Issues after Pediatric Liver Transplantation

Seak Hee Oh
Liver transplantation in children

- has become an effective, definitive, and universally accepted treatment for irreversible liver diseases.

- Long-term survival at Asan Medical Center Children’s Hospital

  Due to:
  - constant surgical advancements
  - improvements in immediate postoperative intensive care
  - better long-term care using better immunosuppressants

1. Oh SH, Transplant Proc 2012;44:484-6
How can we control controllables during PICU?

**Graft Care**
- Primary non-function
- Hemorrhage
- Rejection
- Vascular problems
- Biliary problems

**Patient Care**
- Cardiovascular care
- Respiratory care
- Neuropsychological care
- GI care
- Electrolyte & nephrology
- Infection/Immunosuppression
Graft Care
Early Outcome of Pediatric Liver Transplantation (PLT)

- **30-day Mortality after PLT: OPTN Database**
  
<table>
<thead>
<tr>
<th>Causes</th>
<th>N=2325</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>3.9%</td>
</tr>
<tr>
<td>Graft failure</td>
<td>2.1%</td>
</tr>
</tbody>
</table>

- **Graft failure after PLT**
  
<table>
<thead>
<tr>
<th>Causes</th>
<th>N=246</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular complication</td>
<td>34.9%</td>
</tr>
<tr>
<td>(hepatic artery thrombosis)</td>
<td>(29%)</td>
</tr>
<tr>
<td>Primary non-function</td>
<td>19.1%</td>
</tr>
<tr>
<td>Chronic rejection</td>
<td>14.6%</td>
</tr>
<tr>
<td>Biliary complication</td>
<td>6.9%</td>
</tr>
<tr>
<td>Rejection</td>
<td>3.2%</td>
</tr>
</tbody>
</table>

53.8% among deaths

Primary non-function (PNF)

Definition\(^1,\ 2\)

- aggravated form of reperfusion injury
- results in irreversible graft failure
- no detectable technical or immunological problems
- incidence: 4-8\(^{\circ}\)\(^3\)
- most common reason for early re-transplantation (mortality=practically 100%)

What is PNF like?

- anhepatic condition or acute liver failure

- example¹

  70% centerilobular necrosis
  50% centrilobular steatosis

¹ Liver Transpl 2010; 16: 1428
It is no longer a matter of liver. It is a multisystem disorder.

- **Protein production ↓**
- **Coagulopathy**
- **Immune function ↓ & Infection**
- **Renal function ↓**
- **Clearance of toxin ↓**
- **Vasodilatation & collapse**
- **Encephalopathy & Brain edema**
- **SIRS/Shock**

*Modified by a concept of Pediatr Emerg Care 2007: 23: 129*
Risk factors\textsuperscript{1,2}

- reduced-size liver
- fatty changes on donor liver biopsy
- older donor age
- prolonged cold ischemia times
- intraoperative bile output ↓
- venoveno bypass
- retransplantation
- renal insufficiency
- intraoperative coagulopathy ↓

2. Rev Esp Enferm Dig. 1999;91(6):401
Is it possible to predict PNF?

- LiMAX test\textsuperscript{1,2}

Primary non-function

Therapeutic option
- Re-transplantation ASAP! Put the patient on the waiting list.
- Supportive care with/without hepatectomy
Bridging treatment for liver failure

MARS®

or

Plasma exchange

CVVHD

+

Plasma exchange

by the courtesy of Dr Kasahara
Interim summary

- Do not try to reverse it.
- Early detection is critical.
- PICU care as a bridging therapy before re-LT may delay its progression to multiple organ dysfunction.
Vascular complication

- Types: thrombosis & stenosis

- Location: hepatic artery, portal vein, hepatic vein

- According to locations, in various degrees
  - ↑ liver function tests
  - coagulopathy
  - hypoglycemia
  - large amount of ascites: drain ↑
  - ↓ albumin
  - hypoglycemia
  - bile leak
Hepatic artery thrombosis (HAT): Kyoto study

Total N=382 children
HAT  N=27 (7%)

- **M-group**
  : weak PI < 0.6

- **S-group**
  : loss of arterial signal

Hepatic artery thrombosis (HAT): Kyoto study

- **Risk factors**
  - female, low body weight, high graft-to-recipient weight ratio

- **Outcomes**
  - Re-LT (n=1)
  - had the same survival rate compared to others
  - 33% had biliary complications

Portal vein thrombosis (PVT): Cincinnati study

Total N=417 children
PVT N=32 (7.7%)

⇒ 30% (6/19) were ok among early PVT!

Portal vein thrombosis (PVT): Chang Gung study

Total N=73 children
PVT  N=8 (11%)

- Risk factors of PVT
  - age < 1 yr
  - Body weight < 10kg
  - GRWR > 3
  - PV velocity < 7cm/s
  - PV size < 4mm

→ Infants and young children with graft size mismatch

- Hepatic doppler sonography is mandatory.
- As best as you can, you have to trace any changes of the doppler findings.
- If you can’t, you should freely communicate with your radiologists and surgeons.
Interim summary

- Early detection is critical to avoid reoperation or graft loss.

- Both HAT and PVT are fatal, affecting not only short-term graft survival, but also long-term survival.

- Infants are at a higher risk of critical vascular complications.

- Frequent doppler sonography is mandatory.
Biliary complication: SickKids study\textsuperscript{1}

Total N= 173 children

- **bile leak n= 12 (7%)**
  - anastomotic 75% > cut surface 17% > unknown 8%
  - intervention on 11\textsuperscript{th} day
  - death/graft loss = 50%

- **Biliary stricture n= 22 (13%)**
  - anastomotic 82% > intrahepatic 14% > both 5%
  - intervention on 11\textsuperscript{th} day
  - death/graft loss = 25%

1. Liver Transpl. 2015; 21(8):1082-90
Biliary complication

Signs & symptoms

▪ early sepsis
▪ bile tube drain ↓
▪ bile stained fluid on surgical drains
▪ abdominal distension
▪ liver function tests ↑

Prevention & Therapeutic options

▪ duct tube for anastomotic site
▪ surgical intervention for early bile duct leaks
▪ percutaneous tube placement/stent insertion for duct dilatation
Hyperacute rejection
- can develop even within **several hours** of posttransplantation
- mediated by preformed anti-donor antibodies
- results in endothelial destruction, thrombosis, and hemorrhagic necrosis
- **often fatal** outcome without transplantation
- no effective treatment available

Acute Cellular rejection
- can start after the **1st week** to years (about 45%)
- mediated by alloimmune T-cells
- results in portal inflammation (mixed infiltrate), non-suppurative cholangitis, and endotheliitis
- Untreated, can evolve into cholestasis, and graft failure, but non-cholestatic upfront
- **excellent response to steroids**
### Grading of Acute Liver Rejection by Banff int. Criteria

<table>
<thead>
<tr>
<th>Score</th>
<th>Portal Inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mostly lymphocytic inflammation, involving but not noticeably expanding a minority of the traits</td>
</tr>
<tr>
<td>2</td>
<td>Expansion of most or all triads by a mixed infiltrate</td>
</tr>
<tr>
<td>3</td>
<td>Marked expansion of most or all traits by a mixed infiltrate, with spillover in the parenchyma</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Score</th>
<th>Bile Duct Inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A minority of ducts are cuffed or infiltrated by inflammatory lymphocytes, and show mild reactive changes</td>
</tr>
<tr>
<td>2</td>
<td>Most or all ducts are infiltrated by inflammatory cells. Few of them show degenerative changes</td>
</tr>
<tr>
<td>3</td>
<td>As above, but most or all ducts show degenerative changes, and luminal disruption</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Score</th>
<th>Venous Endothelial Inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Subendothelial lymphocytes infiltrating some of the portal and/or hepatic venules.</td>
</tr>
<tr>
<td>2</td>
<td>Subendothelial lymphocytes infiltration most of the portal and/or hepatic venules.</td>
</tr>
<tr>
<td>3</td>
<td>As above, but infiltrate expands in parenchyma, with associated perivenular hepatocyte necrosis</td>
</tr>
<tr>
<td>Grading</td>
<td>Description</td>
</tr>
<tr>
<td>------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Interminate</td>
<td>portal inflammation that fails to meet the criteria for Dx</td>
</tr>
<tr>
<td>Mild</td>
<td>rejection infiltrate in a minority of the traits, mild, and confined within the portal spaces</td>
</tr>
<tr>
<td>Moderate</td>
<td>rejection infiltrate expanding most or all portal triads</td>
</tr>
<tr>
<td>Severe</td>
<td>as in moderate stage, but infiltrate spilling into the peri-portal areas, presence of peri-venular inflammation, and peri-venular heatocyte necrosis</td>
</tr>
</tbody>
</table>
Calcineurin inhibitors

- Tacrolimus is a mainstay of immunosuppression\(^1\)
- Better in controlling chronic rejection

Rejection & Immunosuppression

TOXICITY¹
- Immune mediated Infection
- Non-immune mediated Nephrotoxicity Cardiovascular disease Neoplasm

EFFICACY
No rejection Tolerance

### Intravenous Immunoglobulins in PLT

Total N=2291 children

<table>
<thead>
<tr>
<th>Factor</th>
<th>A</th>
<th>B (Reference)</th>
<th>Outcome rejection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Category</td>
<td>Relative risk</td>
<td>p-Value</td>
</tr>
<tr>
<td>Recipient’s age</td>
<td>6–11 month</td>
<td>0–5 month</td>
<td>1.39</td>
</tr>
<tr>
<td></td>
<td>1–4 years</td>
<td>0.84</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>5–12 years</td>
<td>1.57</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>≥15 years</td>
<td>1.93</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Primary diagnosis</td>
<td>Other cholestatic or metabolic</td>
<td>0.83</td>
<td>0.037</td>
</tr>
<tr>
<td></td>
<td>Biliary atresia</td>
<td>1.05</td>
<td>0.699</td>
</tr>
<tr>
<td></td>
<td>Fulminant liver failure</td>
<td>0.89</td>
<td>0.408</td>
</tr>
<tr>
<td></td>
<td>Cirrhosis</td>
<td>0.75</td>
<td>0.040</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>0.92</td>
<td>0.430</td>
</tr>
<tr>
<td>Donor-recipient blood match</td>
<td>Compatible</td>
<td>0.55</td>
<td>0.028</td>
</tr>
<tr>
<td></td>
<td>Identical</td>
<td>1.49</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>First immunosuppression</td>
<td>Cyclosporine</td>
<td>0.75</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>Tacrolimus</td>
<td>0.75</td>
<td>0.002</td>
</tr>
<tr>
<td>IVIG use within the first week post-Tx</td>
<td>Yes</td>
<td>0.69</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>0.69</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Year of transplant</td>
<td>2002</td>
<td>0.69</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Patient Care
In the OR, patients already experience hypotensive events usually during the reperfusion of graft.
Cardiovascular care

- Reperfusion of graft
  - Hypotension/Bradycardia
    - Hemorrhage/infection esp. children with Kasai
  - Volume overload
    - Renin excretion
  - Hypertension
    - Drugs (steroid & FK506)
LATE EXTUBATION steps:

- 7PM SIMV mode
- 2AM PS mode
- 6AM CPAP mode & stop fentanyl infusion
- 10-2PM extubation
- Requirements for weaning: PaO2 > 70mmHg, O2 saturation > 95%

OR EXTUBATION indications:

Pre-OP:
- BW > 6-7kg
- No Malnutrition
- No Infection
- Normal cardio-respiratory function

IntraOP:
- GRWR 1-4
- No Vascular graft use
- No re-do vascular anastomosis
- Normal lactate/BE
- No Inotropes

by the courtesy of Dr. Kasahara
## Risk of early extubation failure

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity of liver disease</td>
<td>Renal dysfunction</td>
</tr>
<tr>
<td>UNOS status</td>
<td>Hepatic encephalopathy</td>
</tr>
<tr>
<td>Age</td>
<td>Inotropics</td>
</tr>
<tr>
<td>Duration of graft ischemia</td>
<td>Inadequate oxygenation</td>
</tr>
<tr>
<td>Duration of surgery</td>
<td>Infection</td>
</tr>
<tr>
<td>Intraoperative transfusion</td>
<td></td>
</tr>
</tbody>
</table>

Pulmonary complications of chronic liver disease

■ Portopulmonary hypertension\(^1\)
  mPA Pr > 25mmHg
  moderate (Pr >35 mmHg)
  severe (Pr > 45 mmHg)

■ Hepatopulmonary syndrome\(^2\)
  moderate (PaO2 < 80 mmHg)
  severe (PaO2 <60 mmHg)
### Preoperative

<table>
<thead>
<tr>
<th>Liver failure</th>
<th>Renal disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary biliary cirrhosis</td>
<td>Membranous nephropathy</td>
</tr>
<tr>
<td></td>
<td>Antiglomerular basement membrane disease</td>
</tr>
<tr>
<td></td>
<td>ANCA disease</td>
</tr>
<tr>
<td></td>
<td>Interstitial nephritis</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>Immune complex glomerulonephritis</td>
</tr>
<tr>
<td>Biliary atresia</td>
<td>Membranous nephropathy</td>
</tr>
<tr>
<td>Alagille syndrome</td>
<td>Tubulointerstitial nephropathy</td>
</tr>
<tr>
<td>Methylmalonic acidemia</td>
<td>Interstitial nephritis</td>
</tr>
<tr>
<td>Glycogen storage disease</td>
<td>Glomerulosclerosis</td>
</tr>
<tr>
<td>Caroli, Hepatic fibrosis</td>
<td>ARPKD, nephronopthis</td>
</tr>
<tr>
<td>Primary hyperoxaluria type 1</td>
<td>Nephrolithias</td>
</tr>
</tbody>
</table>

### Postoperative

<table>
<thead>
<tr>
<th>Factor</th>
<th>Renal disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged cold ischemic time</td>
<td>Acute kidney injury</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Short &amp; long term renal insufficiency</td>
</tr>
</tbody>
</table>
**Timeline of infection after SOT**

![Timeline of infection after SOT](image)

### Common Infections in Solid-Organ Transplant Recipients

#### <1 Month
- Infection with antimicrobial-resistant species:
  - MRSA
  - VRE
  - Candida species (non-albicans)
  - Aspiration
  - Catheter infection
  - Wound infection
  - Anastomotic leaks and ischemia
  - *Clostridium difficile* colitis
- Donor-derived infection (uncommon): 
  - HSV, I.CMV, rhabdovirus (rabies), West Nile virus, HIV, *Trypanosoma cruzi*
- Recipient-derived infection (colonization): 
  - Aspergillus, pseudomonas

#### 1–6 Months
- With PCP and antiviral (CMV, HBV) prophylaxis:
  - Polyomavirus BK infection, nephropathy
  - *C. difficile* colitis
  - HCV infection
  - Adenovirus infection, influenza
  - *Cryptococcus neoformans* infection
  - *Mycobacterium tuberculosis* infection
  - Anastomotic complications
- Without prophylaxis:
  - Pneumocystis
  - Infection with herpesviruses (HSV, VZV, CMV, EBV)
  - HBV infection
  - Infection with listeria, nocardia, toxoplasma, strongyloides, leishmaniasis, *T. cruzi*

#### >6 Months
- Community-acquired pneumonia, urinary tract infection
- Infection with aspergillus, atypical molds, mucor species
- Infection with nocardia, rhodococcus species
- Late viral infections:
  - CMV infection (colitis and retinitis)
  - Hepatitis (HBV, HCV)
  - HSV encephalitis
  - Community-acquired (SARS, West Nile virus infection)
  - JC polyomavirus infection (PMI)
  - Skin cancer, lymphoma (PTLD)

Early blood stream infection

- Catheter infection → 58% G (+)
- Biliary complication → 42% G (-)

Table 1. Risk Factors for Early Bloodstream Infections After Pediatric Living Donor Liver Transplant

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Infections Case/Total (%)</th>
<th>Univariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 1 year</td>
<td>23/49 (46.9)</td>
<td>4.20 (1.82–10.24)*</td>
</tr>
<tr>
<td>Bilirubin &gt; 30 mg/dL</td>
<td>20/88 (22.7)</td>
<td>3.20 (1.23–8.23)*</td>
</tr>
<tr>
<td>Albumin &lt; 2.0 g/dL</td>
<td>4/25 (16.0)</td>
<td>1.21 (0.34–3.56)</td>
</tr>
<tr>
<td>Creatinin &gt; 2.0 mg/dL</td>
<td>5/19 (26.3)</td>
<td>2.36 (1.13–6.43)</td>
</tr>
<tr>
<td>Prothrombin time (INR) &gt; 2.0</td>
<td>6/48 (12.5)</td>
<td>0.78 (0.34–2.35)</td>
</tr>
<tr>
<td>PELD ≥ 25</td>
<td>7/32 (21.9)</td>
<td>1.20 (0.45–3.46)</td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
<td>8/21 (38.1)</td>
<td>1.13 (0.35–3.24)</td>
</tr>
<tr>
<td>Living unrelated</td>
<td>0/8 (0)</td>
<td>NA</td>
</tr>
<tr>
<td>ABO incompatibility</td>
<td>3/9 (33.3)</td>
<td>1.40 (0.68–8.32)</td>
</tr>
<tr>
<td>Tacrolimus-based</td>
<td>35/138 (25.4)</td>
<td>5.78 (0.80–42.56)</td>
</tr>
<tr>
<td>ICU stay ≥ 3 weeks</td>
<td>22/79 (27.8)</td>
<td>3.20 (0.85–14.13)</td>
</tr>
<tr>
<td>Catheterization &gt; 10 days</td>
<td>12/37 (32.4)</td>
<td>2.70 (1.68–7.45)*</td>
</tr>
<tr>
<td>Bile duct Cx</td>
<td>7/13 (53.8)</td>
<td>2.54 (1.5–9.78)*</td>
</tr>
<tr>
<td>Vessel Cx</td>
<td>13/32 (40.6)</td>
<td>5.35 (1.93–15.02)</td>
</tr>
<tr>
<td>Early acute rejection</td>
<td>24/67 (35.8)</td>
<td>1.43 (0.68–7.23)</td>
</tr>
</tbody>
</table>

Abbreviations: OR, odds ratio by logistic regression; CI, confidence interval; NA, not available; INR, PELD, preoperative pediatric and end-stage liver disease.
Conclusion

Complication

Successful PLT

Surgeons
Let’s improve our treatment skill from our own experiences!!