Aspects of Combined Pediatric Liver-Kidney Transplantation

September 28, 2012

Jessica Brennan CPNP
Phil Rosenthal MD
Susan Stritzel Diaz CPNP
Objectives

- Review indications for combined liver/kidney transplant
- Review the pre-transplant evaluation and the UNOS waitlist process.
- Describe the disease, diagnosis and management of primary hyperoxaluria
UCSF Pediatric Transplant Program

- Pediatric Kidney Transplant program established 1966
- Pediatric Liver Transplant program established 1988

<table>
<thead>
<tr>
<th></th>
<th>Kidney</th>
<th>Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOTAL TRANSPLANTS</td>
<td>&gt;8000</td>
<td>&gt;2000</td>
</tr>
<tr>
<td>Living donors</td>
<td>&gt;2800</td>
<td>&gt;230</td>
</tr>
</tbody>
</table>

Includes children & adults
One Year Adjusted Patient Survival by Year of Transplantation

Source: SRTR Analysis, Data as of May 2009.
Diagnoses Eligible for Liver Transplant

- *Biliary Atresia*
- Alagille’s syndrome
- Familial cholestasis
- Primary sclerosing cholangitis
- Crytogenic cirrhosis
- Chronic HBV and HCV
- FHF
- AIH
- A1AT
- Wilson’s Disease
- Tyrosinemia
- *Urea Cycle Defects*
- **combined liver/kidney tx**
- GSD
- **Primary Hyperoxaluria Type 1**
- **ARPKD**
- Crigler-Najjar syndrome type 1
- CF
- Neimann-Pick Disease
- Familial amyloidosis
- HCC
- *Hepatoblastoma*
- Budd Chiari syndrome
- PVT
Causes of CKD Stages 2-4 in CKiD Children

- Glomerular: 20%
- Obstruction/Reflux: 38%
- Other Non-Glomerular: 20%
- Hypoplasia/Dysplasia: 18%
- Other Glomerular: 10%
- FSGS: 7%
- HUS: 3%
- Cystic Disease: 4%
Indications for Combined Liver-Kidney Transplant

Pediatrics:
• Autosomal recessive polycystic kidney disease
• Atypical HUS
• Primary hyperoxaluria

Adults:
• Familial amyloidotic polyneuropathy
• Amyloidosis,
• Primary hyperoxaluria
## Contraindications to Transplant

### Relative
- Compliance
- Lack of social support
- Cardiovascular disease

### Absolute
- Malignancy
- Sepsis unresponsive to treatment
- Current Substance Abuse
- Coma with evidence of irreversible brain injury
- No or inadequate social support
- Lack of health insurance or insurability
- BMI > 50 (liver)
- BMI > 38 (kidney)
# SRTR Data

## Multiple Organ Transplants Performed: Age & Gender


<table>
<thead>
<tr>
<th></th>
<th>All Ages</th>
<th>Pediatric</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Genders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Liver-Kidney</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transplants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>3,071</td>
<td>111</td>
<td>2,960</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>1,684</td>
<td>119</td>
<td>1,565</td>
</tr>
</tbody>
</table>

Based on OPTN data as of September 14, 2012
The Liver/Kidney Transplant Evaluation

- HLA+ Pra+ 2 ABO’s
- Transplant surgeon
- Hepatologist
- Nephrologist
- Transplant PNP
- Nutritionist
- Social Worker

- Radiology
- Echocardiogram
- Child Life Specialist
- Financial counselor
- Anesthesiologist
- Additional consults as indicated
Pre Transplant Management

- Collaboration with primary care provider (PCP)
  - Immunizations
  - Dental
- Monitor growth and development
- Optimize Nutritional Status
- Medically manage disease
- Dialysis

- Transplant Education
- Ongoing child/family support
- Collaboration with other specialties: Nephrology and dialysis center
Transplant Selection Committee

- Multidisciplinary team review prior to listing
- Required for transplant insurance authorization
- CMS requirement
- Identify indications for transplant
- Identify contraindications for transplant
  - Medical/Surgical
  - Social
- Assess options for living or cadaveric donation
- Determine when/if to list for transplant
Activation for Transplant

- Secure insurance authorization
- Cell phone availability
- Activation
  - UNOS organ distribution
  - Listing criteria
  - Status 1A/1B
  - PELD/MELD
United Network for Organ Sharing (UNOS)

• Assist in placing donated organs for transplantation

• Assist in gathering donor information and running the donor/recipient computer matching process

• Assist with transportation of organs and tissues for the purposes of transplantation

• Act as a resource to the transplant community regarding organ-sharing policies
UNOS Regional Map
### What’s The Score?

<table>
<thead>
<tr>
<th>MELD</th>
<th>PELD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model for End Stage Liver Disease</strong></td>
<td><strong>Pediatric End Stage Liver Disease</strong></td>
</tr>
<tr>
<td>12 years+</td>
<td>0-&lt;12 years</td>
</tr>
<tr>
<td># 6-40</td>
<td>Negative number- 99</td>
</tr>
<tr>
<td>Bili, INR, Cr, dialysis 2x/wk</td>
<td>Bili, INR, alb, Na, age, growth</td>
</tr>
<tr>
<td><strong>Status 1A</strong></td>
<td><strong>Status 1A and 1B</strong></td>
</tr>
<tr>
<td><strong>MELD/PELD in effect since 2002</strong></td>
<td></td>
</tr>
</tbody>
</table>
Use of Waiting Time

- Only used as a tie breaker for same blood type and same MELD/PELD score
- Waiting time is carried backward and not forward
  - When patient moves to a higher MELD/PELD score, new waiting time clock starts
  - If patient moves to a lower MELD/PELD score time accumulated at higher score or Status 1 is included
Liver Candidates Exceptional Cases

- Exception points awarded at time of listing for certain diagnosis:
  - Hepatopulmonary Syndrome
  - Cystic Fibrosis
  - Cholagioicarcinoma
  - Familial Amyloid Polyneuropathy
  - *Primary Hyperoxaluria*
  - Portopulmonary Syndrome
- There is no exception to Status 1A or 1B criteria
- Requires prospective review by the Regional Review Board
- Center will request specific MELD/PELD score and submit supportive narrative
- Regional Review Board accepts or rejects request

-If rejected can request conference call
Status 1A

- **Fulminant Hepatic Failure**
  - Onset of hepatic encephalopathy within 8 weeks of the first symptoms of liver disease
  - Absence of pre-existing liver disease
- **Primary Non-function (PNF) of a transplanted liver within 7 days**
- **Hepatic Artery Thrombosis (HAT)**
- **Acute Decompensated Wilson’s Disease**
Status 1B

- Chronic Liver Failure
  - Calculated MELD/PELD score >25 and meets specific criteria defined by UNOS
- Hepatoblastoma
  - Objective response to chemotherapy
  - Confined to the liver
Primary Hyperoxaluria
Classification of Primary Hyperoxaluria (PH)

- **PH Type I**
  - Autosomal recessive disorder
  - Mutation in alanine: glyoxylate aminotransferase (AGXT) gene
  - Accounts for 80% of PH
- **PH Type II**
  - Autosomal recessive disorder
  - Mutation in glyoxylate reductase/hydroxypyruvate reductase (GRHPR) gene
  - Accounts for 15% of PH
- **Non-PH I, Non-PH II**
  - Gene?
  - Diagnosis of exclusion
  - Accounts for 5% of PH
- **PH Type III**
  - DHDPSL gene encoding 4-hydroxy-2-oxoglutarate aldolase
  - Likely be further types described
Pathogenesis of PH Type I and II

Type I

Type II

Pyruvate → Alanine → Glyoxylate

Glycinase (DAO)

Glycolate → Glyoxylate

GRHPR

LDH

Oxalate → Oxalate

CaOx stones

Danpure, Biochimica et Biophysica Acta (2006) 1776–1784
Oxalate Synthesis and Metabolism

Gut
- Plants
- Meat (collagen)

Liver
- Glycolate → Glycolate → Glyoxylate
- Glycine → Glyoxylate
- Glycolate → Glyoxylate

Kidney
- Oxalate → Oxalate
- Glycolate
- CaOx kidney stones

Figure showing the pathways of oxalate synthesis and metabolism.

Danpure, Biochimica et Biophysica Acta (2006) 1776–1784
## Primary Hyperoxaluria - Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Type I</th>
<th>Type II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crystalluria</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Urine oxalate</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Urine glycolate</td>
<td>↑</td>
<td>normal</td>
</tr>
<tr>
<td>Urine L-glycerate</td>
<td>normal</td>
<td>↑</td>
</tr>
<tr>
<td>Plasma oxalate*</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>DNA sequencing</td>
<td>AGXT</td>
<td>GRHPR</td>
</tr>
<tr>
<td>Liver biopsy</td>
<td>↓AGT</td>
<td>↓GRHPR</td>
</tr>
</tbody>
</table>

*GFR < 40 ml/min/1.73m²
Primary Hyperoxaluria - Diagnosis

- Crystalluria
- High urine oxalate (type I & II)
- High urine glycolate (type I)
- High urine L-glycerate (type II)
- Plasma oxalate (type I & II, when GFR < 40 ml/min/1.73 m²)
- DNA sequencing (AGXT- type I, GRHPR- type II)
- Decreased alanine:glyoxylate aminotransferase (AGT) activity in liver tissue (type I)
- Decreased glyoxylate reductase/hydroxypyruvate reductase GRHPR activity in liver tissue (type II)
Primary Hyperoxaluria-Type II

- **Age**
  - Early childhood

- **Clinical features**
  - urolithiasis (less stone burden), nephrolithiasis (uncommon), systemic oxalosis, and renal failure (rare)

- **Diagnosis**
  - Increased urinary oxalate, glycerate excretion
  - GRHPR gene mutation analysis (15 mutations identified)

- **Treatment**
  - Stone management
  - Renal transplant only (Liver transplant does not correct hyperoxaluria)
PH Type I- Clinical Features

- **Age of onset**
  - Infantile form (severe)
  - Majority of patients present by 10 years
  - Rarely patients present between 30-50 years

- **Signs and Symptoms**
  - Recurrent urolithiasis
  - Nephrocalcinosis
  - Systemic oxalosis
  - ESRD

- **Time to ESRD**
  - Large intra, interfamilial heterogeneity
  - Usually between 25-45 years
Systemic Oxalosis in PH Type I

- GFR < 30-40 ml/min/1.73 m²
- Plasma oxalate level > 30 μmol/L
- Tissues: retina, skin, myocardium, vessel wall, bone and CNS
- Long term sequelae: visual disturbances, heart block, cardiomyopathy, cardiac conduction disturbance, vasculopathy, treatment resistant anemia, oxalate osteopathy

Stones in Hyperoxaluria

Whewellite Stones in PH type I

Oxalate Crystal in Hepatic Parenchyma

Tanriover, B. Kidney International (2010) 77, 651
PH Type I- Treatment

• **Reduce oxalate burden**
  – Pyridoxine (5-10 mg/kg/day)

• **Stones**
  – Prevention (citrate 100-150 mg/kg/day div TID, fluids 2-3 L/m²/day)
  – Rx (removal, stent)

• **Dialysis**
  – GFR < 30 ml/min/1.73 m²
  – Plasma oxalate > 30 μmol/L

• **Transplantation**
  – Combined liver kidney transplant
PH Type I- Dialysis

- Daily hemodialysis to keep up with oxalate generation rate.
- Aim for pre-HD plasma oxalate of < 30-50 μmol/L.
- If post-HD plasma oxalate < 10-15 μmol/L, then increasing HD duration is not beneficial.
- Add peritoneal dialysis if HD is insufficient and systemic oxalate burden is significant.
- Continue pyridoxine therapy while on dialysis if patient is a responder.
PH Type I- Transplantation

- Kidney transplant only is not recommended due to high recurrence of oxalosis.
- Combined liver kidney transplant is the standard of care.
- Peri-transplant Management:
  - Perform HD within 4 hours of surgery
  - Continue post-transplant HD starting POD ½ until plasma oxalate level < 10 μmol/L consistently
  - Maintain high fluid intake
PH Type I- Transplantation

- Patient and allograft survival rate at 5 years
  - 80% and 72%
- Risk factor for renal allograft failure from recurrence
  - Age < 5 years
  - Long period on dialysis (> 2 years)
- Pre-emptive transplant?
  - Controversial
Pediatric Cases of Primary Hyperoxaluria Type I at UCSF

• Post-transplant  5

• Pre-transplant  3
**SRTR data for 2012**

**Active waitlist for hyperoxaluria in the US**

| Oxalate Nephropathy (including primary oxalosis) | 73 |

http://optn.transplant.hrsa.gov/latestData/rptData.asp

Based on OPTN data as of September 14, 2012
The Case Study
History

- 5 m/o present in renal failure, biopsy performed.
- Initiated hemodialysis (HD) six times per week plus peritoneal dialysis.
- Plasma oxalate level pre-HD 96 μmol/L and post-HD 47.7 μmol/L.
- Gastrostomy tube placed
Pre-transplant Course

• Oxalate-induced retinopathy
• Echocardiogram
• ABO: O+, Pra negative
• Evaluated & approved for listing
• PELD score -10, appealed, awarded 40
• Wt 8.9 kg, (5th %ile) ht 70 cm (3rd %ile)
Peri-operative Course

• Combined deceased donor liver-kidney transplant at age 16 months
• Split liver- segments 2,3
• Primary closure of abdomen not achieved immediately due to size of the allografts
• Immunosuppression
  - Induction: thymoglobulin
  - Maintenance: tacrolimus, mycophenolate mofetil, prednisone
Oxalate Management

Post-transplant renal replacement therapy for oxalate removal:

- CVVH for 4 days post-op
- HD daily for 2 weeks, QOD HD for 1.5 weeks
Post-transplant

- At hospital discharge plasma oxalate level 19.8 μmol/L.
- **Five months** post-transplant, plasma oxalate level 13.6 μmol/L.
- **One year post-transplant**, serum creatinine increased to 0.7 mg/dl from baseline of 0.4 mg/dl.
Differential Diagnosis for ↑Creatinine

- Acute rejection
- Evolving chronicity (interstitial fibrosis and tubular atrophy)
- Infection (bacterial, BK virus, CMV, adenovirus)
- CNI nephrotoxicity
- Oxalate deposition
- Dehydration/ hypoperfusion
- Obstruction
Medications -1 year post

- Tacrolimus 0.9 mg PO BID
- Mycophenolate mofetil 200 mg PO BID
- Lansoprazole 15 mg PO daily
- Magnesium 65 mg elemental PO daily
- Bicitra 10 meq PO BID
- Aspirin 81 mg PO daily
- Trimethoprim/ sulfa 20 mg PO daily
- Nitrofurantoin 15 mg PO daily
Laboratory- 1 year post transplant

- Wbc 4.3, hgb 10.7, hct 30.9, plt 213
- Na 137, K 5.6, Cl 104, tCO₂ 24, BUN 36, Cr 0.7 (eGFR 46.4)
- Tacrolimus trough 6.9 µg/L
- Urinalysis SG ≤ 1.005, otherwise unremarkable
- PT 13.6, INR 1, PTT 24.7
- Urine oxalate: 266 mg/g creat (reference 3-40 mg/g creat)
Biopsy Findings

- Interstitial nephritis
- Interstitial fibrosis
- Oxalosis Crystals
- No evidence of rejection
Post Transplant Continued

1.5 years post-transplant:

• **Episode of acute cellular rejection.**

• **Developed BK nephropathy.**

• **Reflux into transplanted kidney.**
Today... 7 Years Post-transplant

• Persistent BK viruria. BK viremia resolved.
• Serum creatinine 1.3- mg/dl.
• Biopsy 7/2012
• Liver transplant continues to function well.
• Patient thriving
Graft Survival in PH Type I

![Graph showing graft survival over years since transplant](image)

Survival estimate (no. at risk)

<table>
<thead>
<tr>
<th></th>
<th>Years since transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>100 (32) 72 (23) 59 (19) 56 (17) 53 (14) 45 (12)</td>
</tr>
<tr>
<td>Kidney + Liver</td>
<td>100 (26) 95 (14) 95 (9) 95 (8) 71 (3) 71 (3)</td>
</tr>
</tbody>
</table>

P = 0.011

Milliner, AJT 2010; 10:1–9
Post-transplant Primary Hyperoxaluria Management in 2012:

- Post-op plasma oxalate levels.
- Daily hemodialysis post-op while hospitalized.
- 5-6 times/week outpatient hemodialysis after discharge.
- Hemodialysis discontinued when plasma oxalate levels < 10 μmol/L consistently.
- Aggressive fluid management.
Working with 2 services: When it’s good for the kidney and not for the liver...

- **FLUID MANAGEMENT** - walking a fine line
- **Portal congestion vs. renal protection**
- **Immunosuppression**
Cross-match Considerations: Do we care?

- Change to center guidelines.
- Long-term risk of antibody mediated rejection?
- Pra & single antigen data reviewed carefully.
- Single antigen testing performed every 3-6 months on active patients
Clinical Pearls Regarding Multi-organ Transplant

- Fine balance of fluids
- Institution of multi-disciplinary clinic
- Communication & collaboration!