Learning Objectives

• Attendants should understand:
  – Indications and contraindication for liver transplant
  – Organ allocation under the MELD system
  – The role of living donor transplantation
  – Complications of liver transplant
  – Immunosuppression related complications and drug-drug interactions
Disclosure

I have no financial disclosures to report
Prognosis of Compensated Cirrhosis

- Median survival = 9–12 years
- Majority of deaths: Non-liver related
  - Cardiovascular, strokes, etc
  - Liver-related deaths: HCC
- Predictors of decompensation
  - HVPG: HR 1.11
  - MELD score: HR 1.15
  - Serum albumin: HR 0.37
Prognosis of Decompensated Cirrhosis

• Median survival = 2 years
• Causes of deaths:
  – Portal HTN
  – Liver failure
  – Sepsis
  – HCC
• Predictors of death
  – Childs-Turcotte-Pugh score
  – MELD score
  – Serum sodium
Liver Transplant: Indications

- Irreversible acute/fulminant liver failure
- Chronic liver failure
- Metabolic disorders
  - e.g., primary hyperoxaluria, familial amyloidosis
- Hepatobiliary malignancy
  - Hepatocellular carcinoma
  - Cholangiocarcinoma
Liver Transplantation: Timing

• MELD score > 14
• Complications of cirrhosis
  – Ascites/SBP
  – Variceal bleeding
  – Encephalopathy
  – HRS
• Development of hepatobiliary malignancy
• MELD exception cases:
  – Hepatopulmonary syndrome, hepatic hydrothorax, inherited metabolic syndromes
Transplant: Contraindications

- Severe comorbid medical illnesses
  - CAD/CHF
  - Moderate to severe pulmonary HTN
- Extrahepatic malignancies/Advanced HCC
- Uncontrolled systemic infections (except biliary)
- Psychiatric and psychosocial contraindications:
  - Active substance abuse or high recidivism risk
  - Poorly controlled psychiatric illness and/or noncompliance
  - Poor social support
- Technical contraindications:
  - Extensive thrombosis of portal and mesenteric vessels
  - Obesity, BMI > 35
Organ Allocation

• 1997, UNOS criteria for listing
  – Child-Turcotte-Pugh score ≥ 7
• 2002, UNOS adopted the model for end stage liver disease (MELD)
• MELD predicts mortality in patients with chronic liver disease:
  \[ \text{MELD} = 3.78 \log_e (\text{bilirubin}) + 11.2 \log_e (\text{INR}) + 9.57 \log_e (\text{creatinine}) + 6.4 \]
MELD score and estimated 3-month mortality

<table>
<thead>
<tr>
<th>Score</th>
<th>3 month mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>15%</td>
</tr>
<tr>
<td>29</td>
<td>30%</td>
</tr>
<tr>
<td>33</td>
<td>50%</td>
</tr>
<tr>
<td>38</td>
<td>80%</td>
</tr>
</tbody>
</table>
Organ Shortage: Supply vs Demand

UNOS July 2001

Waiting List Registrants
Donors

A MEMBER OF TRINITY HEALTH
LOYOLA MEDICINE
We also treat the human spirit.
Living Donor Liver Transplant (LDLT)

• Living donor liver transplantation (LDLT) has been developed to help overcome the organ donor shortage

• Living donor transplant is based on two main principles:
  – (1) donor morbidity and mortality must be kept to a minimum
  – (2) graft and recipient survival should be as high as in full size cadaveric liver transplant
Essential Concepts of Living Donors

- No conflict of interest
- No coercion
- Minimize donor risks
- Donors must be given every opportunity to change their minds
- Emphasize alternatives
- Living liver donation should be reserved for situations where the benefit to recipient outweighs the risk to the donor
Living Donors Liver Transplant

- Liver = 2% body weight
- Optimal: > 1% liver weight/body weight ratio
- 70 kg recipient needs at least 700 cc (gm)
- Cannot go below 0.7 - 0.8%
Disadvantages of Living Donor

- There is a small risk to the healthy donor and the period of discomfort and recovery for the donor
- Increased rates of biliary complications among recipients and donors
  - 15-30% risk to recipient
- Ethical considerations
Organ Shortage and LDLT: The Reality

The number of patients awaiting a liver transplant at year-end peaked in 2001; this is clearly related to the introduction of the MELD/PELD allocation system in 2002. The number who received a deceased donor liver transplant has gradually increased, reaching a peak in 2006. The gap between the numbers of candidates and recipients has been slowly shrinking since 2002.

Complications of LT

- Rejection
  - Acute
  - Chronic
- Infections
- Biliary complications
  - Strictures
  - Bile leaks
- Vascular Complications
  - Hepatic Artery Thrombosis
  - PV thrombosis/stenosis
  - Hepatic Vein stenosis
### Long Term Complications After LT

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>NODM 15%</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Increased risk in cholestatic liver dz, long term steroids</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>CNI</td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>CNI</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>Sirolimus, CSA</td>
</tr>
<tr>
<td>Neurological</td>
<td>Headache- CNI, neuropathy, confusion</td>
</tr>
<tr>
<td>Hematological</td>
<td>Anemia, neutropenia</td>
</tr>
<tr>
<td>Viruses</td>
<td>CMV, EBV, Herpes viruses</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Skin, hematologic, all solid tumors, PTLD</td>
</tr>
</tbody>
</table>
Acute cellular Rejection

- Occurs in 40-50% of recipients within 1st year post transplant
- Most occur within the first month
- Signs and symptoms
  - Elevated AST/ALT/Alk phos
  - Low grade fever
  - Peripheral eosinophilia
  - Rarely, abdominal pain
- Treatment:
  - IV steroids
  - Adjustment of immunosuppression
Infections Post-Liver Transplant

**Month 1 (Nosocomial infection)**
- Bacteria and Candida are common
- Line infections, wound infections, UTI, pneumonia
- 19-28% of patients develop bacteremia: Staph, Enterococcus (50-60%)
- C. diff

**Month 2-6 (Opportunistic organisms)**
- *Pneumocystis*
- Viruses: CMV, EBV, HHV 3 & 6, VZV
- Fungi: *Aspergillus, Cryptococcus, Histoplasma, and Coccidioides*
- Bacteria: *Nocardia, Listeria, Mycobacterium tuberculosis*

**Month 6 - ∞**
- Influenza, UTI, community-acquired pneumonias
- Herpes zoster
- CMV
Highest risk are recipients from CMV mismatch or Recipients of OKT-3/Thymoglobulin
Without prophylaxis, risk of symptomatic disease 64%
Fever, leukopenia, hepatitis in up to 25%
Pneumonitis, GI infection
Predisposes: chronic rejection, worse HCV recurrence and fungal superinfection
Prophylaxis: Valganciclovir, ganciclovir, acyclovir for 6 months after LT
Treat with IV Ganciclovir/oral Valganciclovir for 3 months
Biliary Anastomotic Strictures

• Incidence
  – 5-15% of cadaveric transplants
  – 15-30% of living donor transplants

• Treatment:
  – Endoscopic:
    • ERCP with stent placement
    • Successful in 75% of cases
  – Surgery:
    • Revision
    • Hepaticojejunostomy
### Disease Recurrence Post-LT

<table>
<thead>
<tr>
<th>Condition</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>30% cirrhotic at 5 years</td>
</tr>
<tr>
<td>HBV</td>
<td>100% without prophylaxis</td>
</tr>
<tr>
<td>AIH/PBC/PSC</td>
<td>20% (graft loss is rare)</td>
</tr>
<tr>
<td>NASH</td>
<td>Up to 80%</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>Common, ?Mayo protocol</td>
</tr>
<tr>
<td>HCC</td>
<td>Depends on tumor size</td>
</tr>
</tbody>
</table>
Advances in Immunosuppression

• Pre-cyclosporine era: 1 year survival 23% to 35%

• Calcineurin inhibitor era:
  – Cyclosprine and tacrolimus
  – 1 year survival 85% to 90%
Cyclosporine (CyA)

- Causes selective suppression of cell-mediated immunity via inhibition of T-cell activation
- Forms a complex with cytoplasmic cyclophilin
  - Binds and inhibits the calcium & calmodulin-dependent phosphatase calcineurin
  - Inhibits IL-2, IL-3, IL-4, IL-8, and various chemotactic factors
- Absorption is dependent on bile flow
- Metabolized primarily by cytochrome P450-3A pathway
- Drug-drug interactions are common
Cyclosporine Toxicity

• Nephrotoxicity: main side effects
  – Post-OLT rate of renal failure up to 20%
• Metabolic abnormalities:
  – Hyperkalemia, hypomagnesemia, hyperlipidemia, hyperglycemia
• Hypertension
• Gingival hyperplasia and hirsutism
• Neurological manifestations: 10% to 28%
  – Tremor, peripheral neuropathy, psychoses, hallucinations, motor weakness, and seizures
Tacrolimus (AKA; TAC, FK506)

- TAC is 100 times more potent than CyA
- Acts by binding to FK binding protein (FKBP12)
  - Complex then inhibits calcineurin
- Absorption occurs in the duodenum and jejunum
  - Unlike CyA, is not dependant on bile flow
  - Food reduces bioavailability (take on an empty stomach)
- Metabolism by cytochrome P450
Tacrolimus Toxicity

• Similar to CyA:
  – Nephrotoxicity
  – Neurotoxicity: tremor, headache
  – Metabolic: hyperkalemia, hypomagnesemia, DM, HTN
  – Nausea, vomiting, diarrhea

• CyA vs. TAC:
  – TAC has a higher rate of diabetes
  – CyA predisposes to more hypertension, dyslipidemia, hirsutism, and gum hyperplasia
### Drug Interactions with Calcineurin Inhibitors

#### Table 1A. Drugs That May Increase Tacrolimus and Cyclosporine Blood Concentrations

<table>
<thead>
<tr>
<th>Calcium Channel Blockers</th>
<th>Antifungal Agents</th>
<th>Macrolide Antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diltiazem</td>
<td>Fluconazole</td>
<td>Clarithromycin</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>Itraconazole</td>
<td>Erythromycin</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Ketoconazole</td>
<td>Troleandomycin</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Voriconazole</td>
<td>Azithromycin</td>
</tr>
<tr>
<td></td>
<td>Clotrimazole</td>
<td>Telithromycin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prokinetic Agents</th>
<th>Miscellaneous Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisapride</td>
<td>Amiodarone</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>Cimetidine</td>
</tr>
<tr>
<td></td>
<td>Methylprednisolone</td>
</tr>
<tr>
<td></td>
<td>Omeprazole</td>
</tr>
<tr>
<td></td>
<td>Protease inhibitors</td>
</tr>
<tr>
<td></td>
<td>Nefazodone</td>
</tr>
<tr>
<td></td>
<td>Ethinyl estradiol</td>
</tr>
</tbody>
</table>

#### Table 1B. Drugs That May Decrease Tacrolimus and Cyclosporine Blood Concentrations

<table>
<thead>
<tr>
<th>Anticonvulsants</th>
<th>Antibiotics</th>
<th>Herbal Preparations</th>
<th>Miscellaneous Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Rifabutin</td>
<td>St. John’s Wort</td>
<td>Probucol</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Rifampin</td>
<td></td>
<td>Terbinafine</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Rifapentine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fosphenytoin</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Corticosteroids

• Block T-cell and antigen-presenting cell-derived cytokine expression
• Corticosteroids are still used in reversing acute rejection and in maintenance therapy
• Side effects: HTN, MS changes, HL, impaired wound healing, DM, ulcers, myopathy, osteoporosis, fluid retention, cataracts
• Most programs wean corticosteroids off within the first year except in cases of autoimmune hepatitis
Antimetabolites

• Azathioprine:
  – Antagonizes purine metabolism
  – Used at < 5% of center due to it’s side effect profile (myelosuppression and hepatotoxicity)

• Mycophenolate (MMF, CellCept) and mycophenolic acid (MPA, Myfortic):
  – Inhibit the de novo purine nucleotide synthesis
  – Causes blockage of DNA replication in T and B cells that lack salvage pathways
  – Adverse effects (nausea, abdominal pain, diarrhea, anemia and neutropenia) occur in 24% to 57%
Rapamycin (Sirolimus, RAP)

• RAP is an antibiotic (structurally related to TAC)
  – Has immunosuppressive, antitumor, and antifungal properties
• Low nephrotoxicity
• Toxicity has limited its use (30% discontinuation rate):
  – Leukopenia, thrombocytopenia, dyslipidemia, anemia, lymphocele, wound dehiscence, oral ulcerations, interstitial pneumonitis
• **Black box warning!!!** = increased risk of hepatic artery thrombosis
Current Therapeutic Strategies

- Steroid Avoidance
- Renal Sparing Protocols
- Conversion from CNI to Sirolimus
- Calcineurin Inhibitor Avoidance
- Individualization of Drug Therapy
Safe Medications Post-OLT

• HTN:
  – Amlodipine, clonidine, ACE inhibitors, ARBs, beta-blockers (excluding carvedilol)
• Diabetes:
  – Metformin, sulfonylureas and thiazolidinediones
• Antibiotics:
  – PCNs, cephalosporins, quinolones, sulfonamides and topical (not oral) anti-fungal
• Seizure:
  – Gabapentin, pregabalin, and levetiracetam
• Hyperlipidemia:
  – Statins, ezetimibe, niacin, bile acids binders
• Pain:
  – Narcotics, Tylenol, tramadol (no NSAIDS!)
Risks of Immunosuppression

• > 50% of deaths post-OLT are related to complications of immunosuppression:
  – Cardiovascular disease
  – Renal failure
  – Infection
  – Metabolic diseases
  – Malignancy
Renal Dysfunction

• Chronic renal failure (GFR of ≤ 29) occurs in 20% after 5 years post-OLT
  – Is associated with a 4.5 x greater probability of death compared to recipients with normal renal function

• Risk factors:
  – Pre-OLT factors:
    • Female sex
    • CKD pre-OLT
    • DM
    • HCV
  – Post-OLT:
    • Immunosuppression (CNIs)
    • HTN
    • DM
Metabolic Disorders

- **Diabetes:** prevalence may be as high as 33%
  - Risk factors include = corticosteroids, TAC, HCV, race, obesity
  - Incidence of de novo post-OLT diabetes
    - Greatest during the first year (26%)

- **Hypertension:**
  - Corticosteroids and CNIs increase the risk
  - CNIs: induce sympathetic stimulation, renal vasoconstriction and sodium retention
  - CyA vs. TAC = 25–82% vs. 17–64%,
  - Calcium channel blockers are effective
  - Beta-blockers are less effective
  - ACE inhibitors and ARBs can be used with caution (CKD & hyperkalemia)
Metabolic Disorders

- **Dyslipidemia:** occurs in 16 to 43%
  - Risk factors: female gender, cholestatic liver disease, pre-OLT HL, DM, obesity, and use CyA, steroids, and sirolimus
  - TAC has a minor effects, MMF and AZA have no significant effect

- **Medical treatment:**
  - Bile acid sequestrants: decrease MMF and MPA levels by 35
  - Fibric acids (gemfibrozil, fenofibrate and clofibrate) can cause myopathy
  - Hydrophilic statins (pravastatin or fluvestatin): not metabolized by the same cytochrome P450-3A as CNIs and sirolimus
  - Lipophilic statins (atorvastatin, lovastatin and simvastatin) are metabolized by cytochrome P450-3A
    - Associated with higher rates of myopathy at dosages > 20mg/day
    - Combined with fibric acid can significantly increase the risk of myopathy
Metabolic Disorders

- **Obesity:** up to 28% of transplant recipients have a BMI > 30
- 22% of nonobese transplant recipients became obese within 2 years
- Risk factors for weight gain:
  - Pre-OLT obesity
  - Use of corticosteroids
  - CsA vs. TAC (46% vs. 27%)
- Treatment:
  - Diet and exercise
  - Considering altering immunosuppressive medications
  - Orlistat may decrease CyA absorption, but not TAC
Metabolic Bone Disease (MBD)

• Risk Factors (general):
  – Pre-OLT MBD
  – ETOH and cholestatic liver diseases
  – Advanced age, physical inactivity
  – Smoking
• Risk factors (transplant related):
  – Corticosteroid use
  – CyA > TAC
• Skeletal fractures prevalence = 13% after 2 years
• Treatment:
  – Lifestyle modification: avoid ETOH, smoking, physical inactivity
  – Pharmacologic: calcium, vitamin D, and bisphosphonates
Cutaneous Malignancies

- Squamous cell carcinomas, basal cell carcinomas and melanomas are frequently observed in transplanted recipients.
- Skin cancers post-OLT (especially SCC):
  - Develop at a younger age
  - Are more aggressive
  - Metastasize
  - Tend to be multiple
- Peak incidence = 3 to 5 years post-OLT
- Risk factors for SCC:
  - History of skin cancer and/or actinic keratosis
  - Fair skin
  - Chronic sun exposure and/or sunburn
  - Older age
  - Duration and intensity of immunosuppression (CD4 lymphopenia)
  - History of HPV infection
Preventative Medicine

- Routine health maintenance
- Vaccinations
- Dental care
- Metabolic syndrome screening:
  - HTN, DM, HL
- Bone density screening (DEXA every 1-2 years)
- Lifestyle screening:
  - Physical activity, drinking, smoking, diet
- Skin cancer screening
THE END