Primary Hyperoxaluria (PH)

- Three currently known types
  - PH I, PH II, PH III
- Autosomal-recessive inherited defects of the glyoxylate-metabolism in the liver
- Endogenous oxalate overproduction
- Clinical symptoms
  - Hematuria
  - Recurrent nephrolithiasis and/or nephrocalcinosis
  - Early end stage renal failure in PH I
  - Multisystemic disease

PH type III

- Defective Hydroxy-2-oxoglutarate aldolase 1
  - HOGA1, 10q24.1
  - Increased urinary oxalate and HOG
- Severe Urolithiasis
- Remission of symptoms despite hyperoxaluria
- No ESRD
**PH type II**
- Defective glyoxylate-reductase
  - GRHPR, 9p11
  - Not liver specific
  - Increased urinary oxalate and glycolate
  - Rec. urolithiasis
  - "benign" follow up
- 20% of patients with ESRF

**PH type I**
- Defective liver specific peroxisomal alanine-glyoxylate aminotransferase (AGT)
  - AGXT, 2q37.3
  - Recurrent calcium-oxalate stones, nephrocalcinosis
  - Systemic oxalosis, end-stage renal failure, death

**Clinical course PH I**
- Nephrocalcinosis
- Urolithiasis
- Systemic Oxalosis
- Heart
- Bone marrow
- Skin
- Eye
Infantile Oxalosis (PH I)

- Symptoms and/or diagnosis within the first 6 months of life
  - 83/688 patients in OxalEurope registry
- Rapid decline of kidney function over time

Follow up

- ESRD in 187 PH I patients
- Transplantation in 133 patients
  - 36 patients with isolated KTx (11 re Tx)
  - 22 isolated liver (3 re Tx, 1 twice re Tx)
  - 2 pre-emptive liver
  - 1 sequential liver/kidney
  - 62 combined liver kidney Tx
  - 9 re combined LKTx, 3 pat. 3 x LKTx

Outcomes

- Cumulative patient survival at ages 5, 10, 30, 50 and 65 years was 93%, 92%, 84%, 70% and 58.5%, respectively
- Patients with onset of ESRD at an early age had worse survival
There are no approved drugs for PH I, current treatments include:

- Vitamin B6, which increases catalytic activity of AGT enzyme in 10-30% of PH1 patients leading to a decrease in urinary oxalate
- Supportive measures: Hyperhydration, potassium citrate
- Dialysis, which is insufficient to clear oxalate as fast as it is produced by the liver
- Dual kidney and liver transplants, which is considered the only "curative" option

As early as in CKD 2 systemic oxalosis develops in PH I

Distinguish infantile oxalosis from other forms

Pre and peri-Transplant management needs to help avoid extreme systemic oxalate depositions

Correlation of $P_{Ox}$ and GFR in CRI

Hager et al, KI 1998
In 22 PH patients, conventional echo parameters as well as peak systolic global (6 myocardial segments) and segmental longitudinal strain (LS) from the apical 4-chamber view were analysed (EchoPac, GE).

GFR > 45 ml/min

Table: Longitudinal strain of patients and controls values in relation to renal function

<table>
<thead>
<tr>
<th>Segment</th>
<th>Patients</th>
<th>Controls</th>
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<tbody>
<tr>
<td>Septal basal</td>
<td>-18.8 ± 4.60</td>
<td>-19.71 ± 3.11</td>
<td>0.124</td>
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<tr>
<td>Lateral basal</td>
<td>-18.34 ± 4.86</td>
<td>-19.29 ± 1.38</td>
<td>0.723</td>
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<td>Septal apical</td>
<td>-17.79 ± 4.85</td>
<td>-20.46 ± 1.44</td>
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<tr>
<td>Lateral apical</td>
<td>-20.79 ± 4.85</td>
<td>-23.22 ± 1.44</td>
<td>0.019</td>
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<tr>
<td>Septal midventr.</td>
<td>-20.94 ± 2.79</td>
<td>-19.63 ± 0.92</td>
<td>0.177</td>
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<tr>
<td>Lateral midventr.</td>
<td>-20.44 ± 2.79</td>
<td>-19.63 ± 0.92</td>
<td>0.177</td>
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Effect of clinical status at time of transplant on outcome

PH1 Transplant Registry Report 1984-2002
Data available on 101 patients

Cumulative Survival

<table>
<thead>
<tr>
<th>Time post transplant (months)</th>
<th>Very good (n=9)</th>
<th>Fair (n=27)</th>
<th>Good (n=37)</th>
<th>Poor (n=28)</th>
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</table>
Effect of period on dialysis on survival

Conclusions

PH1 patients in CKD
- Are on great risk to develop systemic oxalosis
- May need early installment of supportive maintenance dialysis
  - Patient oriented clinical decision
  - Not related to GFR and Pox only
- Time on dialysis before transplantation should be as short as possible

How to dialyse?
- Which form of renal replacement therapy would best be able to sufficiently remove oxalate?
  - Endogenous production of 4-7 mmol/day
  - Elimination per routine dialysis 6-10 mmol/week
  - High Flux filter supposedly with better elimination
  - 5-6 x per week hemodialysis
  - In addition NIPD

Keep quality of life in mind!
Pre-and post HD POx levels in PH I and non-PH patients

Patients with Crohn's disease may have the same levels!
They may also develop systemic oxalosis!
Hoppe et al, KI 1998

Follow up of pre HD POx levels in PH I and non-PH patients

No sufficient oxalate removal over time
Hoppe et al, KI 1998
HD is more effective!

The daily solute elimination rate by CAPD in the non-PH group was 1.89 mmol/l per 1.73 m² by CAPD and 2.95 mmol/l per 1.73 m² by HD. In the PH group, the mean solute elimination rate was 2.19 mmol/l per 1.73 m² by CAPD and 3.77 mmol/l per 1.73 m² by HD. The daily solute elimination rate by the combination of PD and HD was 1.77 mmol/l per 1.73 m². These results suggest that the combination of PD and HD is more effective than HD alone.

Combination of PD and HD
Conclusions

| Short dialysis sessions with higher pre HD(F) Pox lead to better elimination rates
| High flux filter
| Highest surface area possible
| Highest blood flow rate
| PD over night recommendable as early Pox rebound 3-4 hours after HD
19 year old patient, 12 months Pox follow up
HD 3 x 4 h since GFR < 40 ml/min
Urine production: 1500 ml, Uox excretion 0.25 mmol/1.73 m2/d
Reduction: 90 % FX 60, 82 % CorDiax FX 60

Pox follow up, 12 months HD, 22 year old PH I patient, c.508 and c.847-3C>G mutation, no urine, no compliance to B6 medication
Regimen: 6 x 4-5 h, FX 60
Reduction 85.2 % FX 60 vs 87.6 % CorDiax FX 60

Pox in a PH I patient with c.33_34insC mutation
post dilution HDF since 3 months, 5 x 4 h, FX 80

Pox rebound supports combination of PD and HD
Follow up in 18 months old PH I patient CAPD, then HD+CAPD later 6 x/Week HD (BM 25, Fx Ped) post LTx (living related donation, father) HD reduction to 4 x /Week post KTx no further HD

Infantile Oxalosis

6 months old infant, AKF at age 4 months
Exon 3: c.423+1G>T (new splice donor mutation)
Exon 4: p.G156R; known, < 1% AGT activity

HDF 5 x per week 3.5 hours, FX Ped + 12 h NIPD

Patient from University Children's Hospital Zurich, Switzerland
Conclusions

No form or renal replacement therapy will remove sufficient amounts of oxalate
- Endogenous production 4-7 mmol/d
- Elimination per routine dialysis 6-10 mmol/Week
- High Flux Filter with better elimination rates
- 5-6 x per week HD, best 3 hours per session
- In addition NIPD

Conclusions

A maximum of dialysis is necessary to help the patients
- Diagnosis is often delayed and systemic oxalosis is frequently so overt, that even rigid dialysis does not provide adequate care
- Here only rapid, sequential liver and then kidney transplantation are currently helpful!

Outlook

RNA interference treatment
- RNA targets the "genetic instructions" which make protein
- RNA "translation" into proteins
- Glycerol
- Monophosphate
- Glucose
- Oxaloacetate
- Dihydroxyacetone
- Intermediary metabolism
- Oxidation
- RNAi therapy
- RNAi targets the "genetic instructions" which make protein
- RNA "translation" into proteins
- Protein synthesis
- Intracellular protein
- Extracellular protein
- Receptor
Preclinical PH mouse model

- AGXT−/− mice with a significant effect of 0.3 mg/kg DCR-1171X in comparison to controls
  - Reduction of Uox to normal levels after 3 infusions
  - Increase in glycolate (as biomarker)

Preclinical mouse model

- AGXT−/− mice were fed with 0.7% ethylene glycol to induce crystal deposition in kidneys
- DCR-1171X treatment avoided these depositions