PEDIATRIC LIVER TRANSPLANT FOR METABOLIC DISEASE

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George Mazariegos, MD

Hillman Center for Pediatric Transplantation
Children’s Hospital of Pittsburgh, Pittsburgh, PA.
Greetings from the Children’s Hospital of Pittsburgh
Objectives

- Discuss the current state of pediatric liver transplant
- Review indications and outcomes for Tx in IEM
- Compare decision making
  - TX for cure: MSUD
  - Tx for treatment: MMA, PA

Surgical Considerations

- Areas of focus and progress in liver transplant
  - Long term outcomes
  - Investigating Tolerance
Evaluation of the Pediatric Patient for Liver Transplantation: 2014 Practice Guideline by the American Association for the Study of Liver Diseases, American Society of Transplantation and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition

Robert H. Squires, Vicky Ng, Rene Romero, Udeme Ekong, Winita Hardikar, Sukru Emre, and George V. Mazariegos

Diagram:
- Biliary atresia
- Metabolic/Genetic
- Acute liver failure
- Tumor
- Cirrhosis
- Immune
- Other

- OPTN DATA
  - January 2011 through May 31, 2013

Hillman Center for Pediatric Transplantation

Children’s Hospital of Pittsburgh of UPMC
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When do we transplant?: Metabolic disease

Structural liver disease
  Tumor Risk

Extrahepatic manifestations:
  Neurologic
  Systemic (Cardiac, renal, etc)

Quality of Life

How do we time transplant to optimize these outcomes?
# Metabolic conditions with liver injury

## Metabolic defect mainly expressed in the liver
- Alpha-1-antitrypsin deficiency (PiZ)
- Tyrosinaemia type I
- BSEP deficiency
- MDR-3 deficiency
- Primary bile acid synthesis disorders
- Hepatic porphyrias
  - Acute intermittent porphyria
  - Variegate porphyria
- Glycogen storage disease type Ia
- Hereditary fructose intolerance
- Indian childhood cirrhosis
- Mucopolysaccharidoses

## Metabolic defect expressed in other organs or tissues
- Wilson disease
- Cystic fibrosis
- FIC-1 deficiency
- Glycogen storage disease types Ib, III and IV
- Non-alcoholic steatohepatitis
- Lysosomal storage diseases
- Gaucher disease
- Niemann-Pick disease
- Cholesterol ester storage disease
- Mitochondrial cytopathies
- Cerebrotendinous xanthomatosis
- Cytrin deficiency
- Congenital disorders of glycollisation (CGD)
- Galactosemia
- Erythropoietic porphyria

*From Molecular Genetics and Metabolism 111(2014):418-427*
# Metabolic conditions with no liver injury

<table>
<thead>
<tr>
<th>METABOLIC DEFECT MAINLY EXPRESSED IN THE LIVER</th>
<th>METABOLIC DEFECT EXPRESSED IN OTHER ORGANS OR TISSUES</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Crigler-Najjar syndrome type 1</td>
<td>• Citrulinaemia</td>
</tr>
<tr>
<td>• Primary hyperoxaluria</td>
<td>• Cystinosis</td>
</tr>
<tr>
<td>• Urea cycle disorders</td>
<td>• Branched amino acids disorders (organic acidemias)</td>
</tr>
<tr>
<td>• Familial hypercholesterolemia</td>
<td>- Propionic acidemia</td>
</tr>
<tr>
<td>• Fatty acid oxidation defects</td>
<td>- Methyl malonic acidemia</td>
</tr>
<tr>
<td>• Coagulation defects</td>
<td>- Mevalonic acidemia</td>
</tr>
<tr>
<td>- Haemophilia A</td>
<td>- Maple syrup urine disease</td>
</tr>
<tr>
<td>- Factor V and VII deficiency</td>
<td></td>
</tr>
<tr>
<td>- Protein C and S deficiencies</td>
<td></td>
</tr>
<tr>
<td>• Factor H deficiency</td>
<td></td>
</tr>
<tr>
<td>• Afibrinogenenaemia</td>
<td></td>
</tr>
<tr>
<td>• Amyloidosis type 1</td>
<td></td>
</tr>
</tbody>
</table>

*From Molecular Genetics and Metabolism 111(2014):418-427*
RISKS AND BENEFITS

**Medical management**
Natural history - phenotype
Frequency/severity of decompensations
Risks of end organ damage
Quality of life/adherence
Mortality

**Liver transplant**
Local organ availability
Surgical complications
Early mortality
Degree of metabolic correction
Life long immunosupression
Adherence

*Courtesy, D. Hadzic*
OUTCOMES: UNOS Pediatric patient and graft survival

Goh A; Terasaki Foundation Laboratory, Los Angeles, CA, USA. Clin Transpl. 2008:19-34; An analysis of liver transplant survival rates from the UNOS registry.
OUTCOMES: metabolic disease vs. chronic liver disease

UNOS, Kayler, 2003
<table>
<thead>
<tr>
<th>Metabolic disease (N = 446)</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea cycle defects</td>
<td>114</td>
<td>25.6</td>
</tr>
<tr>
<td>Alpha 1 antitrypsin deficiency</td>
<td>88</td>
<td>19.7</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>48</td>
<td>10.8</td>
</tr>
<tr>
<td>Wilson disease</td>
<td>34</td>
<td>7.6</td>
</tr>
<tr>
<td>Maple syrup urine disease</td>
<td>29</td>
<td>6.5</td>
</tr>
<tr>
<td>Tyrosinemia</td>
<td>33</td>
<td>7.4</td>
</tr>
<tr>
<td>Glycogen storage disease</td>
<td>23</td>
<td>5.2</td>
</tr>
<tr>
<td>Crigler-Najjar</td>
<td>21</td>
<td>4.7</td>
</tr>
<tr>
<td>Neonatal hemochromatosis</td>
<td>18</td>
<td>4.0</td>
</tr>
<tr>
<td>Primary hyperoxaluria</td>
<td>9</td>
<td>2.0</td>
</tr>
<tr>
<td>Inborn error in bile acid metabolism</td>
<td>3</td>
<td>0.7</td>
</tr>
<tr>
<td>Other metabolic disease</td>
<td>26</td>
<td>5.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-metabolic disease (N = 2551)</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biliary atresia</td>
<td>1214</td>
<td>47.6</td>
</tr>
<tr>
<td>Fulminant liver failure</td>
<td>421</td>
<td>16.5</td>
</tr>
<tr>
<td>Other cholestatic</td>
<td>386</td>
<td>15.1</td>
</tr>
<tr>
<td>Tumor</td>
<td>212</td>
<td>8.3</td>
</tr>
<tr>
<td>Other</td>
<td>318</td>
<td>12.5</td>
</tr>
</tbody>
</table>
Pediatric LTx, Metabolic and Non-metabolic liver disease

Patient Survival

Graft Survival

Fig. 1. Kaplan–Meier probability of survival after LTx for metabolic vs. non-metabolic liver disease.

Fig. 2. Kaplan–Meier probability of graft survival after LTx for metabolic vs. non-metabolic liver disease.

SPLIT, Arnon, 2010
<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Metabolic liver disease Number (%)</th>
<th>Non-metabolic liver disease Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>37 (100.0%)</td>
<td>302 (100.0%)</td>
</tr>
<tr>
<td>Multi-organ failure</td>
<td>10 (27.0)</td>
<td>40 (13.2)</td>
</tr>
<tr>
<td>Cardiopulmonary</td>
<td>11 (29.7)</td>
<td>32 (10.6)</td>
</tr>
<tr>
<td>Cerebral edema</td>
<td>0 (0)</td>
<td>21 (7.0)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>4 (10.8)</td>
<td>24 (7.9)</td>
</tr>
<tr>
<td>Primary non-function</td>
<td>3 (8.1)</td>
<td>13 (4.3)</td>
</tr>
<tr>
<td>Bacterial infection</td>
<td>0 (0)</td>
<td>21 (7.0)</td>
</tr>
<tr>
<td>Lymphoproliferative disease</td>
<td>2 (5.4)</td>
<td>10 (3.3)</td>
</tr>
<tr>
<td>Hepatic artery thrombosis</td>
<td>3 (8.1)</td>
<td>8 (2.6)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (8.1)</td>
<td>133 (44.0)</td>
</tr>
</tbody>
</table>
Metabolic disease, liver transplant (CHP 1981-2011, n=285)

Disease Indications (%)

- A1AT, 25.6%
- MSUD, 13.3%
- Familial Cholestasis, 13%
- Wilson, 9.8%
- Tyrosinemia, 7%
- CF, 6.7%
- GSD, 5.3%
- CNS, 5.3%
- Urea cycle, 4.9%
- Oxalosis, 3.5%
- Other, 5.6%
- Other, 5.6%

Other, 5.6%
Objectives

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  - Long term outcomes
  - Investigating Tolerance
Liver Transplantation for Classical Maple Syrup Urine Disease: Long-Term Follow-Up in 37 Patients and Comparative United Network for Organ Sharing Experience

George V. Mazariegos, MD,* D. Holmes Morton, MD, Rakesh Sindhi, MD, Kyle Soltys, MD, Navdeep Nayyar, MD, Geoffrey Bond, MD, Diana Shellmer, PhD, Benjamin Shneider, MD, Jerry Vockley, MD, and Kevin A. Strauss, MD

Objective To assess clinical and neurocognitive function in children who have undergone liver transplantation for classical maple syrup urine disease (MSUD).

Study design A total of 35 patients with classical MSUD (age 9.9 ± 7.9 years) underwent liver transplantation between 2004 and 2009. Six patients donated their liver to recipients without MSUD ("domino" transplant). We analyzed clinical outcomes for our cohort and 17 additional cases from the national United Network for Organ Sharing registry; 33 patients completed IQ and adaptive testing before transplantation, and 14 completed testing 1 year later.

Results Patient and graft survival were 100% at 4.5 ± 2.2 years of follow-up. Liver function was normal in all patients. Branched-chain amino acid levels were corrected within hours after surgery and remained stable, with leucine tolerance increasing more than 10-fold. All domino transplant recipients were alive and well with normal branched-chain amino acid homeostasis at the time of this report. Patient and graft survival for all 54 patients with MSUD undergoing liver transplantation in the United States during this period were 98% and 96%, respectively. One-third of our patients were mentally impaired (IQ ≤ 70) before transplantation, with no statistically significant change 1 year later.

Conclusion Liver transplantation is an effective long-term treatment for classical MSUD and may arrest brain damage, but will not reverse it. (J Pediatr 2011; □: ■ - □).
MAPLE SYRUP URINE DISEASE

35 patients + 17 from UNOS

Liver expresses 9-13% of total body branched chain ketoacid dehydrogenase complex activity

Indications  Severe “classical” MSUD

Age at Tx  9.9 years (1.7-32.1y)

Graft type  Cadaveric
        Domino transplant in 6 cases (all alive & well)

Survival  100% patient and graft survival (median f/u 4.5y)

17 UNOS cases  1 death, 1 Re Tx, 1 LRLT

Mazariegos et al, 2012
MAPLE SYRUP URINE DISEASE

METABOLIC CONTROL

Plasma leucine
Leucine/isoleucine
Leucine/valine

35 cases

Mazariegos et al, 2012
MAPLE SYRUP URINE DISEASE
Neurological outcomes: IQ and adaptive score pre and 1 year post Tx (n=14)

Mazariegos et al, 2012
### MSUD Perioperative and Post-Operative Complications in 37 Patients

<table>
<thead>
<tr>
<th>Post-Surgical Interventions</th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed wound closure</td>
<td>10</td>
<td>27</td>
</tr>
<tr>
<td>Ventral hernia repair</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>Gastrocutaneous fistula closure&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Exploratory laparotomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• hepatic artery thrombosis with successful revision</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>• hepatic artery revision or graft revision</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>• intra-abdominal bleeding</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>• partial small bowel obstruction</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Pleurocentesis</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Chest tube drainage</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Bronchoscopy</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

#### Medical Complications

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Acute rejection&lt;sup&gt;b&lt;/sup&gt;</td>
<td>15</td>
<td>40</td>
</tr>
<tr>
<td>• EBV disease</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>• CMV disease</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>• Post-transplant lymphoproliferative disease&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

<sup>a</sup> At prior gastrostomy tube sites  
<sup>b</sup> Antibody therapy for steroid-resistant rejection in 3/15 (8% of all patients)  
<sup>c</sup> Intestinal PTLD developed in one patient transplanted at another center; it resolved with transient withdrawal of immunosuppression and she has been disease-free for 12 years.
## Patient survival ped & adult LTx MSUD

<table>
<thead>
<tr>
<th>Cohort</th>
<th>N</th>
<th>Patient survival (%)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 year</td>
<td>5 years</td>
</tr>
<tr>
<td>Peds&lt;21</td>
<td>76</td>
<td>98.6</td>
<td>98.6</td>
</tr>
<tr>
<td>Adults&gt;=21</td>
<td>13</td>
<td>99.9</td>
<td>99.9</td>
</tr>
</tbody>
</table>

*p-value of log rank test of equality of survival distributions b/w age groups
PROPIONIC ACIDEMIA

26 cases

Indications
- neonatal onset
- poor metabolic control

Age at Tx
- 7m-9y median 2y

Graft type
- LRLT 8 (30%)
- APOLT 1
- Re-Tx 3 (11%)

Survival
- 19 (73%) 6 deaths at <1 year post Tx
- follow up: 7m-15y

PROPIONIC ACIDEMIA

19 survivors

Metabolic control

- 2 children further decompensation
- 1 metabolic stroke
- 50-60% reduction in serum metabolites
- Persistence of propionyl-carnitine and methyl-citrate in urine

PROPIONIC ACIDEMIA

19 survivors

Growth  improved, some better feeding

Diet  Normal - variable protein restriction +/- L carnitine

Neurodevelopment  Decline halted (one metabolic stroke; MRI)

Immunity  2 PTLD/CMV/HSV

Renal function  no documented major changes

Cardiomyopathy  reversed after Tx  Romano et al, 2010

PA – King’s experience

5 pts

• 4 neonatal presentation, 1 antenatal dg
• Main LT indication: metabolic instability
• All had some neurodevelopmental delay
• Median age at tx: 1.5 yrs (0.8-7)
• 1 re-Tx (HAT)
• PTLD (1), recurrent HS (1)
• All a/w after median 7.3 yrs (2.2-15)

Courtesy, D Hadzic
Patient survival pediatric LTx: Other Organic Aciduria (PA)

<table>
<thead>
<tr>
<th>Cohort</th>
<th>N</th>
<th>Patient survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peds&lt;21</td>
<td>24</td>
<td>1 year: 76.5, 5 years: 76.5, 10 years: NA</td>
</tr>
</tbody>
</table>

![Peds < 21 Survival Graph](image-url)
METHYL-MALONIC ACIDEMIA

22 survivors

KT (n=6)
2 died sepsis
1 diabetes
1 acidosis
1 chronic rejection

LT (n=15)
2 died infection, 1 acidosis
4 progressive renal failure
3 neurological disorder (one late stroke)
3 infection - bronchiolitis/CMV/EBV
1 acidosis

CLKT (n=6)
1 infection - CMV
2 neurological disorder

METHYL-MALONIC ACIDEDEMIA

22 survivors

Metabolic control

- 3 episodes of acidosis/decompensation (1 death)
- Serum MMA decreased to 13.8% of pre-op values in LT pts - better in CLKT pts
- Protein restriction 1g/kg/d to 2/g/kg/d in LT group

Developed in context of en bloc liver intestinal transplantation and as a technical solution to lack of abdominal venous access in renal recipients

- En bloc Liver/kidney (n=4)
  - MMA -3
  - Congenital hepatic fibrosis/ARPCKD -1

- En Bloc liver/intestine/kidney (n=6)
Lt FOR MMA - Conclusions

- LT does not cure the disease
  - May decrease the disease activity
  - May improve quality of life
- Early LT might be recommended to reduce the magnitude of progressive neurological disability
- Combined L-K is an effective treatment modality in patients with MMA and renal failure
- Progressive renal and neurological deterioration post-LT may not be prevented
### Patient survival pediatric & adult LTx: MMA

<table>
<thead>
<tr>
<th>Cohort</th>
<th>N</th>
<th>Patient survival (%)</th>
<th>p-value*</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 year</td>
<td>5 years</td>
</tr>
<tr>
<td>Peds&lt;21</td>
<td>32</td>
<td>93.4</td>
<td>93.4</td>
</tr>
<tr>
<td>Adults&gt;=21</td>
<td>3</td>
<td>99.9</td>
<td>NA</td>
</tr>
</tbody>
</table>

*p-value of log rank test of equality of survival distributions b/w age groups

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**Graph:**

- **Patient Survival**
- **Axes:** Days on the x-axis and Cum Survival on the y-axis.
- **Legend:**
  - Peds < 21
  - Adults >= 21
  - Peds < 21 - censored
  - Adults >= 21 - censored
Objectives

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- Compare decision making
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- Surgical considerations
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  - Long term outcomes
  - Investigating Tolerance
How to perform transplant in metabolic conditions?

- Technical aspects; size, age
- Choosing graft type
  - Impact of local donor availability
  - Understanding specific disease to estimate sufficient enzyme activity required
  - Assessing impact of heterozygous phenotype + stress

Courtesy D. Hadzic
Graft type in pediatric liver transplant
Kaplan-Meier probability of first allograft survival by graft type among 5-year survivors of pediatric LT

Ng, V. L. et al. Pediatrics 2008;122:e1128-e1135
Auxiliary liver transplantation

- Metabolic liver-based conditions
  - C-N type 1
  - Organic acidemias
  - Urea cycle disorders
  - Coagulation factor deficiencies

- Acute liver failure (non-A-E)
  - Living-related option
  - Prospects of IS withdrawal

Courtesy D. Hadzic
What about living donors?

Living Donor Liver Transplantation for Pediatric Patients with Inheritable Metabolic Disorders

Daisuke Morioka*,a,c, Mureo Kasaharaa, Yasutsugu Takada,b, Jose Pablo Garbanzo Corralesb, Atsushi Yoshizawaa, Seisuke Sakamotoa, Kaoru Taira,b, Elena Yukie Yoshitoshib, Hiroto Egawa,a, Hiroshi Shimadac and Koichi Tanakab

Received 13 May 2005, revised 12 July 2005 and accepted for publication 27 July 2005

Introduction

The use of liver transplantation (LT) has steadily increased, including for the treatment of some inborn metabolic deficiencies, irrespective of whether the liver is predominantly or only partly involved in disorder (1, 2). In some cases, however, there is a shortage of deceased donor organs and a living donor who is heterozygous for the disorder in question must be employed (3, 4). In pediatric cases of autosomal recessive disorder in particular, the donor is almost always a heterozygote because a parent is usually employed in such cases.
Indications for living donor liver tx in IEM (Morioka, 2007)
LRLT In MMA and PA

- **MMA (Morioka et al):**
  - 7 pediatric patients (7 months-7.5 yrs)
  - Follow up 4-21 months, median 10.5 months
  - 6/7 patient survival
  - ? Assessing need for simultaneous Renal Tx

- **PA (Kasahara et al, 2012):**
  - 3 patients, 3/3 survivors
  - Recommendation for early TX in neonatal onset PA

LRLTx for metabolic disease
(Kasahara, 2014, 10-year patient survival 82%)

### Table 1: Pediatric LDLT for metabolic disorders in Japan

<table>
<thead>
<tr>
<th>Original liver disease</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilson’s disease</td>
<td>59</td>
<td>30.4</td>
</tr>
<tr>
<td>Ornithine transcarbamylase deficiency</td>
<td>40</td>
<td>20.6</td>
</tr>
<tr>
<td>Carbamoyl phosphate synthetase 1 deficiency</td>
<td>9</td>
<td>4.6</td>
</tr>
<tr>
<td>Argininosuccinic aciduria</td>
<td>2</td>
<td>1.0</td>
</tr>
<tr>
<td>Methylmalonic academia</td>
<td>20</td>
<td>10.3</td>
</tr>
<tr>
<td>Propionic academia</td>
<td>9</td>
<td>4.6</td>
</tr>
<tr>
<td>Citrininemia</td>
<td>6</td>
<td>3.1</td>
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<tr>
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<td>9</td>
<td>4.6</td>
</tr>
<tr>
<td>Bile acid synthetic defect</td>
<td>4</td>
<td>2.1</td>
</tr>
<tr>
<td>Crigler-Najjar syndrome type 1</td>
<td>3</td>
<td>1.5</td>
</tr>
<tr>
<td>Mitochondrial respiratory chain disorders</td>
<td>2</td>
<td>1.0</td>
</tr>
<tr>
<td>Familial hypercholesterolemia</td>
<td>2</td>
<td>1.0</td>
</tr>
<tr>
<td>Erythropoietic protoporphyna</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Total</td>
<td>194</td>
<td>100</td>
</tr>
</tbody>
</table>

Graph showing trends in patient and graft survival.
Living related liver transplantation in MSUD

- Feier et al Hospital Sirion-Libanes, Sao Paulo Brasil
  - 2 yo child with MSUD
  - Maternal donor
  - DNA analysis post transplantation
MSUD: Domino Transplant

- 7 domino transplants
- Recipients 6.97 – 64.59 (Y)
- HCV, PSC, PFIC, CF, CHF, PBC, EC
- F/U 12.06 – 72.12 (M)
Less invasive transplant options?

Hepatocyte transplantation
Objectives

- Discuss the current state of pediatric liver transplant
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- Compare decision making
  - TX for cure: MSUD
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- Surgical considerations
- Areas of focus and progress in liver transplant
  - Long term outcomes
  - Investigating Tolerance
Late Graft Loss or Death in Pediatric Liver Transplantation: An Analysis of the SPLIT Database

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Suppressive protocols have also contributed greatly to the routine survival of many children after their first postoperative year with 1-year survival rates increasing from 35% in 1982 to 88% in 2002\textsuperscript{11}. Despite the improvement in early
Etiology of late mortality and graft loss (Soltys et al, 2007)

Table 6: Etiology of late mortality after LT (n = 34)

<table>
<thead>
<tr>
<th>Condition</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignancy</td>
<td>7</td>
<td>20.6</td>
</tr>
<tr>
<td>Recurrence/metastasis</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Denovo malignancy</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Sepsis/infection</td>
<td>5</td>
<td>14.7</td>
</tr>
<tr>
<td>MSOF</td>
<td>5</td>
<td>14.7</td>
</tr>
<tr>
<td>PTLD</td>
<td>4</td>
<td>14.7</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>8.8</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Aplastic anemia</td>
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<td></td>
</tr>
<tr>
<td>Cardiopulmonary</td>
<td>3</td>
<td>8.8</td>
</tr>
<tr>
<td>Cerebral edema/infarct</td>
<td>3</td>
<td>8.8</td>
</tr>
<tr>
<td>Portal vein thrombosis</td>
<td>1</td>
<td>2.9</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>1</td>
<td>2.9</td>
</tr>
<tr>
<td>Liver failure</td>
<td>1</td>
<td>2.9</td>
</tr>
<tr>
<td>Chronic rejection</td>
<td>1</td>
<td>2.9</td>
</tr>
</tbody>
</table>

Table 3: Etiology of late graft loss after LT (n = 35)*

<table>
<thead>
<tr>
<th>Condition</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic rejection</td>
<td>13</td>
<td>37.1</td>
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<tr>
<td>Other</td>
<td>5</td>
<td>14.3</td>
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<tr>
<td>Venoocclusive disease</td>
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<td></td>
</tr>
<tr>
<td>Parenteral nutrition</td>
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<td></td>
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<tr>
<td>Regenerative nodular hyperplasia</td>
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<td></td>
</tr>
<tr>
<td>Fulminant liver failure</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Chronic cholangitis</td>
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<td></td>
</tr>
<tr>
<td>Acute rejection</td>
<td>4</td>
<td>11.4</td>
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<tr>
<td>HAT</td>
<td>4</td>
<td>11.4</td>
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<tr>
<td>Biliary</td>
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<td>8.6</td>
</tr>
<tr>
<td>Missing</td>
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<td>8.6</td>
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<tr>
<td>HCV</td>
<td>1</td>
<td>2.9</td>
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<tr>
<td>Recurrent disease</td>
<td>1</td>
<td>2.9</td>
</tr>
<tr>
<td>Stopped immunosuppression</td>
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<td>2.9</td>
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</tbody>
</table>

EVIDENCE OF OVER IMMUNOSUPPRESSION (INFECTION) AS WELL AS UNDER IMMUNOSUPPRESSION (IMMUNE INJURY)
Extra-Hepatic Morbidity at the 10-Year Anniversary Clinic Visit

- cGFR < 90
- PTLD
- ↑ BMI
- ↑ choles
- ↑ triglyceride

% of patients

SPLIT
Contributors to late allograft dysfunction

- Technical
- Immune
- Infection
- Recurrent disease
- Ischemia (non-technical)
- Non-adherence
Monotherapy FK Dosing of liver transplanted MSUD patients with 3 year follow-up
Need for improved immune monitoring

Rejection risk assessment

Measuring antiviral (CMV) immunity
Complete Immunosuppression Withdrawal and Subsequent Allograft Function Among Pediatric Recipients of Parental Living Donor Liver Transplants

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Context Although life-saving, liver transplantation burdens children with lifelong immunosuppression and substantial potential for morbidity and mortality.

Objective To establish the feasibility of immunosuppression withdrawal in pediatric living donor liver transplant recipients.

Design, Setting, and Patients Prospective, multicenter, open-label, single-group pilot trial conducted in 20 stable pediatric recipients (11 male; 55%) of parental living donor liver transplants for diseases other than viral hepatitis or an autoimmune disease who underwent immunosuppression withdrawal. Their median age was 6.9 months (interquartile range [IQR], 5.5-9.1 months) at transplant and 8 years 6 months (IQR, 6 years 5 months to 10 years 9 months) at study enrollment. Additional entry requirements included stable allograft function while taking a single immunosuppressive drug and no evidence of acute or chronic rejection or significant fibrosis on liver biopsy. Gradual immunosuppression withdrawal over a minimum of 36 weeks was instituted at 1 of 3 transplant centers between June 5, 2006, and November 18, 2009. Recipients were followed up for a median of 32.9 months (IQR, 1.0-49.9 months).

Main Outcome Measures The primary end point was the proportion of operationally tolerant patients, defined as patients who remained off immunosuppression therapy for at least 1 year with normal graft function. Secondary clinical end points included the durability of operational tolerance, and the incidence, timing, severity, and reversibility of rejection.

Results Of 20 pediatric patients, 12 (60%; 95% CI, 36.1%-80.9%) met the pri-
Closing thoughts and acknowledgements

- Liver transplant for Metabolic Disease
  - Complex, individualized decision making
  - Optimal results require multidisciplinary, comprehensive care with a long term view
  - We must aim for the “ideal” survivor

- Acknowledgements
  - SPLIT (Ronan Arnon)
  - King’s College UK (Dino Hadzic)
  - Clinic for Special Children (Kevin Strauss and Holmes Morton)
“We don’t have the luxury of choosing what we need to study… The problems that drive us in our research are the problems that our patients face every day”

Kevin Strauss
“Children are the trailblazers”...Dr Starzl
Thank you.