Post-Liver-Transplant Complications
Medical Disorders

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Post-Transplant Complications

**Time**
- Early: 0-1 month
- Intermediate: 1-6 months
- Late: > 6 months

**Type**
- Infection
- Allograft dysfunction
- Biliary tract dz.
- Disease recurrence
Post Liver Transplant Complications: Early: 0-1 Month

- **Infections:**
  - **Bacterial:** related to procedure →
    - pneumonia;
    - biliary sepsis;
    - wound infection;
    - catheter related,
    - c. difficile PMC
  - **Viral:**
    - HSV stomatitis,
    - HCV,
    - Hepatitis B (if without prophylaxis)
  - **Fungal:**
    - Candida,
    - Aspergillus
  - **Parasites:**
    - Strongyloides
Post Liver Transplant Complications: Early: 0-1 Month

• **Allograft dysfunction:**
  – PNF in first two weeks
  – Acute cellular rejection
  – Small-for-size Syndrome

• **Biliary tract:**
  – Bile leaks
  – Anastomosis disruption
  – Hepatic duct stricture/hepatic artery thrombosis

• **Disease recurrence:** unusual
Post Liver Transplant Complications: Intermediate: 1-6 Months

- **Infections**:
  - **Viral**:
    - HHV6, - Adenovirus,
    - RSV, - Viral reactivation (CMV, EBV, VZV, HCV, HBV),
  - **Bacterial**:
    - Listeria, - Nocardia,
    - TB,
  - **Fungal**:
    - Pneumocystis, - Aspergillus,
    - Cryptococcus, - Hystoplasma,
    - Coccidioides,
  - **Parasites**:
    - Toxoplasma, - Strongyloides,
    - Leishmania, - Trypanosoma
Post Liver Transplant Complications: Intermediate: 1-6 Months

- **Allograft dysfunction:**
  - Recurrent HCV
  - Rejection
  - Hepatic artery thrombosis

- **Biliary tract:**
  - Biliary stricture
  - Leak associated with T-tube removal

- **Disease recurrence:**
  - HCV,
  - PBC,
  - PSC (if after > 90 days),
  - Alcohol (rarely)
Post Liver Transplant Complications:

Late: > 6 Months

- **Infections:**
  - Community acquired infections (UTI, pneumonia)
  - VZV, CMV, influenza, papillomavirus, PTLD
- **Allograft dysfunction:**
  - Chronic Rejection
  - Lymphoproliferative Syndrome (PTLD)
  - Underlying Disease
- **Biliary tract:** < 4% per year
- **Disease recurrence:** HCV, PBC, PSC, alcoholism within two years
Allograft Dysfunction
Graft Complications
0-1 month

- **Primary Nonfunction:**
  - Occurs in 4-10% LTX.
  - **Features:** hepatic encephalopathy, coagulopathy, minimal bile output, renal & multisystem failure, persistent hypothermia, hemodynamic instability, high lactate & liver enzymes, and hepatocyte necrosis, *without* vascular complication.
  - Those with hemodynamic instability or multiorgan failure need urgent retransplantation.
Primary Nonfunction:

- Donor risk factors:
  - prolonged cold ischemia,
  - unstable donor,
  - high steatosis,
  - older age,
  - hypernatremia,
  - non-heartbeating
Allograft Complications 0-1 month
“Small-for-Size” Syndrome

- Partial liver graft unable to meet functional demands of recipient: poor early graft function in absence of ischemia.
- Prevention: in cirrhotic GWBWR must be $\geq 0.85\%$
- Manifestations:
  - Poor bile production
  - Prolonged cholestasis
  - Significant ascites
  - Coagulopathy
Allograft Complications 0-1 month
“Small-for-Size” Syndrome

• Biochemical profile:
  – Elevated Direct (& total) bili
  – Mild/moderate elevation of ALT & AST
  – Prolonged PT

• Histologic Features:
  – Cholestasis with “bile plugs”
  – Areas of regeneration & ischemia with patchy necrosis.

• Prognosis: 50% of recipients will die of sepsis within 4-6 weeks.
Acute Allograft Rejection

• **Features:**
  - Portal infiltrate with mixed inflammatory cells
  - Bile duct injury
  - Endothelialitis

• **Grades (Banff Criteria)**
  - **I (mild):** cellular infiltrate in < 50% triads, mild, and within portal spaces.
  - **II (moderate):** cellular infiltrate in > 50% triads
  - **III (severe):** as in moderate + spillover into periportal areas + moderate/severe perivenular inflammation with perivenular-hepatocyte necrosis.
**Post-Transplant Lymphoproliferative Disorder**

T-lymphocytes are supposed to regulate B-cell proliferation due to EBV; in PTLD immunosuppression affects T-cell immunity allowing unregulated proliferation.

- B-cell proliferation in nodal & extranodal sites; may involve transplanted organ.
- Median time: 10 mo post-LTx.
- Child/adult = 3/1.
- Survival: 1-y = 85%; 20-y = 45%.
- Better survival if:
  - limited dz, - polymorphic/polyclonal dz,
  - in children, - on tacrolimus.
**PTLD**

- **...PTLD**

**DX:** Bx with hyperplastic or neoplastic growth of B-cells which are receptor CD20(+) .

- **Risk factors:**
  - pre-LTx EBV sero-negativity,
  - steroid bolus,
  - CMV disease,
  - blood products.
  - excessive immunosuppression (OKT3, ATGAM, Thymoglobulin),
Allograft Complications at any time

PTLD

- **THERAPY OF PTLD**
- **Limited Disease (one site only)**
  - Surgical extirpation or localized radiation
  - Minor/moderate immunosuppression reduction (25%)
- **Extensive disease (more than 1 site)**
  - Intense immunosuppression reduction (50%)
  - Extirpation of local disease.
  - Rituximab
  - Chemotherapy, for Rituximab failure or poor prognosis
  - In CNS involvement, radiation without chemotherapy.
- **Critically ill**
  - Stop all immunosuppression except Prednisone
Infections
Post Liver Transplant Complications: Infections

• More than 2/3 patients will develop infections in the 1st year.
• Infections are the leading cause of death.
• Complication of overimmunosuppression
• Risk increased by:
  – acute rejection,
  – re-transplantation,
  – HIV,
  – hepatitis B or C.
Bacterial Infections
Post Liver Transplant Complications: Bacterial Infections

- More common in 1st two months & most frequently located in the abdomen.
- General Risk factors:
  - rejection, - s/p acute liver failure,
  - high bilirubin, - prolonged hospitalization,
  - long OR time, - long ICU stay.
Post Liver Transplant Complications: Bacterial Infections

- **Bacteremia:**
  - Most common pathogens:
    - S. aureus
    - Enterococcus.
  - Risk factors:
    - DM, - IV catheter,
    - CMV, - low albumin,
    - roux-en-y, - biliary stricture.
Post Liver Transplant Complications: Bacterial Infections

- **Intra-abdominal & wound infections**
  - *do not decrease patient nor graft survival.*
  - **Risk factors:**
    - bile anastomotic leak, - high pre-op WBC,
    - long OR time, - ascites,
    - severe obesity, - low albumin,
    - high transfusion need, - OKT3 use.
Post Liver Transplant Complications: Bacterial Infections

• **Pneumonia:**
  - Bacteria & aspergillus in 1\textsuperscript{st} month.
  - Legionella may be the cause early post-OLTx or post rejection therapy.
  - Splenectomy increases risk of opportunistic infection.
  - BAL & Bx are helpful.

• **Hepatic Artery Thrombosis (HAT)**
  occur in 7%; associated with:
  - bacteremia, - cholangitis,
  - liver abscess, - graft loss.
Post Liver Transplant Complications: Bacterial Infections

- **Legionella:**
  - Usually early post-OLTx or after rejection therapy
  - Fever, chills, malaise, dyspnea, non-productive cough, diarrhea.
  - CXR: unilateral or bilateral dense lung infiltrate.
  - **DX:** Legionella Ag in urine, fluorescent Ab in respiratory secretion
  - **Treatment:** fluoroquinolone or erythromycin
Post Liver Transplant Complications: Bacterial Infections

- **Nocardia**: 
  - 0.7-3% of patients. N. asteroides is most common. 
  - From 2nd month until years later. 
  - May give: pneumonia, pulmonary nodules, lung abscess, brain abscess, meningitis, or skin lesions. 
  - *All patients should have brain imaging to R/O abscess.* 
  - **DX**: branching gram(+) bacteria; positive culture. 
  - **Treatment**: Bactrim or Minocycline.
Post Liver Transplant Complications: 
Bacterial Infections

- **Listeria monocytogenes:**
  - Usually from weeks to initial 2 months; infrequently years later.
  - Acquired from contaminated food.
  - May give: meningitis, meningo-encephalitis, encephalitis, bacteremia.
  - Rarely: pneumonia, arthritis, endophthalmitis, endocarditis, peritonitis, myocarditis, or hepatitis.
  - **Presentation:** fever, headache, meningismus, altered mentation, focal CNS findings, or seizures.
  - **DX:** Listeria in CSF or blood culture.
  - **Treatment:** Amp + Gent, or Bactrim
Post Liver Transplant Complications: Mycobacterial Infections

- **Tuberculosis**: Incidence is 1-6% in developed countries; high morbidity & mortality (up to 40%).
  - Mean onset is 9 months (15 days to years).
  - 50-66% have pulmonary TB.
  - Usually is reactivation of “dormant TB”.
  - Symptoms: fever, night sweats, weight loss.
  - **Pulmonary**: cough, dyspnea, pleuritic pain; may be miliary, focal or nodular; cavitary in 4%.
  - **Extrapulmonary**: gastrointestinal (ileitis, colitis, hepatitis, peritonitis; may cause GI bleed), genitourinary, skin, muscles, bones, lymph nodes, CNS.
- **Other Mycobacteria**: unusual in liver transplant. Most commonly pulmonary, pleural, or cutaneous.
Parasitic Infections
Post Liver Transplant Complications: Protozoal Infections

- **Toxoplasma gondii:**
  - uncommon except in heart Tx with allograft from infected donor.
  - TMP/SMX has decreased the risk.
  - May cause pneumonia as reactivated disease.
  - Diagnosis by BAL with direct immunofluorescence or PCR.

- **Others:**
  - *Strongyloides* (autoinfestation)
  - Giardia, Cryptosporidium, Isospora, Cyclospora, Microspora
  - Nematodes, Leishmania, Trypanosoma.
Fungal Infections
Post Liver Transplant Complications: Fungal Infections

- **Risk factors:**
  - invasive infection likely with two of the following factors:
    - creat > 3 mg/dL,
    - re-transplantation,
    - fungal colonization
  - OR time > 11 hours,
  - need for transfusion,

Other factors: CMV, HHV-6, HCV
Post Liver Transplant Complications: Fungal Infections

- **Candida**: most common fungal infection.
  - Risk factors: SBP prophylaxis, post-Tx dialysis, re-Tx.

- **Aspergillus**:
  - Second most common fungal infection.
  - High mortality (90%).
  - Median time: 17 d post-LTx.
  - Causes angioinvasion with tissue necrosis.
  - Aspergillus in sputum in Tx patient is probably invasive infection.
Post Liver Transplant Complications: Fungal Infections

- **Cryptococcus:**
  - most common cause of post-Tx meningitis.
  - Incidence=12/1000.
  - Mean time 30 mo post-LTx (1-146 mo).
  - May cause pneumonia (46%), meningitis (36%), other organ (11%), multiorgan (11%).
  - Mortality: 25%.
  - Infection may be subacute.
  - Cryptococcal serum Ag is good in meningitis, but only 40% (+) in pneumonia.
Post Liver Transplant Complications: Fungal Infections

- **Pneumocystis jiroveci:**
  - now very rare b/o TMP/SMX prophylaxis (5-10% of LTx in the past).
  - Most common 1-6 mo post Tx (up to 1 y).
  - Indolent fever, dyspnea, dry cough & hypoxemia.
  - CXR: Bilateral lung infiltrates.
  - BAL with immunofluorescence.
  - **Treatment:** TMP/SMX; if intolerant, aerosolized pentamidine.
Viral Infections
Post Liver Transplant Complications: Viral Infections

- **Cytomegalovirus**: Is immunomodulator virus; it is associated with fungal infections and chronic rejection.
  - CMV syndrome with fever, leukopenia & thrombocytopenia.
  - Pneumonia with diffuse infiltrates. Hepatitis. Retinitis.
  - Diagnosis by Bx findings, ophtalmoscopic exam, pp65 antigenemia, and/or quant PCR.
  - Risk factors: D+/R-, D+/R+, OKT3, Thymoglobulin, ATGAM.
  - **Treatment**: Ganciclovir IV or Valganciclovir po.
  - **Prophylaxis**: ganciclovir 1 gm TID po x 3 mo decreased CMV disease from 48.9% to 4.8%.
  
  Preemptive therapy is a reasonable alternative.
Post Liver Transplant Complications: Viral Infections

- **Epstein-Barr Virus:**
  - Signs & symptoms similar to CMV (fever, leukopenia, thrombocytopenia & atypical lymphocytosis in 50%; atypical presentation in 50%).
  - Reactivation most common in adults (90% sero-positive) & primary infection most common in children.
  - Most PTLD are due to EBV.
Post Liver Transplant Complications: 

Viral Infections

**HSV & VZV:**
- Pre-prophylaxis 1/3 patients had HSV disease.
- Now HSV & VZV are rare b/o acyclovir or famciclovir use.
- Hepatitis & pneumonitis may occur without skin lesions.
- VZV vaccine can be given before Tx.
- Post contact prophylaxis with VZV immunoglobulin is useful.
Post Liver Transplant Complications: Viral Infections

- **Adenovirus:**
  - More common in children.
  - May cause colitis, hepatitis, pneumonitis, hemorrhagic cystitis, encephalitis. FHF may occur.
  - Mimics CMV with fever, leukopenia, intranuclear inclusion bodies, and negative bacterial cultures.
  - Asymptomatic infection in 8-10% pediatric liver recipients.
  - Cidofovir or ribavirin may help.
Post Liver Transplant Complications: Viral Infections

- **Human Herpesvirus 6**: is an immunomodulator virus and the agent of Roseola Infantum.
  - Most children sero-positive by age 2.
  - Reactivates wk 2-8 post-LTx.
  - Incidence: 14-82%.
  - **Symptoms**: fever, rash, pneumonitis, hepatitis, encephalitis.
  - Increases risk of invasive fungal infections.
  - **DX**: shell vial culture. Serology is not reliable. Antigenemia may be helpful. Serum PCR is too sensitive (overdiagnosis).
  - **Treatment**: ganciclovir, foscarnet, cidofovir.
Post Liver Transplant Complications: Viral Infections

- **Human Herpesvirus 8**: causes Kaposi sarcoma, Castleman dz, and Primary Effusion Lymphoma.
  - Very rare; occurs in Liver Tx on CSA or Tacrolimus;
  - KS lesion in skin, viscera/liver.
  - Overimmunosupression increases risk.
  - **Treatment**: d/c or decrease immunosupression; bleomycin, doxorubicin, vincristine may help. Unknown if antivirals help.
Recurrent Disease
HBV prevention Post-OLTx
HBsAg(+) Recipient
Benefits of HBIG Prophylaxis
HBsAg(+) Recipient

• Without Prophylaxis: 5 year survival 40-60%
• With Prophylaxis survival is: 1 y = 91%, 5 y = 81%,
  10 y = 73%
• Anti-HBs titer goals post-OLTx (in HBIG monotherapy):
  – a) first week: >500 IU/L,
  – b) week 2-4: >500 IU/L in high-replic; >100-150 in low-replic
  – c) day 28-180: >250 IU/L in high-replic; >100-150 in low-replic
  – d) thereafter: >100-150 IU/L
• Escape occurs b/o:
  – a) “inadequate anti-HBs titer”, or
  – b) “pre-S/S mutation” causing reduced binding of anti-HBs.
### HBsAg (+) Liver Transplant Recipient

<table>
<thead>
<tr>
<th>Recipient’s Status</th>
<th>Anhepatic Phase</th>
<th>First week</th>
<th>Thereafter</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV-DNA &gt; 2000 IU/mL</td>
<td>HBIG 10000 IU, IV</td>
<td>HBIG 10000 IU, qd IV, x 6 days</td>
<td>HBIG 936 IU (3 mL Nabi-HB), IM on day 7, and q month for life</td>
<td>HBsAg, HBe/anti-HBe, HBV-DNA quantitation q month x 3, and then q 3 months for life</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adefovir+Lamivudine, or Entecavir, or Tenofovir, <strong>for life</strong></td>
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<td></td>
</tr>
<tr>
<td>HBV-DNA ≤2000 IU/mL, or Fulminant HBV, or HBV + Delta</td>
<td>HBIG 936 IU (3 mL Nabi-HB), IM</td>
<td>HBIG 936 IU (3 mL Nabi-HB), qd IM, x 7 days</td>
<td>HBIG 936 IU (3 mL Nabi-HB), q month IM. Immunize after 1 year, and if anti-HBs response &gt; 100 IU/L, d/c HBIG</td>
<td>HBsAg, HBe/anti-HBe, HBV-DNA quantitation q month x 3, and then q 3 months for life</td>
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</tbody>
</table>
Anti-HBc(+) organ given to HBsAg(-) Recipients
Anti-HBc(+) organ donors
Risk of HBV acquisition

- Anti-HBc (+) or anti-HBs (+) donors: 33-100%
- Anti-HBc(+) organ given to:
  - HBV naïve recipient: 30-72%.
  - Anti-HBc(+) recipient: 13%.
Anti-HBc(+) Organ Donors
Risk of HBV Infection
Dodson et al. Transplantation 1997

No HBV prophylaxis was given
Anti-HBc(+) Donor To Naïve Recipient
Effect of Prophylaxis
UCLA Experience

Ghobrial RM; Transplant Hepatology CAQ Course - 2006

<table>
<thead>
<tr>
<th>Therapy</th>
<th>% Anti-HBc (+) to Naïve</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Therapy</td>
<td>29</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>44</td>
</tr>
<tr>
<td>HBIG</td>
<td>17</td>
</tr>
<tr>
<td>HBIG + Lam</td>
<td>0</td>
</tr>
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</table>
### Anti-HBc(+) organ given to HBsAg(-) Recipient

<table>
<thead>
<tr>
<th>Recipient Status</th>
<th>Donor Status</th>
<th>Oral Agent</th>
<th>Immunization</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peak anti-HBs &gt; 10 mIU/mL, or anti-HBc(+)</strong></td>
<td>Serum HBV-DNA(+)</td>
<td>High “barrier-resistance”, [(Adefovir+Lamivudine), Entecavir, or Tenofovir] for life.</td>
<td>HBV-vaccine 40 mcg @ 0,1,2,6 mo x 1-3 times until anti-HBs &gt; 100 mIU/mL</td>
<td>HBsAg, HBe/anti-HBe, HBV-DNA quantitation q month x 3, and then q 3 months for life</td>
</tr>
<tr>
<td><strong>Peak anti-HBs &gt; 100 mIU/mL</strong></td>
<td>Serum HBV-DNA(-)</td>
<td>Lamivudine 150 BID, until anti-HBs &gt; 100 mIU/mL, or for life</td>
<td>HBV-vaccine 40 mcg, until anti-HBs &gt; 100 mIU/mL</td>
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HCV Recurrence Post Liver Transplant Natural History
Post-OLTx HCV Recurrence

- Infection occurs during graft reperfusion.
- Negative-strand HCV-RNA (replication) as early as 48h post-LTx.
- 25% have HCV core Ag in hepatocyte 10 d post-LTx, & > 90% @ 3 months post-LTx
- Pre-LTx HCV-RNA level may be reached by day 4.
- Peak titers reached at 1-3 mo post-Tx.
- 1-y post-LTX, HCV-RNA level are 10-100X pre-LTx
- Failure to develop a HCV-specific MHC-complex class II-restricted CD4+ T-cell response contributes to graft-injury.
**Acute HCV Recurrence**

- Mild to moderate ALT/AST elevation
- Total bilirubin < 6 mg/dL
- Liver Bx in acute HCV:
  - mononuclear lobular infiltrate, variable hepatocyte necrosis, and fatty infiltration;
  - Il-2, IFN-gamma, and TNF gene expression dominate.
- Liver Bx in Acute Cellular Rejection:
  - endothelitis, severe bile duct damage, and *mixed-cell* infiltrate;
  - Il-4 & Il-10 gene expression dominate.
- Portal lymphocytic infiltrate and lymphocyte aggregates are seen in HCV & ACR.
Post-OLTx HCV Recurrence
Factors That Affect Outcome

- Pre-OLTx HCV-RNA > 600000 IU (1 M copies)
- Advanced Donor Age (> 50) (increase 1%/y after age 25; very poor if donor > 65 y)
- Treatment of ACR (do not treat mild rejection)
- High-average daily steroid dose
- T-cell depleting therapy
- CMV disease
- Non-caucasian recipient
- Year of OLTx (?) (worse in recent years)
Fibrosing Cholestatic Hepatitis

- Bilirubin > 6 mg/dL without biliary or vascular complications.
- Usually in 1st year
- Begins about 1 mo post LTx; liver failure in 3-6 months.
- ALT & AST elevated 2-5X; alk. phosph. > 500 U/L & GGT > 1000 U/L
- Very high serum (> 30-50 million IU/mL) & intrahepatic HCV-RNA
Fibrosing Cholestatic Hepatitis

- Liver Bx: severe perivenular hepatocyte ballooning, intrahepatic cholestasis, pericellular & portal fibrosis, ductular proliferation, and paucity of inflammation.
- Probably due to high immunosuppression; stable quasispecies; $T_H^2 > T_H^1$ cytokine response; direct cytotoxic injury.
- Prognosis: very serious illness with extremely high mortality.
- Treatment: Decrease immunosuppression and Peg-IFN + RBV (but is poorly tolerated) long term.
Chronic HCV Recurrence

- There is portal-portal bridging fibrosis and portal & lobular infiltration; variable degrees of hepatocyte necrosis.
- Progressive, non-specific $\text{Th}^1$ inflammatory response.
- Treatment recommended for stages METAVIR 2 / ISHAK 3 or higher.
Post-OLTx HCV Recurrence

- Risk of death (hazard ratio 1.23) & of graft-loss (hazard ratio 1.3) is higher in HCV(+) than in HCV(-), at 1, 3, & 5 years; (but patient survival similar to ALD, & cryptogenic liver disease).

- Fibrosis progression in HCV:
  - LTx = 0.3-0.8 stage/y vs
  - Immunocompetent = 0.1-0.2 stage/year.

- Median time to cirrhosis:
  - LTx = 10y;
  - Immunocompetent = 20-40 y.
Post-OLTx HCV Recurrence

• Cirrhosis:
  – 6-23% in 3-4 y,
  – 30% by 5 y.

• Risk of decompensation:
  – 1y = 42% (< 5% immunocompetent) &
  – 3y = 62% (< 20% in Immunocompetent)

• Approximately 10-25% of post-LTx HCV-liver disease will need re-Tx or will be dead within initial 5 years.
Survival After Liver Transplantation


The bar chart shows the survival rates after liver transplantation for non-HCV and HCV patients at various time intervals: 1 year, 2 years, 3 years, 4 years, and 5 years. The survival rates are indicated with orange and maroon bars, respectively.
Patient Survival After Liver Transplantation

![Graph showing patient survival rates over 1 year, 3 years, and 5 years for different causes of liver disease: HCV, ALD, and Cryptogenic.](Image)
Graft Survival After Liver Transplantation

![Bar chart showing graft survival rates after liver transplantation. The chart compares survival rates for different causes of liver disease: HCV, ALD, and Cryptogenic. The rates are given for 1 year, 3 years, and 5 years post-transplantation.](image-url)
Progression to F3-F4 Fibrosis and to Decompensated Cirrhosis Post OLTx HCV
Survival in Post-OLTx HCV-Cirrhosis
Berenguer et al. Hepatology 2000;32:852-858

![Graph showing survival rates in Post-OLTx HCV-Cirrhosis](image)

- **Compensated**
- **Decompensated**

- **1 year**
- **2 years**
- **3 years**

- **Survival Rates**
  - 1 year: Compensated 80%, Decompensated 20%
  - 2 years: Compensated 70%, Decompensated 30%
  - 3 years: Compensated 60%, Decompensated 40%
Treatment of Recurrent HCV
Preemptive

- Starts therapy shortly post LTx.
- Treatment is poorly tolerated.
- Discontinuation rate: 33%
- Reported SVR: 10-25%
Treatment of Recurrent HCV After METAVIR Stage 2

- Interferon or RBV monotherapy have not improve fibrosis nor induce SVR.
- With Peg-IFN + RBV, SVR has been 26-45%
- 60% of patients with SVR improve histology; 20 % remain stable.
- 30-60% require RBV dose reduction; 30% need discontinuation of therapy.
- There is no increase in rate of Acute nor Chronic Rejection.
## Histologic Scoring of Fibrosis

<table>
<thead>
<tr>
<th>FIBROSIS</th>
<th>METAVIR</th>
<th>Ishak</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Portal fibrosis (some p. areas)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Portal Fibrosis (most p. areas)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Bridging fibrosis (occasional)</strong></td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Bridging fibrosis (marked)</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Incomplete cirrhosis</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>4</td>
<td>6</td>
</tr>
</tbody>
</table>

Treat METAVIR $\geq 2$, or Ishak $\geq 3$
Peg-IFN + RBV for HCV Recurrence in OLTx Recipients

- 36 patients
- Median time OLTx-Rp = 513 d
- Cirrhosis 15%, cholestatic HCV 9%
- 88% off steroids
- Premature D/C 40%
- ADEs 57%
- Rejection 14%
- EPO increased SVR
- HCV-RNA drop < 2 log @ 12 wks = non-response
Predictors of Poor Outcome in HCV Re-Transplantation

- Bilirubin > 10 mg/dL
- Creatinine > 2 mg/dL
- Creatinine clearance < 40 mL/min
- Recipient > 55 years
- Cirrhosis < 1 year post-LTx
- Donor > 40 years
Patients: 32 HCV infected s/p OLTx who developed graft failure and needed re-transplantation.

Mean time to re-transplant: 41 months

Indications: ch. rejection 37%, HCV infection 28%, both 31%

Causes of death post re-OLTx: Sepsis 25%, HCV 15%, MOF 6%

Treatment against HCV given to 56%; 38% of them had SVR
Recurrent PBC
Neuberger J. Liver Transplantation 2003

- **Rate:**
  - 17% with strict criteria;
  - 26% with expanded criteria

- **Diagnostic Criteria:**
  - OLTx for PBC, and
  - AMA persistence, and
  - Histology (2/4 = probable; 3/4 = definitive)
    - Mononuclear cell infiltrate
    - Lymphoid aggregates
    - Epitheloid granulomas
    - Bile duct lesions
<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Little mismatch of HLA-A, HLA-B, and HLA-DR</td>
<td>Increased</td>
</tr>
<tr>
<td>Living donor recipient</td>
<td>Increased</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Increased ?</td>
</tr>
<tr>
<td>Warm/cold ischemia time</td>
<td>Increased ?</td>
</tr>
<tr>
<td>Young donor/recipient</td>
<td>Increased ?</td>
</tr>
<tr>
<td>Steroid discontinuation</td>
<td>Unclear</td>
</tr>
</tbody>
</table>
Recurrent PBC
Treatment & Prognosis

- UCDA commonly used; decreases alkaline Phosph & ALT in 52% @ 36 month.
- No change in graft nor patient survival.
- Infrequent need for late re-transplantation (4% from recent UNOS database)
Recurrent PSC
Diagnostic Criteria
Graziadei I. Liver Transplantation 2002

- OLTx for confirmed PSC
- Absence of Exclusion Criteria
- Cholangiography
  - Intrahepatic and/or extrahepatic strictures/beading/irregularities > 90 days after OLTx
- Histopathology
  - Fibrous cholangitis and/or fibro-obliterative lesions +/- ductopenia, fibrosis, or cirrhosis
Recurrent PSC
Exclusion Criteria
Graziadei I. Liver Transplantation 2002

- Hepatic artery thrombosis or stenosis.
- Chronic ductopenic rejection
- Anastomotic stricture alone.
- Non-anastomotic stricture < 90 days post-OLTx
- Donor/Recipient ABO incompatibility.
Recurrent PSC

Predictors, Prognosis, & Therapy

- **Incidence:** 10-27% ; onset: 6 mo 5y.
- **Predictors:**
  - UC with intact colon,
  - Steroid resistant rejection,
  - Albumin given at OLTx,
  - HLA-DR matching, and/or HLA-DRB1*08
  - Cholangio-Ca before OLTx.
- **Prognosis:**
  - 7.5% re-transplantation rate.
- **Treatment:**
  - none proven;
Recurrent AIH
Suggested Diagnostic Criteria

- OLTx for AIH
- Persistence of autoantibodies
- Hypergammaglobulinemia and/or high IgG
- Characteristic Histology
  - Prominent portal interface hepatitis
  - Lymphoplasmocytic infiltrate
  - Lobular involvement
  - Occasional: bile-duct lesion, endothelialitis.
- Response to Steroids
- Exclusion of other causes.
Recurrent AIH
Risk Factors

- Discontinuation of steroids; low-dose immunosuppression.
- Type-I AIH = 34%; Type-II AIH = 5%
- HLA-DR3/DR-4 recipient?
- Severe necroinflammatory activity?
- Unaffected by Tacrolimus vs CyA
Recurrent AIH

- Incidence: 23% (patients should stay with steroids in immunosuppressant protocol).
- Interval to Dx: 26.4 mo (14-55)
- Autoantibodies: most commonly ANA \(\geq\) 1:40, anti-SLA. May have (+) ASMA, anti-LKM1, ANCA.
Recurrent AIH
Treatment & Prognosis

- Prednisone +/- Azathioprine
- Switch from CyA to Tacrolimus potentially effective.
- Sirolimus in non-responders to steroids.
- Graft & patient survival unaffected at medium-term.
- Long-term progression to cirrhosis: 40%.
- May need re-transplantation.
- Rarely recurs in new allograft.
Recurrent NASH

- Found in “Protocol Biopsies”
- Clinical evidence of weight gain, hyperglycemia, hypertriglyceridemia.
- At 1 year: NASH in 25%
- At 4 years: NASH in 50%
Re-Transplantation
Survival after Liver Transplant & Re-Transplant

![Bar graph showing survival rates after liver transplant and re-transplant over time.](image)
Re-LTX 1-year Survival by UCLA Class

- **POINTS (1 each)**
- Age > 18
- Liver ischemia > 12 h
- Pre-op in ventilator
- Creatinine > 1.6mg/dL
- Bilirubin > 16mg/dL
Long-Term Follow-Up

• Labs:
  – CBC + diff
  – CMP
  – CSA or tacrolimus levels

• Vaccines:
  – Yes: HBV, pneumococcus, influenza
  – No: live/attenuated → measles, mumps, rubella, oral polio, BCG
Long-Term Follow-Up

- **Metabolic Syndrome:** any 3 of the following
  - Abdominal girth: males > 40 in, female > 35 in
  - Lipid panel after 14 h fasting:
    - Triglycerides > 150 mg/dL
    - HDL: < 40 mg/dL in males, < 50 in females
    - LDL > 100 mg/dL
  - Fasting blood sugar >/= 100 mg/dL
  - BP > 130/85 mm Hg
Long-Term Follow-Up

• Hyperlipidemia:
  – Hyperlipidemia with Sirolimus > CSA > Tacrolimus.
  – Change to Tacrolimus, minimize dose, or change to MMF regimen.
  – Mediterranean diet.
  – Best choice is Pravastatin 20 mg; others are simvastatin 40 mg, or atorvastatin 40 mg
General Plan for the Stepwise Management of Dyslipidemia

- Elevated low-density lipoprotein cholesterol level > 100 mg/dL (with or without elevated triglycerides)
  - 1. Therapeutic lifestyle and dietary changes
  - 2. Statins
  - 3. Addition of ezetimibe

- Hypertriglyceridemia with normal cholesterol
  - 1. Fish oil at 1000 mg twice daily to 4 g daily if tolerated
  - 2. Fibric acid derivatives

- Refractory hyperlipidemia: consider changes in

- immunosuppression
  - 1. Conversion of cyclosporine to tacrolimus
  - 2. CNI reduction (eg, add mycophenolate mofetil)
  - 3. Discontinuation of sirolimus
Long-Term Follow-Up

- **Hypertension:** (BP > 130/80 mm Hg).
  - Goal: 125/75 for renal impairment; others 130/80
  - Steroid reduction or withdrawal, change CSA to tacrolimus, change CNI to sirolimus, or MMF.
  - Best are Ca channel blocker (amlodipine or nifedipine, that decrease vasoconstriction from CNI), plus diuretics
  - Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and direct renin inhibitors should be used as first-line antihypertensive therapy in LT recipients with DM, CKD, and/or significant proteinuria (grade 1, level A); addition of diuretics mitigate volume retention from CNI.
Long-Term Follow-Up

• **Insulin Resistance** (HOMA $\geq 2.5$)
  - Avoid, or taper & discontinue steroids rapidly (within 3 months).
  - Tacrolimus depletes pancreatic beta-cell mRNA; change to CSA
  - ADA weight control Diet + Exercise $\geq 4000$ steps/d
  - Metformin if creat $\leq 1.5$ mg/dL in males, & $1.25$ in females.
  - Glinides: repaglinide (Prandin).
Long-Term Follow-Up

- **Dental:**
  - Periodontal prophylaxis every 6 months

- **Bone:**
  - Calcium = 1200 mg/d
  - Vitamin D = 400-800 IU/d
  - Bone densitometry (DXA)
Long-Term Follow-Up

• Colorectal:
  – Colonoscopy every 10 years (>50 y/o)
  – In U.C. → colonoscopy every year

• Contraception → High Risk Pregnancies
Long-Term Follow-Up
Risk of oro-pharyngeal Neoplasm

45 months

ALD
Other cirrhosis
Questions ?
Combination HBIG + Oral agent

High Replicators (> $10^4$ copies or > 2000 IU/mL)

- **Anhepatic phase:** HBIG 10000 IU IV
- Continue effective “high resistance-barrier” oral agent, post-OLTx, **for life**.
  - Give either (Adefovir + Lamivudine), Entecavir, Tenofovir, or combination regimen that was effective pre-Tx.
- **First week:** daily 10000 IU HBIG IV x 6 days
- **Thereafter:** 936 IU IM q month (3 mL Nabi-HB), starting on day 7 post-op.
- **Monitoring:**
  - HBsAg, HBe Ag & Ab, and HBV-DNA quant q month x 3; then
  - HBsAg, HBe Ag & Ab, and HBV-DNA quant q 3 months for life.
Combination HBIG + Oral agent

Low replicators (\( \leq 10^4 \text{ copies/mL or } < 2000 \text{ IU/mL} \)),
Fulminant HBV, and HBV+Delta

Angus PW. Liver Transpl 2000;6:429-433; Gane EJ. Gastroenterology 2007;132:931-937

- **Anhepatic phase**: HBIG 936 IU IM (3 mL Nabi-HB)
- Start/continue “high resistance-barrier” oral agent post-OLTx for life:
  - Either (Adefovir + Lamivudine), Entecavir, or Tenofovir, or the combination that was effective before transplant.
- **First week**: daily 936 IU HBIG (3 mL Nabi-HB) IM x 7 days.
- **Thereafter**: HBIG 936 IU IM q month (3 mL Nabi-HB)
- If after 1 year HBV-DNA is still “non-detectable”, consider to discontinue HBIG after vaccination + boosters (40mcg @ 0,1,2 & 6 mo) x 1-3 courses, if patient responds with anti-HBs > 100 mIU/mL.
- **Monitoring**:
  - HBsAg, HBe Ag & Ab, and HBV-DNA quant q month x 3; then
  - HBsAg, HBe Ag & Ab, and HBV-DNA quant q 3 months for life.
Definitions for Oral Antivirals

Pre-OLTx anti-HBV Therapy

- **High replicators** $> 10^4$ copies/mL or $> 2000$ IU/mL:
  - high risk for graft re-infection and death;
  - all cirrhotics with $> 10^4$ copies/mL (2000 IU/mL) need therapy with “high resistance-barrier agent” (Tenofovir, Entecavir, or Lamivudine+Adefovir).

- **Low replicators** $< 10^4$ copies/mL ($< 2000$ IU/mL):
  - moderate/low risk re-infection & death;
  - if $< 10^2$ copies/mL, may be candidates for post-OLTx [short-term HBIG + oral agent], or [oral “high resistance-barrier” agent monotherapy].
Definitions for Oral Antivirals

Pre-OLTx anti-HBV Therapy

- **Primary non-response:** drop of HBV-DNA < 1 log after 12 wks of therapy
  - Check for viral resistance (INNO-Lipa HBV DR v2). May be compliance issue, or host pharmacologic effect.
  - Change or **add second drug without cross-resistance.**

- **Partial Response:** HBV-DNA > 2000 IU/mL after 24 weeks of therapy.
  - Predicts high risk for resistance. (Resistance risk is low if HBV-DNA is < 200 IU/mL).
  - Change or **add second drug without cross-resistance.**

- **Breakthrough:** increase of HBV-DNA > 1 log from nadir, at any time, or reappearance of HBV-DNA(+) after 2 negative HBV-DNA at least 1 month apart.
  - Check for viral resistance (INNO-Lipa HBV DR v2). May be compliance problem.
  - Change or **add second drug without cross-resistance.**
# Drug Cross-Resistance Profile

*(reverse transcriptase mutations)*


<table>
<thead>
<tr>
<th>Reverse Transcriptase Mutations</th>
<th>Lamivudine</th>
<th>Telbivudine</th>
<th>Entecavir</th>
<th>Adefovir</th>
<th>Tenofovir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>M204I</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>L180M + M204V</td>
<td>R</td>
<td>R</td>
<td>I</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>A181T/V</td>
<td>I</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>N236T</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>I</td>
</tr>
<tr>
<td>I169T + V173L + M250V</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>T184G + S202I/G</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>I233V</td>
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<td>Resistance ?</td>
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<tr>
<td>A194T</td>
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# Treatment Options for Antiviral Resistance

<table>
<thead>
<tr>
<th>Resistance to</th>
<th>Rescue Therapy</th>
</tr>
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<tbody>
<tr>
<td>Lamivudine or Telbivudine</td>
<td><strong>Add:</strong> Adefovir, or Tenofovir, or</td>
</tr>
<tr>
<td></td>
<td><strong>Switch to:</strong> Tenofovir + Emtricitabine (Truvada)</td>
</tr>
<tr>
<td>Adefovir</td>
<td><strong>Add:</strong> Lamivudine, or Entecavir, or</td>
</tr>
<tr>
<td></td>
<td><strong>Switch to:</strong> Tenofovir + Emtricitabine (Truvada)</td>
</tr>
<tr>
<td>Entecavir</td>
<td><strong>Add:</strong> Adefovir, or Tenofovir</td>
</tr>
<tr>
<td>Multidrug</td>
<td>?</td>
</tr>
</tbody>
</table>
Anti-HBc(+) liver donors

- **Primary candidates:**
  HBsAg(+) recipients
  - Follow protocols for Low, or High Replicators as described in previous section (“HBsAg(+) Recipient”).
Anti-HBc(+) organ donors

• **Secondary candidates:**
  1) anti-HBs(+) recipients (with titer > 10 IU/L),
  2) anti-HBc(+) recipient

  – Before OLTx or other Tx:
    • Order HBV-DNA in donor’s serum (to detect “pre-S/S mutant virus” = HBsAg(-) mutant), and
    • Check or order recipient’s “peak” anti-HBs titer (if not known, obtain pre-op anti-HBs titer)
Anti-HBc(+) organ donors

Secondary candidates management:
- Donor’s serum HBV-DNA (+) & any Recipient’s peak anti-HBs titer (despite absence of HBsAg):
  - Highly active, “high resistance-barrier”, oral agent (Lamivudine+Adefovir combination, or Tenofovir or Entecavir) for life;
  - Booster vaccinate after 1 year, if HBV-DNA is still (-), with HBV-vaccine 40mcg @ 0,1,2 & 6 mo x 1-3 courses, until anti-HBs > 100 IU/mL (but continue oral agent for life; likely “pre-S/S mutant virus”)

Anti-HBc(+) organ donors

– Secondary candidates management:
  – Donor’s serum HBV-DNA (-) & Recipient’s peak anti-HBs titer > 100 IU/L:
    • Lamivudine 150 mg BID (until anti HBs > 100 mIU/mL, or for life).
    • Booster vaccinate x 1 dose and check anti-HBs.
    • Discontinue oral agent after 1 year if good anti-HBs response is maintained (> 100 mIU/mL) ?
  – Donor’s serum HBV-DNA (-) & Recipient’s peak anti-HBs titer is < 100 IU/L:
    • Lamivudine 150 BID (until anti HBs > 100 mIU/mL, or for life).
    • Booster vaccinate after 1 year, if HBV-DNA is still (-), with HBV-vaccine 40mcg @ 0,1,2 & 6 mo x 1-3 courses, until anti-HBs > 100 mIU/mL.
    • Discontinue oral agent after 1 year if good anti-HBs response is achieved (> 100 mIU/mL) ?
Anti-HBc(+) organ donors

- **Secondary candidates management:**

- **Choice of oral agent:**
  - If donor HBV-DNA in serum is (+) give Tenofovir or Entecavir.
  - If donor HBV-DNA in serum is negative, give Lamivudine 150 mg BID (corrected by renal function).

- **Monitoring:**
  - HBsAg, HBe Ag & Ab, and HBV-DNA quant q month x 3; then
  - HBsAg, HBe Ag & Ab, and HBV-DNA quant q 3 months for life.
Anti-HBc(+) organ donors

- Tertiary candidates:
  - HBV naïve patients [anti HBc(-) & anti-HBs(-)]
    - Before OLTx, check/order HBV-DNA in donor’s serum.
    - **If Donor’s serum HBV-DNA is (+):**
      - High resistance-barrier oral agent (Entecavir, or Tenofovir) for life; [to give HBIG will not help if donor’s HBsAg was (-); likely “pre-S/S mutant virus”]
      - Vaccinate after 1 year, if HBV-DNA is still(-).
      - Independently of anti-HBs response, give oral agent for life.
    - **If Donor’s serum HBV-DNA is negative:**
      - Lamivudine 150 mg BID for life.
      - Vaccinate after 1 year, if HBV-DNA is still (-), with HBV-vaccine 40mcg @ 0,1,2 & 6 mo x 1-3 courses, until anti-HBs > 100 mIU/mL.
      - Discontinue oral agent after 1 year if good anti-HBs response is achieved (anti-HBs > 100 mIU/mL)?
Anti-HBc(+) organ donors

- **Tertiary candidates:**
  - **Choice of oral agent:**
    - If HBV-DNA in serum is (+) give Tenofovir or Entecavir.
    - If HBV-DNA in serum is negative, give Lamivudine.
  - **Monitoring:**
    - HBsAg, HBe Ag & Ab, and HBV-DNA quant q month x 3; then
    - HBsAg, HBe Ag & Ab, and HBV-DNA quant q 3 months for life.
Risk Factors Associated to Severity of Recurrence

- **Recipient related**
  - Female gender: lower survival
  - Age: lower survival
  - Non-white race: lower survival, more severe
  - Severity of illness: lower survival
  - Hepatitis B co-infection: controversial

- **Donor Related**
  - Age: lower survival, more severe
  - HLA-mismatch: controversial
  - Living donor: controversial
  - Donor-liver fat: controversial
  - Genetic factors: controversial
Risk Factors Associated to Severity of Recurrence

**Virological**
- Pre-LTx viral load (>1M): more severe
- Early post-LTx load: more severe
- CMV infection (+ g-1a): more severe
- HIV co-infection: more severe
- Genotype 1b: controversial
- Quasispecies: controversial

**Other**
- Time to recurrence: more severe
- Steroid bolus, OKT3: more severe
- Short time to recurrence: more severe
- Cold ischemia time: controversial