Liver transplantation in primary cholestatic liver diseases

Transplant forum
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Cholestatic indications for OLT

- Pediatric
  - Alagille syndrome
  - PFIC
  - Non-syndromic biliary hypoplasia
  - Nutrition related cholestasis
- Adult
  - Primary biliary cirrhosis
  - Primary sclerosing cholangitis
Indications for transplant

- Survival benefit: risk of death without Tx greater than risk with Tx
  - Generic models- MELD
  - Disease specific models- Mayo score
- Quality of life
  - √ Intractable pruritis
    - Refractory to medical Rx (cholestyramine, refampicin, naltrexone etc.)
  - ? Recurrent, debilitating nontraumatic bone fractures
  - ? Recurrent episodes of cholangitis
- X Fatigue- not reversed with OLT. Try Modafinil
  - Goldblatt J et al. Gastroenterology. 2002 May;122(5):1235-41
Timing of transplant

- Both MELD and Mayo scores superior to CTP for predicting mortality
  - Kamath PS et al. Hepatology 2001;33:464–70
  - Kim WR et al. Hepatology 1999;29;1643-1648
- No head to head comparison b/w MELD and Mayo
- MELD scores used in most programs
  - Underestimate disease severity in patients with primarily fatigue and pruritis- delay in Tx
  - Favor critically ill patient- poorer outcome, higher cost of Tx
Mayo scores for OLT in PBC

- Based on bilirubin, albumin, age, edema, and PT
- OLT advised when 6m survival expected to be less than 80% (score ≈ 9.4, bilirubin >10mg/dl))

- Survival benefit of OLT evident 3-6m after Tx
• Earlier Tx may be beneficial with improved OLT survival currently
• Late transplant (R>7.8) leads to increased mortality and resource usage

• OLT advocated when score between 6-7.8
  • Kim WR et al. Liver Transpl 2000; 6: 489-494
Mayo scores for OLT in PSC

- Based on age, bilirubin, albumin, AST and variceal bleed

- Similar to PBC: benefit evident 6m post Tx.

- Tx when expected survival less than Tx survival for a given centre (Score of >2 used in Japan)
  - Tamura S et al. World J Gastroenterol 2008;14:5105-9
Results of OLT

Average life expectancy for male recipients by age group and primary liver disease
- 1, 5 and 10-year survival rates in PBC- 80-90%, 77%-88%, and 70-80%, respectively
  - Liermann Garcia RF et al. Hepatology 2001; 33:22
- 1-year and 5-year survival rates of 90–97% and 80–85% respectively in PSC

### Table 4. Median Preoperative MELD Score and 1-Year Survival of Liver Transplant Recipients Analyzed by Principal Diagnosis

<table>
<thead>
<tr>
<th>Median MELD Scores (Interquartile Range) and 1-Year Survival</th>
<th>Viral Liver Disease</th>
<th>Alcoholic Liver Disease</th>
<th>Cholestatic Liver Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States MELD score 15.6 (12.4–21)</td>
<td>16.7 (13.1–23.2)</td>
<td>16.1 (12.1–21.3)</td>
<td></td>
</tr>
<tr>
<td>1-year survival (%)</td>
<td>86.8</td>
<td>88.2</td>
<td>92.9</td>
</tr>
<tr>
<td>Canada MELD score 16.2 (12.1–20.8)</td>
<td>16.5 (13.5–22.8)</td>
<td>18.8 (14.1–21.7)</td>
<td></td>
</tr>
<tr>
<td>1-year survival (%)</td>
<td>88.4</td>
<td>94.1</td>
<td>95.1</td>
</tr>
<tr>
<td>United Kingdom MELD score 10.2 (8.4–13)</td>
<td>15.7 (12–20)</td>
<td>8.5 (7.5–11.1)</td>
<td></td>
</tr>
<tr>
<td>1-year survival (%)</td>
<td>84.6</td>
<td>91.6</td>
<td>88</td>
</tr>
</tbody>
</table>

Abbreviation: MELD, model for end-stage liver disease.
Differences in MELD score within countries not significant except for the United Kingdom where cholestatic vs alcoholic liver disease (95% confidence interval of difference = −8.17 to −4.32) and viral vs alcoholic liver disease (95% confidence interval of difference = −6.69 to −2.77).
• Prompt reversal of pruritis, encephalopathy, UGI bleed and HRS
• Jaundice and ascites resolve over weeks to months
• 12 -18 months for improvement in osteodystrophy
  • Eastell R et al. Hepatology 1996;14:296
• Fatigue responds poorly
• ?Increase in IBD/Ca colon post Tx
  • Dvorchik I et al. Hepatology 2002; 35:380
  • Vera A et al. Transplantation 2003; 75:1983
## Recurrence- PSC

### Mayo criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed diagnosis of primary sclerosing cholangitis prior to liver transplantation</td>
<td>Hepatic artery thrombosis/stenosis</td>
</tr>
<tr>
<td>Cholangiography: intrahepatic and/or extrahepatic biliary stricturing, beading and irregularities at least more than 90 days following transplantation</td>
<td>Established chronic ductopenic rejection</td>
</tr>
<tr>
<td>Histology: fibrous cholangitis and/or fibro-obliterative lesions with or without ductopenia, biliary fibrosis or biliary cirrhosis</td>
<td>Anastomotic strictures alone</td>
</tr>
<tr>
<td></td>
<td>Nonanastomotic strictures before posttransplantation day 90</td>
</tr>
<tr>
<td></td>
<td>ABO incompatibility between donor and recipient</td>
</tr>
</tbody>
</table>


- Difficult diagnosis:
  - May have normal LFT
  - Many causes of secondary cholangitis to be excluded
  - Histology/imaging not specific
• 1, 5, and 10 years post-transplantation: 2, 12, and 20%
  • Campsen J et al. Liver Transpl 2008; 14:181
• Risk factors:
  • gender mismatch, male recipient
  • coexistent IBD, presence of an intact colon after Tx
  • Related LDLT
  • CMV infection, recurrent cellular rejection
  • use of OKT3, prolonged use of steroids
  • CCR5 Δ32 mutation, HLA-DRB1*08
    • Graziadei IW et al. Curr Opin Gastroenterol 2011;27:301–305
    • op den Dries S et al. Liver Int. 2011;31(8):1102-9
Recurrence- PBC

- Diagnostic criteria
  - Transplant for PBC and
  - Persistence of AMA and
  - Histology showing the characteristic portal tract lesions
    - Mononuclear inflammatory infiltrate
    - formation of lymphoid aggregates
    - epithelioid granulomas
    - bile duct damage
    - (3/4 for definite, 2/4 for probable)

- LFT neither specific nor sensitive
- AMA titre/subtype not predictive
- Anti-GPC- non-specific, 100% sensitive for recurrence
8-18% at 5 year and 22-30% at 10 years

- Liermann Garcia RF et al. Hepatology 2001; 33:22
- Abu-Elamgd et al. Hepatology 1997; 26:176A

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No. of patients</th>
<th>Median follow-up after transplantation (mo)</th>
<th>Recurrence (%)</th>
<th>Median time to recurrence (mo)</th>
<th>Risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liermann-Garcia et al [8]</td>
<td>2001</td>
<td>400</td>
<td>56</td>
<td>17</td>
<td>36</td>
<td>Tacrolimus-based immunosuppression</td>
</tr>
<tr>
<td>Sanchez et al [54]</td>
<td>2003</td>
<td>156</td>
<td>72</td>
<td>11</td>
<td>50</td>
<td>—</td>
</tr>
<tr>
<td>Sylvestre et al [55]</td>
<td>2003</td>
<td>100</td>
<td>44</td>
<td>17</td>
<td>56</td>
<td>—</td>
</tr>
<tr>
<td>Neuberger et al [26]</td>
<td>2004</td>
<td>485</td>
<td>79</td>
<td>23</td>
<td>—</td>
<td>Tacrolimus-based immunosuppression</td>
</tr>
<tr>
<td>Jacob et al [25]</td>
<td>2006</td>
<td>100</td>
<td>118</td>
<td>14</td>
<td>61</td>
<td>Tacrolimus-based immunosuppression</td>
</tr>
<tr>
<td>Charatcharoenwithaya et al [23]</td>
<td>2007</td>
<td>154</td>
<td>—</td>
<td>34</td>
<td>—</td>
<td>Recipient age Tacrolimus-based immunosuppression Male recipient</td>
</tr>
</tbody>
</table>
Impact of disease recurrence

- No difference in patient/graft survival with rPBC
  - Liermann Garcia RF et al. Hepatology 2001;33:22-7

- rPSC may affect graft survival- controversial
  - Graziadei IW. Hepatology 1999;29:1050-6
Rx of recurrent disease

- Biliary dilatation for recurrent strictures in PSC
  - Difficult, may not be effective
- UDCA improves LFT but no effect on outcome in recurrent PBC
- Retransplantation if significant graft dysfunction
  - Liermann Garcia RF et al. Hepatology 2001;33:22-7
- Prevention of recurrence- no proven strategy
  - CyA instead of Tac
  - Slower steroid taper
  - UDCA
Conclusions

- Definite advantage of OLT vs. medical management in decompensated primary cholestatic diseases
- Tx when expected survival less that OLT survival/intractable symptoms
- Results as good/better than other indications of OLT
- Disease recurrence not uncommon
- Difficult to diagnose without Bx
- Impact of recurrence on graft/patient survival minimal
- No definite Rx for recurrent disease- successful re-transplantation possible