respectively, and is still poorly reimbursed in DEing.

Conclusions Over the last decade, access to investigations (namely genetics and IL-CL) and to cysteamine have improved in DEing and TrE. However, discrepancies remain with DEed: access to delayed released cysteamine is limited, and reimbursement is still profoundly insufficient, therefore limiting their current use.

Keywords Nephropathic cystinosis · Cysteamine availability · Developing economies · Worldwide disparities

How to bridge the gap?
Oxal'in the world study





Results (preliminary)

- 51 countries participating
- 103 responding (pediatric) nephrologists, geneticists and urologists
- 12 low income countries (24%)
- 13 middle income countries (25%)
- 26 high income countries (51%)

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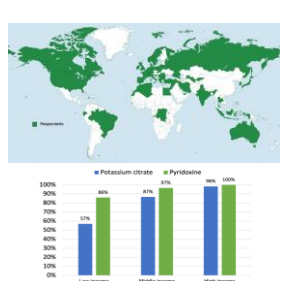
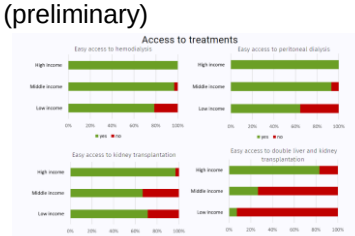


1 lemon => citrate content = 2.5-3 grams

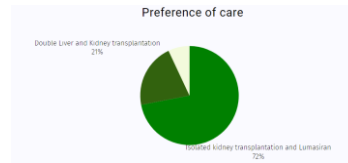
Results (preliminary)



Results (preliminary)

- 22% of the respondents had access to Lumasiran in a commercial setting
- 31 countries access to Nedosiran in industry-sponsored trials or as compassionate use products

Results (preliminary)



Conclusion

- Large variation in the accessibility to diagnostics and treatments between countries
- Low- and middle-income countries have less access to diagnostic tools and treatments compared to high-income countries

- Laila Oubram, MD
- Prof. Jaap Groothoff
- Prof. Justine Bacchetta
- Ella Metry, MD
- OxalEurope, ESPN and all respondents

Scan to participate in the

OxalEurope: we are rare, we care