Hot topics

Lumasiran in Kidney-Only Transplantation in Oxalosis, with a focus on the 2023 European guidelines

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Kansas City March 2023

Disclosures

- **Consultancy and speaker**
- Kyowa Kirin
- Alnylam
- Dicerna/Novonordisk
- Biocodex
- Amgen
- Pfizer
- Alexion
- Bayer
- Lilly
- Vifor
- Mylan
- Amolyt

- **Research grants**
- Kyowa Kirin
- Amgen
- Horizon
- Novartis
- Crinex

- **Travel grants**
- Kyowa Kirin
- Alnylam

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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Transplantation	Liver and kidney	Kidney	Not required — no reported cases of renal failure to date

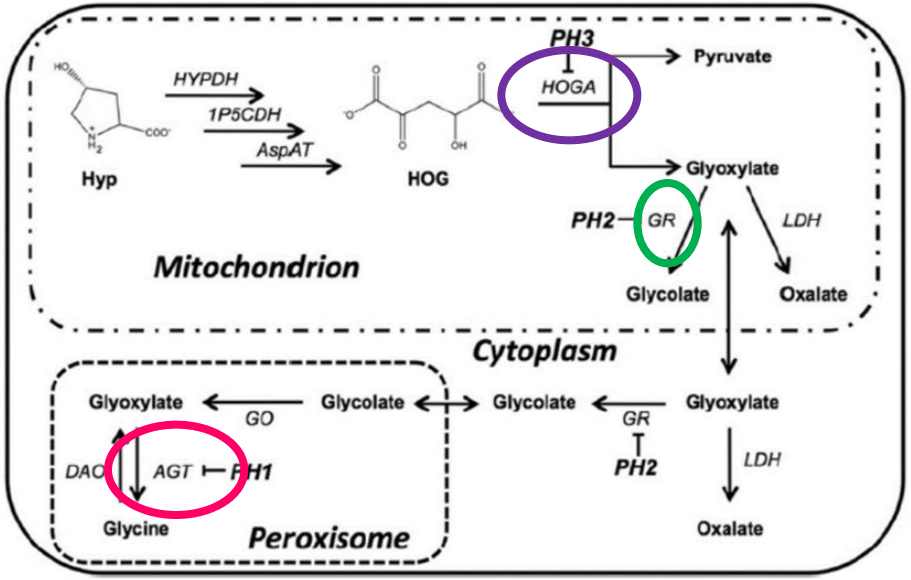
Type 1

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

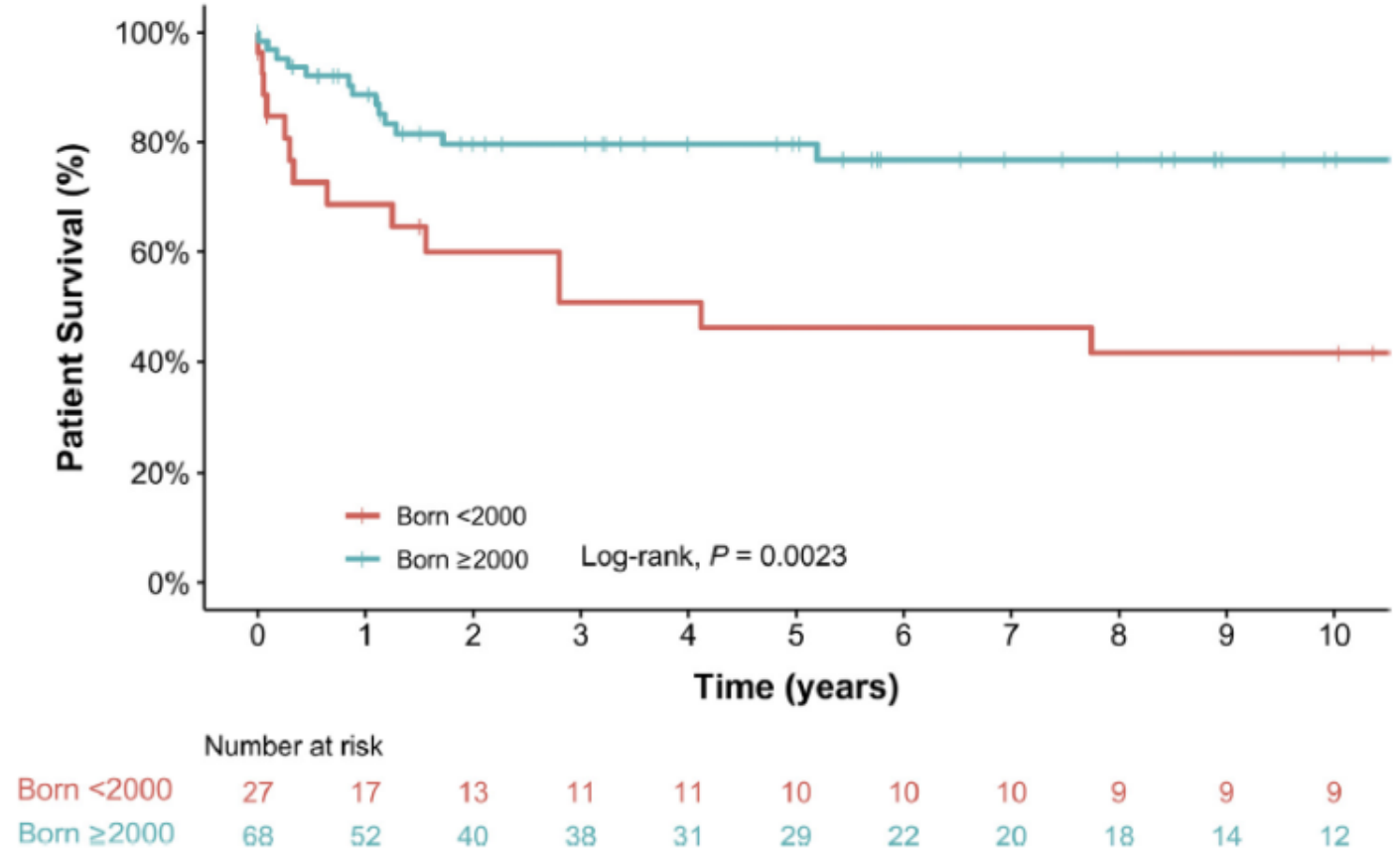
Increased Oxalate and HOG/DHG

Increased Ox and glycolate

Cochat, NEJM 2013; Hoppe 2012

Infantile oxalosis: the most severe form of PH1

- **OxalEurope registry**
- 95 patients
- Born between 1980 and 2018



Deesker KIR 2022

PH1: a severe renal disease with a significant mortality

- **ESPN-ERA-EDTA Registry**

- 9247 patients < 19 years
- ESRD 1979 - 2009
- 31 countries
- 100 PH1

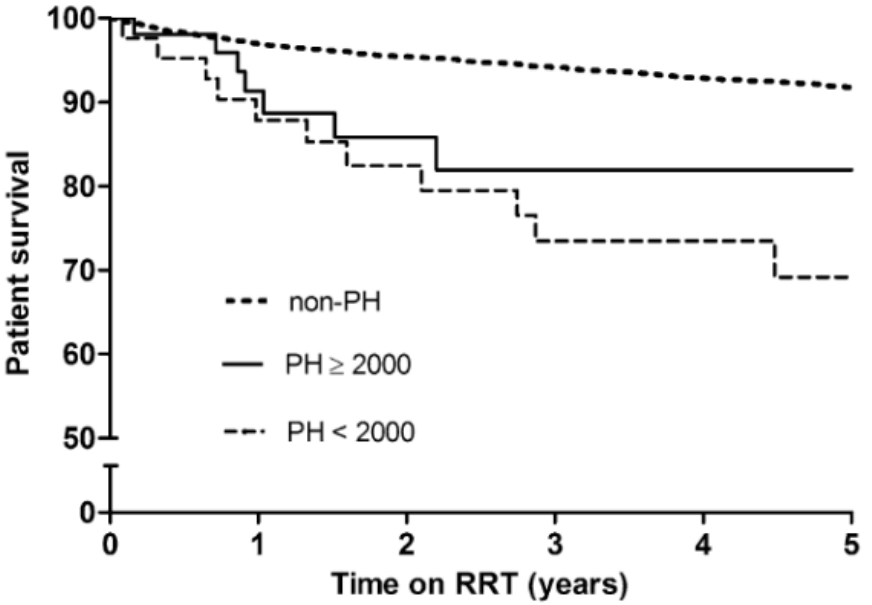
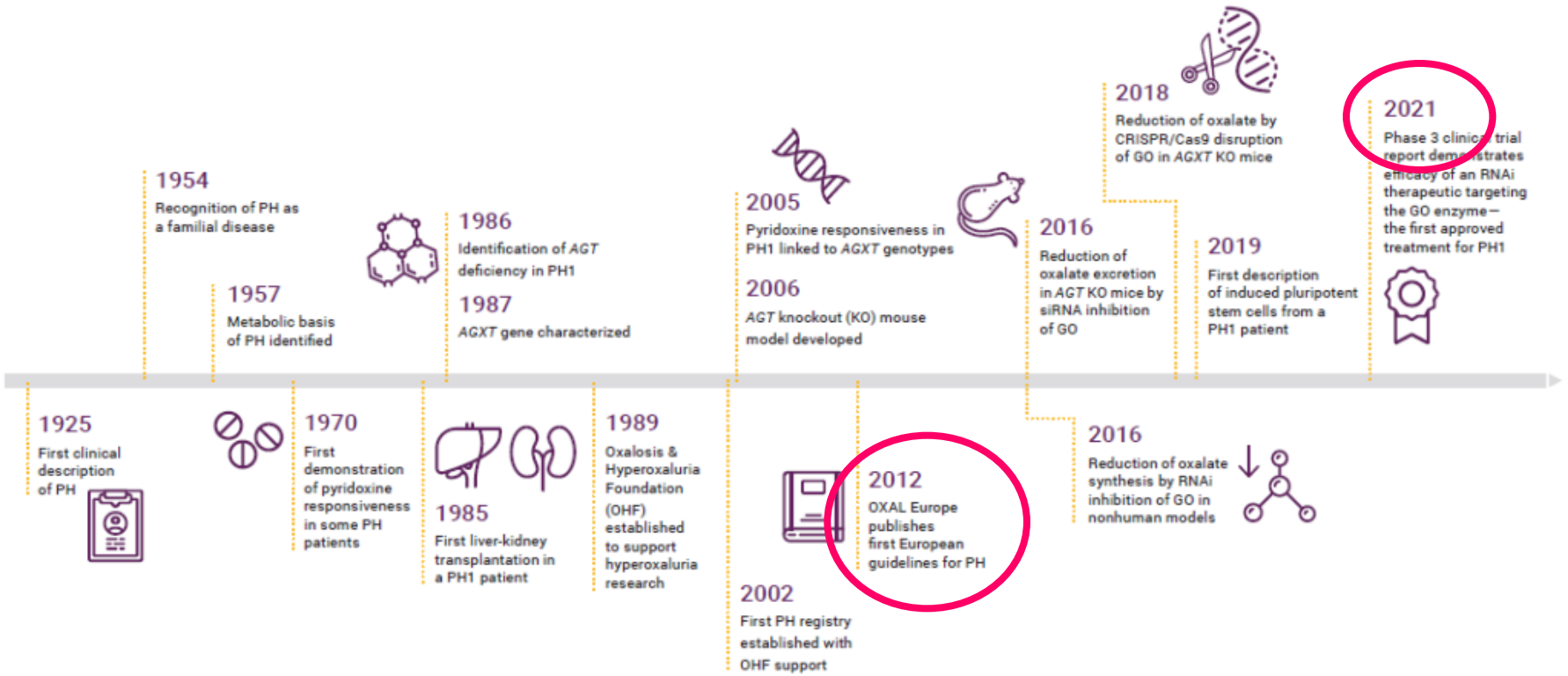


Table 3. Causes of death in 22 patients with primary hyperoxaluria on renal replacement therapy

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	5 (23)

Harambat cJASN 2012

The timeline of hyperoxaluria



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

Jaap Groothoff[1†], Ella Metry[1], Lisa Deesker[1], Sander Garrelfs[1], Cecile Acquaviva[2], Reham Almardini[3], 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

Methods (1)

- Objective : **to delineate diagnosis, management, and follow-up of patients with PH**

- **Consensus document established by a multi-disciplinary team from ERKNet and Oxaleurope**

- **First a core working group (i.e., the authors of the manuscript)**
- Pediatric and adult nephrologists and urologists, biochemists and geneticists
- From 8 European countries
- All members of OxalEurope and ERKNet
- Together responsible for performing a literature review, rating the quality of evidence and writing/grading statements
- During 6 zoom sessions 2021

- + 2 physicians with experience in PH from low resource countries

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Methods (2)

- **Second an external voting panel**
- Members of different international working groups on inherited kidney diseases (OxalEurope, ESPN, ERKNet, ERA), N=36
- 20 pediatric nephrologists, 11 nephrologists, 5 scientists or geneticists
- From 14 countries
- All with an expertise in PH
- Delphi method
- 5-point scale: strongly disagree, disagree, neither agree/disagree, agree, strongly agree
- Requiring at least 70% of agreement for each statement
  - First round for 46 statements
  - 2 statements were discussed again, reworded, agreed among the core working group and re-sent to the working panel

- As such, **we propose 48 practical statements** on diagnosis and management, including conventional therapy (pyridoxine, hyperhydration, alkalinisation, dialysis & transplantation), new therapies and follow-up of patients with PH

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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/s00467-022-05613-2

REVIEW

Check for updates

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[5] on behalf of the OxalEurope Consortium/Erknet Guideline Workgroup On Hyperoxaluria

Received: 29 March 2022 / Revised: 23 April 2022 / Accepted: 29 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.404+3_404+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

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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 PH[1]	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

Table 1. Age-Related Reference Ranges of Metabolites in Patients with Primary Hyperoxaluria.*

Urinary Excretion	Reference Range	Source
24-Hr specimen		
Oxalate, all ages	<45 mg (0.5 mmol)/1.7 m²	Hoppe[42]
Glycolate, all ages	<45 mg (0.5 mmol)/1.73 m²	Hoppe[42]
Random ("spot") specimen		
Oxalate:creatinine		Barratt et al.[43]
<1 yr	11.9–207 µg/mg (15–260 µmol/mmol)	
1 to <5 yr	8.7–95.6 µg/mg (11–120 µmol/mmol)	
5 to 12 yr	47–119 µg/mg (60–150 µmol/mmol)	
>12 yr	1.6–63.7 µg/mg (2–80 µmol/mmol)	
Glycolate:creatinine		Barratt et al.[43]
<1 yr	5.4–47.0 µg/mg (8–70 µmol/mmol)	
1 to <5 yr	4.0–61.4 µg/mg (6–91 µmol/mmol)	
5 to 12 yr	4–31 µg/mg (6–46 µmol/mmol)	
>12 yr	2.7–27.0 µg/mg (4–40 µmol/mmol)	
Glycerate:creatinine		Dietzen et al.[44]
0 to 5 yr	12–177 µg/mg (13–190 µmol/mmol)	
>5 yr	19–115 µg/mg (22–123 µmol/mmol)	
HOG:creatinine, adults	0.1–3.9 µg/mg (0.07–2.8 µmol/mmol)	Belostotsky et al.[14]

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

Cochat, NEJM 2013

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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/m^2 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)**

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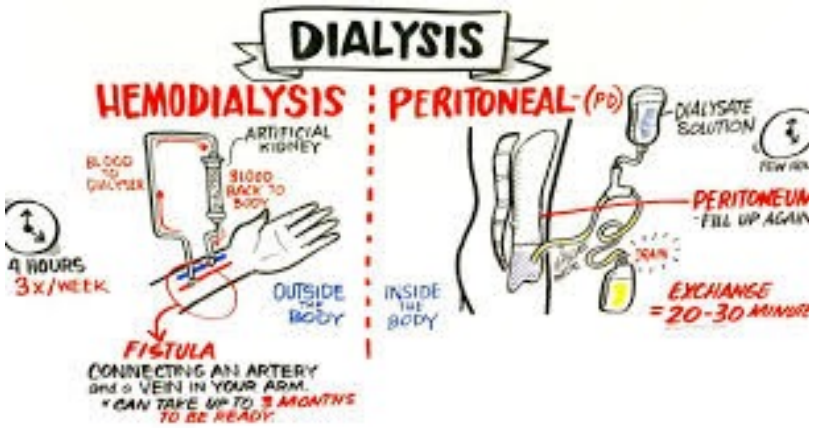
A vicious circle in hemodialysis

At least before RNAi therapies?

ENDOGENOUS LIVER PRODUCTION

4-7 mmol/1.73 m^2 per day



DIALYSIS REMOVAL

HD= 1-2 mmol/1.73 m^2 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)

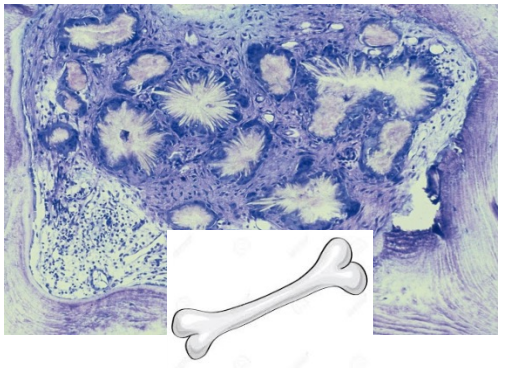
Weekly clearance = 2-3 days of endogenous oxalate production

Accumulation of oxalate in target organs

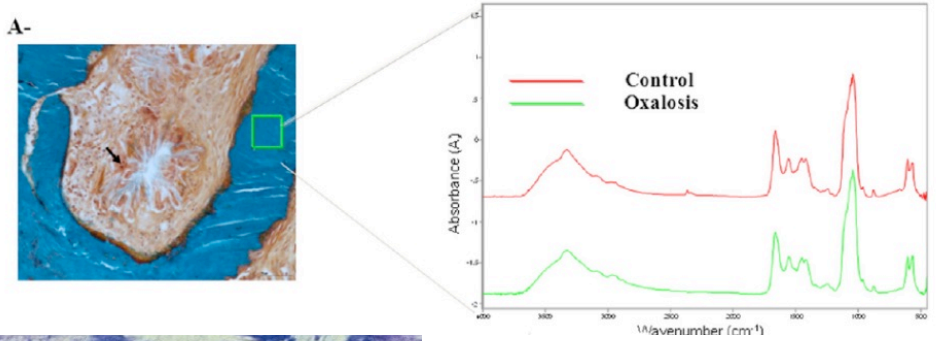
Bone, vessels, eyes, etc…

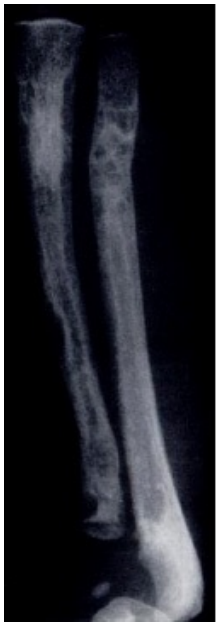
Systemic oxalosis worsens in dialysis!

RNAi therapies will have no effect on oxalate release from bone…



Oxalate osteopathy as the hallmark of systemic oxalosis



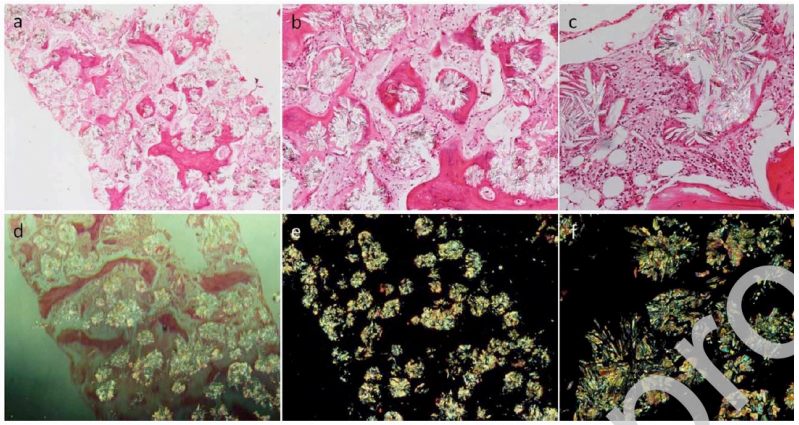


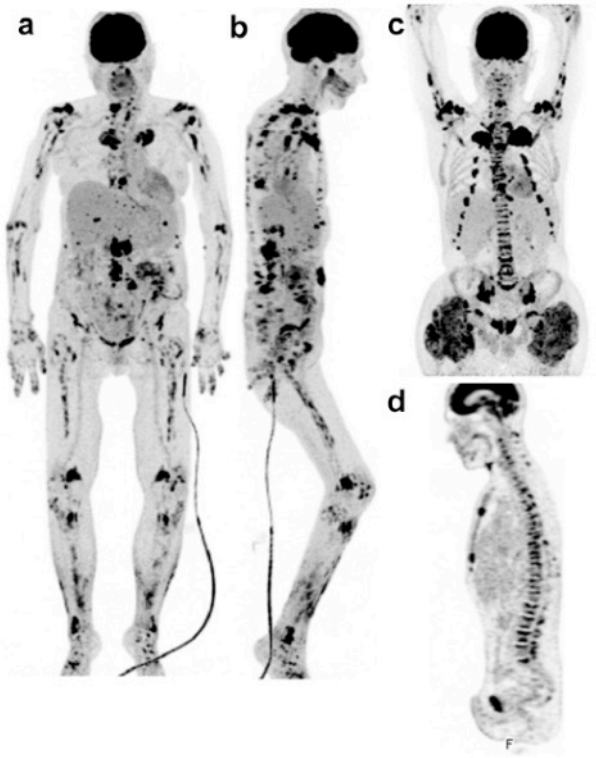
Patients often present with recurrent low-trauma fractures, bone deformities, and severe bone pains: decreased QoL

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

Practical consequences for the management (1)

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





- **How to evaluate systemic bone storage?**
  - No gold standard
  - No interest of DXA
  - Bone biopsy?
  - 3T bone MRI?
  - 18F-FDG PET/CT and 99mTc-HMDP Bone Scan ?

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

Practical consequences for the management (2)

- Even intensive hemodialysis regimens remove far less oxalate than is endogenously produced
- The frequency of dialysis sessions is more important than the duration of each session or even the membrane type

- **Intensive dialysis strategies**: 2-3 hours x 6 to 7 days per week

- **Additional risk of hypophosphatemia and further mineralization defects +++**
- Especially in the **infantile forms of PH1** undergoing intensive dialysis
- Phosphate supplementation: 1 mmol/kg during the entire session

- **Try to optimize the control of other CKD-MBD parameters**: acidosis, PTH, 25-D, etc..

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 (>1m^2 capillary surface per 1m^2 BSA) with maximal blood flow (>150-200 $cm^3/min/m^2$ 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)

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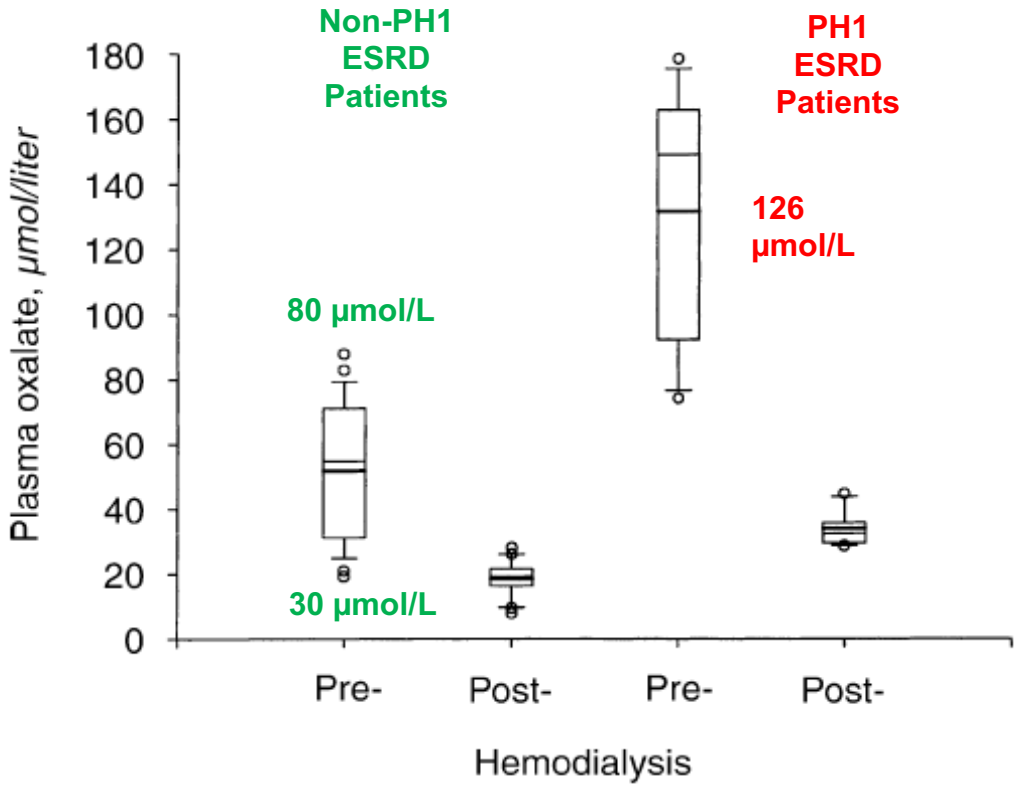
Specificities of plasma oxalate measurements

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

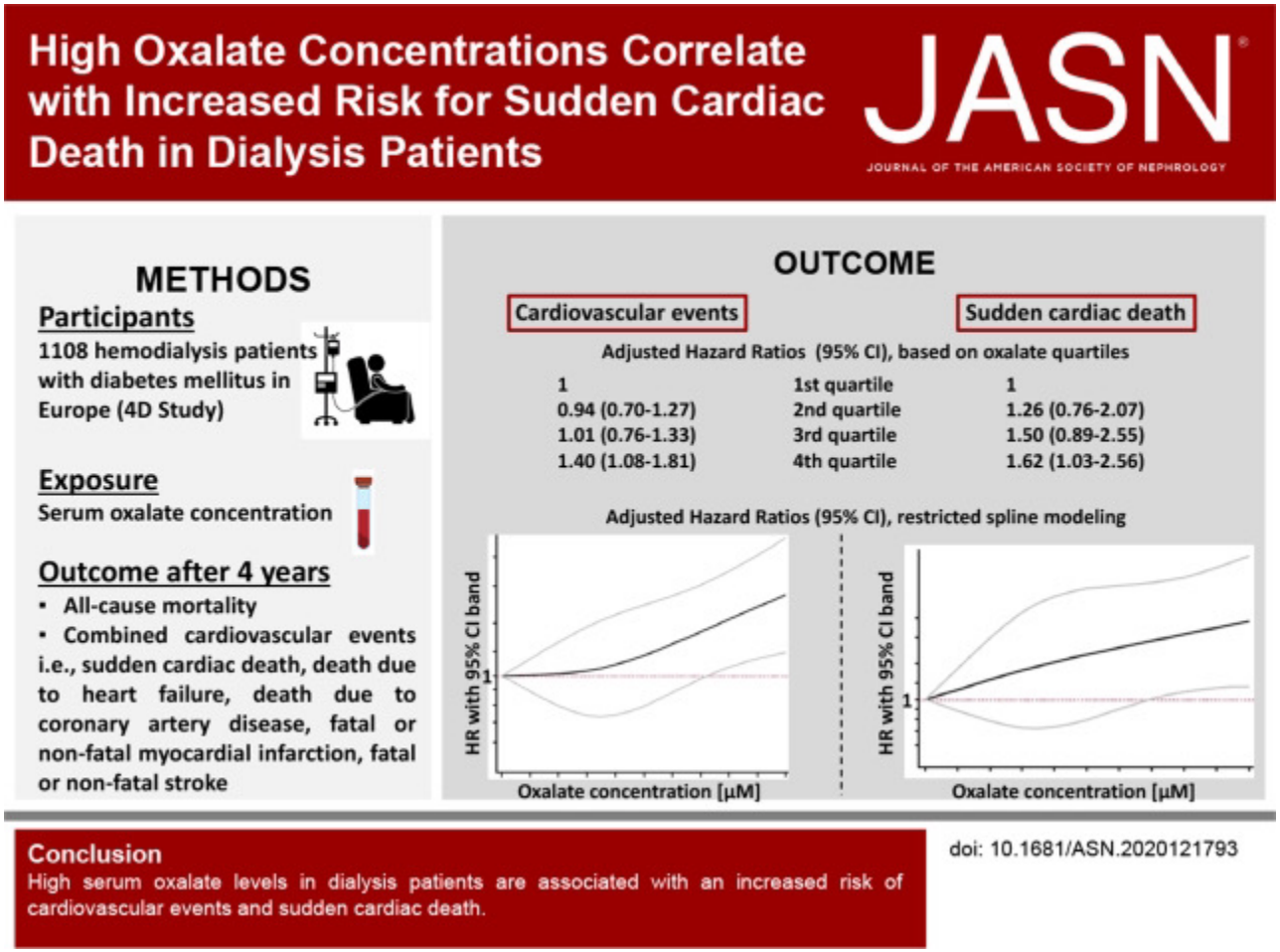
- **The follow-up of POx should be performed <u>at the beginning of the dialysis session</u> whatever the type of management**
- **A non-PH patient in dialysis has Pox levels well above the upper normal limit +++**



Publication	POx
POx in 1108 non PH dialysis patients (4D study), *Pfau 2021 JASN*	**42.4 µmol/L** (median)
POx in 93 non PH hemodialysis patients, *Metry NDT Epub 2023*	**47.3 µmol/L** (mean)
POx in 23 non PH hemodialysis patients, *Marangella et al, Clinical Science, 1991*	**49.8 µmol/L** (mean)

Groothoff Nature Reviews Nephrology 2023; Hoppe 1999

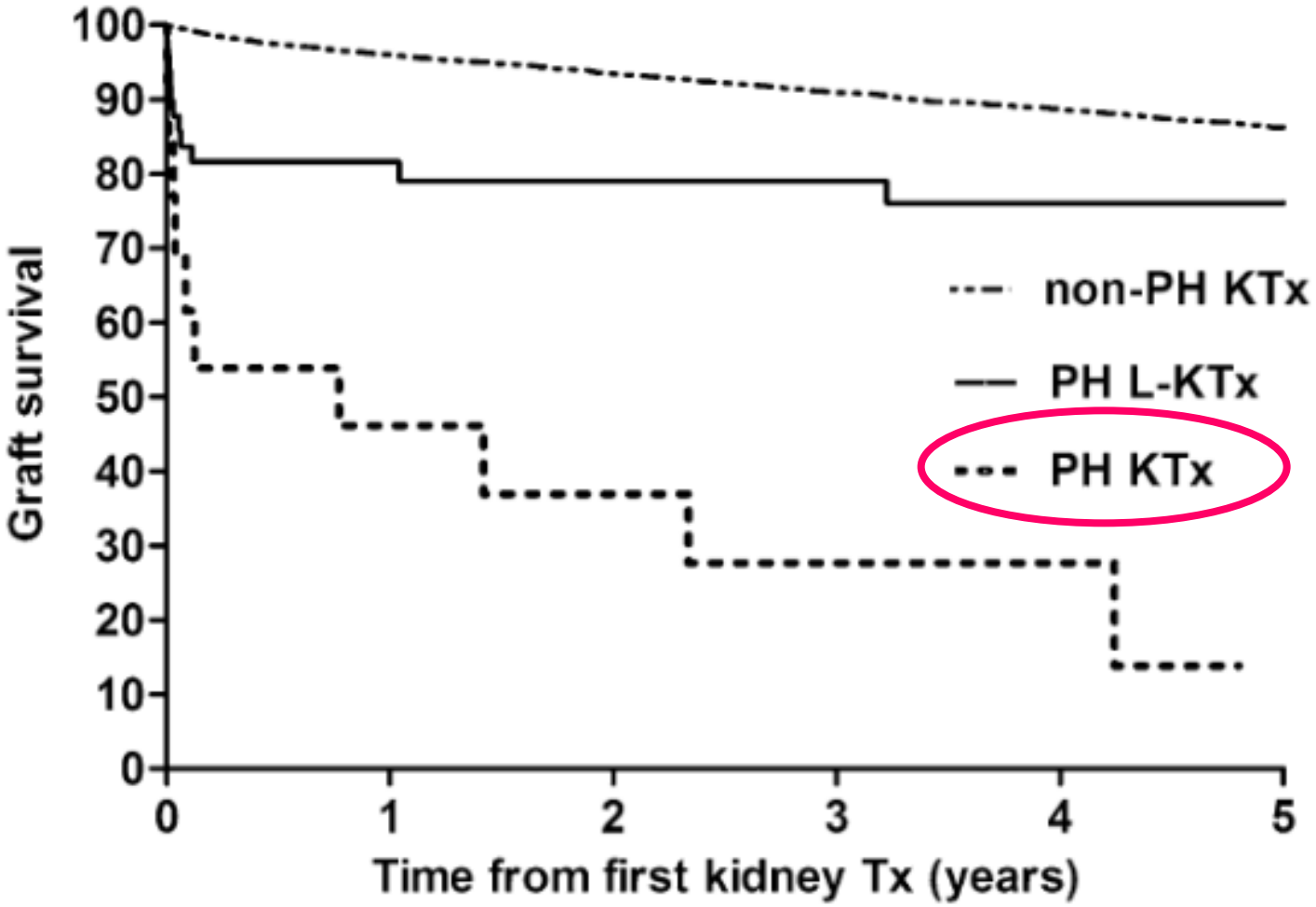
P-Ox and cardiovascular outcomes in non PH patients…



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

Pfau JASN 2021

PH1: a severe renal disease requiring liver/kidney Tx

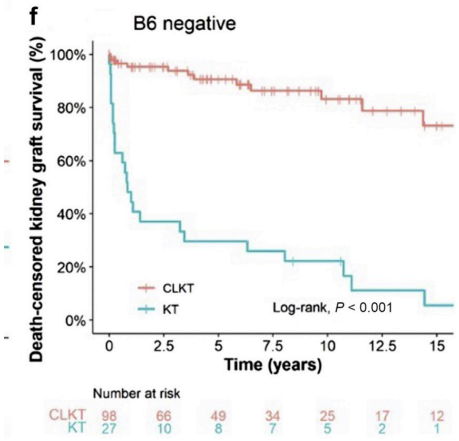


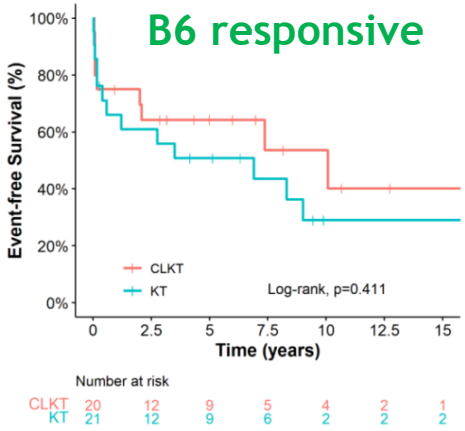
Harambat cJASN 2012

PH1 and transplantation: a few facts

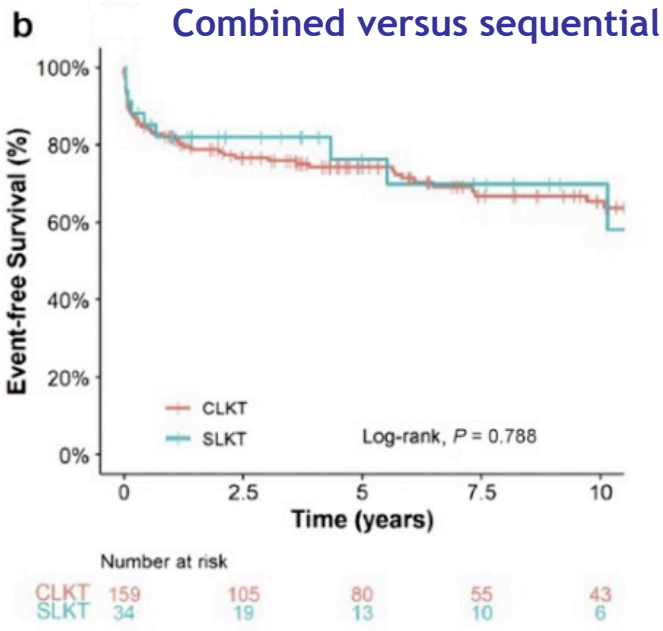
- **Data from OxalEurope**
- 267 patients with PH1 underwent transplantation between 1978 and 2019
- Data of 244 patients analyzed: 159 CLKTs, 48 isolated KTs, 37 SLKTs

B6 non-responsive





Combined versus sequential

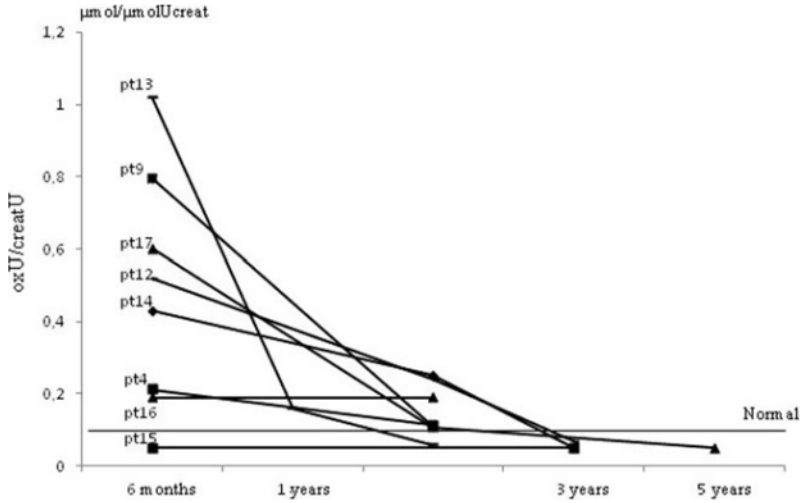


Metry, Kidney Int Reports 2022

PH1 and transplantation: lessons from combined kidney/liver transplantation in pediatrics

- **Immediate post-operative period**
- **Dialysis to discuss even in the absence of delayed graft function**
- **Hyperhydratation:** 3L/m²/day
- **Alcalinisation**: citrate K (100-150 mg/kg/day)
- **Pyridoxine (B6)?**

- **"Patience and time are more important than strength or rage"**
- Even in pediatrics, it may take years to correct Uox because of bone release
- Adage from the pioneers « time of hyperhydration after Tx = time spent in dialysis before Tx »



Loras-Duclaux Ped Neph 2016

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)

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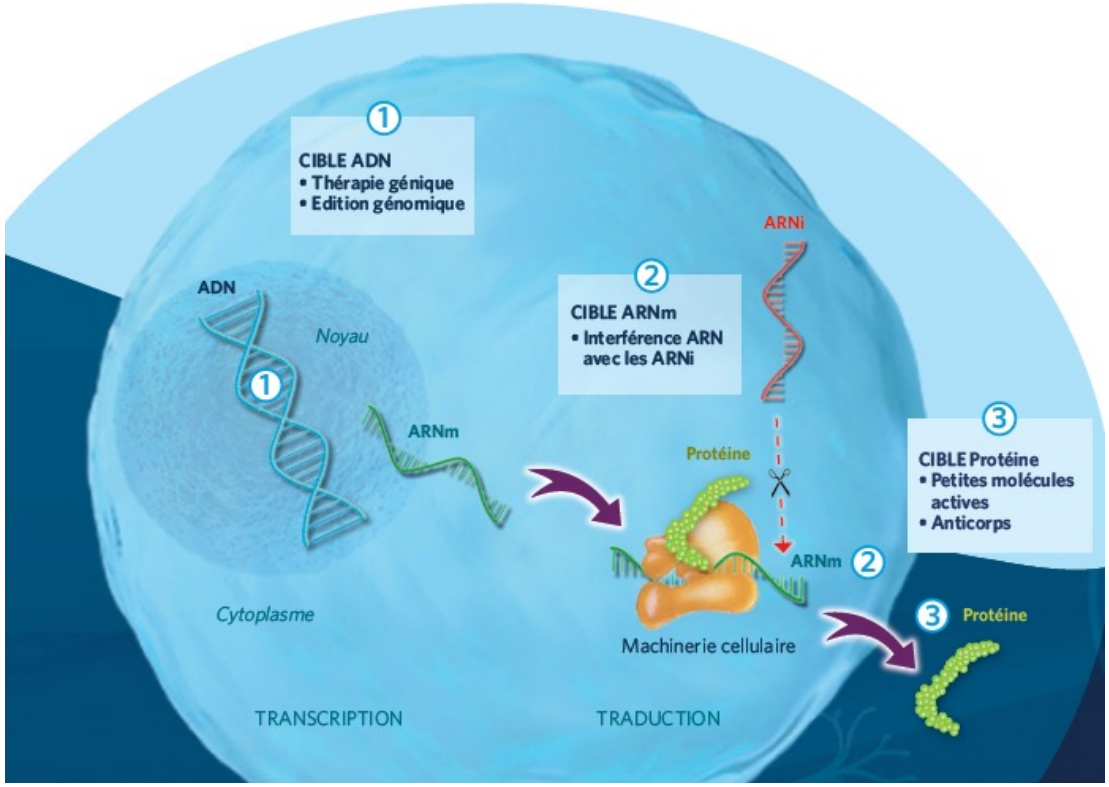
RNAi therapies: a novel therapeutic group targeting mRNAs



1 **TECHNOLOGY**

To synthesize RNAi complementary to the mRNA to destroy

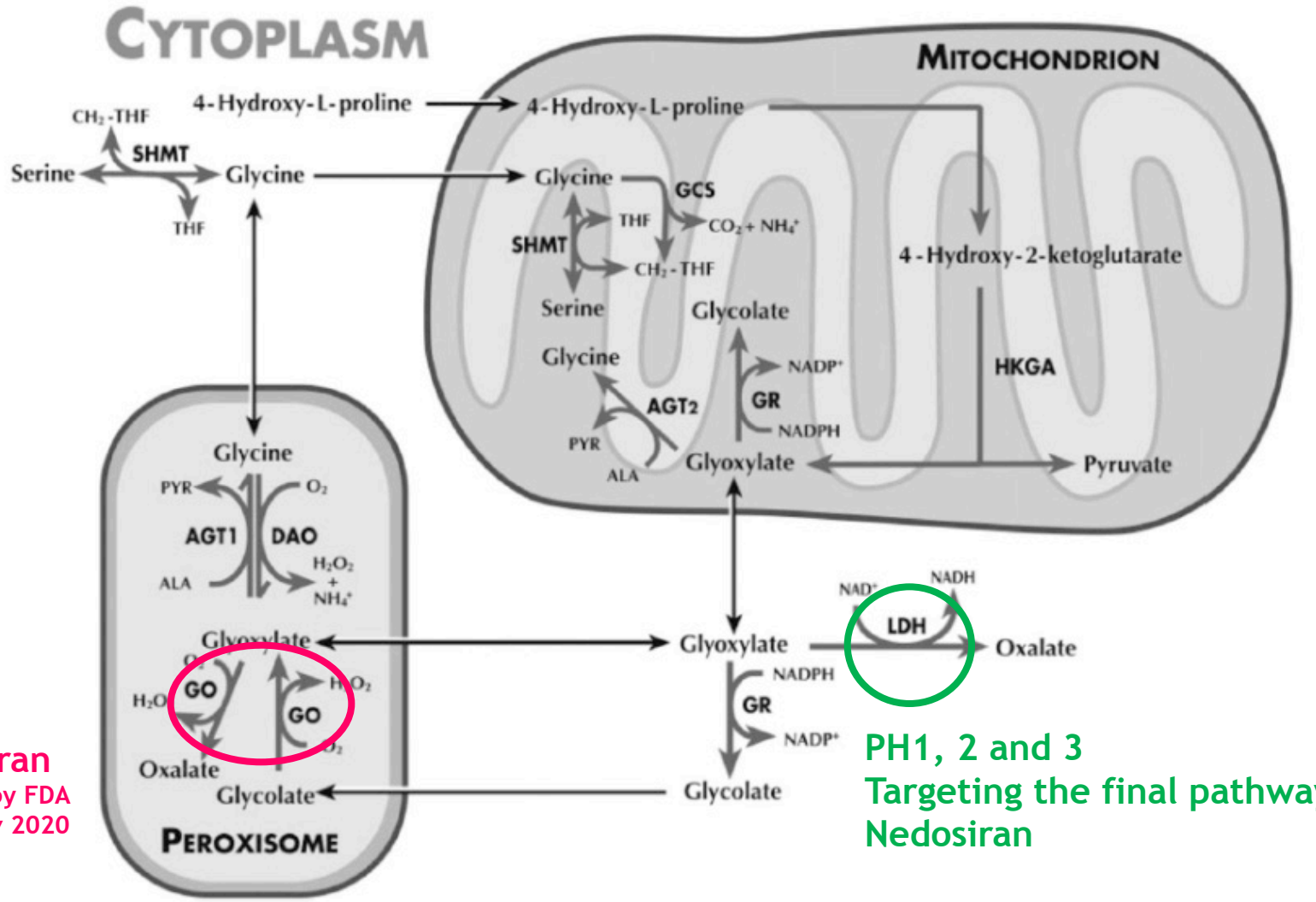
2 **VECTORS**

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

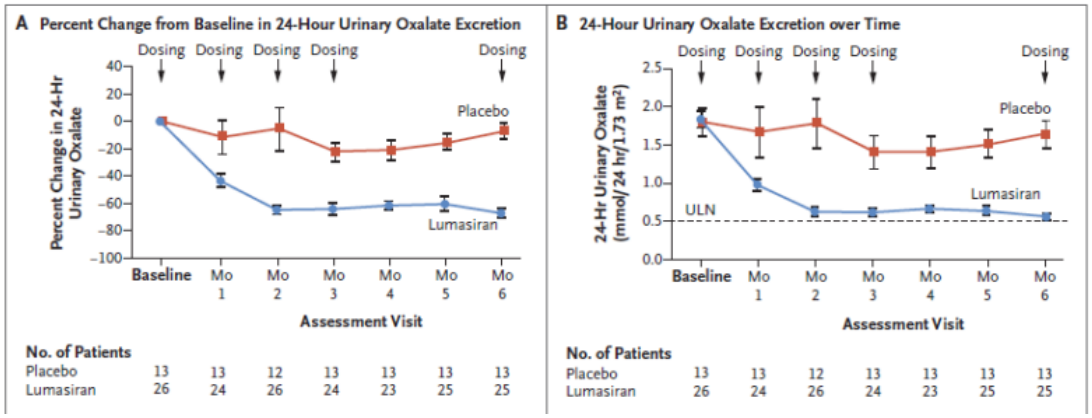
Figure 1. Hepatic oxalate synthesis pathway. ALN-GO1 targets hepatic GO.[27] Copyright clearance center license number 3863190482947.

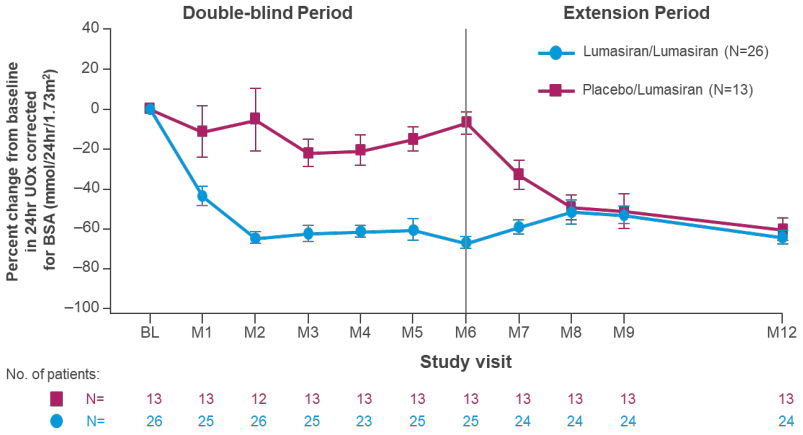
Liebow J Am Soc Nephrol. 2017 ; Garrelfs, NEJM 2021; Shee Urology 2021; Hoppe Kidney Int 2021; Baum Kidney Int 2022

Lumasiran: the Illuminate A-B-C studies

ILLU-A

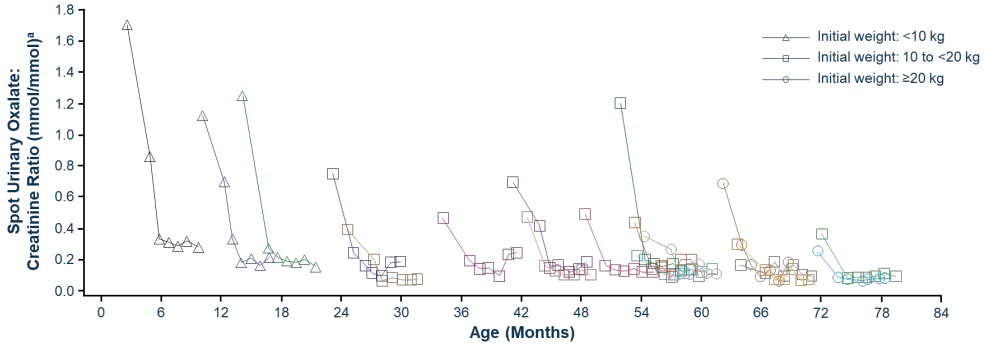
- Randomized placebo controlled trial 2:1
- 26 lumasiran / 13 placebo
- Age > 6 years
- eGFR > 30 mL/min per 1.73 m^2
- Uox 24hr > 0.70 mmol/day per 1.73 m^2
- Primary endpoint: % reduction of Uox





ILLU-B

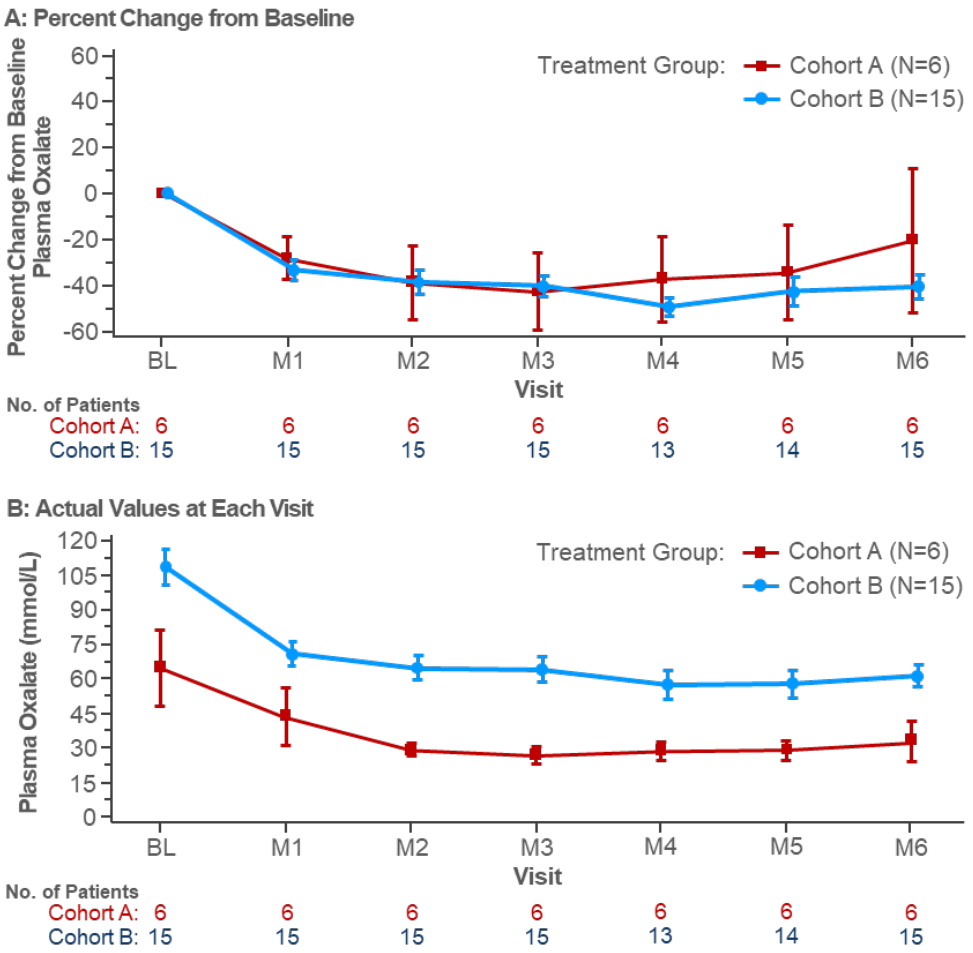
- Phase 3 Single-Arm Open-Label Study
- In Young Children < 6 years
- eGFR > 45



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

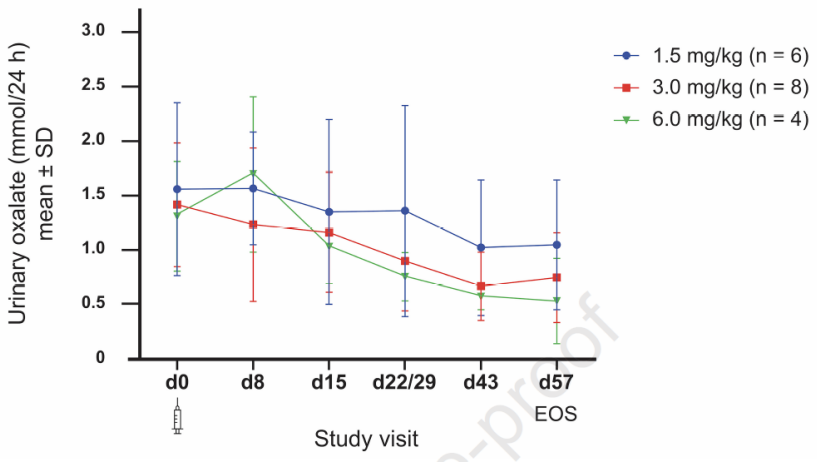


Michael AJKD 2022

Nedosiran: the PHYOX studies

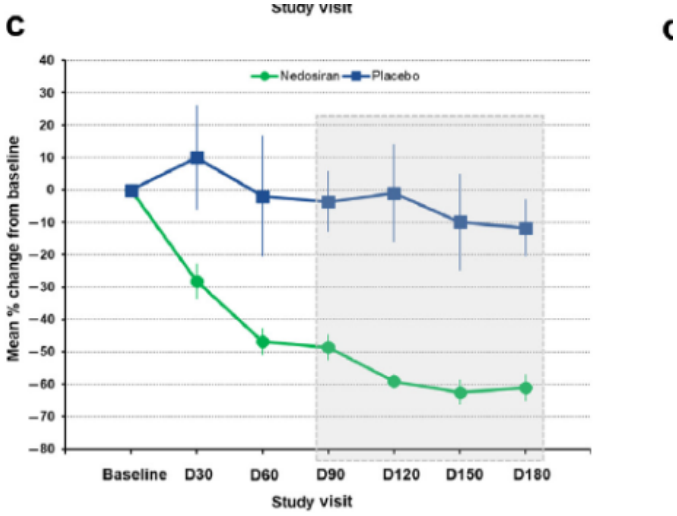
PHYOX 1

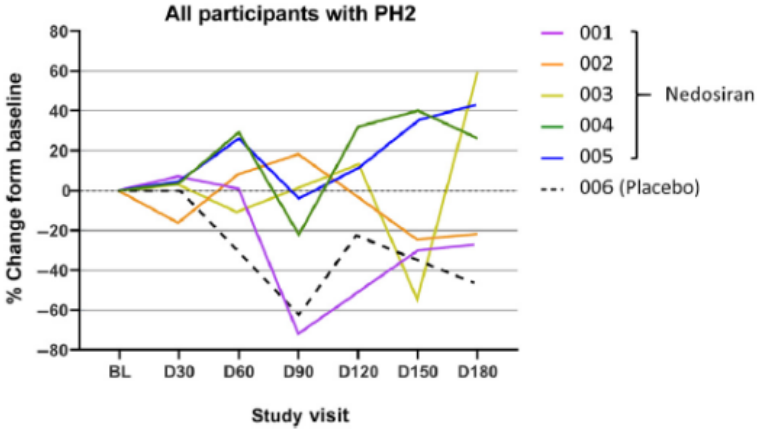
- Randomized, single-ascending-dose, phase 1 study: PHYOX1
- Safety, pharmacokinetics, pharmacodynamics, and exposure-response of subcutaneous nedosiran
- 25 healthy participants (Group A)
- 18 patients with PH1 or PH2 (Group B)
- Model: fixed monthly dose of 160 mg in adults
- Mean maxiumum reduction 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





Hoppe Kidney Int 2021; Baum Kidney Int 2022

Pros and cons of RNAi therapies…

- Clinical trials to date have described the evolution of an **intermediate end-point**, namely U Ox and/or POx
- The association between Uox and slope of decline of renal function remains to be completely proved
- No data demonstrating an effect **to preserve renal function on the long term** yet
- **No long term safety data**, but other « more ancient » RNAi used for other orphan diseases since 2013 do not yield any safety warning (patisiran and amylosis)
- This kind of therapy is really really **expensive**…
- And not available everywhere…
- And if available not necessarily available for all patients…
- So, yes we have to agree with all the points listed above…
- **But…**

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[d,e]. 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,f] 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%[2,4]; discuss options if the decrease in Pox is <30%[d,f]. 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

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Follow-up for patients receiving RNAi

Recommended biochemical analyses in patients on RNA interference therapy

Patients with PH and eGFR >30 ml/min/1.73 m^2

- Should be monitored every 3–6 months during the first year or therapy and thereafter every 6 months for 5 years, and thereafter once yearly
- Analyses should include assessment of urinary levels of oxalate, glycolate, citrate, calcium and creatinine (2×24 h), as well as assessment of kidney function, electrolytes, vitamin B6 level (if indicated), liver enzymes, ultrasonography of bone and heart (including speckle tracking) and an eye examination

Patients with PH and eGFR <30 ml/min/1.73 m^2 or stage 5D chronic kidney disease

- Analyses that should be performed every 3 months include assessment of plasma oxalate level, kidney function, electrolytes, vitamin B6 level (if indicated), liver enzymes
- Ultrasonography of bone and heart (including speckle tracking) and an eye examination should be performed yearly

Kidney transplant recipients with PH

- Assuming estimated glomerular filtration rate (eGFR) of the transplanted kidney is >30 ml/min/1.73 m^2, follow the guidance outlined for patients with primary hyperoxaluria (PH) and eGFR >30 ml/min/1.73 m^2 with the addition of plasma oxalate measurements, until parameters are normalized

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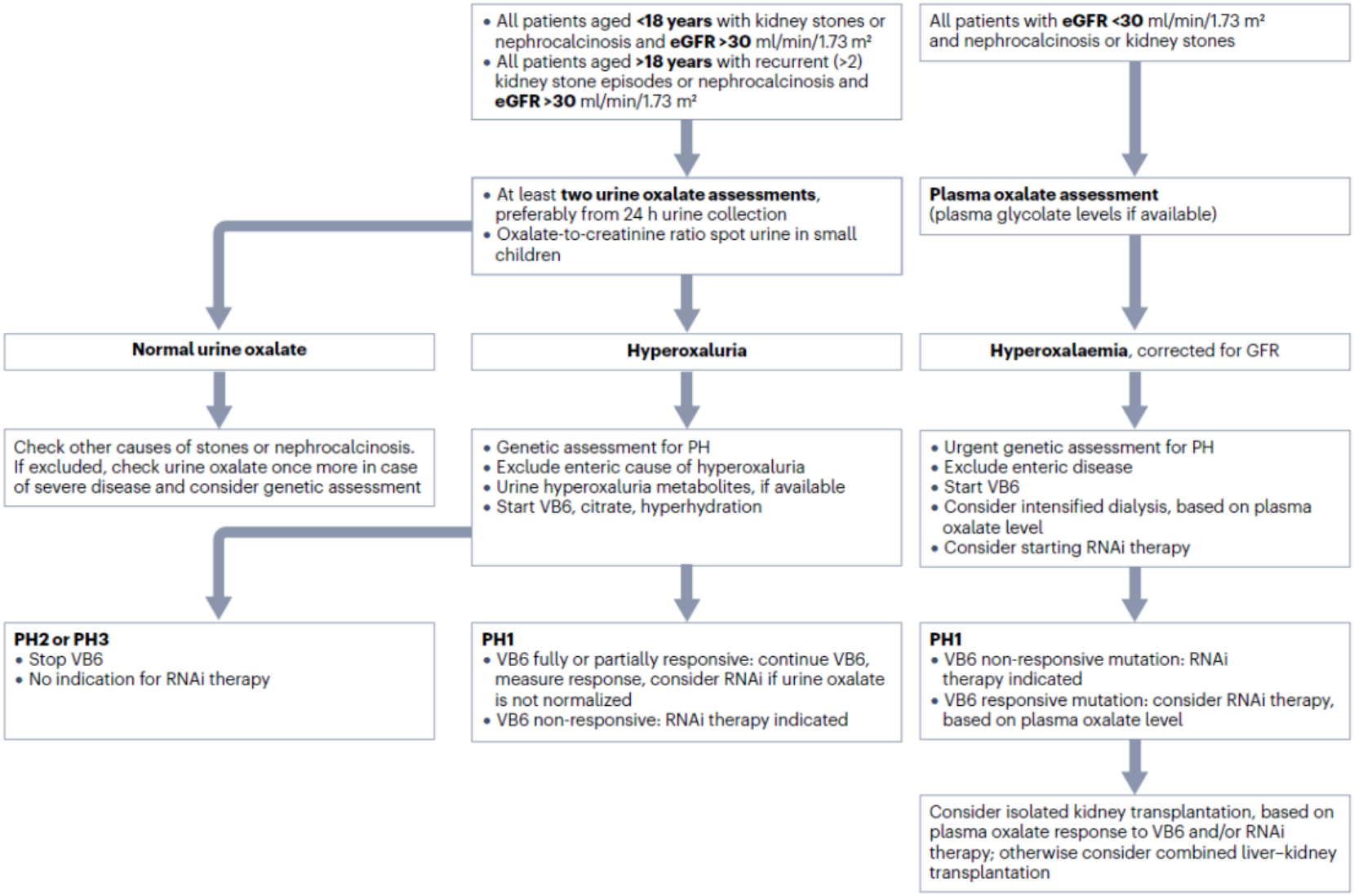
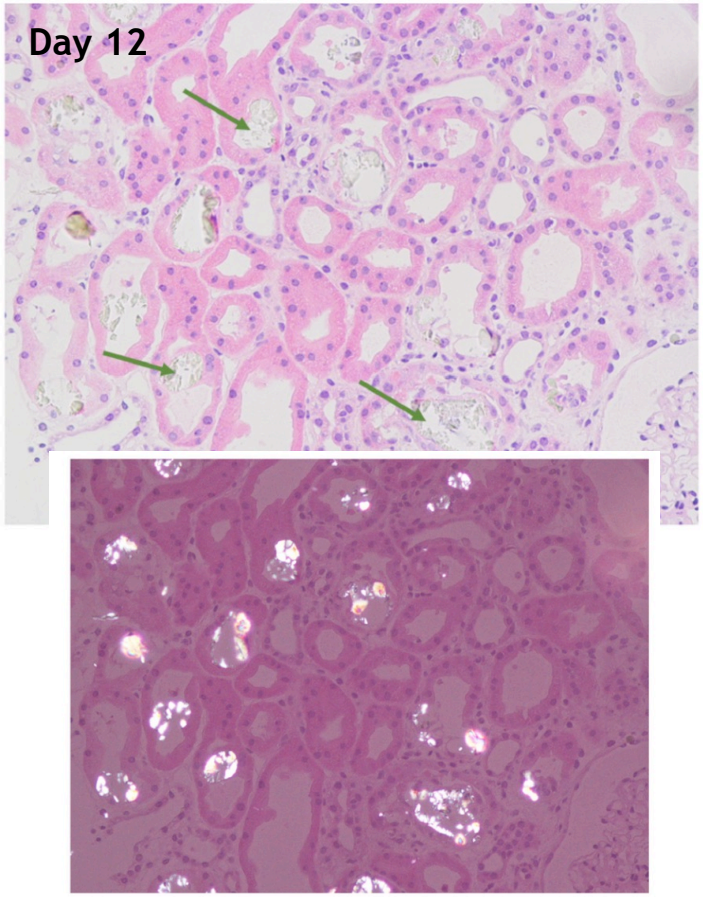
Proposed algorithm: management in case of PH suspicion

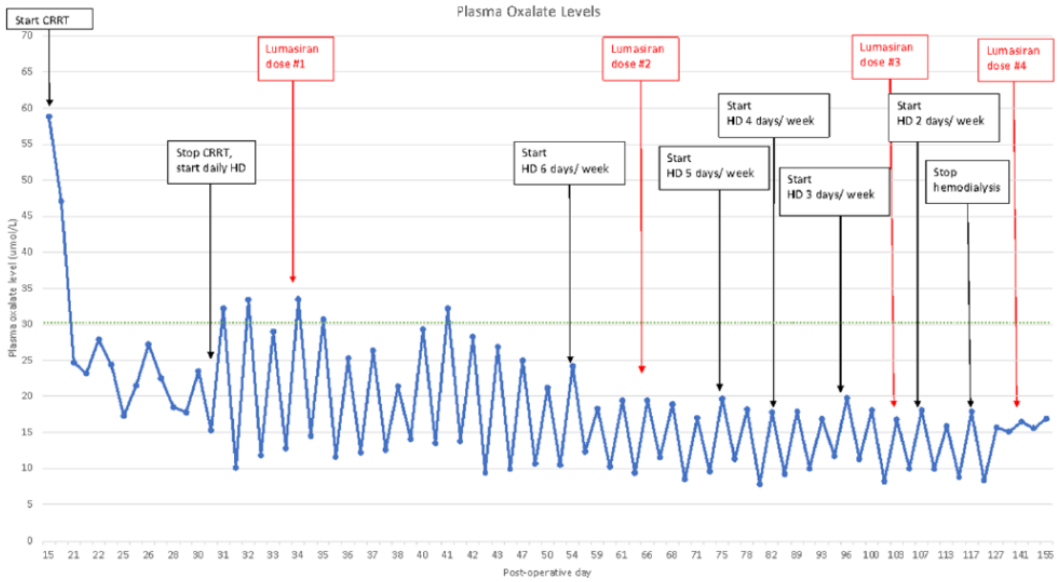


Groothoff Nature Reviews Nephrology 2023

Isolated renal transplant without previous diagnosis of PH1, and lumasiran as rescue

- Case report of a child diagnosed with PH1 after kidney transplant
- Able to maintain kidney function, thanks to aggressive renal replacement therapy and lumasiran

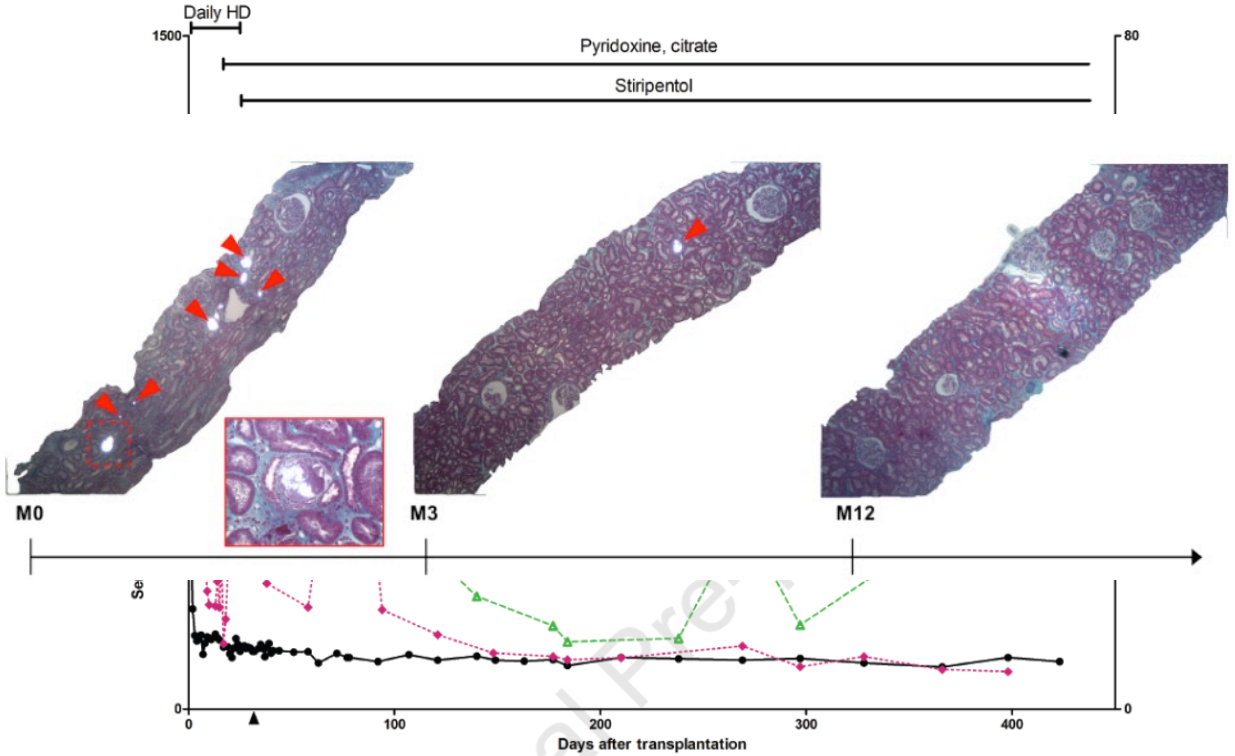




Stone, Am J Transplant 2021

Isolated renal transplant with a previous diagnosis of PH1, and lumasiran/stiripentol as rescue

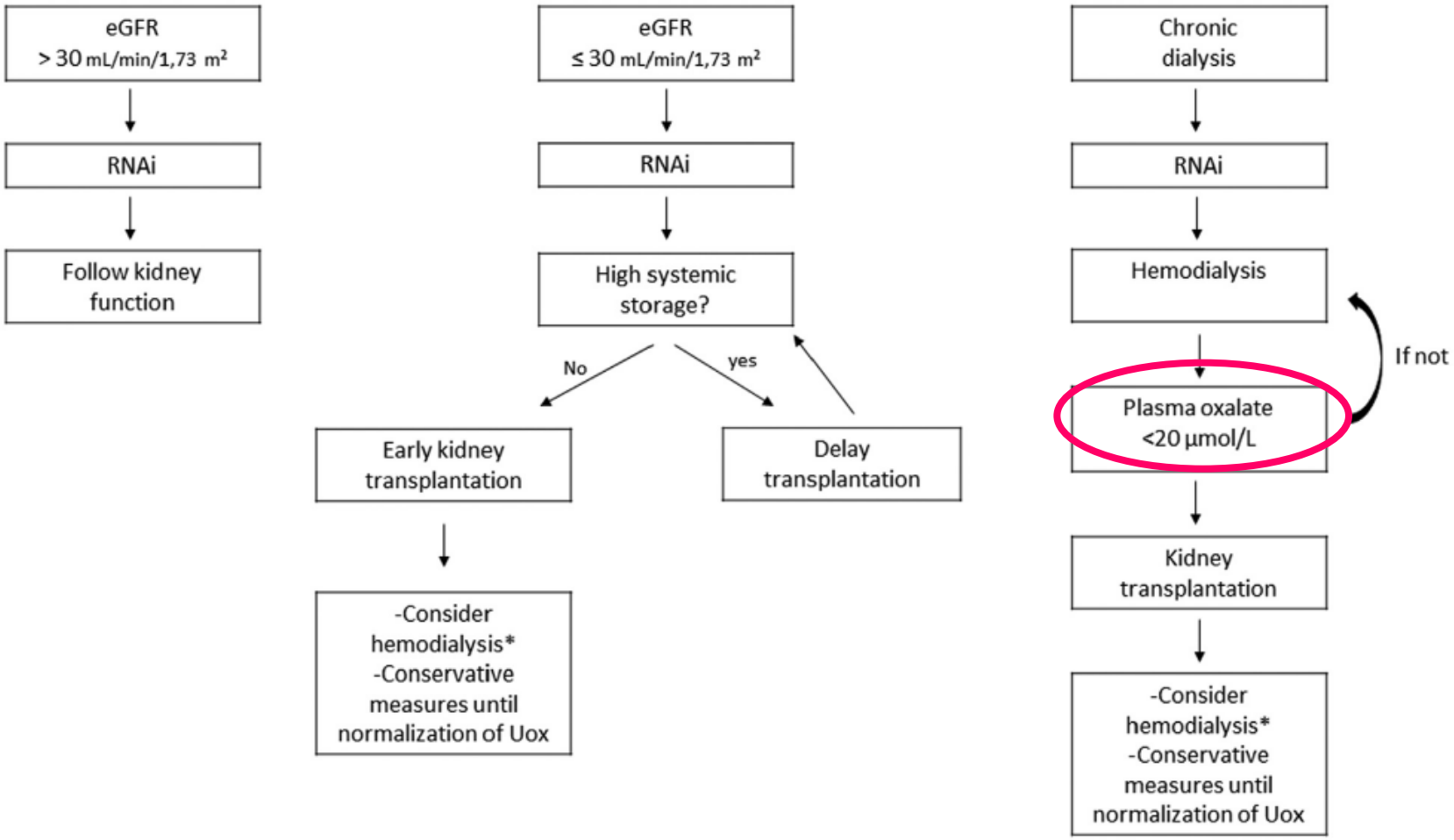
- PH1 diagnosis before Tx (family screening, p.G170R), decision of isolated kidney Tx because of the absence of extra-renal manifestations and late disease onset
- 51-year-old patient with a biopsy-proven recurrence of oxalate nephropathy after a kidney-only transplantation.
- Combination of stiripentol and lumasiran without adverse events.
- Fourteen months after transplantation, graft function, serum and urinary oxalate levels have remained stable, and kidney biopsy showed a complete regression of oxalate crystals.



Lombardi, AJKD 2023

And now… isolated renal Tx under RNAi?

Despite algorithms with quite optimistic thresholds of Pox…



Devresse Kidney Int Rep 2020

Real-life data: isolated renal transplant and lumasiran, first data published in adults

- 39 year-old women with PH1
- 3 years of conventional dialysis
- 1 year of intensive dialysis (among which 7 months of lumasiran)
- Then isolated kidney transplantation

- Delayed graft function, 1 HD session
- Hyperhydration: + 3.5 L / day
- Potassium citrate
- Pyridoxine
- Low-oxalate diet

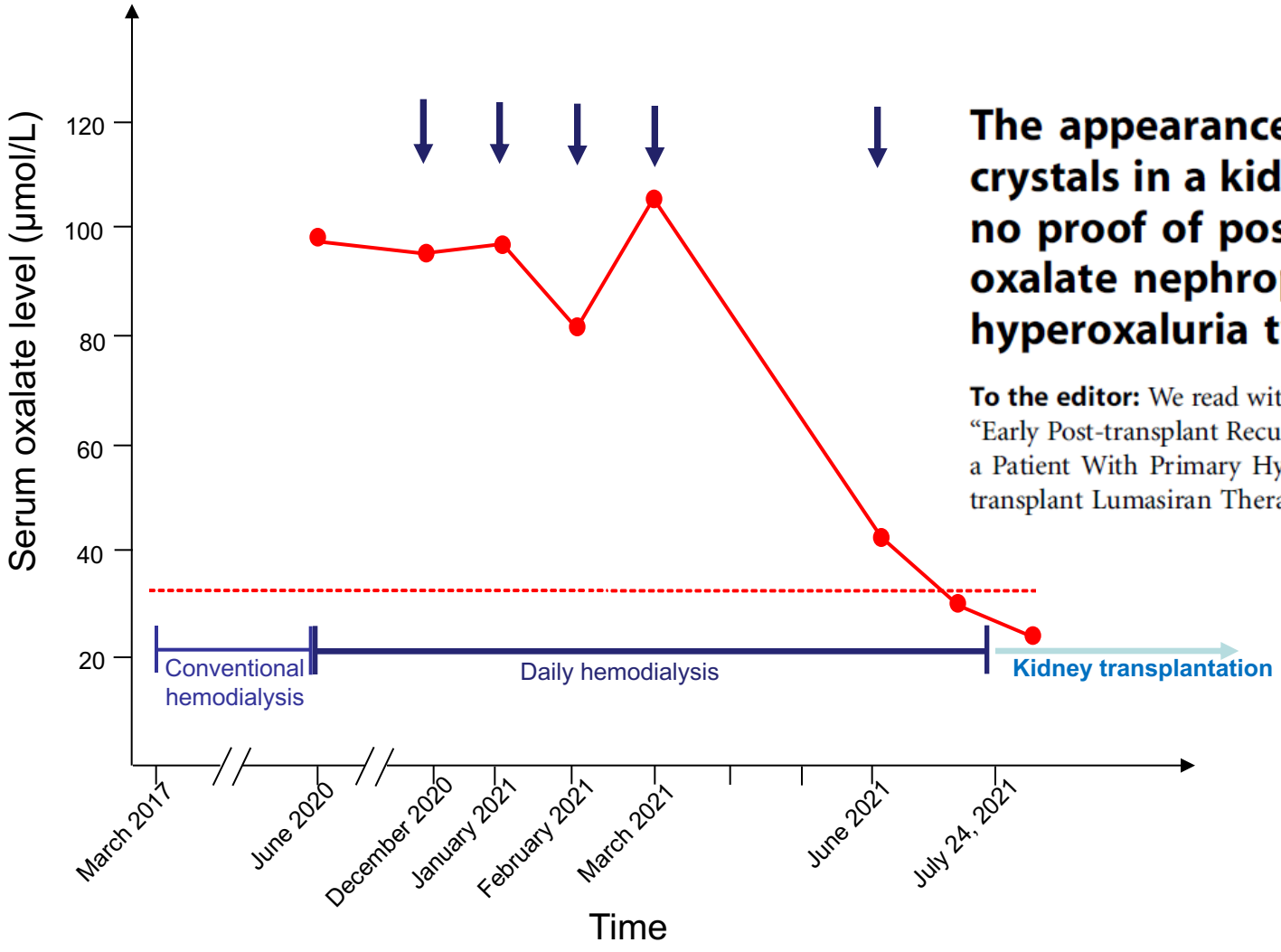
- Minimum 140 µmol/L
- Biopsy D25: rejection Banff IIA + oxalate deposits
- Corticosteroids pulses + thymoglobulins
- In parallel hyperhydrat + citrate + lumasiran

- 10 sweeks post Tx: creat 169 µmol/L, Pox 21 µmol/L

Early post-transplant recurrence of oxalate nephropathy in a patient with primary hyperoxaluria type 1, despite pretransplant lumasiran therapy

Joher N et al, Kidney Int 2022

Real-life data: isolated renal transplant and lumasiran, first data published in adults



The appearance of oxalate crystals in a kidney biopsy is no proof of post-transplant oxalate nephropathy in primary hyperoxaluria type 1

To the editor: We read with interest the letter by Joher *et al.*: "Early Post-transplant Recurrence of Oxalate Nephropathy in a Patient With Primary Hyperoxaluria Type 1, Despite Pre-transplant Lumasiran Therapy."[1]

Joher N, Kidney Int 2022; Metry Kidney Int 2022

Real-life data: our 5 cases from 4 centers

- 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/m^2/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 m^2
  - 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)**

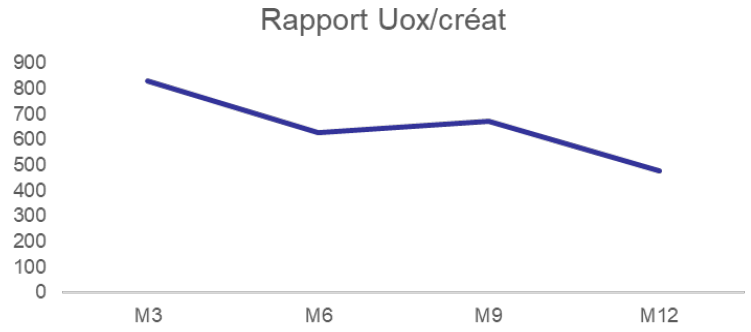
Leclerc and al, NDT 2022, collaboration between Lyon, Marseille, Strasbourg and Amsterdam

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age at diagnosis (years)	1.5	17	6	8	8
Age of ESKD (years)	0.5	23	12	27	43
Genotype	Homozygous c.731T>C	Compound heterozygous c.[508G>A]; [847-1G>C]	Compound heterozygous c.[33del];[731T>C]	Compound heterozygous c.[33dup];[847-11G>C]	Compound heterozygous c.[33del] ;[454T>A]
Predicted pyridoxin sensitivity	Unclear	Responsive	Unclear	Non responsive	Partly responsive
Time on dialysis before lumasiran initiation (months)	10	36	60	0	8
POx (µmol/l) before lumasiran initiation	110	20	128	150	91
Plasma Glycolate (µmol/l) before lumasiran initiation	598	<8	229	460	49
Time between lumasiran initiation and Tx (months)	13	10	17	13	5
Age at Tx (years)	3	26	18	28	45
Renal graft	Deceased donor	Living donor	Deceased donor	Living donor	Living donor
Pox at Tx (µmol/l)	53	10	65	72	49
Plasma Glycolate (µmol/l) at Tx	>150µmol/L	114 µmol/l	> 150 µmol/l	>150	68.6
Delayed graft function	No	No	No	No	No
Dialysis after Tx	Yes	No	Yes	Yes	No
SOC hyperhydration	Yes	Yes	Yes	Yes	Yes
SOC urine alkalinization	Yes	No	After month 4	Yes	Yes
Pyridoxine	Yes	Yes	Yes	No	Yes
Renal lithiasis after Tx on renal US	Yes	No	No	No	No
Nephrocalcinosis of the graft on renal US	No	No	No	No	No
Biopsy of the graft	Yes (M3 and M7) No oxalate deposit	Yes (M2) No oxalate deposit	No	Yes (M1.5) Oxalate deposit (N=1) At M4 : no oxalate deposit	Yes No oxalate deposit

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Evolution at 1 month post Tx			*Under dialysis*		
Pcreat (µmol/l)	30	133	345	140	142
eGFR (mL/min/1.73 m²)	125	48	22	60	38
Pox (µmol/L)	14	<5	28	5	14
Uox (µmol/mmol)	519	67	245	78	90
24-hour UOx (µmol/day)	NA	396	NA	1035	1152
Plasma glycolate (µmol/L)	>150	>150	>150	>150	73.9
Evolution at 3 months post Tx					
Pcreat (µmol/l)	29	150	93	145	144
eGFR (mL/min/1.73 m²)	125	41	88	60	38
Pox (µmol/L)	14	<5	26	7	7
Uox (µmol/mmol)	830	103	345	67	90
24-hour UOx (µmol/day)	NA	180	NA	1278	1369
Plasma glycolate (µmol/L)	>150	>150	> 150	>150	21.3
Normal UOx/creat depending on age and local values (µmol/mmol)	11-120	2-80	2-80	<40	60

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

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Evolution at 6 months post Tx					
Pcreat (µmol/l)	34	140	98	154	180
eGFR (mL/min/1.73 m²)	125	44	88	52	29
Pox (µmol/L)	11	6	ND	7	21
Uox (µmol/mmol)	619	40	283	39	ND
24-hour UOx (µmol/day)	NA	101	NA	840	2046
Plasma glycolate (µmol/L)	>150	>150	>150	>150	39.9
Evolution at 12 months post Tx					BK virus nephropathy
Pcreat (µmol/l)	35				203
eGFR (mL/min/1.73 m²)	124				25
Pox (µmol/L)	11				19
Uox (µmol/mmol)	479				120
24-hour UOx (µmol/day)	NA				1872
Plasma glycolate (µmol/L)	>150				91.1
Normal UOx/creat depending on age and local values (µmol/mmol)	11-120	2-80	2-80	<40	60



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

Take home messages

- **New guidelines recently released for diagnosis and management (including RNAi)**

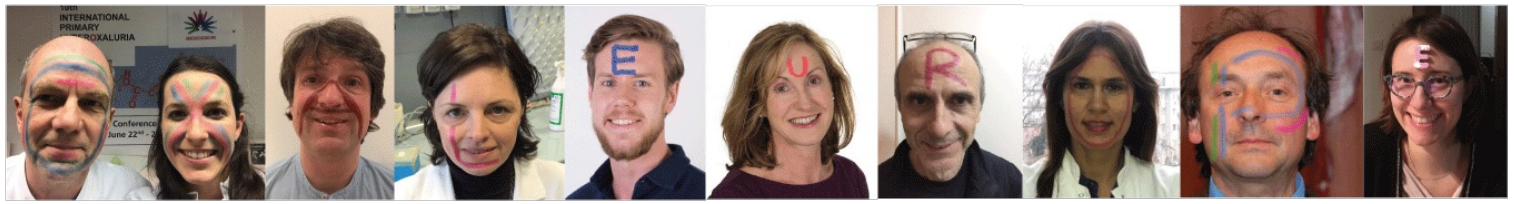
- **A non-PH patient in dialysis has Pox levels well above the upper normal limit +++**
- **Dialysis in PH1**
  - The shorter the better, propose intensive dialysis
  - This is not because a patient receives RNAi therapy that intensive HD should be stopped: beware of systemic and bone release!

- **After transplantation**
  - Even in pediatrics, it may take years to correct Uox because of bone release
  - RNAi therapies will not have effects on bone release
  - Adage from the pioneers « time of hyperhydration after Tx = time spent in dialysis before Tx » that may be improved by RNAi therapies
  - Be pro-active in the immediate post-operative period +++
    - Hyperhydration
    - Alkalinization
    - B6?
    - RNAi at the time of transplant to block hepatic synthesis?

- **A lot of questions remain open**
  - Pending ancillary analyses in Illu-C: bone release, outcomes after Tx (if performed)
  - We need to confirm the feasibility of isolated renal Tx under RNAi therapies on larger cohorts
  - Could we imagine performing isolated renal Tx with RNAi and then stop RNAi when the post-operative situation is stabilized in B6 sensitive patients ?

Knowledge in the field is changing quickly…

#rarediseaseday19



OxalEurope: we are rare, we care