Medical Care of Liver Transplant Patients

Omar Massoud, MD, PhD
6/13/2015
## Registered U.S. Patients Waiting for Transplants

<table>
<thead>
<tr>
<th>Organ Type</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>79,357</td>
</tr>
<tr>
<td>Liver</td>
<td>15,835</td>
</tr>
<tr>
<td>Heart</td>
<td>2,772</td>
</tr>
<tr>
<td>Lung</td>
<td>1,945</td>
</tr>
<tr>
<td>Kidney/Pancreas</td>
<td>2,262</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1,525</td>
</tr>
<tr>
<td>Heart/Lung</td>
<td>85</td>
</tr>
<tr>
<td>Intestine</td>
<td>215</td>
</tr>
<tr>
<td><strong>Total patients</strong></td>
<td><strong>101,728</strong></td>
</tr>
</tbody>
</table>

Source: UNOS 4/16/09
Survival after Liver Transplantation

Outline

I. Immunosuppression
II. Liver allograft dysfunction
III. Renal dysfunction
IV. Metabolic disorders
V. Malignancies
VI. Preventive medicine
I. Immunosuppression
Immunosuppression

- Calcineurin inhibitors (CNIs)
- Antimetabolites
- m TOR inhibitors
- Corticosteroids
Immunosuppression

- Calcineurin inhibitors (CNIs):
  - Cyclosporine (Neoral, Gengraf)
  - Tacrolimus (Prograf)
- Common side effects:
  - Nephrotoxicity
  - Neurotoxicity
  - Hyperkalemia
  - Hypertension
  - Dyslipidemia (cyclosporine)
  - Diabetes (tacrolimus)

Alloway. Am J Transplant 2003
Meier-Kriesche, Am J Transplant 2006
Immunosuppression

- **Antimetabolites:**
  - Mycophenolate Mofetil (Cellcept)
  - Azathioprine (Imuran)

- **Common side effects:**
  - Bone marrow suppression
  - GI symptoms
Immunosuppression

- m TOR inhibitors:
  - Sirolimus (Rapamycin)

- Side effects:
  - Hepatic artery thrombosis
  - Rash
  - Dyslipidemia
  - Cytopenia
  - Poor wound healing
  - Oral ulceration
  - Interstitial pneumonitis

Massoud and Wiesner, *J Hepatol.* 2012
Augustine, *Drugs* 2007
Immunosuppression

- Corticosteroids
Immunosuppression

- Drug interactions:

Table 1: Drugs and substances that may decrease levels of cyclosporine, tacrolimus and sirolimus¹

<table>
<thead>
<tr>
<th>Anti-convulsants</th>
<th>Antibiotics</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Rifabutin</td>
<td>St. John’s Wort</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Rifampin</td>
<td>Orlistat</td>
</tr>
<tr>
<td>Phenytoin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹This table is not all inclusive.

Drug interactions:

<table>
<thead>
<tr>
<th>Antifungals</th>
<th>Antibiotics</th>
<th>Calcium channel blockers</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caspofungin</td>
<td>Azithromycin</td>
<td>Diltiazem</td>
<td>Protease inhibitors for HBV</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Clarithromycin</td>
<td>Verapamil</td>
<td>Protease inhibitors for HIV</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Erythromycin</td>
<td></td>
<td>Grapefruit products</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td></td>
<td></td>
<td>Danazol</td>
</tr>
<tr>
<td>Terbinafine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voriconazole</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 This table is not all inclusive.

64 y.o. woman who had liver transplant 4 mos ago and has had worsening renal insufficiency. Had been well with stable labs and creat 1.4 and tacrolimus level 6.7 one mo ago. Two weeks ago, diagnosed with bronchitis and given amoxicillin-clavulanate. One week ago, developed Candida vaginitis and started on fluconazole. Other meds are tacrolimus and labetalol, the doses of which have not been changed. Exam: Tremor, otherwise well.

Lab: Liver tests normal, creatinine 2.1.

Which of the following is the most likely explanation for elevation in creatinine?

- 1. Interstitial nephritis
- 2. Candida cystitis
- 3. Tacrolimus toxicity
- 4. Intravascular volume depletion
64 y.o. woman who had liver transplant 4 mos ago and has had worsening renal insufficiency. Had been well with stable labs and creat 1.4 and tacrolimus level 6.7 one mo ago. Two weeks ago, diagnosed with bronchitis and given amoxicillin-clavulanate. One week ago, developed Candida vaginitis and started on fluconazole. Other meds are tacrolimus and labetalol, the doses of which have not been changed. Exam: Tremor, otherwise well.

Lab: Liver tests normal, creatinine 2.1.

Which of the following is the most likely explanation for elevation in creatinine?

1. Interstitial nephritis
2. Candida cystitis
3. Tacrolimus toxicity
4. Intravascular volume depletion
II. Liver Allograft Dysfunction
Liver Allograft Dysfunction

Causes:

1. Rejection
2. Infection including CMV
3. Recurrence of primary liver disease
4. Vascular complications
5. Biliary complications

Dasai and Neuberger, Transplant Proc 2009
Liver Allograft Dysfunction

1. Rejection:
   Acute cellular rejection
   - Occurs in 30% of transplant patients
   - Most common during the first 6 weeks
   - Suspected by elevated LFTs
   - Diagnosed by liver biopsy
   - Managed by transplant center by adjusting immunosuppression and/or steroids

A combination of $C_4 \leq 0.31$ gm/L and alanine aminotransferase (ALT) $\geq 70$ IU/ml (two times the upper limit of normal) had a sensitivity of 96%, a specificity of 81%, a positive predictive value of 86% and a negative predictive value of 94%.

<table>
<thead>
<tr>
<th>C4 and C1q results</th>
<th>ACR</th>
<th>Controls</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive C4 and positive C1q*</td>
<td>13</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>Negative C4 and negative C1q*</td>
<td>0</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Positive C4 and negative C1q*</td>
<td>11</td>
<td>8</td>
<td>19</td>
</tr>
<tr>
<td>Negative C4 and positive C1q*</td>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>21</td>
<td>46</td>
</tr>
</tbody>
</table>

*Positive C4: C4 ≤ 0.31 gm/l, Negative C4: C4 > 0.31 gm/l  
Positive C1q: C1q ≤ 30.6 ng/ml, Negative C1q: C1q > 30.6 ng/ml
Liver Allograft Dysfunction

1. Rejection:

Chronic rejection

- Occurs in 3 – 5 % of transplant patients.
- Few months to several years after transplant.
- Bile ducts injury and disappearance followed by fibrosis.
- Patients may need re-transplant.

Liver Allograft Dysfunction

2. Cytomegalovirus

- Common cause of acute graft dysfunction.
- Reactivation of a remote infection or a new infection.
- 1-4 months post-transplant.
- Fever, headache, myalgia, nausea, diarrhea, leukopenia, and thrombocytopenia.
- Diagnosis: PCR and/or CMV antigenemia.
- Treatment: IV ganciclovir.

Kusne and Blair, Liver Transplantation 2006
Liver Allograft Dysfunction

3. Recurrence of primary liver disease:
   - HCV
   - HBV
   - Autoimmune liver disease
   - Alcohol-related liver disease
   - Hepatocellular carcinoma

Dasai and Neuberger, Transplant Proc 2009
Liver Allograft Dysfunction

4. Vascular Complications:

Porrett and Shaked, Liver Transpl 2009
Liver Allograft Dysfunction

5. Biliary Complications

Table 1. Reported Series of Biliary Complications After Liver Transplantation

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of Transplants</th>
<th>Complication Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D’Alessandro et al, 6 1991</td>
<td>227</td>
<td>15</td>
</tr>
<tr>
<td>Colonna et al, 4 1992</td>
<td>738</td>
<td>15</td>
</tr>
<tr>
<td>Rossi et al, 7 1994</td>
<td>224</td>
<td>15</td>
</tr>
<tr>
<td>Grief et al, 5 1994</td>
<td>1,792</td>
<td>12</td>
</tr>
<tr>
<td>Neuhaus et al, 8 1994</td>
<td>340</td>
<td>9</td>
</tr>
<tr>
<td>Verran et al, 9 1997</td>
<td>502</td>
<td>13</td>
</tr>
</tbody>
</table>

- leaks - several sources
- anastomotic strictures

- sequelae of “early” complications
  - anastomotic
  - hilar
  - intrahepatic
- stones, sludge
- mucocoele, ampullary stenosis

Perrakis et al. Transplant Proc 2010
Biliary Reconstruction

Duct-to-duct

Roux Y
III. Renal Dysfunction
Figure 1. Cumulative Incidence of Chronic Renal Failure among 69,321 Persons Who Received Nonrenal Organ Transplants in the United States between January 1, 1990, and December 31, 2000.

The risk of chronic renal failure was estimated with a noncompeting-risk model. Measurements of renal function were obtained at six-month intervals during the first year and annually thereafter.
Renal Dysfunction

- Risk factors for renal dysfunction:
  
  A) Pre-transplant:
  - Female
  - Chronic kidney disease prior to OLT
  - Diabetes mellitus
  - HCV
  
  B) Post-transplant:
  - Calcineurin inhibitors (CNIs)

Renal Dysfunction

Recommendations:
- Avoid nephrotoxic drugs (e.g. NSAIDs)
- Monitor renal function
- Consider reducing CNIs dose
- Consider early referral to a nephrologist
IV. Metabolic Disorders
Metabolic Disorders

1. Hypertension
2. Diabetes
3. Dyslipidemia
4. Obesity
5. Metabolic bone disease
Metabolic Disorders

Hypertension

- Affects more than 50% of liver transplant recipients
- Risk factors:
  - Reversal of the cirrhotic hemodynamic state
  - Initiation of immunosuppression

Sheiner, Transplantation, 2000
Gorwa, Liver Transpl, 2001
Neal, Transplantation, 2005
### Useful antihypertensive agents in OLT recipients

<table>
<thead>
<tr>
<th>Antihypertensive Agent</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium-channel blockers</td>
<td>Decrease in CNI-induced vasoconstriction</td>
<td>Edema, tachycardia, headach, Cytochrome P450 interactions</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>Decrease LVH</td>
<td>Impotence, bronchospasm</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>Renal sparing effect in diabetics</td>
<td>Hyperkalemia, azotemia, acidosis</td>
</tr>
<tr>
<td></td>
<td>Decrease CNI-induced renal fibrosis</td>
<td></td>
</tr>
<tr>
<td>ATII receptor antagonists</td>
<td>Decrease in CNI-induced vasoconstriction</td>
<td>Hyperkalemia</td>
</tr>
<tr>
<td>α- Adrenergic agonists (clonidine)</td>
<td>?Decrease CNI-induced neurogenic renal vasoconstriction</td>
<td>Sedation</td>
</tr>
</tbody>
</table>
Metabolic Disorders

1. Diabetes
   - 15-38% of liver transplant recipients, within the first year after OLT
   - Risk factors: steroids, tacrolimus, HCV recipient, pre-transplant DM and obesity
   - Management: similar to non transplant patients

Saliba, Liver Transpl 2007
Kuo, Transplantation 2010
Navasa, Diabetes Metab 2011
Metabolic Disorders

Dyslipidemia

- One-third to one-half of liver transplant patients
- Risk factors: female, cholestatic liver disease, diabetes, obesity and use of cyclosporine, steroids and sirolimus
- Management, life style changed, IS modifications, and statins.

Metabolic Disorders

Obesity

- In one study, up to 28% of patients who had a liver transplant had a BMI > 30
- 22% of non-obese transplant recipients became obese over a 2 year follow up
- Risk factors: steroid and cyclosporine use
- Management: similar to non-transplant patients

Metabolic Bone Disease

Many patients with chronic liver disease have decreased bone density as compared with age-matched control.

After transplantation, bone loss occurs at an accelerated rate for 6-12 months.

Transplant patients should be screened by DEXA scan and treated (as in non-transplant patients).

Cunningham, Transplantation, 2005.
V. Malignancies
Malignancies

- De novo malignancies are the 2\textsuperscript{nd} most common cause of late mortality.
- Cumulative risk 5-50%.
- The most common: skin, PTLD, lung, esophagus and head & neck cancer.
- Why?

Chak, Liver Int 2010
Feng, Am J Transplant 2003
Oo, Transplantation 2005
Haagsma, J Hepatol 2001
Malignancies

Skin Cancer

- The incidence is up to a hundred times as that observed in the general population.
- Skin cancers most frequently seen are squamous cell carcinoma, basal cell carcinoma and melanoma.
- The peak incidence is 3-5 years after transplantation.
- All transplant patients should have annual skin exam.

Sanchez. Liver Transpl, 2002
Stasko. Dermatol Surg, 2004
VI. Preventive Medicine
Preventive Medicine

- Vaccination
  - Do I need to take the vaccine?
  - Does it work?
  - Is it safe?
Preventive Medicine

- Vaccination
- A study in 165 renal transplant recipients vaccinated with trivalent inactivated influenza vaccine, showed the vaccine was safe with seroprotection rates of 79-93%

Preventive Medicine

- Vaccination

Table 3: Vaccines that are safe to give to immunosuppressed patients or household contacts

- Diphtheria
- Hepatitis A, B or the combination of A and B
- Haemophilus influenzae type b (Hib)
- Human papillomavirus
- Influenza inactivated
- Meningococcal
- Pertussis
- Pneumococcal
- Tetanus
- Tick-borne encephalitis

Preventive Medicine

- Vaccination

Table 4: Live attenuated vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacille calmette-guerin (BCG)</td>
</tr>
<tr>
<td>Live attenuated influenza (LAIV)</td>
</tr>
<tr>
<td>Measles</td>
</tr>
<tr>
<td>Mumps</td>
</tr>
<tr>
<td>Polio (oral)</td>
</tr>
<tr>
<td>Rotavirus</td>
</tr>
<tr>
<td>Rubella</td>
</tr>
<tr>
<td>Typhoid (oral-TY21a)</td>
</tr>
<tr>
<td>Vaccinia (smallpox vaccine)</td>
</tr>
<tr>
<td>Varicella</td>
</tr>
<tr>
<td>Yellow fever</td>
</tr>
</tbody>
</table>

Liver transplantation is the treatment of choice for ESLD and selected cases of liver cancer.

One year survival rate is 90% and 3-year survival rate is 80%.
Summary

- Immunosuppressive drugs have extensive drug-drug interactions.

- The most common causes of liver allograft dysfunction are: acute rejection, infection, recurrence of the primary disease, vascular complications and biliary complications.
Renal failure occurs in 20% of liver transplant patients within 5 year of transplantation.

There is increased prevalence of metabolic disorders including: hypertension, diabetes, dyslipidemia, obesity and metabolic bone disease after liver transplantation.
Summary

- All preventive measures that apply to the general population, also apply to liver transplant patients, especially vaccination and screening for cancer.
“Be ready to say, ‘I do not know’.”
Dr. William Osler, 1849-1919