PH: Current and future treatment options
History...

1927. Lepoutre M. *Journal d’Urologie Médicale et Chirurgicale* 20: 424
*Calculs multiples chez un enfant ; infiltration du parenchyme rénal par des dépôts cristallins*

The metabolic error in primary hyperoxaluria: $\alpha$-cetoglutarate-glyoxylate-carboligase deficiency

Failure of: Calcium carbimide, Disulfiran, Glutamic acid, Allopurinol, Malonic acid, Pyridoxin
Benefit of: Magnesium hydroxyde, Sodium phosphate, Low calcium diet
Frequent recurrence after kidney transplantation...

Primary hyperoxaluria (type I): attempted treatment by combined hepatic and renal transplantation
Interestingly... (1)

The action of pyridoxine in primary hyperoxaluria

Failure of: Calcium carbimide, Disulfiran, Glutamic acid, Allopurinol, Malonic acid, **Pyridoxin**
Benefit of: Magnesium hydroxyde, Sodium phosphate, Low calcium diet
Frequent recurrence after kidney transplantation...

2013. **Pyridoxin responsiveness depends on genotype!**
Interestingly... (2)

The metabolic error in primary hyperoxaluria: α-cetoglutarate-glyoxylate-carboligase deficiency

Primary hyperoxaluria (type I): attempted treatment by combined hepatic and renal transplantation

Liver peroxisomal alanine:glyoxylate aminotransferase deficiency in primary hyperoxaluria type I
More recently...

The gene encoding hydroxypyruvate reductase (GRHPR) is mutated in patients with primary hyperoxaluria type II

*Hum Mol Gen* 8: 2063-9

Mutations in DHDPSL are responsible for primary hyperoxaluria type III.

*Am J Hum Genet* 87: 392-9
**Representation of the AGT 3D structure**

**PH1**

1:120,000 live births

Ca Ox monohydrated

Uox < 0.7 mmol/1.73 m² per day

*Cellini Biochim Biophys Acta 2011*
Primary hyperoxaluria Type 1: indications for screening and guidance for diagnosis and treatment

Pierre Cochat¹, Sally-Anne Hulton², Cécile Acquaviva³, Christopher J. Danpure⁴, Michel Daudon⁵, Mario De Marchi⁶, Sonia Fargue⁴, Jaap Groothoff⁷, Jérôme Harambat⁸, Bernd Hoppe⁹, Neville V. Jamieson¹⁰, Markus J. Kemper¹¹, Giorgia Mandrile⁶, Martino Marangella¹², Stefano Picca¹³, Gill Rumsby¹⁴, Eduardo Salido¹⁵, Michael Straub¹⁶ and Christiaan S. van Woerden⁷; on behalf of OxalEurope (http://www.oxaleurope.com/)
Conservative treatment

As soon as a diagnosis of PH1 has been suggested

- **High fluid intake** $\geq 3 \text{ L/m}^2 \text{ per 24 h}
- **Tube feeding** for adequate hydration in infants
- **Vitamin B6 (pyridoxine)** in any patients with proven PH1
  - Starting at a dose of 5 mg/kg per day
  - Not exceeding 20 mg/kg per day
  - Aiming to decrease Uox by $< 30\%$

- **Calcium oxalate crystallization inhibition**
  - Alkalization with oral potassium citrate
  - 0.10–0.15 g/kg BW per day as long as GFR is preserved

- **No special dietary interventions in the absence of CKD**
Early conservative measures
[Hydration – vitamin B6 – citrate]

- N= 27
- Age at start: 4.1 yrs
- Follow-up: 7.7 yrs

GFR at start: 92 mL/min per 1.73 m²
Final GFR (N= 23, without ESRD): 110
- 19 pts: stable GFR
- 8 pts: progressive CKD
- 4 pts: progression to ESRD

N= 27
Age at start: 4.1 yrs
Follow-up: 7.7 yrs

Fargue Kidney Int 2009
Original Article

Efficacy and safety of *Oxalobacter formigenes* to reduce urinary oxalate in primary hyperoxaluria

Bernd Hoppe¹, Jaap W. Groothoff², Sally-Anne Hultön³, Pierre Cochat⁴, Patrick Niaudet⁵, Markus J. Kemper⁶, George Deschênes⁷, Robert Unwin⁸ and Dawn Milliner⁹
Surgical management of urolithiases

- **Avoid any kind of surgical intervention** in patients with uncomplicated urinary stone disease, except when there is obstruction, infection or multiple urolithiasis.

- **Endoscopic procedure is the preferred strategy** in patients who require intervention.
RRT: unadjusted 5-year patient survival
Dialysis procedures

- Avoid any form of dialysis and consider pre-emptive Tx

- High efficacy dialysis when pre-emptive Tx is not an option
  - Daily HD
  - Nocturnal dialysis
  - Combination of HD and PD

- Avoid dialysis in the early postoperative Tx

- HD/F for oxalate clearance during and after organ Tx in patients with systemic involvement and/or insufficient urine outflow in the early post-Tx period
Transplantation strategy

- Plan preemptive organ Tx at CKD Stage 3b to avoid the complications of systemic oxalosis

- Avoid isolated kidney Tx unless there is no other option

- Combined liver–kidney Tx is recommended in most patients, either simultaneously or sequentially

- Avoid preemptive isolated liver Tx unless in very well-defined and selected patients
Unadjusted 5-year kidney graft survival
PH1 among indications of combined liver-kidney Tx

Table 4. Reported indications for combined liver kidney transplantation (CLKTx) in 1007 cases

<table>
<thead>
<tr>
<th>Indications for CLKTx</th>
<th>No. of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperoxularia Type 1</td>
<td>430</td>
<td>42.7</td>
</tr>
<tr>
<td>Liver cirrhosis + chronic renal failure</td>
<td>237</td>
<td>23.5</td>
</tr>
<tr>
<td>Polycystic kidney and liver diseases</td>
<td>156</td>
<td>15.5</td>
</tr>
<tr>
<td>Liver cirrhosis + hepatorenal syndrome</td>
<td>72</td>
<td>7.1</td>
</tr>
<tr>
<td>Unspecified end-stage insufficiency of both organs</td>
<td>60</td>
<td>6</td>
</tr>
<tr>
<td>Viral cirrhosis + cyclosporine A nephrotoxicity</td>
<td>19</td>
<td>1.9</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>9</td>
<td>0.9</td>
</tr>
<tr>
<td>Congenital hepatic fibrosis + polycystic kidney disease</td>
<td>7</td>
<td>0.7</td>
</tr>
<tr>
<td>α1 antitrypsin deficiency + chronic glomerulonephritis</td>
<td>6</td>
<td>0.6</td>
</tr>
<tr>
<td>Caroli's disease</td>
<td>5</td>
<td>0.5</td>
</tr>
<tr>
<td>Liver graft rejection + unknown end-stage renal insufficiency</td>
<td>2</td>
<td>0.2</td>
</tr>
<tr>
<td>Viral cirrhosis + polycystic kidney disease</td>
<td>2</td>
<td>0.2</td>
</tr>
<tr>
<td>Primary sclerosing cholangitis + interstitial nephritis</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>Cystinosis</td>
<td>1</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Table 5. Reported post-operative complications after combined liver kidney transplantation (CLKTx)

<table>
<thead>
<tr>
<th>Complications after CLKTx</th>
<th>No. of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>86</td>
<td>27.5</td>
</tr>
<tr>
<td>Bleeding</td>
<td>39</td>
<td>12.5</td>
</tr>
<tr>
<td>Biliary complications</td>
<td>38</td>
<td>12.2</td>
</tr>
<tr>
<td>Re-LTx</td>
<td>38</td>
<td>12.2</td>
</tr>
<tr>
<td>Acute thrombosis of the hepatic artery</td>
<td>28</td>
<td>8.9</td>
</tr>
<tr>
<td>Relapse of the underlying disease</td>
<td>22</td>
<td>7.1</td>
</tr>
<tr>
<td>Re-KTx</td>
<td>13</td>
<td>4.2</td>
</tr>
<tr>
<td>Intestinal perforation</td>
<td>7</td>
<td>2.3</td>
</tr>
<tr>
<td>Urologic complications</td>
<td>0</td>
<td>1.9</td>
</tr>
<tr>
<td>Renal failure</td>
<td>5</td>
<td>1.6</td>
</tr>
<tr>
<td>Others</td>
<td>29</td>
<td>9.6</td>
</tr>
</tbody>
</table>
Preemptive liver Tx can arrest GFR deterioration

But...
# Suggested Tx options

*according to residual GFR, systemic involvement and local facilities*

<table>
<thead>
<tr>
<th>Tx strategy</th>
<th>Simultaneous liver + kidney</th>
<th>Sequential liver–kidney</th>
<th>Isolated kidney</th>
<th>Isolated liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD Stage 3 (30 &lt; GFR &lt; 59)</td>
<td>Red</td>
<td>Green</td>
<td>Red</td>
<td>Yellow</td>
</tr>
<tr>
<td>CKD Stage 4 (15 &lt; GFR &lt; 29)</td>
<td></td>
<td></td>
<td>Red</td>
<td>Yellow</td>
</tr>
<tr>
<td>CKD Stage 5 (GFR &lt; 15)</td>
<td></td>
<td></td>
<td>Red</td>
<td>Yellow</td>
</tr>
<tr>
<td>Infantile form (ESRD &lt; 2 years)</td>
<td></td>
<td></td>
<td>Red</td>
<td>Yellow</td>
</tr>
</tbody>
</table>

**HD strategy**

- Perop + postop according to POx and GFR
- Standard HD following liver Tx aiming at POx < 20 µmol/L
- Preop + perop
- Sometimes peroperative
But strategy should be adapted to individuals... (1)

30 year-old patient from C Hiesse, Paris

Tunisian female, born 1983
History of nephrolithiasis
- 1991 Diagnosis of PH
  Homozygous I244T AGXT mutation
- 2003 CKD stage 4
- 2013 Symptom-free
  No systemic oxalosis (eye, bone, etc.)
  No nephrocalcinosis
  Pox: 13 to 31 µmol/L

Options
- Combined liver-kidney Tx?
- Isolated kidney Tx?
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Options

- Combined liver-kidney Tx
- Isolated kidney Tx
But strategy should be adapted to individuals... (2)

Surg Today
DOI 10.1007/s00595-012-0310-x

CASE REPORT

An adult with primary hyperoxaluria type 1 regrets not receiving preemptive liver transplantation during childhood: report of a case

Tomohide Hori · Toshimi Kaido · Nobuyuki Tamaki · Yasuko Toshimitsu · Kohei Ogawa · Shinji Uemoto
But strategy should be adapted to individuals... (3)

Email, to-day 08:12
J vande Walle, Gent

“Dear Pierre,
Two days ago a child of 2 months, 4 kg, entered the hospital without clinical history... until the 2 days before (vomiting) with a creatinine of 530 µmol/L, oliguria, white kidneys. Diagnosis: hyperoxaluria.
What would be your treatment strategy in the first year?
Thanks,
Johan”
But strategy should be adapted to individuals... (3)

08:34

“Dear Johan,

In case of pyridoxine responsiveness, I suggest to give IV B6 and citrate for 1 or 2 weeks (same dose as oral) to provoke some degree of recovery. But you should start as early as to-day! Then you may adapt to genotype...

Otherwise you will have to start intensive PD, and even try HD.

Tx will depend on local facilities but can be considered early, sequential or synchronous...

Good luck...

Best,

Pierre”
## Therapeutic goals

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Conservative</th>
<th>Dialysis</th>
<th>Transplantation</th>
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<tr>
<td><strong>Urine oxalate</strong></td>
<td>$&lt; 0.4$ mmol/L</td>
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<tr>
<td></td>
<td>B6 response if $\downarrow$ 30%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Plasma oxalate</strong></td>
<td>---</td>
<td>$&lt; 40-50$ µmol/L</td>
<td>$&lt; 20$ mmol/L</td>
</tr>
<tr>
<td><strong>Urine calcium</strong></td>
<td>$&lt; 4$ mmol/L</td>
<td></td>
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</tr>
<tr>
<td><strong>Urine crystal volume</strong></td>
<td>$&lt; 200$ /mm$^3$</td>
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PH2

- Phenotype
  - Can mimic PH1
  - Usually less severe

- Higher incidence in Asians

- No rational for using pyridoxin nor other enzyme booster

- No rationale for combined liver-kidney Tx
PH3

- Phenotype
  - Sometimes limited to predisposition to stone formation
  - No ESRD reported so far

- No specific population

- No rationale for using pyridoxin nor other enzyme booster
Future options for diagnosis

- Urine phenotyping using ‘omics’

- Preimplantation diagnosis

- Screening program in countries with a high rate of PH

- Noninvasive assessment of systemic oxalosis
  - Bone imaging (HRpQCT)
  - Cutaneous blood flow assessment using pressure-induced vasodilation
Future options for treatment - 1

- New trial with *Oxalobacter formigenes*

- Aluminum citrate to prevent oxalate-induced tubular injury

- IL-1β blockade to prevent inflammasome damage induced by nephrocalcinosis
Future options for treatment - 2

Animal models for PH1, PH2, PH3
The problem in PH is not the lack of enzyme *per se* but the accumulation of precursors requiring sufficient replacement to overcome residual enzyme inactivity.

- **Cell [hepatocyte transplantation] therapy**

  Jiang *Transplantation* 2008
  Beck *Nephrol Dial Transplant* 2012

- **Somatic gene therapy using adenovirus-associated vector**

  2013 *OXALgTHER* Project

- **Identification of chaperones to restore correct protein folding may be applicable to some genotypes**

  Hopper *J Biol Chem* 2008
Conclusions

- 2 priorities:
  - Identification of PH type
  - Early conservative measures

- Management of PH requires technical and ethical resources

- Reference to large databases is a cornerstone

- Various treatment options may help in the future
Thank you for your attention!