Recurrence of disease post liver transplant: diagnosis and management

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Liver Transplant Around the World

United States
7000 per yr

Brazil
2005: 949 and 2014: 1756
Indications for liver transplant

• Hepatitis C is the most common etiology worldwide

• Germany
  – HCV < 1% of the population
  – Alcohol related liver disease
  – NAFLD

• United Kingdom similarly ALD > HCV
Impact of primary indication for LT

Log-Rank: p<0.001

Months after LT

CD / AI
ALF
HBV
ALD
HCV
HCC

%
20 year Survival Post LT

Main causes of death and time after LT

<table>
<thead>
<tr>
<th>Time after LT (yrs)</th>
<th>Others</th>
<th>CVE</th>
<th>De-novo malignancy</th>
<th>Infection</th>
<th>Recurrent disease</th>
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Recurrent liver disease post LT

• Viral Hepatitis
  – Hepatitis C
  – Hepatitis B
• Alcohol related liver disease
• Autoimmune related liver diseases
RECURRENT  HEPATITIS B POST LT
Risk factors identified for recurrence of HBV post LT

- High viral load at time of LT
  - (100,000 copies/mL the recurrence rate was 50% higher (p=0.003)
- HBeAg positivity
- History of HBV drug resistance
- HCC at the time of LT
- HCC recurrence post LT
- Chemotherapy use
Prevention of recurrence of HBV

• High dose Intravenous HBIG
• Low dose IM or SQ HBIG
• Oral Nucleoside Analogs
  – Entecavir
  – Tenofovir
Algorithm for HBV prevention post LT

Start patient on NA when listed for LT
Monitor HBV DNA while listed

Assess Risk Status

Low-Risk Patients
- Undetectable HBV DNA levels at LT
- No HB Ig
- High potency NAs [Tenofovir or Entecavir]

High-Risk Patients
- Detectable HBV DNA levels at LT
- Presence of drug-resistant HBV
- HIV/HDV coinfection
- HCC at LT
- Poor compliance to antiviral therapy
- 10,000 IU IV HB Ig in an hepatic phase followed by 600-1000 IU intramuscularly/IV daily for 7 days, weekly for 3 weeks, and then monthly, to keep anti-HBs levels >100 mIU/mL for 1 year
- High potency NAs [Tenofovir or Entecavir]
Algorithm to treat HB core positive donors

Anti-hepatitis B core positive liver grafts

- HBsAg (+) recipients
  - Anti-HBc (+)
  - Anti-HBs (+)
    - HBIG + antivirals
  - Anti-HBc (+)
  - Anti-HBs (-)
    - No prophylaxis
  - Anti-HBc (-)
  - Anti-HBs (+)
    - Antivirals
- Anti-HBc (-) and anti-HBs (-) recipients
  - Antivirals
<table>
<thead>
<tr>
<th>Recipient</th>
<th>HBV Antiviral Therapy</th>
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</thead>
<tbody>
<tr>
<td><strong>HBs Antibody</strong></td>
<td></td>
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<tr>
<td><strong>Positive</strong></td>
<td>Lamivudine 100 mg oral daily(^2) starting the first dose on-call to operating room&lt;br&gt;Reassess at 1 year&lt;br&gt;HBsAb(+), consider discontinuing lamivudine(^3)&lt;br&gt;HBsAb(−), continue lamivudine, order HBV vaccine (dialysis dose) x 3 doses</td>
</tr>
<tr>
<td><strong>Negative</strong></td>
<td>Tenofovir 300 mg oral daily(^2) or entecavir 0.5 mg oral daily(^2) starting the first dose on-call to operating room&lt;br&gt;HBsAb(+) at 1 year after LT, consider discontinuing antiviral treatment(^3)&lt;br&gt;HBsAb(−) at 1 year after LT, continue antiviral treatment, order HBV vaccine (dialysis dose) x 3 doses</td>
</tr>
</tbody>
</table>
Treatment of recurrent HBV post LT

– Noncompliance or viral mutations
– HBV recurrence in the setting of Lam therapy use
  Tenofovir not Entecavir
RECURRENT ALCOHOL RELATED LIVER DISEASE POST LT
We are naive if we think our patients do not drink after transplant.
Recurrent ALD post LT

- Duration of abstinence pre-transplant does not necessarily predict recurrence
- Stronger negative predictors include
  - Lack of Psychosocial support and Psychiatric comorbidities
- Graft loss is rare in patients that drink after LT
- But cirrhosis can occur in those that drink more heavily
RECURRENT AUTOIMMUNE RELATED LIVER DISEASE POST LT
Probability of Developing Recurrent PBC

Charatcharoenwitthaya P. Lvr Transpl 2007;13:1236-1245
Recurrent PBC: Diagnosis

3 Diagnostic Criteria

- OLT for PBC and
- AMA persistence and
- Characteristic histology

Histology diagnostic hallmark is identification of granulomatous cholangitis or the florid duct lesion.

2/4 probable
3/4 definite

Hubacher S et al, J Hepatol 1993; Neuberger J, L Transpl 2003
Sylvestre P et al, L Transpl 2003
Impact of Recurrent PBC on Patient Survival

Recurrence vs. Recurrence free over the years after OLT. The graph shows a decrease in patient survival with increasing years after OLT, with a notable difference between recurrence and recurrence-free groups. The p-value is reported as P = NS.
Probability of Freedom from Fibrosis Progression in Patients with Recurrent PBC Treated with URSO vs Untreated

Charatcharoenwitthaya P. Lvr Transpl 2007;13:1236-1245
Conclusions

- Incidence of recurrent PBC increases with time: 30-35% at 15 yrs

- Risk factors – male gender, older donor age and early steroids withdrawal

- Recurrent PBC has minimal impact on patient and graft survival up to 15 yrs post transplant

- URSO seems to have minimal impact if started at time of diagnosis of recurrent PBC.

- If URSO started immediately after liver transplantation??
Recurrent AIH: Histopathology

Features:
- Lymphoplasmocytic infiltrate
- Interface hepatitis
- Lobular involvement

Occasionally
- Bile duct lesions
- Endothelialitis

Differential Diagnosis
- Acute rejection
- Chronic rejection
- Viral hepatitis (CMV, etc)
- Drug-induced hepatotoxicity

Faust TW, Semin Liver Dis 2000
## Prevalence of Recurrent AIH

<table>
<thead>
<tr>
<th>Location</th>
<th>Count/Total</th>
<th>Percentage</th>
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</thead>
<tbody>
<tr>
<td>Madrid</td>
<td>9/27</td>
<td>33%</td>
</tr>
<tr>
<td>Paris</td>
<td>3/35</td>
<td>12%</td>
</tr>
<tr>
<td>Birmingham</td>
<td>13/47</td>
<td>27%</td>
</tr>
<tr>
<td>Boston</td>
<td>5/14</td>
<td>36%</td>
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<tr>
<td>Los Angeles</td>
<td>13/40</td>
<td>32%</td>
</tr>
<tr>
<td>Hanover</td>
<td>9/28</td>
<td>32%</td>
</tr>
<tr>
<td>Mayo</td>
<td>7/41</td>
<td>17%</td>
</tr>
<tr>
<td>NIH</td>
<td>24/46</td>
<td>53%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>83/268</strong></td>
<td><strong>31%</strong></td>
</tr>
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</table>
Graft loss after recurrence
Treatment of Recurrent AIH

• Most respond to increasing corticosteroids--azathioprine – treat indefinitely

• Sirolimus – successful in non-responders to steroids--(AJT: 2005)

• Steroid withdrawal should be performed with caution—maintain prednisone 5 mg/day

• Recurrent AIH can affect 2\textsuperscript{nd} graft

• Success depends on early intervention
Diagnostic criteria for de novo AIH

• No evidence pre-op for AIH
• Elevated LFTs
• Elevated gammaglobulins
• Autoimmune antibodies (ANA, ASmAb)
• Biopsy consistent with AIH
  – plasma cell–rich central perivenulitis
• Treatment is steroids, azathioprine or MMF
Rejection may trigger de novo AIH
Recurrent PSC

Diagnostic Inclusion Criteria

• OLT for confirmed PSC

• Cholangiography
  
  Non-anastomotic intrahepatic and/or extrahepatic strictures, beading and irregularities >90 days after OLT

• Histopathology
  
  Fibrous cholangitis and/or fibro-obliterative lesions with or without ductopenia, fibrosis or cirrhosis

Graziadei IW et al. Hepatology 1999
Graziadei IW et al. L Transpl 2002
# Prevalence of Recurrent PSC

<table>
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<tr>
<th></th>
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<th>Recurrence</th>
<th>F/U</th>
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<tr>
<td>NIH-data</td>
<td>124</td>
<td>36%</td>
<td>12 yrs</td>
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<tr>
<td>Mayo / Columbia</td>
<td>346</td>
<td>24%</td>
<td>9 yrs</td>
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<tr>
<td>Columbia</td>
<td>130</td>
<td>17%</td>
<td>5.2 yrs</td>
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<tr>
<td>Birmingham</td>
<td>152</td>
<td>37%</td>
<td>10 yrs</td>
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<tr>
<td>Kings</td>
<td>69</td>
<td>13.5%</td>
<td>9 yrs</td>
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<td>Washington</td>
<td>69</td>
<td>10%</td>
<td>4 yrs</td>
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<tr>
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<td>49</td>
<td>18%</td>
<td>7 yrs</td>
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<tr>
<td>Boston</td>
<td>42</td>
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<tr>
<td><strong>Total</strong></td>
<td>237 / 956</td>
<td>24%</td>
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PSC recurrence post LT
Recurrent PSC post LT

• Risk of recurrence of PSC (1,3,5, 10 years)
  – 0.3%, 4.0%, 8.7%, and 22.4%

• Risk of re-transplant (1,3,5, 10 years)
  – 5.4%, 5.8%, 5.8%, and 7.5%

• Probability of being alive with original graft no recurrence (1,3,5, 10 years)
  - 92.7%, 87.7%, 82.5%, and 67.0%
There is no difference between LDLT and DDLT in recurrence rate.
Recurrent PSC: Therapy

• Dilatation and stenting of biliary strictures

• Antibiotics - cholangitis

• Ursodeoxycholic acid - ? Efficacy

• Retransplantation for recurrent PSC

(Recurrence with 2nd graft)
WE SHIFT OUR FOCUS NOW FROM IMMEDIATE SURVIVAL TO SURVIVAL 10 YEARS, 20 YEARS POST LT.
THANK YOU

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