MANAGING THE TRANSPLANT PATIENT

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OCTOBER 25, 2015
Pre 1. What is the backbone anti-rejection drug for most organ transplant recipients in the United States today?

A. Mycophenolate Mofetil
B. Prednisone
C. Azathioprine
D. Tacrolimus
E. Sirolimus
Pre 2. Which medication, if given, is most likely to increase levels of tacrolimus and possibly lead to toxicity?

A. Carbamazepine
B. Fluconazole
C. Rifampin
D. Penicillin
E. Phenytoin
Pre 3. All of the following are potential side effects of tacrolimus except:

A. Chronic kidney disease
B. Diabetes
C. Hypertension
D. Elevated triglycerides
E. Tremor
Transplant Timeline

First Corneal Transplant 1906
Blood Transfusion 1918
Kidney Transplant from Identical Twin 1954
First DD Kidney Transplant 1962
Kidney Transplant from Identical Twin 1954
First DD Kidney Transplant 1962
Skin Allograft 1908
First Dialysis Machine 1943
Cardiopulmonary Bypass 1953
First Liver Transplant 1963
First Heart Transplant 1967
Uniform Anatomical Gift Act 1968
FDA approves cyclosporine 1983
National Organ Transplant Act 1984
UNOS gets contract to run organ database 1984
First single lung transplant 1983
First small bowel transplant 1991
Final Rule 2000
Transplant Immunosuppression

• 1960s: Azathioprine and steroids
• 1979: Cyclosporine
• 1990s: Tacrolimus, mycophenolate mofetil
• 2000: Sirolimus
• 2013: Everolimus
Pre-Transplant
MANIFESTATIONS OF LIVER DISEASE

- Hemodynamic Abnormalities
- Coagulopathy
- Ascites/ SBP
- Hepatopulmonary Syndrome
- Hepatic Encephalopathy
- Variceal Hemorrhage
- Hepatorenal Syndrome

HEPATIC FAILURE
INDICATIONS FOR ORTHOTOTOPIC LIVER TRANSPLANTATION (OLT)

<table>
<thead>
<tr>
<th>Hepatitis C</th>
<th>Nonalcoholic fatty liver disease</th>
<th>Polycystic liver disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholic liver disease</td>
<td>Cryptogenic cirrhosis</td>
<td>Familial Amyloidosis</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Alpha-1 Antitrypsin deficiency</td>
<td>Glycogen storage diseases</td>
</tr>
<tr>
<td>Autoimmune liver disease</td>
<td>Wilson’s disease</td>
<td>Urea Cycle Defects</td>
</tr>
<tr>
<td>Primary Biliary Cirrhosis</td>
<td>Hemochromatosis</td>
<td>Cystic Fibrosis</td>
</tr>
<tr>
<td>Primary Sclerosing Cholangitis</td>
<td>Acute Liver Failure</td>
<td>Budd Chiari</td>
</tr>
<tr>
<td>Biliary Atresia</td>
<td>Hepatoblastoma</td>
<td>***Cholangiocarcinoma</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>Hemangioendothelioma</td>
<td>***HIV patients with cirrhosis</td>
</tr>
</tbody>
</table>
DEMAND FOR HCV-RELATED LIVER TRANSPLANTS IS ON THE RISE

Among HCV patients aged 55–64 years

Controversial Indications for OLT

- Acute Alcoholic Hepatitis
- Advanced hepatocellular carcinoma
- Peripheral Cholangiocarcinoma
- Metastatic Neuroendocrine Tumors
- Fontan Associated Liver Disease
- Metastatic Colon Cancer
Hilar Cholangiocarcinoma
No Priority for Transplant

Ascites
SBP
Esophageal and gastric varices
Hepatic encephalopathy
Muscle cramps
Fatigue
Insomnia
Cold intolerance
Hernias
Erectile Dysfunction/Low libido
Depression
Hyponatremia
MELD score

\[ 3.8 \times \log (e) \ (\text{bilirubin mg/dL}) + 11.2 \times \log (e) \ (\text{INR}) + 9.6 \log (e) \ (\text{creatinine mg/dL}) \]
MELD score and 1 year survival

Merion, R  Am J Transpl 2005; 5:307
SURVIVAL AFTER TRANSPLANT

A. Patients with MELD > 30  Post-transplant survival 1994-2008

B. Patients with MELD < 15  Post-transplant survival 1994-2008
LOSS OF LIFE YEARS AFTER OLT

Milan Criteria for HCC

- Tumor ≥ 2 cm but < 5 cm
- Up to 3 tumors, the largest < 3 cm
- No evidence of extrahepatic spread
# MELD Exception for HCC

<table>
<thead>
<tr>
<th>Then</th>
<th>Now</th>
</tr>
</thead>
</table>
| • Within Milan?  
  • Automatic MELD of 22  
  • Increase of 10% every 90 days  
  • No MELD Cap | • Within Milan?  
  • List with raw MELD  
  • After 180 days, automatic MELD of 28  
  • Increase of 10% every 90 days without a donor  
  • MELD Cap of 34 |
Patients on the Active Waiting List

[Graph showing trends in patients by organ type from 1998 to 2010]

SRTR Annual Report 2012
Transplants performed during the year (adult & pediatric combined)
Liver Transplant in the U.S.

LI 4.1 Total adult liver transplants
Patients receiving a transplant. Retransplants are counted.
# Transplant Survival

Table 1. Mean Rates of Graft and Patient Survival for Transplantations in the United States from 1993 through 2002.

<table>
<thead>
<tr>
<th>Organ</th>
<th>Survival</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 Yr</td>
<td>5 Yr</td>
<td>10 Yr</td>
<td></td>
</tr>
<tr>
<td></td>
<td>% of</td>
<td>% of</td>
<td>% of</td>
<td>% of</td>
<td>% of</td>
</tr>
<tr>
<td></td>
<td>grafts</td>
<td>patients</td>
<td>grafts</td>
<td>patients</td>
<td>grafts</td>
</tr>
<tr>
<td>Kidney</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cadaveric</td>
<td>88.7</td>
<td>94.2</td>
<td>65.7</td>
<td>80.7</td>
<td>36.4</td>
</tr>
<tr>
<td>donor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living</td>
<td>94.3</td>
<td>97.5</td>
<td>78.6</td>
<td>90.1</td>
<td>55.2</td>
</tr>
<tr>
<td>donor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreas*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>77.3</td>
<td>98.6</td>
<td>41.0</td>
<td>79.2</td>
<td>20.5</td>
</tr>
<tr>
<td>With kidney</td>
<td>85.1</td>
<td>94.7</td>
<td>69.8</td>
<td>84.0</td>
<td>46.6</td>
</tr>
<tr>
<td>Liver†</td>
<td>80.6</td>
<td>86.3</td>
<td>64.1</td>
<td>72.1</td>
<td>45.5</td>
</tr>
<tr>
<td>Heart*</td>
<td>85.3</td>
<td>85.6</td>
<td>70.6</td>
<td>72.1</td>
<td>45.6</td>
</tr>
<tr>
<td>Lung†</td>
<td>77.0</td>
<td>78.1</td>
<td>43.6</td>
<td>45.1</td>
<td>18.6</td>
</tr>
</tbody>
</table>

* These transplants were from cadaveric donors.
† Most of these transplants were from cadaveric donors.

Sayegh et al, NEJM 2004 : 351; 2761-2766
Immunosuppression

- Calcineurin inhibitors (at tx)
  - Tacrolimus
  - Cyclosporine

- Anti-metabolites (at transplant)
  - Mycophenolate
  - Azathioprine

- mTOR inhibitors
  - At transplant
  - 1 year post-tx

SRTR Annual Report 2012
Immunosuppression

Steroids

Percent

- At transplant
- 1 year post-tx

Induction agents

- IL2-RA
- T-cell depleting
- None

SRTR Annual Data 2012
Current Challenges After OLT

- Surgical Complications
- Medical Complications (e.g. renal disease)
- Organ rejection
- Infections
- Recurrent Diseases
  - HCV
  - HBV
  - NASH
  - Autoimmune disease
SURGICAL COMPLICATIONS

**EXTRAHEPATIC**
1. Hernias 5-25%
2. Bowel obstruction 1-2%

**VASCULAR**
1. Hepatic artery thrombosis 1-4%
2. Hepatic artery aneurysm 1%
3. Hepatic artery stenosis 2-4%
4. Portal vein stenosis 2-3%
5. Hepatic vein stenosis 1-5%

**BILIARY**
1. Biliary anastomotic strictures 0.5-18%
2. Non-anastomotic biliary strictures 5-10%
3. Sludge/stones/casts 5%
Hepatic Artery Thrombosis
Hepatic Artery Stenosis and Balloon dilatation
Cholangiopathy
Portal Vein Stenosis
BILIARY COMPLICATIONS

Anastomotic stricture

Ischemic type diffuse biliary strictures
HYPERTENSION AND CARDIOVASCULAR DISEASE

Cumulative rate of cardiovascular events in liver transplant recipients

DIABETES

- Common complication after OLT
- Incidence may be as high as 30%
- Main predictors of new onset DM after OLT
  - ethnicity
  - family history of DM
  - glucose intolerance
  - age > 45
  - obesity
  - metabolic syndrome
  - long term use of corticosteroids
  - hepatitis C
  - tacrolimus
OBESITY

Frequency of obesity among LT recipients

CHRONIC KIDNEY DISEASE

CHRONIC KIDNEY DISEASE

Incidence of KTX, ESRD, and CRF plus ESRD after liver transplantation

Current Challenges After OLT
Renal Dysfunction

- Predictors of renal dysfunction
  - Higher pre-operative Cr levels
  - Higher % of patients with HRS
  - Higher % of patients requiring post-op dialysis
  - Higher Cr at 1 year post-op

- Survival @ year 13
  - 28% for ESRD patients
  - 54.6% for controls

Gonwa, Liver Transpl, 2001
# Osteoporosis Following OLT

## Pretransplant Factors

1. Older age  
2. Female  
3. Poor nutritional status  
4. Low bone density  
5. Existing osteoporotic fractures  
6. Cholestatic liver disease

## Post Transplant Factors

1. Cumulative dose of corticosteroids  
2. Rejection episodes  
3. Low bone density
BONE DISEASE FOLLOWING OLT
CAUSES OF DEATH POST-OLT

Causes of death after liver transplantation over a 10 year period

Conventional nosocomial infections

Viral
- HSV
  - Onset of CMV
    - EBV, HHV3, influenza, RSV, adenovirus
  - Onset of hepatitis B or hepatitis C

Bacterial
- Wound infections, catheter-related infections, pneumonia
  - Nocardia
  - Listeria, tuberculosis

Fungal
- Pneumocystis
- Aspergillus
- Cryptococcus
- Geographically restricted, endemic fungi
  - Candida

Protozoal
- Strongyloides
- Toxoplasma
- Leishmania
- Trypanosoma cruzi

Time after transplantation, mo

Community-acquired or persistent infections

CMV retinitis or colitis
- Papillomavirus, PTLD
## Malignancy Post-OLT

<table>
<thead>
<tr>
<th>Type of Neoplasia</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>2-4</td>
</tr>
<tr>
<td>Squamous and basal cell skin cancer</td>
<td>20-70</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>10-30</td>
</tr>
<tr>
<td>Head and Neck cancer</td>
<td>4-7</td>
</tr>
<tr>
<td>In alcoholic liver disease</td>
<td>25</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>1.7-2.5</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>3-12</td>
</tr>
<tr>
<td>In ulcerative colitis</td>
<td>25-30</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>Not increased</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Not increased</td>
</tr>
<tr>
<td>Kidney cancer</td>
<td>5-30</td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td>100</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>3.4</td>
</tr>
</tbody>
</table>
### Post Liver Transplant Morbidity

<table>
<thead>
<tr>
<th>Disease</th>
<th>Prevalence post transplant</th>
<th>Rate in US population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (BP &gt; 140/90)</td>
<td>41-81%</td>
<td>15.7%</td>
</tr>
<tr>
<td>Hypercholesterolemia (&gt;240mg%)</td>
<td>20-66%</td>
<td>14.9%</td>
</tr>
<tr>
<td>HDL &lt; 35mg%</td>
<td>52%</td>
<td>12%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>21-32%</td>
<td>3.7%</td>
</tr>
<tr>
<td>Obesity (BMI &gt; 30)</td>
<td>39-43%</td>
<td>16.1%</td>
</tr>
<tr>
<td>Skin cancer (BCC and SCC)</td>
<td>10%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Other Cancers</td>
<td>2%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Renal Impairment</td>
<td>77%-80%</td>
<td>4%</td>
</tr>
<tr>
<td>Symptomatic Fractures</td>
<td>10%</td>
<td>.04%</td>
</tr>
</tbody>
</table>
LIFE AFTER LIVER TRANSPLANTATION

- There is a survival benefit to liver transplantation
- However, life expectancy and QOL are NOT equivalent when compared to matched controls
- We must treat co-morbid conditions aggressively and in a multi-disciplinary fashion
3 Signal Pathway

Signal I
- TCR
- CD3
- CD4/8

Signal II
- CD28
- CD154
- CD2
- CD11a
- CD54
- IL-2 receptor

Signal III
- Growth factor receptors

De novo pyrimidine synthesis
- IMPDH

Calcineurin activation
- NFAT
- NFAT-P-P
- mTOR
- Ca++ independent
- Costimulation
- PI-3K protein kinases
- p70S6 kinase
- 40S6-P
- CREM

Cytokine and growth factor transcription
- IL-2 mRNA
- Growth factors mRNAs

DNA synthesis
- (G1-S phase)

Mitosis
- Mitosis

IL-2, growth factors
Goals of Immunosuppression

- Minimize rejection
- Minimize toxicity
- Improve long-term graft and patient survival
- Improve quality of life
## Maintenance Immunosuppression

<table>
<thead>
<tr>
<th>Calcineurin Inhibitors (CNI)</th>
<th>Anti-proliferatives</th>
<th>Corticosteroids</th>
<th>m-Tor inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tacrolimus (Prograf®)</td>
<td>Mycophenolate mofetil (CellCept®)</td>
<td>Prednisone (Deltasone®)</td>
<td>Sirolimus (Rapamune®)</td>
</tr>
<tr>
<td>Cyclosporine, modified (Gengraf®, Neoral®)</td>
<td>Mycophenolate sodium (Myfortic®)</td>
<td>Methylprednisolone (Solu-Medrol®)</td>
<td>Everolimus (Zortress®)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Azathioprine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Costimulation inhibitors**

Belatacept (Nulojix®)
Immunosuppression in the U.S.

The first cadaveric renal allograft survival and rejection episodes over time. This figure demonstrates the best reported 1-year cadaveric survival and incidence of rejection over the last 45 years. The time that various immunosuppression medications were introduced is position on the graph.
LIVER TRANSPLANTATION WITH USE OF CYCLOSPORIN A AND PREDNISONE

Thomas E. Starzl, M.D., Ph.D.,
Göran B. G. Klintmalm, M.D.,
Kendrick A. Porter, M.D.,
Shunzaburo Iwatsuki, M.D.,
and Gerhard P. J. Schröter, M.D.
Calcineurin Inhibitors (CNIs)

- **Tacrolimus** (FK506, FK, Prograf®)
  - Binds to FKBP-12

- **Cyclosporine** (Gengraf®, Neoral®, Eon, Sandimmune®)
  - Binds to cyclophilin
Mechanism of action of cyclosporine or tacrolimus (FK506)
Tacrolimus (TAC) and Cyclosporine

- Dose every 12 hours
- Trough levels are important to follow
- Goal trough levels of 3-12 for TAC depending on time from transplant and risk of rejection
- Goal trough levels of 50-250 for cyclosporine
- Random levels can be sent to assess for toxicity
CNI Adverse Effects

- Renal Toxicity
- Neurotoxicity (TAC > Cyclo)
- Hyperglycemia (TAC > Cyclo)
- Hypertension
CNI Adverse Effects

- Acne and hirsutism (Cyclosporine)
- Gingival Hyperplasia (Cyclosporine)
- Hypomagnesemia
- Hyperkaleemia
- Hair loss (TAC)
- Increased risk of malignancy
Chronic Renal Failure after Transplantation of a Nonrenal Organ

Akinlolu O. Ojo, M.D., Ph.D., Philip J. Held, Ph.D., Friedrich K. Port, M.D., M.S., Robert A. Wolfe, Ph.D., Alan B. Leichtman, M.D., Eric W. Young, M.D., M.S., Julie Arndorfer, M.P.H., Laura Christensen, M.S., and Robert M. Merion, M.D.

Table 2. Cumulative Incidence of Chronic Renal Failure According to the Type of Transplanted Organ.*

<table>
<thead>
<tr>
<th>Type of Organ</th>
<th>Cumulative Incidence of Chronic Renal Failure after Transplantation</th>
<th>Relative Risk of Chronic Renal Failure (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12 Mo percentage ±SE</td>
<td>36 Mo percentage ±SE</td>
</tr>
<tr>
<td>Heart</td>
<td>1.9±0.1</td>
<td>6.8±0.2</td>
</tr>
<tr>
<td>Heart–lung</td>
<td>1.7±0.5</td>
<td>4.2±0.9</td>
</tr>
<tr>
<td>Intestine</td>
<td>9.6±2.0</td>
<td>14.2±2.4</td>
</tr>
<tr>
<td>Liver</td>
<td>8.0±0.1</td>
<td>13.9±0.2</td>
</tr>
<tr>
<td>Lung</td>
<td>2.9±0.2</td>
<td>10.0±0.4</td>
</tr>
</tbody>
</table>
Drug Interactions with CNIs

- **CNI – Increased levels**
  - Erythromycin, clarithromycin
  - Amiodarone
  - Diltiazem, nicardipine, verapamil
  - Azoles: Fluconazole, itraconazole, ketoconazole, voriconazole
  - Grapefruit juice, pomegranate
  - PI: Saquinavir, indinavir, nelfinavir, ritonavir

- **CNI – Decreased levels**
  - Carbamazepine
  - Phenobarbital
  - Phenytoin
  - Rifampin
  - St. John’s Wort
Drugs that potentiate CNI toxicity

- Nephrotoxic agents
  - NSAIDs, Amphotericin, IV contrast, aminoglycosides
- K-sparing diuretics/potassium supplementation
  - Increased risk of hyperkalemia
- Statins
  - Increased risk of rhabdomyolysis
  - Pravastatin/fluvastatin best choice
Purine Antagonists

- **Mycophenolate mofetil (CellCept®, MMF)**
  - Inhibits inosine monophosphate dehydrogenase (IMPDH)
  - Blocks de novo pathway of purine synthesis
  - Inhibits late T cell activation

- **Mycophenolate sodium (Myfortic®)**
  - Enteric coated

- **Azathioprine (Imuran®)**
Mechanism of action of mycophenolate mofetil

Expert Reviews in Molecular Medicine © 2000 Cambridge University Press
MMF

- Administration
  - Usually BID dosing

- Monitoring
  - Drug levels are not required
MMF Adverse Effects

- GI Side Effects
- Bone Marrow Suppression
- Bad for Pregnancy (miscarriage; birth defects)
Corticosteroids
(methylprednisolone, prednisone)

- Steroids should be minimized
- Steroids may need to be long term in autoimmune type diseases or renal transplant patients
- First line treatment of acute cellular rejection
<table>
<thead>
<tr>
<th>Adverse Effects of Steroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Hyperglycemia</td>
</tr>
<tr>
<td>Dyslipidemia</td>
</tr>
<tr>
<td>Osteoporosis</td>
</tr>
<tr>
<td>Psychosis</td>
</tr>
<tr>
<td>Glaucoma</td>
</tr>
<tr>
<td>Edema</td>
</tr>
<tr>
<td>Acne</td>
</tr>
<tr>
<td>Cushingoid appearance</td>
</tr>
<tr>
<td>Cataracts</td>
</tr>
<tr>
<td>Growth retardation in children</td>
</tr>
<tr>
<td>Leukocytosis</td>
</tr>
</tbody>
</table>
mTOR Inhibitors

- Sirolimus (Rapamune®, Rapamycin)
- Everolimus (Zortress)
Sirolimus (Rapamune®)

- Binds/inhibits mammalian target of rapamycin (mTOR)
  - Binds FKBP-12
  - Blocks IL-2 induced cell cycle progression
  - Halts G1 to S phase
  - Long half-life
Mechanism of action of sirolimus (rapamycin)

Expert Reviews in Molecular Medicine © 2000 Cambridge University Press
Sirolimus Adverse Effects

- Hyperlipidemia
- Leukopenia
- Thrombocytopenia
- Rash
- Mouth ulcers
- Delayed wound healing
- Edema
- Hepatic Artery Thrombosis (HAT)
- Interstitial pneumonitis
- Proteinuria
Belatacept

- Selective co-stimulation blocker (CD80 and CD86)
  - Inhibition of T-cell activation
- FDA approved in June 2011
- Less nephrotoxic than calcineurin inhibitors
- Monthly infusions
- Increased risk of rejection
- Increased risk of PTLD and PML
  - Use only if recipient is EBV positive
Belatacept
GFR: Bela vs CSA

Mean calculated GFR (mL/min/1.73m²)

Month

12 18 24 30 36 42 48 54 60

Belatacept n= 102

CsA n= 23

95 91 85 86 82 79 78 76

19 17 13 18 19 14 12 12
<table>
<thead>
<tr>
<th>Condition</th>
<th>TAC</th>
<th>CYA</th>
<th>MPA</th>
<th>AZA</th>
<th>SRL/EV</th>
<th>Pred</th>
<th>Bela</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTN</td>
<td>++</td>
<td>++</td>
<td></td>
<td></td>
<td></td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>++++++</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Renal toxicity</td>
<td>+++</td>
<td>+++</td>
<td></td>
<td></td>
<td>+</td>
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<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>++</td>
<td>+</td>
<td></td>
<td></td>
<td>+++</td>
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<td></td>
</tr>
<tr>
<td>Cosmetic</td>
<td></td>
<td>+++</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>GI Upset</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td></td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS/tremor</td>
<td>+++</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
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<td>+</td>
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<tr>
<td>Alopecia</td>
<td>+</td>
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<tr>
<td>Osteopenia</td>
<td>+</td>
<td>+</td>
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<td>+++</td>
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</tr>
</tbody>
</table>
"BOY! TALK ABOUT ORGAN REJECTION!"
Acute Cellular Rejection

- Liver: Increased Bilirubin, AST/ALT, Alk Phos, GGT
- Kidney: Increased serum creatinine
- History of non-adherence
- Suboptimal immunosuppression

How to diagnose? Biopsy
Other common medications

- Antibiotic prophylaxis
- Acid suppression
- Anti-hypertensives
- Pain medications
Prophylaxis After Transplant

- **Anti-bacterial**
  - Pneumocystis jiroveci pneumonia (PJP) prevention

- **Anti-viral**
  - Cytomegalovirus (CMV) and Herpes Simplex Virus (HSV) prevention

- **Anti-fungal**
  - Thrush prevention
  - Systemic prevention if high risk
PJP Prophylaxis

- Sulfamethoxazole/trimethoprim (Bactrim SS) daily for 6 months
- Adverse effects:
  - Bone marrow suppression, allergic reactions, photosensitivity
  - Adjust dose for renal insufficiency
PJP Alternatives

- If allergy or intolerance to Bactrim:
  - **Atovaquone (Mepron®)** 1500 mg PO daily
    - Headache
    - Increased LFTs
    - Only available in liquid
  - **Inhaled pentamidine (NebuPent®)** 300 mg every month
    - Check PFTs prior to administration
    - Leukopenia, thrombocytopenia
  - **Dapsone (Dapsone®)** 100 mg PO daily
    - Hemolytic anemia
    - Methemoglobinemia
    - Check G6PD
CMV/HSV Prophylaxis—high risk

- Valganciclovir (Valcyte®) for 3 months

- Common side effects
  - Neutropenia/leukopenia
  - Headache
  - GI upset

- Adjust dosing for renal insufficiency
CMV/HSV Prophylaxis—lower risk

- **Acyclovir** 400mg -800mg PO TID x 3 months

- **Valacyclovir**
  - 500mg po qday
  - Pro-drug of acyclovir
  - Less frequent dosing, but more expensive

- **Common side effects**
  - Headache
  - GI upset
Anti-fungal prophylaxis

- **Nystatin (Mycostatin®) swish and swallow**
  - 5ml four times daily

- **Clotrimazole (Mycelex®) troche**
  - Dissolve 10mg troche 5 x day

- **Fluconazole (Diflucan®)—High risk patients**
  - 200-400mg daily
    - Renally adjust
Typical Discharge Medications: Liver

- Tacrolimus (Prograf) 5 mg po q12hr
- Mycophenolate (CellCept) 1000mg po q12hr
- Prednisone 20mg po daily
- SMZ/TMP SS po daily
- Valganciclovir 900mg
- Nystatin s/s 5ml QID
- Protonix 20 mg daily
- Amlodipine 10mg po daily
- Docusate sodium 100mg po q12hr
- Oxycodone 5mg po q6hr prn pain
- Baby aspirin daily
Typical Discharge Meds: Kidney (Bela)

- Belatacept
- Mycophenolate mofetil 1000mg po q12hr
- Prednisone 5mg po qday
- Tacrolimus q12hr
- SMZ/TMP SS po qday
- Valcyte 900 mg daily
- Nifedipine XL 60mg po q12hr
- Metoprolol 25mg po q12hr
- Protonix 20 mg daily
Kidney Transplantation

Diseased kidneys
- Inferior vena cava
- Aorta
- Ureters

Transplanted kidney

Transplanted ureter
Bladder

Donor kidney

Renal artery

Renal vein

Right iliac artery

Ureter

Right iliac vein

Bladder
Graft Survival: Living vs Deceased Donor Kidney

One Year Unadjusted Graft Survival by Year, Living and Deceased Donor Kidney Transplants

Year of Transplant

Source: OPTN/SRTR Annual Report Tables 1.11b
Renal Transplant Allograft Survival

The graph shows the percentage of allografts surviving over time for living donors and cadaveric donors. The survival rate decreases over the years after transplantation.
## Indications for Kidney Transplant

- Diabetes mellitus
- Hypertension
- Glomerulosclerosis
- Glomerulonephritis
  - Focal glomerulosclerosis
  - Membranous
  - IgA nephropathy
- Polycystic Kidney
- Nephritis
- Hyperoxaluria
- Fabry’s disease
- Porphyria
- Drug induced
- Lupus (SLE)
- Tumors
Post-Transplant Complications

- Acute rejection
- Early allograft failure
- Late allograft failure
- Recurrence of kidney disease
HYPER

ATN
Acute humoral

Acute cellular

Chronic allograft nephropathy

Immediate / first week

First 2 weeks

1 week – 3 months

> 1 year
Medical Complications

- Hypertension
- Diabetes
- Cardiovascular disease
- Hyperlipidemia
- Infections
- Malignancy
Chronic allograft nephropathy

Immunologic factors:
- Poor HLA matching and previous sensitization
  - Delayed graft function
  - Episodes of acute rejection
- Subacute and chronic alloimmune response
- Noncompliance of patient
- Suboptimal immunosuppression

Nonimmunologic factors:
- Older donor or poor graft quality
  - Brain-death injury, preservation injury, or ischemic injury
- Acute peritransplantational injuries
  - Delayed graft function
- Hypertension
- Hyperlipidemia
- Chronic toxic effects of ciclosporine or tacrolimus

Chronic allograft nephropathy

NEJM 2002: Pascal et al 346; 580-590
Kaplan-Meier analysis of renal allograft loss

Briganti EM et al NEJM 2002; 347:103-109
Management of hypertension

- Hypertension occurs in 60-80% of renal transplant recipients.
- Associated with increased risk for graft failure and patient death.
- All classes of antihypertensive agents can be used to lower BP in renal transplant recipients.
<table>
<thead>
<tr>
<th>Common Types of Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cytomegalovirus</td>
</tr>
<tr>
<td>• <em>Polyomavirus (BK virus)</em></td>
</tr>
<tr>
<td>• Epstein-Barr virus</td>
</tr>
<tr>
<td>• Bacterial infections</td>
</tr>
<tr>
<td>○ <em>Pneumocystis</em></td>
</tr>
<tr>
<td>○ <em>Listeria</em></td>
</tr>
<tr>
<td>• Urinary tract infection</td>
</tr>
<tr>
<td>• Wound infections</td>
</tr>
<tr>
<td>• Fungal infections</td>
</tr>
<tr>
<td>○ <em>Aspergillus</em></td>
</tr>
<tr>
<td>○ <em>Candida</em></td>
</tr>
<tr>
<td>○ <em>Cryptococcus</em></td>
</tr>
<tr>
<td>• Viral infections</td>
</tr>
<tr>
<td>○ Herpes simplex</td>
</tr>
<tr>
<td>○ Varicella zoster virus</td>
</tr>
<tr>
<td>○ Hepatitis B virus</td>
</tr>
<tr>
<td>• Parasitic infections</td>
</tr>
<tr>
<td>○ Toxoplasmosa</td>
</tr>
</tbody>
</table>
BK virus

- Monitor serum BK PCR every month post transplant for the first 12 months.
- Definitive diagnosis: renal biopsy.
- Pathology: tubular cells enlarged with nuclear viral inclusion bodies and associated lymphocytic infiltrate.

<table>
<thead>
<tr>
<th>Type of neoplasm</th>
<th>Number of tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin and lip cancers</td>
<td>3897</td>
</tr>
<tr>
<td>PTLD</td>
<td>1108</td>
</tr>
<tr>
<td>Lung cancers</td>
<td>515</td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td>422</td>
</tr>
<tr>
<td>Uterus cancers</td>
<td>402</td>
</tr>
<tr>
<td>Kidney</td>
<td>393</td>
</tr>
<tr>
<td>Colo-rectal cancers</td>
<td>342</td>
</tr>
<tr>
<td>Breast cancers</td>
<td>330</td>
</tr>
<tr>
<td>Vulva/perineum/ scrotal</td>
<td>272</td>
</tr>
</tbody>
</table>
Risk factors for post transplant malignancies

- Cumulative effects of immunosuppression
- Age (older than 60 years)
- Cigarette smoking
- UV radiation
- Viruses associated with cancers
  - EBV → NHL and PTLD
  - HPV → Cervical cancer
  - HHV → Kaposi’s sarcoma
Skin Cancers
**Table 1. Skin Tumors in Transplant Recipients and Cells of Origin.**

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Cell of Origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal-cell and squamous-cell carcinoma, actinic keratosis, Bowen's disease</td>
<td>Epidermal and hair-follicle keratinocytes</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Melanocytes, nevus cells</td>
</tr>
<tr>
<td>Kaposi's sarcoma, angiosarcoma</td>
<td>Endothelial cells</td>
</tr>
<tr>
<td>Neuroendocrine skin carcinoma</td>
<td>Neuroendocrine (Merkel) cells</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>B and T lymphocytes</td>
</tr>
<tr>
<td>Malignant fibrous histiocytoma</td>
<td>Histiocytic or fibroblastic cells</td>
</tr>
</tbody>
</table>

Euvrard S et al NEJM 2003 : 348; 1681-1691
• Transplant-related health issues are not limited to graft function and rejection

• Significant health issues are introduced by transplantation and immunosuppression
When to call the liver transplant team?

- **Pre-transplant:** Management of liver decompensation, changing MELD score, high MELD score, new complication that may require removal from transplant waiting list
- **Post-transplant:** Assistance with immunosuppression, abnormal liver tests
When to call the renal transplant team?

- Pre-transplant: Any patient with medical complications who is listed for future transplant
- Post-transplant: Any change in serum creatinine; assistance with immunosuppression
Post 1. What is the backbone anti-rejection drug for most organ transplant recipients in the United States today?

A. Mycophenolate Mofetil
B. Prednisone
C. Azathioprine
D. Tacrolimus
E. Sirolimus
Post 1. What is the backbone anti-rejection drug for most organ transplant recipients in the United States today?

- Mycophenolate Mofetil: 24%
- Prednisone: 26%
- Azathioprine: 6%
- Tacrolimus: 38%
- Sirolimus: 6%

Chart shows:
- 95% for Tacrolimus (First Slide)
- 5% for Sirolimus (Second Slide)
Post 2. Which medication, if given, is most likely to increase levels of tacrolimus and possibly lead to toxicity?

A. Carbamazepine  
B. Fluconazole  
C. Rifampin  
D. Penicillin  
E. Phenytoin
Post 2. Which medication, if given, is most likely to increase levels of tacrolimus and possibly lead to toxicity?

- Carbamazepine: 6%
- Fluconazole: 97%
- Rifampin: 21%
- Penicillin: 0%
- Phenytoin: 24%
Post 3. All of the following are potential side effects of tacrolimus except:

A. Chronic kidney disease
B. Diabetes
C. Hypertension
D. Elevated triglycerides
E. Tremor
Post 3. All of the following are potential side effects of tacrolimus except:

- Chronic kidney disease: 15% (First Slide) 6% (Second Slide)
- Diabetes: 24% (First Slide) 0% (Second Slide)
- Hypertension: 15% (First Slide) 6% (Second Slide)
- Elevated triglycerides: 6% (First Slide) 54% (Second Slide)
- Tremor: 39% (First Slide) 34% (Second Slide)
Evaluation

- Please take < 90 seconds to evaluate this session.
- Time permitting, speaker will take questions following evaluation.
- Responses are not displayed and are important in maintaining high quality education.
The overall performance of the speaker:

1. Poor
2. Fair
3. Average
4. Good
5. Excellent
How well were the learning objectives met?

1. Poor
2. Fair
3. Average
4. Good
5. Excellent

Poor: 0%
Fair: 0%
Average: 0%
Good: 0%
Excellent: 79%
Did speaker present a balanced view of therapeutic options?

1. Yes
2. No
3. N/A

91% Yes, 9% No, 0% N/A
How useful will this session be in your practice?

1. Poor
2. Fair
3. Average
4. Good
5. Excellent

[Bar chart showing distribution percentages: 0% for Poor, 3% for Fair, 24% for Average, 21% for Good, 52% for Excellent]
As a result of this program, do you intend to change your patient care?

1. Yes
2. No

87%
13%
Thank you!