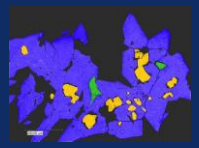
German Hyperoxaluria Center

Drug treatment of PH

Bernd Hoppe, MD, Bonn, Germany



Specific Treatment

- Daily fluid intake > 3 Liter
  - Via (naso)gastral tube in small infants and children
- Pyridoxine in PH type I
- Alkaline citrate or orthophosphate
- Magnesium
- Avoid diet with high oxalate content

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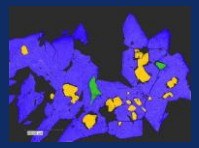

Treatment in normal kidney function

1. Fluids

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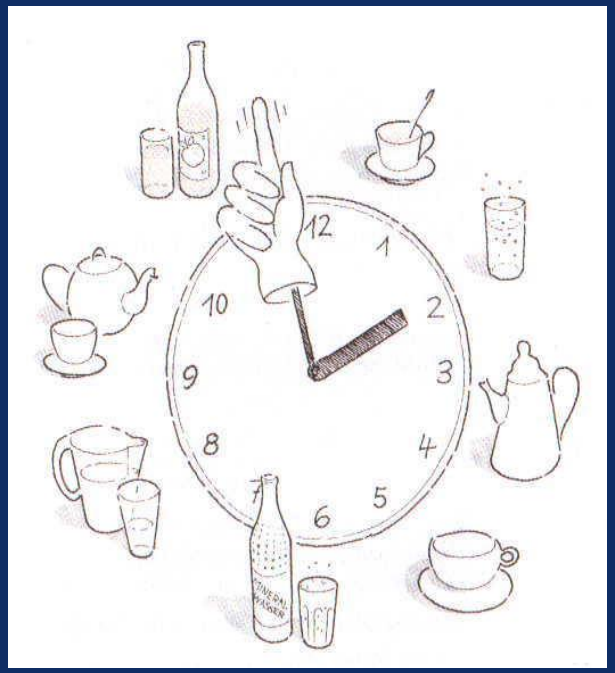
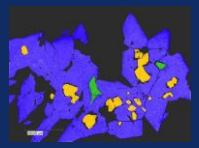
Drink as much as you can!

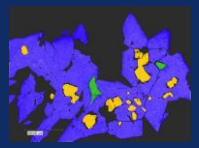
All other treatment efforts are „worthless“, if daily fluid intake is insufficient!



German Hyperoxaluria Center 

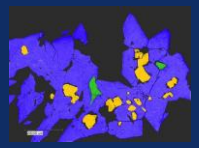
Drink, drink, drink.....

- Repeated, means continuous daily fluid intake of at least > 1 -1.5 Liter/per m^2 BSA
- the earlier young patients accept the necessity to drink the better they get used to it!
- Older kids, adolescents and adults should drink > 2-3 liter per day.



...drink...

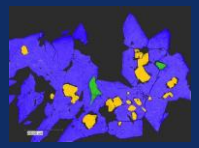
- Increase fluid intake at great heat, fever, fluid loss, e.g. severe diarrhea
- If oral fluid intake is no longer sufficiently possible, prompt i.v. (re-)hydration is necessary!
- A gastrostomy tube may sometimes be helpful in small infants and children

German Hyperoxaluria Center 

Oxalate reduced diet?

- Oxalate absorption in healthy children:
  - 10.1 +/- 3.8 %
- Oxalate absorption in patients with PH I
  - 6.77 +/- 3.3 %

- Hence, only diet with extreme oxalate content should be avoided!



Diet?

Food	Ox content mg/100 g	Food	Ox content mg/100 g
Beans (fresh)	43.7	Cacao powder	623
Spinach (cooked)	356-780	Coffee	1.0
Rhubarb	537	Coffee powder	57-230
Potatoes (cooked)	14.5	Beer	1.7
Apple	1.5	Wine	3.1
Orange	6.2	Tea (2 Min.)	7.0-10.8
Strawberry	15.8	Tea leaves	375-1450

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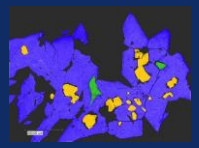

Treatment in normal kidney function

2. Pyridoxine in primary hyperoxaluria type I

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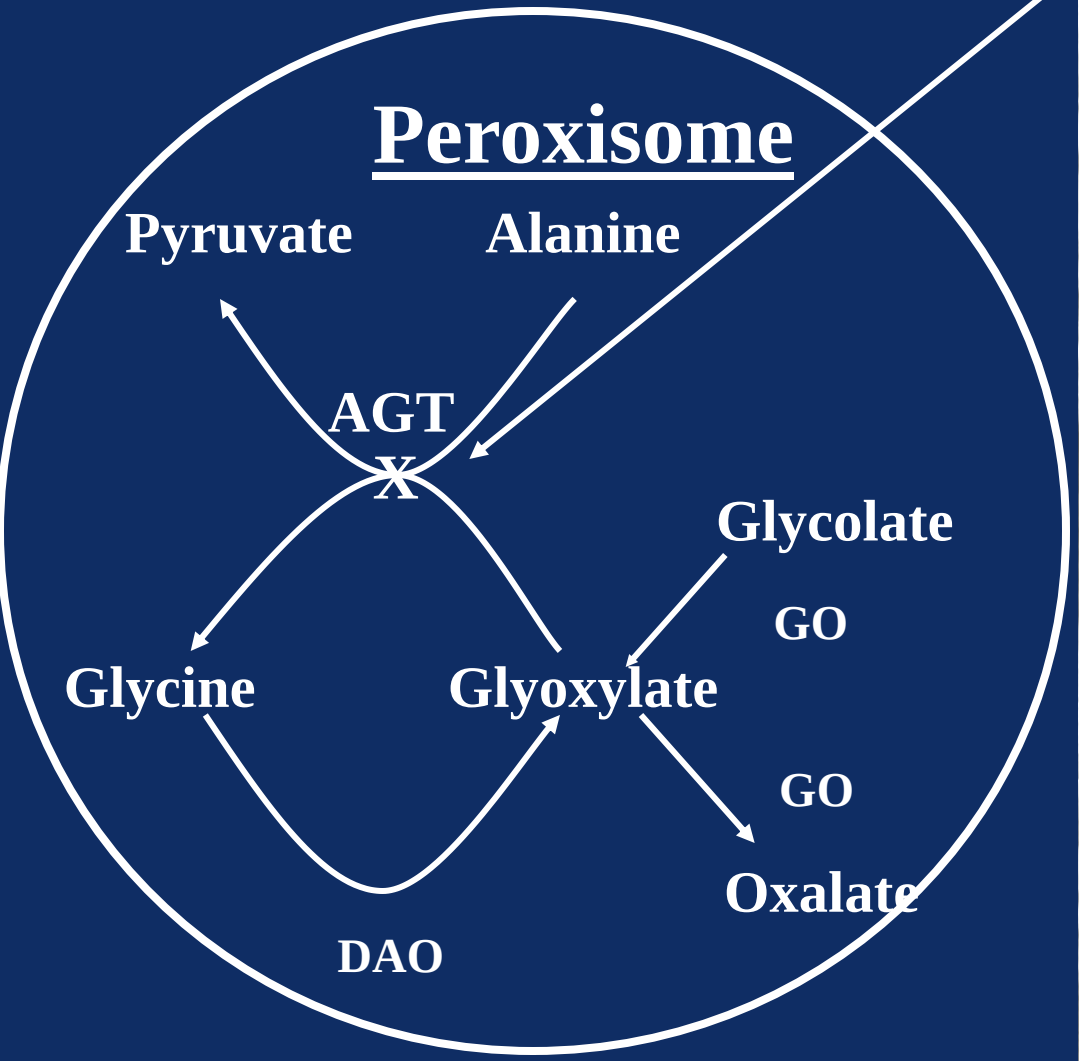
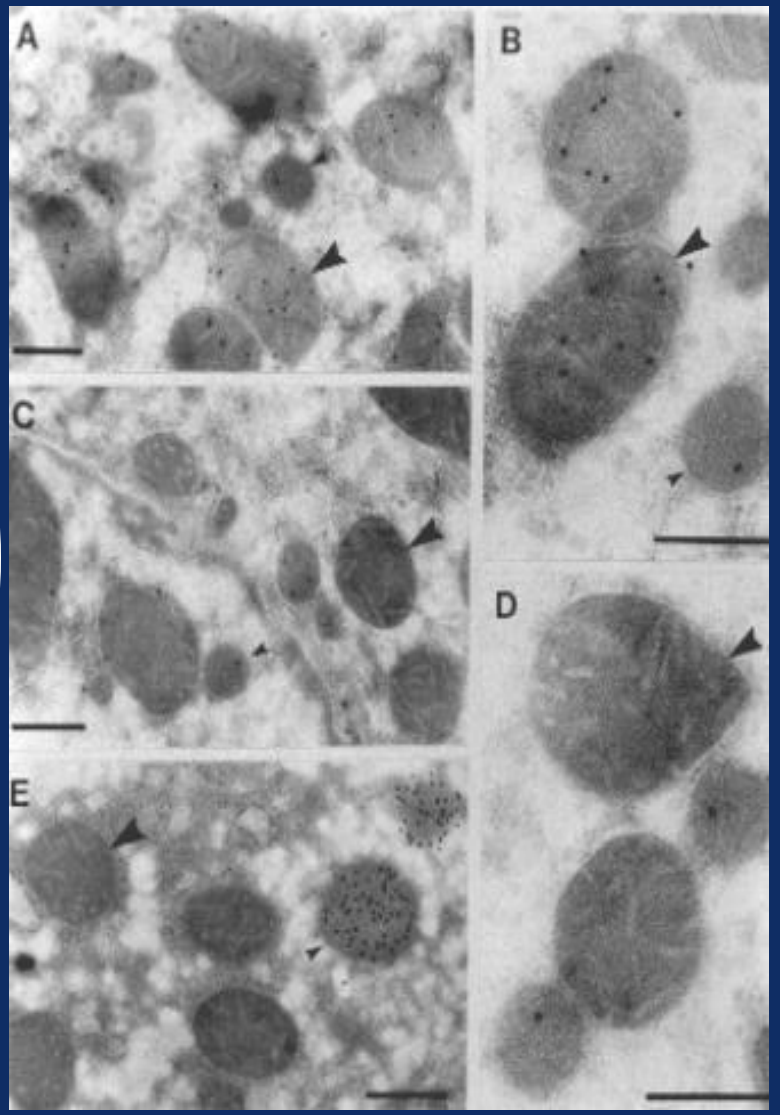
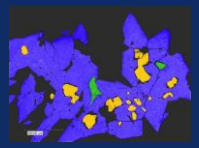
When and why helps Vitamin B6?

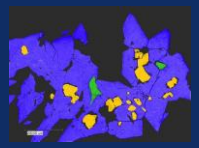






Dosage?

- Vitamin B6 should be administered in every patient with PH I
- Result of liver biopsy, or molecular genetic testing may give evidence on therapeutic efficiacy
- Dosage: 5-20 (30) mg/kg body weight/day
- Attention: side effects



Treatment control?

- 24 h urine analysis before/under treatment
- How much reduction of urinary oxalate excretion is achieved?
- Stop of treatment when no success?
- In end stage renal failure => control of plasma oxalate levels?!

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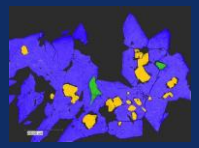

PHOX-B6 **PILOT**

- **Investigation of the <u>relative reduction of UOX</u> excretion under increasing dosages of vitamine B6 at study week 24 compared to baseline in a prospective setting.**
- **Correlation of serum B6 level with urinary oxalate excretion**
- **Differences in genotype/phenotype correlation**
- **12 patients included**

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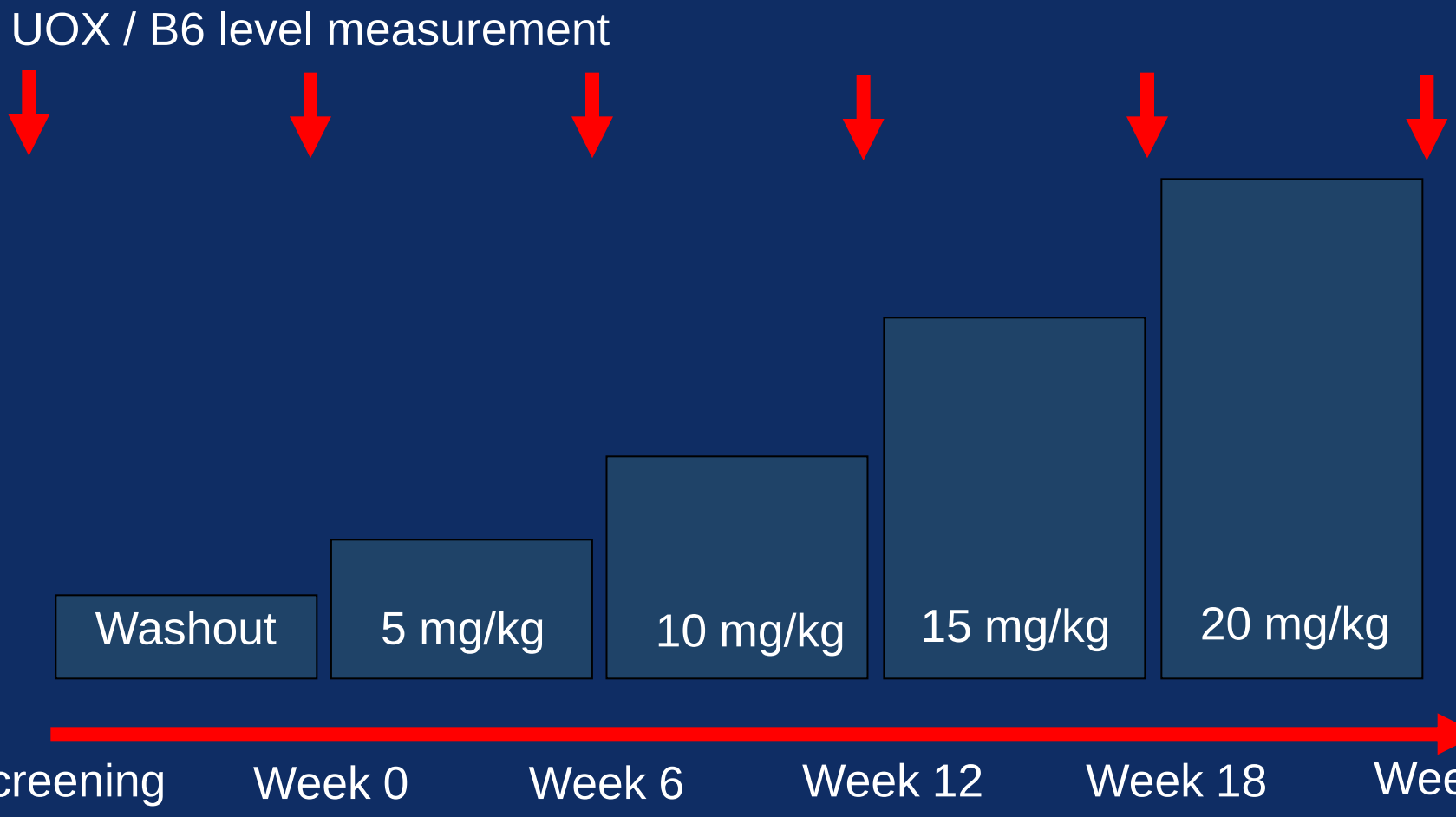
Study Design



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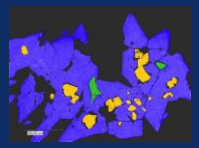

Results

Baseline- characteristics

Variable	PH I patient (n=12)
Female/ male (n)	7/ 5
Age (yr) (mean +/- SDS)	13.5 ± 3.3
GFR (ml/min*1.73m^2) (mean +/- SDS)	139 ± 37
c.508G>A homozygous (n)	3
c.508G>A heterozygous (n)	5
c.508G>A negative (n)	4
Nephrocalcinosis (n)	6
Urolithiasis (n)	8
Vit B6 before study entry (n)	8

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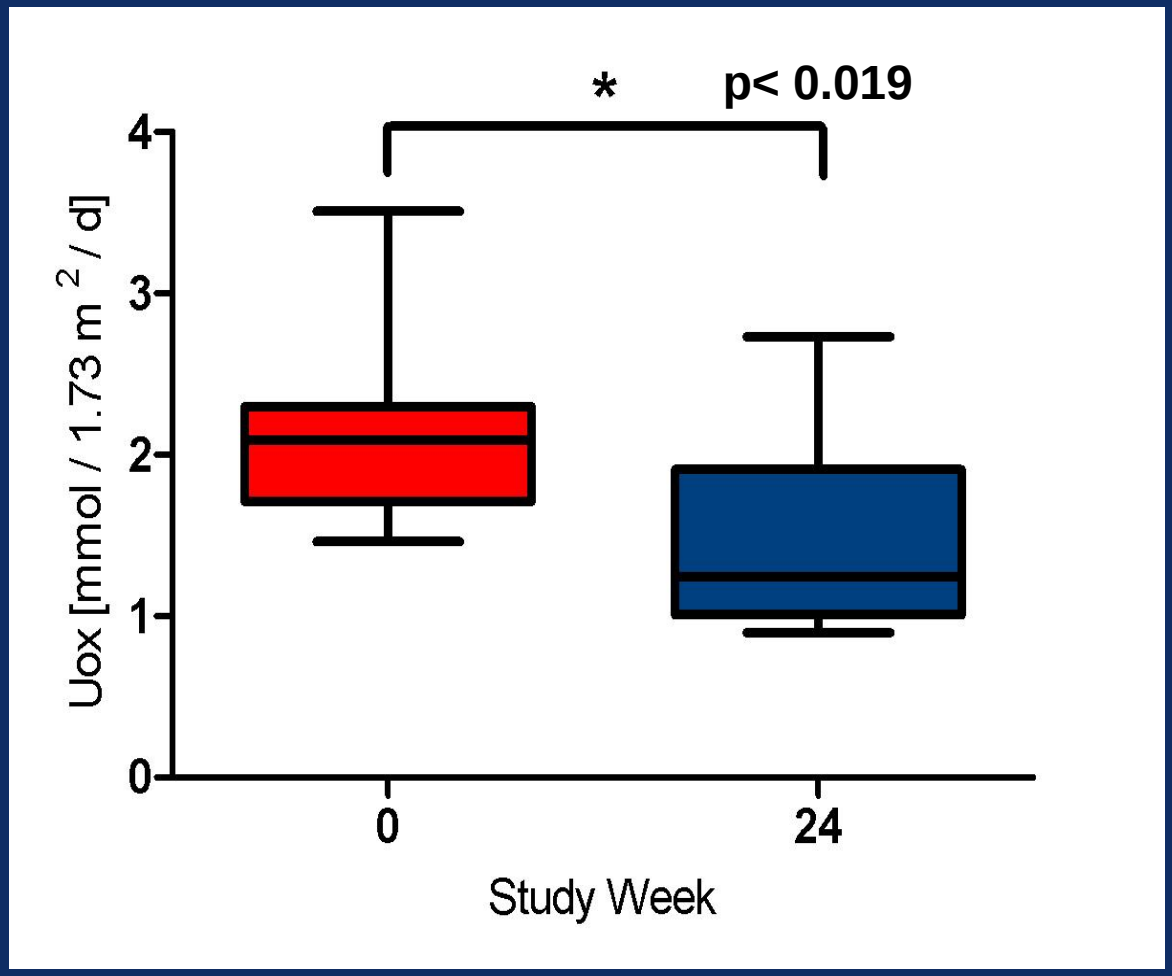
Results

Primary objective- relative reduction of UOX excretion



Relative UOX reduction of the whole group 25.0%!

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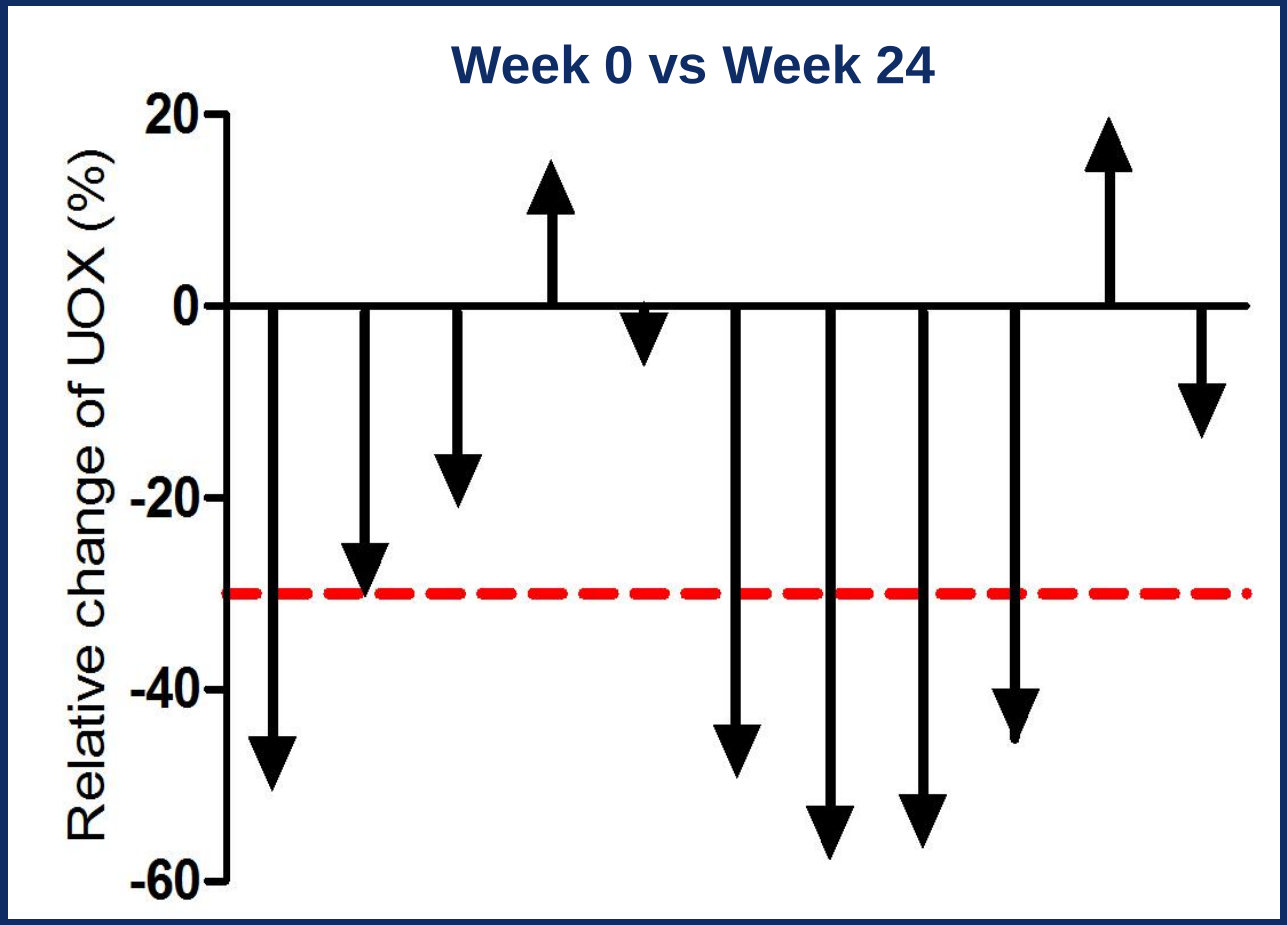
Results

Primary objective- individual relative change of UOX excretion



5/12 UOX

reduction > 30%

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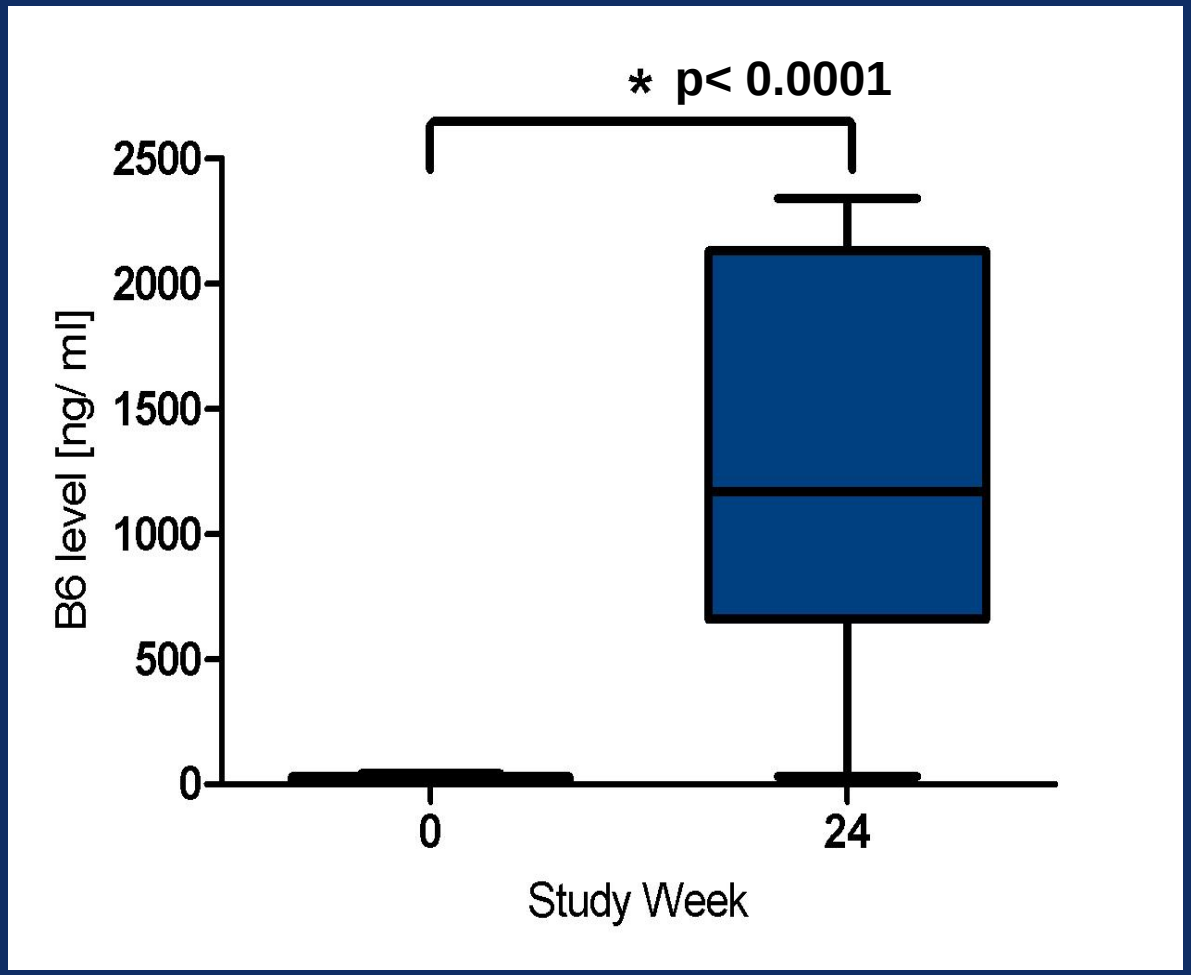
Results

Secondary objective: Vitamine B6 levels serum



B6 levels variable!

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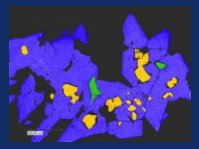

Results

Patient	5mg/kg	10mg/kg	15mg/kg	20mg/kg	Genotype
12	+	+			c.508G>A homoz.
06	+	+	+	+	c.508G>A homoz.
07	+	+	+	+	c.508G>A homoz.
09	+	+	+	+	c.508G>A heteroz.
03	+	+	+	-	c.508G>A heteroz.
11	+	+	+	-	c.508G>A heteroz.
01	+	+	+	+	c.508G>A heteroz.
02	-	-	-	-	c.508G>A heteroz.
08	-	-	+	+	c.508G>A negative
05	+	+	+	-	c.508G>A negative
10	-	-	-	-	c.508G>A negative
04	-	-	-	-	c.508G>A negative

Brothers!

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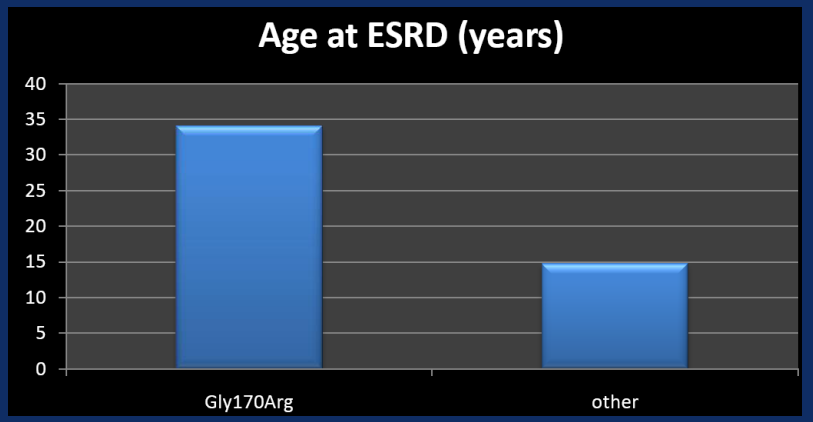
Outcome prediction (kidney function)

28% Gly170Arg
Phe152Ile

Pyridoxine reduces
Oxalate excretion

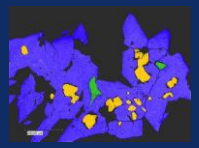
good:

AGXT gene mutations:



bad:

OXALEUROPE

German Hyperoxaluria Center 

Conclusions

- **Vitamine B6 reduces Uox in some patients with PH I**
- **No dose/response relationship detectable**
- **Reasonable dosage recommendations remain unclear**
- **No safety problem**

- **Further modifiers must be identified to realize an individual translational concept**

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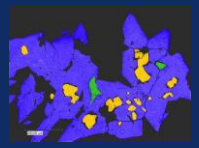

Treatment in normal kidney function

3. Alkaline citrate/Orthophosphate

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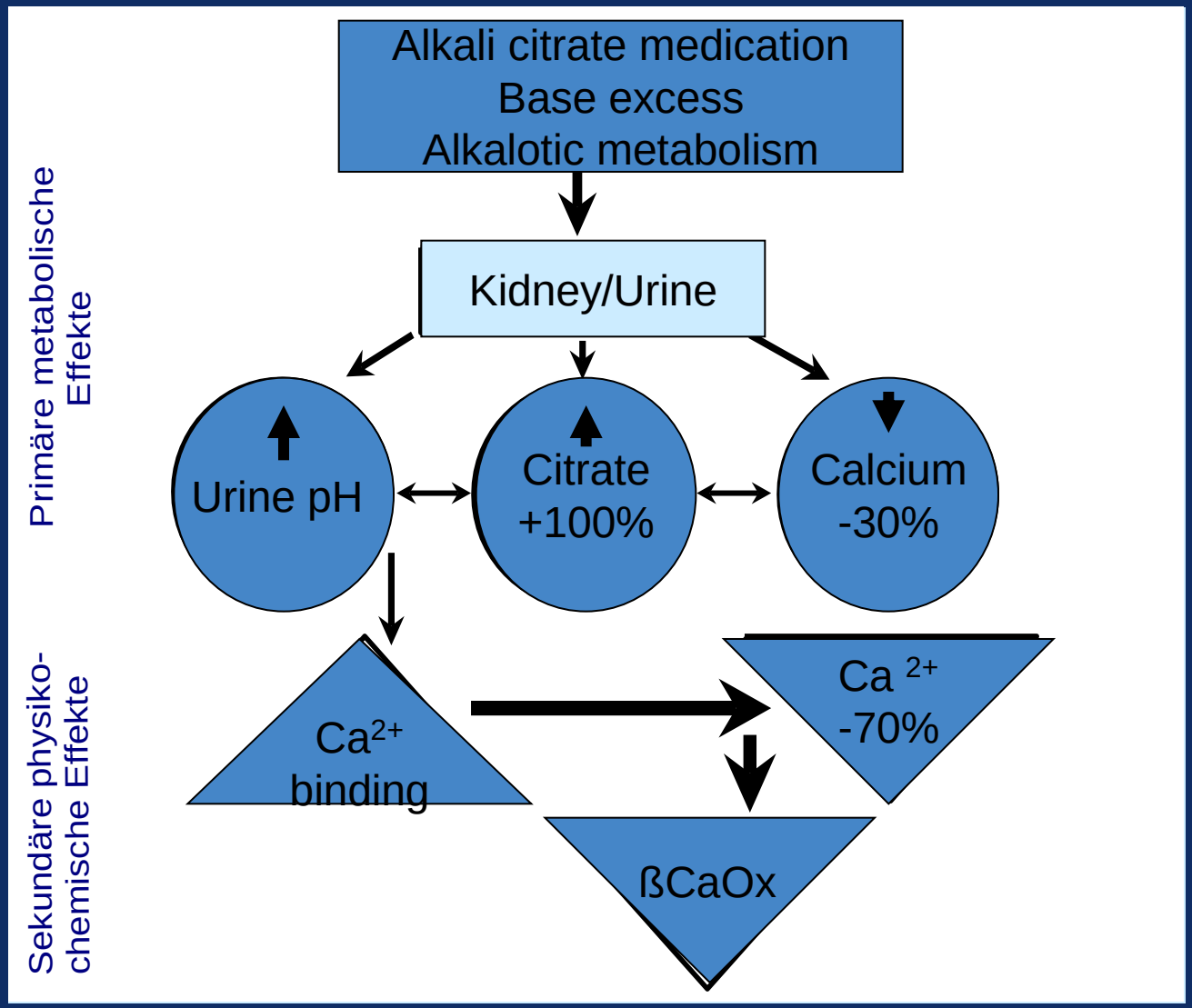
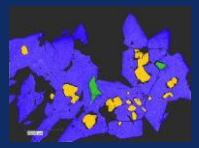
Background





Dosage?

- **Alkaline citrate**
  - **0.1-0.15g/kg body weight/d (or 1-1.5 meq/kg/d)**
- **Preparations**
  - **Bicitra**
  - **Shol‘s solution**

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Results?

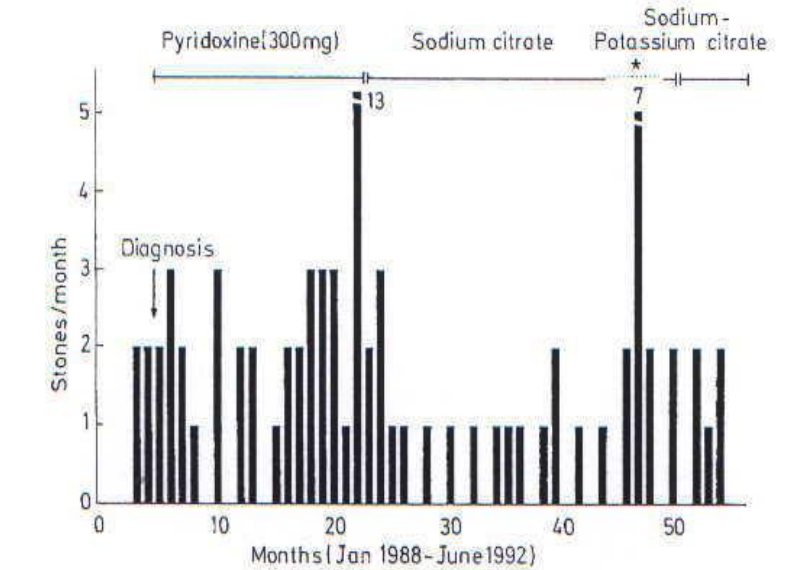
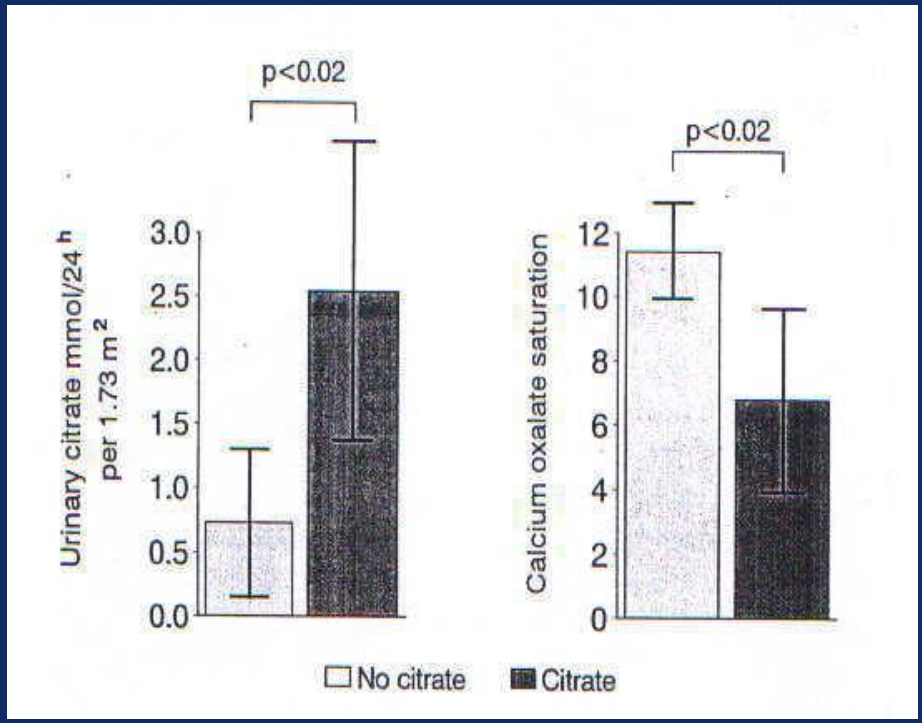
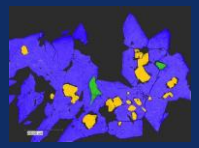
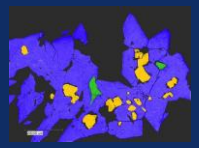


Fig. 1. Spontaneous passage of stones in patient no. 1 with primary hyperoxaluria type I without and during administration of alkali citrate. _*_, Non-compliance





Future treatment options



- **Oxalobacter formigenes**
  - **New phase III study starting 05/2013**
- **Small molecules (chaperones)**
  - **Studies/Research ongoing**
- **Hepatocyte transplantation**
  - **Performed in other metabolic diseases**
- **Gene/stem cell therapy**
  - **Performed in other metabolic diseases**

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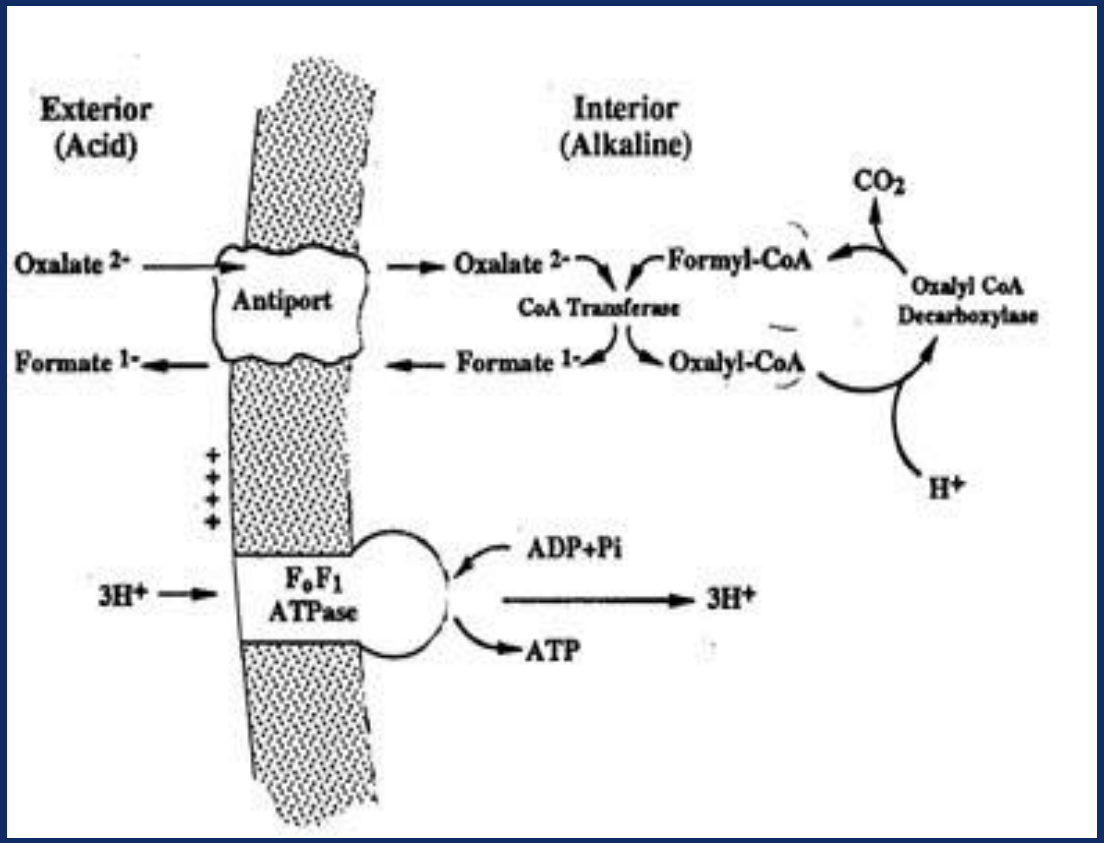
Oxalobacter formigenes (Oxf): Oxalate degrading enzymes

Oxf metabolises Oxalat to CO_2 + Formate



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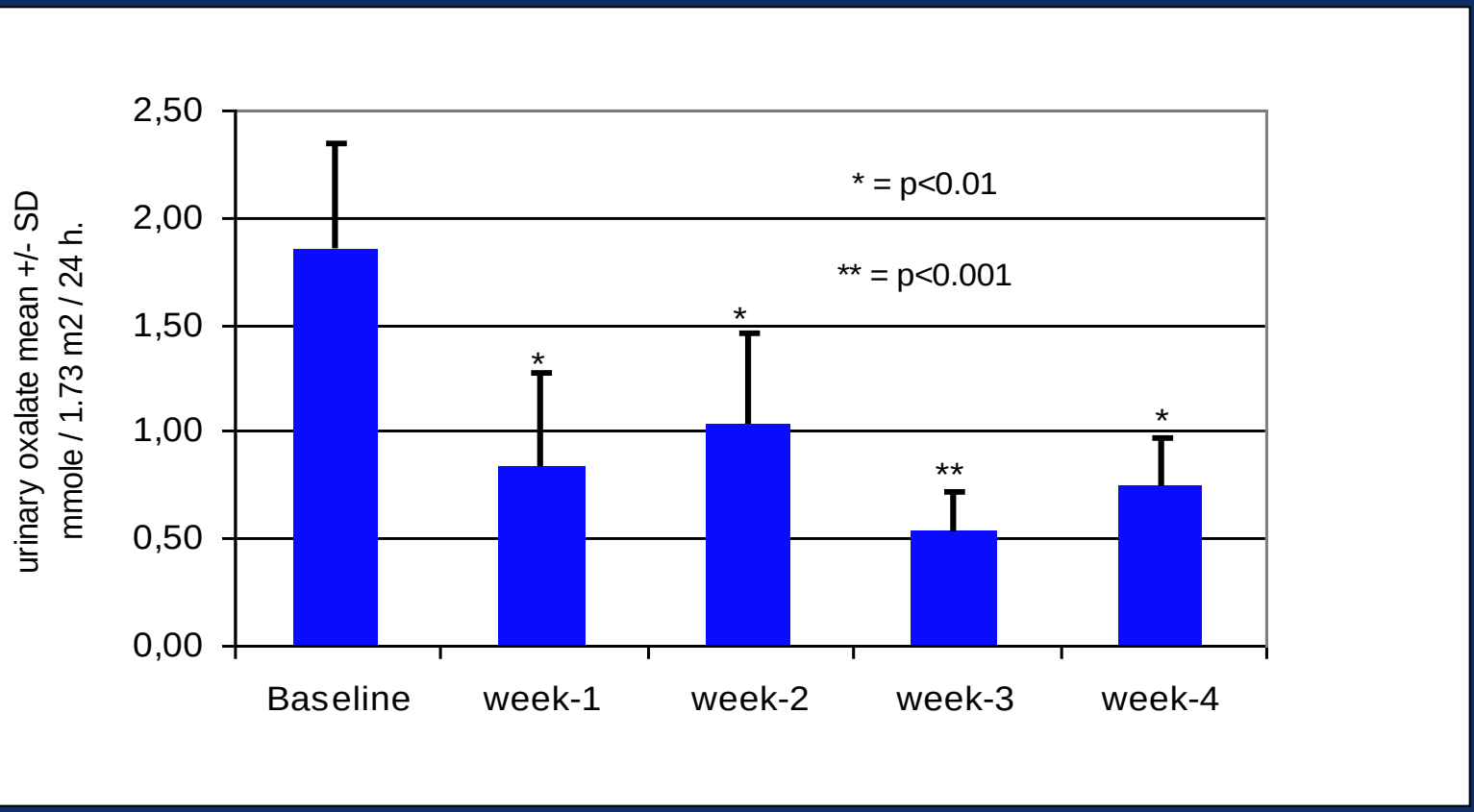
Urinary oxalate excretion of 7 PH patients with normal renal function under Oxalobacter formigenes treatment



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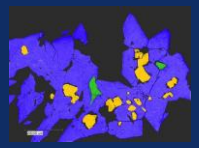

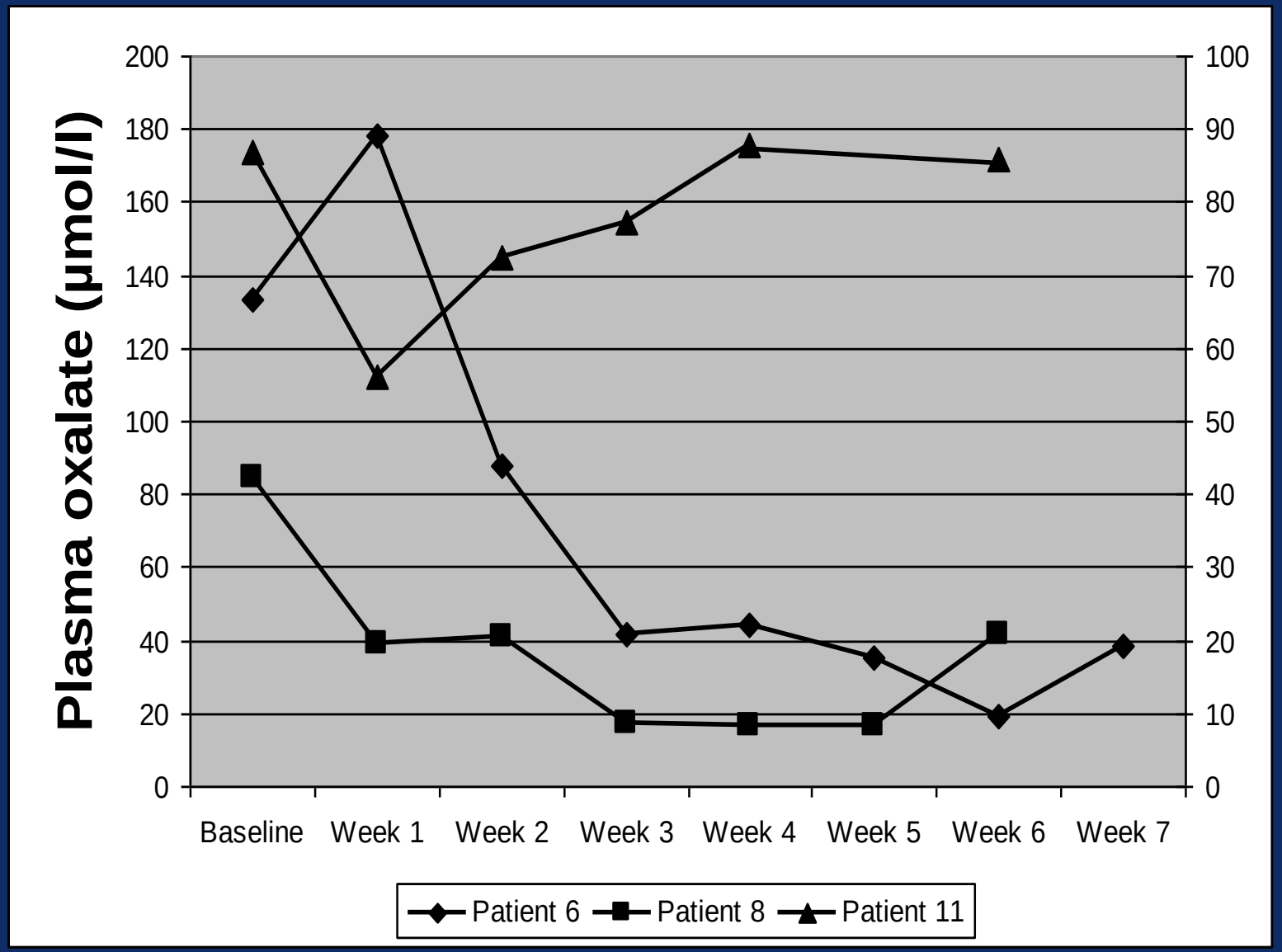

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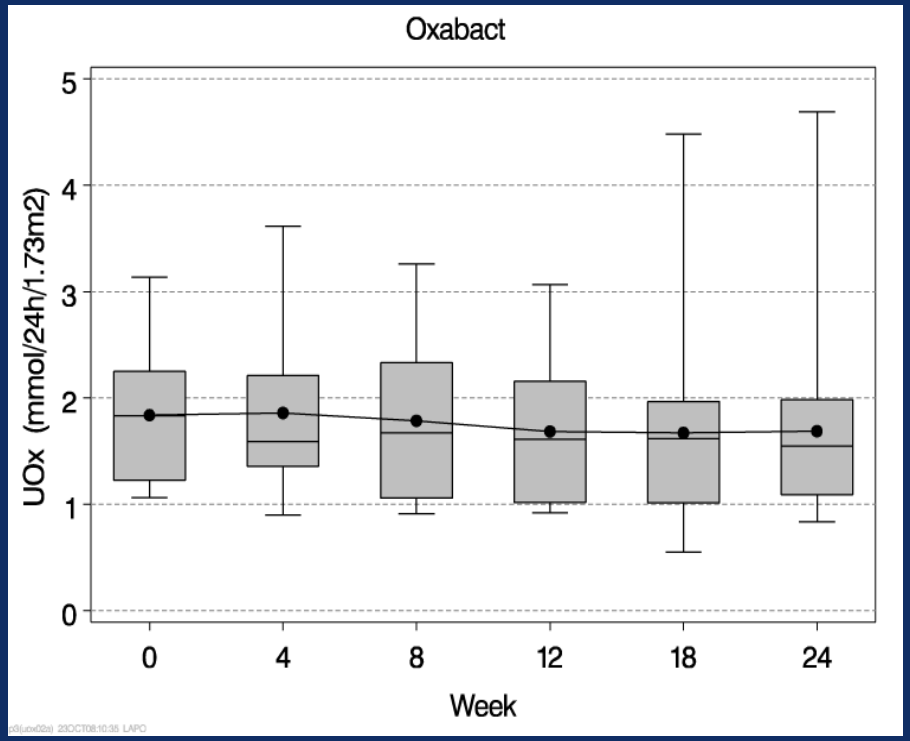
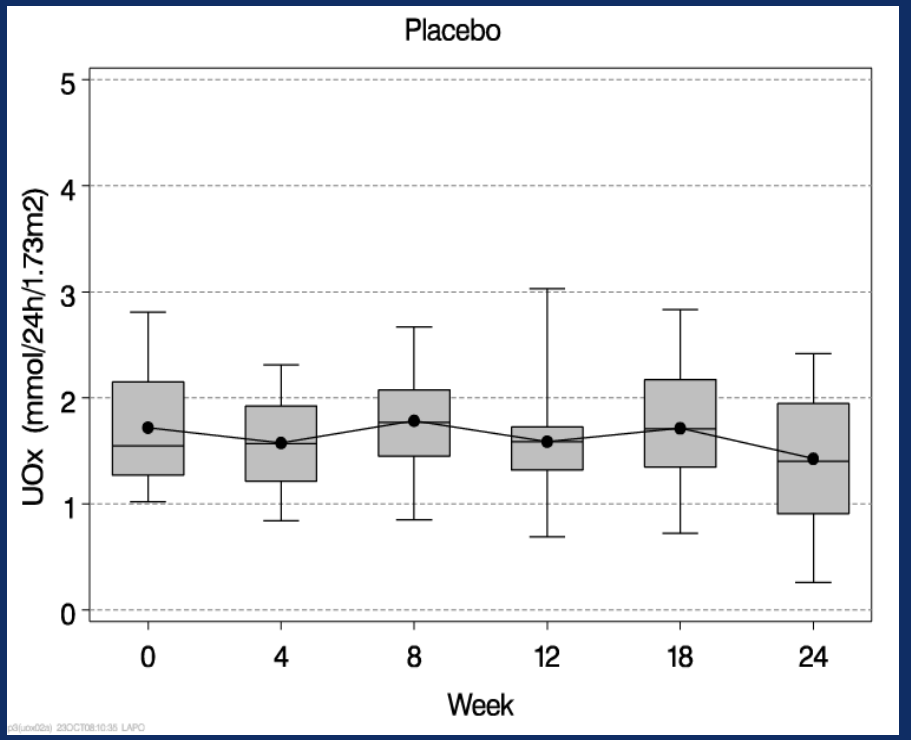
Phase III Oxalobacter Study

Urine oxalate (mmol/24h/1.73m²)
n = 42





Hoppe et al, NDT 2011

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- Drink as much as possible
- (Diet)
- Increase urine solubility
- Pyridoxine (in PH I)
- Hope for new treatment options