Long Term Complications Post Liver Transplant

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ABIM Blueprint for Transplant Hepatology Exam
240 questions

Post-Transplant 25%, 60 questions
Long-Term Complications 15%, 36 questions
- Nonimmune 5%
- Diabetes, Renal, Bone, Growth, Cardiovascular
- Recurrent Disease 3%
- HCV, cancer, PBC, AIH
- Post-Transplant cancer 2%
- PTLD
- Surveillance
- Indications for RE-OLT, Adherence 2%, QOL 2%
Long Term Complications Post Liver Transplant

- >110,000 liver transplants since 1985
- 88,715 liver transplant recipients alive in U.S. in 2018
- 30,000 liver transplant recipients >5 years post
- 10,000 liver transplant recipients >10 years post

Complications post liver transplant

- 0-3 months
  - HAT
  - Acute cellular rejection
  - Bacterial infections
  - Candidiasis
  - Biliary stricture/leak
  - Acute kidney injury
- 3-12 months
  - CMV
  - Biliary strictures
  - ACR
- 1-5 years
  - Chronic kidney injury
  - Metabolic syndrome
  - Hypertension
- Beyond 5 years
  - Diabetes
  - Cardiovascular disease
  - Cancer
  - Recurrent disease

Russo MW J Clin Gastro 2017;51:683

Liver transplant recipients, by age
Most patients >50 years old

Risk Factors for mortality >1 year post liver transplant
- Male
- Older Age
- Diabetes (pre or post)
- Hypertension (post)
- Renal failure (pre or post)
- Pretransplant malignancy


Probability of death, by causes 1 year and 12 years after liver transplant

Metabolic Complications
Prevalence of conditions pre and post liver transplant

**PRE-OLT** 1 - 3 years  
**POST-OLT**

- **Hypertension** 15%  
- **Diabetes** 15%  
- **Hyperlipidemia** 20%  
- **Metabolic syndrome** 15%

- **Hypertension** 60%  
- **Diabetes** 30%  
- **Hyperlipidemia** 50%  
- **Metabolic Syndrome** 50%

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**Hypertension**

- Leading metabolic complication ~60-70% OLT recipients
- <2000 mg/d sodium
- First line therapy-dihydropyridine calcium channel blockers unless proteinuria

HTN  
Proteinuria: ARB or ACE inhibitor

Intolerant  
Amlodipine

Effective 33%  
Intolerant 12.5%  
(Liver Transpl 2008;14:1020-8)

Unresponsive

Carvedilol  
Nifedipine

Effective 32%  
Intolerant 20%

ACE inhibitors (Lisinopril) superior to beta blocker (bisoprolol)  
(Transplantation 2004;77:748-50)

If combination therapy is needed: calcium channel blocker+ACE Inhibitor  
30% recipients require 2 or more agents

Goal <140/90  
if proteinuria<130/80

Hyperlipidemia

- 50% prevalence
- 14% 5 year risk cardiac event after liver transplant

Measure lipids 14 hours after fasting

LDL>100 mg/dL

Triglycerides>200

Dietary & Lifestyle changes
- Statins + ezetimide
- Omega-3 fatty acids
- Gemfibrozil
- Fenofibrate

Change cyclosporine to tacrolimus
- Reduce CNI, add MMF
- Stop sirolimus

Cardiovascular events after liver transplant

<table>
<thead>
<tr>
<th>Event</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any CV event</td>
<td>10%</td>
</tr>
<tr>
<td>Any CV event in NASH recipient</td>
<td>25%</td>
</tr>
<tr>
<td>Any CV event in recipient with post transplant metabolic syndrome</td>
<td>30%</td>
</tr>
</tbody>
</table>

Most common cardiovascular events

- Acute coronary syndrome: 42%
- Congestive heart failure: 22%
- Stroke: 11%
- Arrhythmia: 11%
- Peripheral vascular disease: 10%

Cardiovascular disease after liver transplantation
Management

- Convert from tacrolimus to cyclosporine in recipients with poor glycemic control (HgbA1C>9%) for >6 months despite optimal antidiabetic therapy
- Convert from cyclosporine to tacrolimus in recipients with refractory hyperlipidemia. Avoid sirolimus
- Target BP ≤130/80
- Lifestyle modifications, follow recommendations for general population

Transplantation 2017;101:S1-S56.

A primary care provider calls you to discuss a liver transplant recipient with diabetes mellitus. She is on tacrolimus. The patient has normal liver tests. Her creatinine is 1.5 mg/dL with an estimated GFR of 50 mL/min/1.73m².

What do you advise?
A. Avoid metformin
B. Avoid insulin
C. Convert to cyclosporine
D. Avoid glipizide
Diabetes Post-Liver Transplant

- 15% new onset diabetes post transplant
- Risk factors: corticosteroids, tacrolimus>cyclosporine, hep c, obesity
- DM lower survival vs No DM, 10 yr 78% vs 69%
- Increase in fibrosis progression
- HgbA1c goal<7%
- If renal dysfunction avoid metformin
  - If GFR<30 avoid acarbose, exenatide, pramlintide, gliptins

Factors associated with diabetes post liver transplant

<table>
<thead>
<tr>
<th>Factors</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>Increased leptin, Decreased adiponectin, Increase TNF alpha</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Decrease beta cell production, Increase gluconeogenesis, Decrease peripheral glucose uptake</td>
</tr>
<tr>
<td>Tacrolimus, cyclosporine</td>
<td>Increase oxidative stress, Increase mitochondrial dysfunction, Increase lipid peroxidation</td>
</tr>
</tbody>
</table>
Cumulative Incidence of Chronic Renal Failure Among Recipients of Non-Renal Organ Transplants in the US

5 years postOLT
Stage 2 or 3 50%
Stage 4 20%

Pathogenesis and Prognosis of Renal Injury in Liver Transplant Recipients

Calcineurin inhibitors

Other factors:
- Peri-transplant renal failure
- Diabetes
- Hypertension

Glomerular injury

Parenchymal fibrosis

25% liver transplant recipients have ESKD 7-10 years post transplant

Afferent arteriolar constriction

Reversible (decrease CNI)

Tubular ischemia

Irreversible

Courtesy of Todd Stravitz
Post Transplant Chronic renal failure, by GFR at liver transplant

- % Chronic renal failure
- 10 mL in GFR OLT
- 33% CRF
- 1% of kidney transplants in liver transplant recipients


Renal preserving strategies
Implemented month 1 - 3

- Reduce TAC+MMF
  - TAC level 4-8 vs TAC only
  - Increase GFR at 1 yr
  - No difference in rejection

- BAS induction then Everolimus vs Everolimus + TAC (3-5) vs Standard TAC (6-10)
  - Increase GFR with everolimus + reduced TAC
  - Increase rejection with everolimus only

- Reduce TAC or CYA +MMF vs MMF+sirolimus
  - Increase GFR CNI+MMF MMF+sirolimus- increase in rejection, side effects (leukopenia, mouth ulcers)

Belotacept was associated with increase risk of rejection, HCV recurrence.
Renal preserving regimens
Implemented 6 months or more post liver transplant

- Convert CNI to sirolimus vs TAC
- Increase rejection with sirolimus monotherapy
- Everolimus+ low dose TAC vs Everolimus only 12-60 months post OLT
- No difference in GFR or rejection
- Low dose CNI+ MMF vs Standard CNI
- Increase GFR with low dose CNI + MMF No increase in rejection

**Summary: Renal preserving strategies**

- To preserve long term renal function then target lower CNI level and use MMF early post-transplant
- Implement renal preserving regimens such as low dose CNI+MMF or mTORi before GFR<50
- Conversion to mTORi monotherapy or MMF monotherapy has been associated with increase in rejection
- MMF+mTORi associated with side effects, leukopenia, mouth ulcers
- Conversion to low dose CNI+MMF>1 year post liver transplant has been associated with preserved renal function
Bone Health

- 68% OLT recipients have osteopenia
- Vertebral, nonaxial fracture risk 15%-60%
- Bone loss accelerated first 4 months post transplant


Recommendations

- Bone density study q 1-3 years and 25-hydroxyvitamin D levels
- Elemental calcium 1000(19-50)-1200 mg/d + vitamin D 600-1000 U/d
- Thoracolumbar radiographs
- Thyroid function, PTH, free testosterone (males)
- Bisphosphates (not in CKI):
  - T-score< -2.5 or atraumatic fractures
  - T-score-1.5-2.5 & risk factors (FRAX formula)

Selected therapy for prevention or treatment of osteopenia and osteoporosis

<table>
<thead>
<tr>
<th>Generic/Trade</th>
<th>Class/Mechanism</th>
<th>Adverse event examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zolendronic Acid/Reclast, once a year infusion</td>
<td>Bisphosphonate Inhibit bone resorption</td>
<td>Renal impairment Osteonecrosis of jaw</td>
</tr>
<tr>
<td>Denosumab/Prolia/ Xgeva, q6 month injection</td>
<td>Monoclonal antibody RANK ligand on osteoclasts</td>
<td>Serious infections in patients with impaired immune system,</td>
</tr>
<tr>
<td>Teriparatide/Forteo (injection)</td>
<td>Synthetic PTH, promotes new bone</td>
<td>Osteosarcoma, hypercalcaemia</td>
</tr>
<tr>
<td>Raloxifene/Evista, Bazedoxifene/conj estrogen/Duavee</td>
<td>Selective estrogen receptor modulator, prevent osteoporosis</td>
<td>Increase risk DVT, stroke, pulm embolus</td>
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Malignancy post liver transplant

### Most common malignancies after liver transplant

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>Risk factors</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonmelanoma skin cancers</td>
<td>&gt;40, male, sun exposure, smoking, alcohol use</td>
<td>Annual skin exams, abstinence from alcohol, tobacco, sun screens</td>
</tr>
<tr>
<td>PTLD</td>
<td>&gt;50, EBV infection</td>
<td>Minimize immunosuppression</td>
</tr>
<tr>
<td>Head, neck, lung cancer</td>
<td>Alcohol, tobacco use</td>
<td>Abstain from alcohol, tobacco, ENT exam,</td>
</tr>
<tr>
<td>Colorectal</td>
<td>PSC and IBD</td>
<td>Annual colonoscopy</td>
</tr>
</tbody>
</table>

Follow cancer screening guidelines for general population

Transplantation 2017;101:S1-S56.

PTLD and EBV Status

Treatment
First start with reducing or stopping immunosuppression

*Figure 11.85. Incidence of PTLD among adult liver transplant recipients by recipient EBV status at transplant, 2012-2016. AJT 2020;20 supppl s1:193-299.*
Late Acute Allograft Rejection

- Variable definitions, >1 month to 12 months post LT
- Incidence 7%-23%
- Characterized central venulitis, centrilobular necroinflammation
- Highest rates in AIH, PSC, PBC
- LAR associated with ductopenic rejection, patient and graft survival


Late hepatic artery thrombosis

☐ >21-180 days post liver transplant
☐ 41% retransplant rate (vs 71% with early HAT)
☐ 30% late HAT managed conservatively (anticoagulation)
☐ 50% develop biliary complications
☐ Risk factors for late HAT:
  - prior abd surgery
  - prior hx HAT
  - low donor weight
  - recipient age<50

Liver Transpl 2014;20:713-23.
Retransplant

- Retransplant (>14 days post)
- Recurrent disease (PSC highest recurrence)
- Chronic rejection
- Ischemic cholangiopathy
- Late vascular complications

MELD Exception for Ischemic cholangiopathy

Adherence

- Adherence tools-ITAS,SMAQ
- Variability in drug levels may indicate nonadherence
- Simplify medication regimen, once a day options
- Patient education small part of adherence
- Behavioral interventions (reminders) and simplifying medical regimens are effective in improving adherence

Transplantation 2017;101:S1-S56.
Quality of Life

- Physical activity strongly associated with high QOL
- Employment associated with improved QOL
- Employment highest in patients transplanted for PSC
- Sexual problems in 25%-50% of recipients

Liver Int 2014;34:1298-1313.

Growth and Development

Pediatrics
Ongoing height and weight recovery 10-15 years post transplant
- 26th-46th percentile for height 15 years post transplant
- 9% overweight by BMI
- Weight status at transplant predicts post transplant obesity
- 12-38% develop fractures (vertebral)
- Increase in cognitive and academic deficits 42% receive special education

Summary

- Metabolic syndrome is common after liver transplantation. Hypertension is the most common metabolic condition. Dihydropyridine calcium channel blocker, ACE Inhibitor preferred.

- Low dose CNI+MMF is an effective renal preserving regimen >1 yr post OLT with favorable side effect profile. Most effective if GFR>50.

- Risk for some malignancies is increased post transplant, recipients transplanted for PSC with IBD should undergo annual colonoscopy.