2021 Fourth Annual National Conference

September 9-11, 2021

Red Rock Hotel – Las Vegas, NV
Liver Transplant, Now What?
Post-Liver Transplant Management

Corrie Berk, DNP, MBA, APRN
Loma Linda University Health
Disclosures

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Disclosures

Corrie Berk, DNP, MBA, APRN
Speakers Bureau: Gilead, Clinical Area- HCV
Speakers Bureau: Salix, Clinical Area- HE
Speakers Bureau: Abbvie, Clinical Area- HCV
Consultant (spouse): Bausch, Best Doctors, Biovie
Liver Transplant as a Treatment for ESLD

• From 1985 – 2011, approximately 100,000 persons in the United States underwent LT

• On December 30, 2011, there were 30,000 LT recipients who were alive and had survived at least 5 years, and there were more than 16,000 recipients with 10 or more years’ survival
Long-term mortality after liver transplantation

Causes of death

- Non hepatic: 63.30%
- Hepatic: 23.90%
- Unknown: 12.80%

Non hepatic causes of death

- Malignancy: 29, 50%
- Renal: 6, 80%
- Infection: 25, 10%
- Other: 19, 30%
- CVD: 19, 30%
Laboratory Monitoring

• Frequency of laboratory monitoring individualized by the transplant center
  – Time from LT, complications from LT, stability of testing, underlying cause of liver disease

• Abnormal liver tests – pattern is important
  – Doppler US
  – CT
  – MRI/MRCP or ERCP

• Obtain liver histology when parenchymal injury suspected
## Causes of Liver Test Abnormalities in LT Recipient

<table>
<thead>
<tr>
<th>TABLE 3. Causes of Liver Test Abnormalities in the Asymptomatic Recipient</th>
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</thead>
<tbody>
<tr>
<td><strong>Allograft parenchymal damage</strong></td>
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<tr>
<td>Immune-mediated disease</td>
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<tr>
<td>Recurrent disease</td>
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<tr>
<td>Drug toxicity</td>
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<tr>
<td>Alcohol</td>
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<tr>
<td>De novo infection</td>
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<tr>
<td>Recurrent cancer</td>
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<tr>
<td><strong>Biliary damage</strong></td>
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<tr>
<td>Biliary Strictures</td>
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<tr>
<td>Recurrent PSC</td>
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<tr>
<td><strong>Vascular disease</strong></td>
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<tr>
<td>Hepatic artery stenosis, PVT</td>
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<tr>
<td><strong>Metabolic Disease in the allograft</strong></td>
</tr>
<tr>
<td><strong>Nonhepatic disease mimicking liver disease</strong></td>
</tr>
<tr>
<td><strong>Nonhepatic disease causing liver test abnormalities</strong></td>
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</tbody>
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Immunosuppression: Which Agent?

- Consider:
  - Indication for transplant
    - HCV? Malignancy? Autoimmune?
  - Comorbidities
  - IS side effects (ie: renal impairment)
  - History of rejection
  - History of or risk for cancer
  - History of or risk for infection
  - Likelihood of pregnancy?
    - mTORi and mycophenolate are potential teratogens

Immunosuppression

- The current gold standard of care is based on the triple combination regimen of:
  - Calcineurin inhibitors (CNI)
  - Mycophenolate mofetil (MMF)
  - Corticosteroids
Corticosteroids

- Induction: IV corticosteroids for several days post transplant
- Transition to oral corticosteroids
- Most LT recipients should be tapered off of corticosteroids after 3 months post LT
  - Patients at higher immunological risk (eg, immune-mediated diseases) should be considered for long-term low-dose steroids
- SE: HLD, HTN, obesity, DM

Calcineurin Inhibitors

- Tacrolimus (Prograf®, Envarsus XR®) and cyclosporine (Gengraf®, Sandimmune®, Neoral®)
Calcineurin Inhibitors

- SE: renal toxicity, DM (tacrolimus)
- Monitoring: typical trough levels (>3 months after LT)
  - ~5 to 10 ng/mL for tacrolimus
  - ~100 to 150 ng/mL for cyclosporine

Mycophenolate

- Mycophenolate mofetil (Cellcept®) and mycophenolate sodium (Myfortic®)
Mycophenolate

- SE: GI disturbances, bone marrow suppression
- Need for therapeutic drug monitoring not certain
mTOR Inhibitors

- Sirolimus (Rapamune®), everolimus (Zortress®)
mTOR Inhibitors

- SE: hypercholesterolemia, proteinuria
- Therapeutic drug monitoring (>3 months after LT)
  - Target trough level for sirolimus is ~5 ng/mL
  - Target trough level for everolimus is ~3-8 ng/mL
## TABLE 5. Unwanted Side Effects of Immunosuppressives

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Corticosteroids</th>
<th>CNIs</th>
<th>mTORi</th>
<th>Mycophenolate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney disease</td>
<td>-</td>
<td>+++</td>
<td>+ (proteinuria)</td>
<td>-</td>
</tr>
<tr>
<td>Bone disease</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Bone Marrow Suppression</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Diabetes</td>
<td>++</td>
<td>+ (tacrolimus)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hypertension</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

Acute Rejection

- Usually asymptomatic until late stages
- Requires histology for diagnosis prior to treatment
- Rejection scored by Banff Criteria
  - Rejection Activity Index (RAI):
    - Portal inflammation
    - Bile duct inflammation/damage
    - Venous endothelial inflammation

Acute Rejection

- **Two main types:**
  - **T-cell mediated rejection (TCMR)**
    - Formerly known as acute cellular rejection (ACR)
  - **Antibody-mediated rejection (AMR)**
    - Formerly known as humoral rejection
    - Rare in LT recipients

Acute T-Cell Mediated Rejection (TCMR)

- **Laboratory abnormalities**
  - Nonspecific, bilirubin and aminotransferase elevation

- **Histology**
  - Inflammatory bile duct damage
  - Subendothelial inflammation
  - Predominantly lymphocytic portal inflammatory infiltrate with neutrophils and eosinophils
Acute T-Cell Mediated Rejection (TCMR)

• **Risks**
  – Reduced IS (iatrogenic or noncompliance)
  – Transplantation for autoimmune disease

• **Treatment**
  – Based on degree of liver injury and histological activity
  – Increase in IS +/- short course of corticosteroids
Infectious Prophylaxis

- Interval between 3-6 months after transplant is high risk period for infections with opportunistic pathogens
  - Viruses: CMV*, EBV, HSV
  - Fungi: *Aspergillus* and *Cryptococcus*
  - Rare bacteria
- Risk reduction
  - Prophylaxis
  - Avoidance of high-risk exposures
  - Minimizing IS

CMV

- Most significant opportunistic pathogen affecting LT recipients
- Clinical syndromes: viremia, bone marrow suppression and involvement of the GI tract and liver
- Risks:
  - Low risk (D-/R-)
  - Intermediate risk (D-/R+ or D+/R+)
  - High risk (D+/R-)
  - Increased IS
  - Allograft rejection

CMV

**Diagnosis:**
- Nucleic acid testing (PCR)
- Tissue biopsy sometimes required
- Some LT patients with low level viremia are asymptomatic

**Treatment**
- Initiated when symptomatic, persistent/increased viremia or evidence of tissue injury
- Consider IS reduction until viremia resolved
- IV ganciclovir (5 kg/mg BID*) minimum 14 days
- PO valgancyclovir (900 mg daily*) minimum 14 days

*adjust for renal impairment
Kidney Disease

- The cumulative incidence of chronic renal failure (eGFR <30 ml/min/1.73 m²) after liver transplantation (LT) is 22% after 5 years and this is significantly higher than after lung or heart transplantation.
Kidney Disease

- Etiology of renal disease post LT is multifactorial
  - Chronic exposure to CNI
  - Metabolic risks (HTN, DM, HLD)
  - Pre-transplant renal dysfunction
  - Allocation system: high MELD, donor after cardiac death (DCD)
Kidney Disease

- Creatinine late and insensitive indicator for CKD in this population
  - Use estimating equation to calculate GFR
  - Urine protein quantification once yearly
- Consider reduction or withdrawal of CNI
- Consider kidney transplantation in LT recipients who develop ESRD
Malignancy/De Novo Cancers

• The cumulative incidence of de novo cancer after LT increases from 3% to 5% at 1 to 3 years to 11% to 20% at 10 years after LT

• Cutaneous malignancies most common form of malignancy in solid organ transplant recipients

• PSC – risk for colorectal cancers

• Tobacco users – increased risk for lung and oropharyngeal cancers
Malignancy – Surveillance

- Dermatologic skin exam at least annually five years or more after LT
- PSC/IBD patients- screening colonoscopy annually with biopsies
- Liver Transplant for HCC
  - Chest and abdomen CT every 6 months for 2-3 years
  - Beyond minimizing overall IS, the optimal IS strategy for minimizing the recurrence of HCC (including the use of mTOR inhibitors) has not been determined

Metabolic Control

- **DM:** goal HgbA1c <7%
- **HTN:** goal BP <130/80
- **HLD:** goal LDL <100 mg/dL
  - Lifestyle changes, statin, consider ezetimibe
  - Refractory HLD: consider changes to IS
- **Avoid obesity (BMI >30 kg/m2)**
  - Dietary counseling
  - Consideration of bariatric surgery in patients who fail behavioral weight loss programs

Bone Health

• In the first 5 years after LT, screening by BMD should be done:
  – Yearly for osteopenic patients
  – Every 2-3 years for patients with normal BMD

• The osteopenic LT recipient
  – Should perform regular weight-bearing exercise
  – Receive calcium and vitamin D supplementation

• Bisphosphonate therapy should be considered in LT recipients with osteoporosis or recent fractures

Alcohol Liver Disease

- In patients who undergo LT for ESLD 2/2 ALD:
  - 20 to 50% acknowledge some alcohol use in the first 5 years after LT
  - 10%-15% will resume heavy drinking
- All patients with prior diagnosis of ALD should be encouraged to remain abstinent from alcohol
- Resuming ETOH consumption after LT may damage graft due to poor compliance with IS and ETOH-related liver injury
- Encourage counseling in cases of alcohol relapse

Vaccinations

- All LT recipients should receive annual influenza vaccination
- All LT recipients should avoid live virus vaccines
- Pneumococcal vaccine every 3-5 years

fda.gov.
According to the American Society of Transplantation (AST):

- Pre-transplant vaccination of all SOT candidates as a priority whenever feasible.
- Continued SARS-CoV-2 vaccination in SOT recipients and priority for vaccination of their household members and caregivers to reduce exposure risk for these vulnerable patients.
- Continuation of a stable immunosuppression regimen at the time of vaccination to avoid the risk of organ rejection.
- Continued adherence of all transplant recipients to protective measures including masking and social distancing regardless of vaccination status.