Primary Care of Organ Transplant Recipients

Shawn Floyd MSN, ACNP-BC, CCTC
Nurse Practitioner
University of Virginia

Objectives

- Discuss the number of transplant patients in the United States and who is taking care of post transplant patients.
- Outline what preventive care transplant patients should be receiving on a routine basis and special considerations for the transplant population.
- Develop a working understanding of co management of the post transplant patient with transplant teams.
- Discuss common interactions of medications used in the primary care setting and transplant immunosuppression.
- Discuss common prophylaxis medications post transplant.
- To help facilitate sharing between primary care providers, specialty care providers, and transplant teams.

University of Virginia Health System
the only comprehensive transplant program in the Commonwealth of Virginia
Transplant History

- Ancient Greek, Roman and Chinese myths feature fanciful accounts of transplants performed by gods and healers often involving cadavers or animals.
- While these tales are considered questionable in history.
- It is known that by 800 B.C. Indian doctors had likely begun grafting skin—technically the largest organ—from one part of the body to another to repair wounds and burns.

- 16th Century: Italian surgeon Gasparo Tagliacozzi, sometimes known as the father of plastic surgery, reconstructed noses and ears using skin from patients' arms. He found that skin from a different donor usually caused the procedure to fail, observing the immune response that his successors would come to recognize as transplant rejection.
- Early 1900s: European doctors attempted to save patients dying of renal failure by transplanting kidneys from various animals, including monkeys, pigs and goats. None of the recipients lived for more than a few days.
Transplant History

- 1905: Eduard Zirm, an Austrian ophthalmologist, performed the world’s first corneal transplant, restoring the sight of a man who had been blinded in an accident.
- 1912: Transplant pioneer Alexis Carrell received the Nobel Prize for his work in the field. The French surgeon had developed methods for connecting blood vessels and conducted successful kidney transplants on dogs.
- 1936: Ukrainian doctor Yu Yu Voronoy transplanted the first human kidney, using an organ from a deceased donor.
  - The recipient died shortly thereafter as a result of rejection.

Charles O. Strickler Transplant Center

Game Changer
Richard and Ronald Herrick

The first successful living-related kidney transplant in the United States done in 1954. This was done in identical twins, which helped overcome the immune challenges.

Charles O. Strickler Transplant Center

Transplant History in the U.S.

- 1954- First successful kidney transplant performed.
- 1966- First simultaneous kidney/pancreas transplant performed.
- 1967- First successful liver transplant performed.
- 1968- First successful isolated pancreas transplant performed. First successful heart transplant performed.
- 1981- First successful heart-lung transplant performed.
- 1983- First successful single-lung transplant performed.
- 1984- National Organ Transplant Act (NOTA) passed.
- 1986- First successful double-lung performed.
- 1987- First successful intestinal transplant performed.
- 1988- First split-liver transplant performed.

Timeline of Key Events in U.S. Transplantation provided by UNOS.org

Charles O. Strickler Transplant Center
Transplant History in the U.S.

- 1954- First successful kidney transplant performed.
- 1966- First simultaneous kidney/pancreas transplant performed.
- 1967- First successful liver transplant performed.
- 1968- First successful isolated pancreas transplant performed. First successful heart transplant performed.
- 1981- First successful heart-lung transplant performed.
- 1983- First successful single-lung transplant performed.
  - *Cyclosporine introduced* - *This is a key to what we do today*
- 1984- National Organ Transplant Act (NOTA) passed.
- 1986- First successful double-lung transplant performed.
- 1987- First successful intestinal transplant performed.
- 1988- First split-liver transplant performed.

Timeline of Key Events in U.S. Transplantation provided by UNOS.org

- 1989- First successful living donor liver transplant performed.
- 1990- First successful living donor lung transplant performed.
- 1998- First successful adult-to-adult living donor liver transplant performed.
- 2000- U.S. Department of Health and Human Services publishes Final Rule (federal regulation) for the operation of the OPTN.
- 2001- For the first time, the total of living organ donors for the year (6,528) exceeds the number of deceased organ donors (6,081).
- 2013- This trend has reversed once again and now we have less living donation.

Timeline of Key Events in U.S. Transplantation provided by UNOS.org

The Numbers

- Number of people waiting for organ transplants on UNOS database:
  - Waiting list candidates as of 1/5/14 @ 2:05pm: 121,075
  - Active waiting list candidates as of 1/5/14 @ 2:05pm: 77,143
  - Transplants January - September 2013: 21,659
  - Donors January - September 2013: 10,587

Taken from: http://www.unos.org/index.php 1/5/14 @ 14:56
The Numbers

- Transplant done in the United States 1998-2013
- All Donor Types: 585,294
- Deceased Donor: 459,001
- Living Donor: 126,293

Taken from: http://optn.transplant.hrsa.gov/latestData/rptData.asp 01/05/2014

UNOS Regions

- Region 1: Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Eastern Vermont
- Region 2: Delaware, District of Columbia, Maryland, New Jersey, Pennsylvania, West Virginia, Northern Virginia
- Region 3: Alabama, Arkansas, Florida, Georgia, Louisiana, Mississippi, Puerto Rico
- Region 4: Oklahoma, Texas
- Region 5: Arizona, California, Nevada, New Mexico, Utah
- Region 7: Illinois, Minnesota, North Dakota, South Dakota, Wisconsin
- Region 8: Colorado, Iowa, Kansas, Missouri, Nebraska, Wyoming
- Region 9: New York, Western Vermont
- Region 10: Indiana, Michigan, Ohio
- Region 11: Kentucky, North Carolina, South Carolina, Tennessee, Virginia
Care of the transplant recipient

**CLINICAL TRANSPLANT BASICS**

Charles O. Strickler Transplant Center

---

### Transplanted Solid Organs In the U.S.

- Heart - Heart and Heart/lung
- Lungs - Single, Lobar, and Bilateral
- Liver - Split liver, Whole liver
- Kidney - only one at a time.
- Pancrease - Whole and Islet cells
- Hands - still in the early stages
- Face - very limited still in the early stages

Charles O. Strickler Transplant Center

---

### Transplanted Tissue

- Bone - Many different uses
- Skin - Grafting, burns, reconstructive
- Tendons - Injury, trauma
- Bone Marrow - Done regularly by oncologist
- Cornea Transplant - multiple reasons

Charles O. Strickler Transplant Center
Transplant Complications

- Bleeding
- Rejection
- Infection
- Graft versus host disease
- Side effects from immunosuppression
- Recurrence of disease
- Organ failure

Rejection

- Hyperacute rejection:
  - The antibodies on the endothelium within hours or even minutes. This is prevented by cross-matching donors and recipients.
- Antibody Mediated rejection:
  - Donor antibodies in circulation cause damage to the transplant organ.
- Acute Cellular rejection:
  - Transplant organ tissue starts to show inflammation and injury due to recipient native immune response.
- Chronic rejection:
  - Chronic allograft vasculopathy (heart) or bronchiolitis obliterans (lungs)
  - A transplant that functions initially may gradually lose function in a slow scarring process that sometimes cannot be controlled.

Bleeding

- Medications used to help prevent problems can actually cause problems.
  - Anticoagulation
  - Immunosuppression
  - ASA
Infection

- Donor derived
  - Even with the best screening transmission occurs.
  - Screen for Hep B, C, HIV, Toxo, EBV, CMV and others based on Donor Hx.
- Related to immune compromised host
  - Any infection that the recipient might have had can become worse once we start giving immunosuppression

Medication Side effects

<table>
<thead>
<tr>
<th>Routine Medications</th>
<th>Transplant Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>Nausea</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Vomiting</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Headaches</td>
<td>Headaches</td>
</tr>
<tr>
<td>Ect</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Ect</td>
<td>Anemia</td>
</tr>
<tr>
<td>Ect</td>
<td>Neutropenia</td>
</tr>
</tbody>
</table>

Graft Versus Host Disease

- Acute GVHD happens within the first 3 months after a transplant.
  - Abdominal pain or cramps, nausea, vomiting, and diarrhea
  - Dry or irritated eyes
  - Jaundice (yellow coloring of the skin or eyes)
  - Skin rash, itching, redness on areas of the skin
- Chronic GVHD starts more than 3 months after a transplant, and can last the rest of the patients post transplant course.
  - Dry eyes or vision changes
  - Dry mouth, white patches inside the mouth, and sensitivity to spicy foods
  - Fatigue, muscle weakness, and chronic pain
  - Skin rash with raised, discolored areas, as well as skin tightening or thickening
  - Shortness of breath
  - Vaginal dryness
  - Weight loss
- This can be mistaken for a very long time as viral illness.


Charles O. Strickler Transplant Center
Recurrence of disease

- Although most transplants are done with the hope that disease will not reoccur it can.
  - Hepatitis
  - Sarcoidosis
  - Vascular Disease (CAD, PHTN)
  - Renal Disease

Charles O. Strickler Transplant Center

Transplant organ failure

- Despite all the advancements that we have achieved sometimes the best organs that are procured do not work.
  - This could be related to ischemic time.
  - Could be a technical problems with surgery.
  - Could be a error at time of procurement.

Charles O. Strickler Transplant Center

Post transplant liver specific issues

- Hepatic artery thrombosis
- Bleeding
- Shock liver
- Elevation in liver enzymes

Charles O. Strickler Transplant Center
Post transplant heart specific issues

- Anastomotic complications
- Fatal rhythms
- EKG’s might be misleading due to changes in the electrical conduction of the transplant organ.

Post transplant lung specific issues

- PA clot/PE
- Ischemic reperfusion injury
- Unexplainable hypoxia

Post transplant kidney specific issues

- Surgical complications
- Poor organ function
- Elevation in serum creatinine
Post transplant pancreas specific issues

- Vascular Clots
- Drainage issues
- Unexplainable blood sugar elevations and drops

Diabetes

- Post transplant organ recipients are at higher risks than general population.
  - Use of calcineurin inhibitors and steroids.
  - Obesity BMI > 30
  - Advanced age

Renal Failure

- Higher rates of elevated creatine and renal failure due to:
  - Use of Calciurin inhibitors
  - Use of nephrotoxic prophylaxis
Cardiovascular

- Use of immunosuppression medications result in cardiovascular comorbidities
  - Hypertension
  - Hyperlipidemia
  - Early and close treatment are key.

Lyu et al. 2009
Charles O. Strickler Transplant Center

Osteoporosis

- Osteoporotic bone loss is accelerated in the first few months post transplant.
  - Chronic long term steroid use
  - Need for weight bearing exercise
  - Bisphosphates
  - Vitamin D levels

Lyu et al. 2009
Charles O. Strickler Transplant Center

Avascular Necrosis

- 3-22% of post transplant patients develop AVN of the femoral head.
  - Early evaluation of hip pain is key
  - Early referral to orthopedics for consideration of joint replacement

Zamora et al. 2009
Charles O. Strickler Transplant Center
Hematologic

- Hematologic issues are common due to antirejection medications.
- Erythrocytosis
- Anemia
- Neutropenia
- Thrombocytopenia


Charles O. Strickler Transplant Center

Thromboembolic disease

- 6-8% of patients that have undergone organ transplant have a high incidence of thromboembolic events.
- Lung transplant patients 8.6-29%
- Could be related to hypercoagulable state post transplant.

Lee et al, 2011

Charles O. Strickler Transplant Center

Gastrointestinal

- Gastrointestinal complaints after transplant are reported in 20% to 35% of recipients, with a frequency as high as 60%
**Neurologic**

- Neuro complications can be attributed to both drugs and infection, 30 to 60% of patients may develop:
  - Headaches
  - Seizures
  - Strokes
  - Altered Mental Status

**Malignancy**

- Solid organ transplant patients have higher prevalence of cancer than general population
  - High frequency of aggressive skin, GI, and lung cancers.

---

Charles O. Strickler Transplant Center

Post transplant patient care

WHY DO I NEED THAT?

Charles O. Strickler Transplant Center

Care of the transplant patient

- Organ transplant is not for all patients, it has to be the right patient at the right time. (i.e., if a patient with ETOH Cirrhosis is still drinking)
- Solid organ transplant patients trade one set of problems for another!
  - Most transplants are palliative not curative. They have relief from the symptoms of end stage organ disease.
  - They may have complications or side effects from medications or surgery, that the patient did not have prior.

Charles O. Strickler Transplant Center

Care of the transplant patient

- Ideally transplant centers want primary care providers to provide general preventive care:
  - Pap Smears
  - Mammograms
  - PSA’s
  - Lipid profiles
  - Skin surveillance

Charles O. Strickler Transplant Center

-- McLaughlin, 2001 --
What care do transplant centers need referring primary care physicians to manage?

- Preventive medicine 100%
- Annual examinations 65%
- Vaccination 65%
- Diabetes 60%
- Bone disease 40%
- Hypertension 37%
- Pregnancy 28%
- Sexual issues 15%

McCashland, 2001

Every Transplant Center is Different

- Depending on the center postoperative patients might be cared for by:
  - Surgeons
  - Specialist
  - Generalist
  - Nurse Practitioners
  - Transplant Coordinators.

PREVENTATIVE SCREENINGS FOR ORGAN TRANSPLANT RECIPIENTS
General Guidelines for Screening

- Post transplant disease screening and surveillance is very important due to the chronic use of immunosuppressive medications.
  - The use of triple and double immunosuppression regimens increase development of co-morbid conditions.

Cardiovascular

- Lipids
  - Check every 3 to 4 months
  - LDL >130
  - HDL >30

- Blood Pressure:
  - Weekly home monitoring
  - Systolic <130
  - Diastolic <80

Dental

- Semi annual dental screens for patients with and without natural dentation.
  - Dentist can see microvascular changes in the oral cavity before systemic changes or signs start.
### Dermatologic
- Annual skin screenings.
  - Cancers
  - Vascular changes
  - Infections
  - Rashes

### GI
- High risk patients should undergo colonoscopy at least every 3 to 5 years post transplant.
- EGD if clinic s/s suggest esophagitis or treatment resistant GERD.

### Pulmonary
- Chest film
  - To evaluate infection/malignancy.
- Pulmonary Function Testing
  - If hx of smoking and/or still smoking.
Endocrine

- HA1C every 3 to four months to screen for new onset Diabetes
- Bi-annual bone density studies.
- Vitamin D levels at least 2 times a year.

Ophthalmology

- Annual vision testing
  - Cataracts
  - Vision changes due to steroids

GU/GYN

- Annual or bi-annual
  - Pap
  - Rectal exam
  - PSA
  - Mammo
Reproductive

- All transplant patients of child bearing age.
  - Birth Control
  - Family Planning

Caveat....

- This is not an all inclusive drug interaction list.
- It will have some of the more common interactions that occur.
- Unfortunately, interactions are unavoidable in this population.
  - We routinely use these interactions to our advantage.
Immunosuppression

- Complex medication regimens that must be monitored by the transplant team.
- This is a requirement at the beginning of transplant and is reportable to UNOS by transplant centers.

Induction

- This is the beginning of the madness, used at the time of transplant to suppress the recipients immune system.
- Can be complex depending on the protocol being used.

Induction

- Induction immunotherapy is intense immunosuppression in the perioperative or immediate post operative phase.
- Common drugs used for induction:
  - Polyclonal Antibodies
  - Rabbit ATG (thymoglobulin)
  - Equine ATG
    - Monoclonal Antibodies
      - Basiliximab
      - Daclizumab (no longer available in the U.S.)
  - Steroids
  - Methyprednisolone or Prednisone
### Polyclonal Antibodies

**ATG**

**Mechanism of Action**
- Exact mechanism of action unknown; reduces number and alters function of circulating T-lymphocytes

**Side effects**
- Hypersensitivity
- Increased risk of opportunistic infections

---

### Monoclonal Antibodies

**Mechanism of Action**
- Binds to activated T-lymphocyte IL-2 receptor alpha chains, antagonizing IL-2

**Side effects**
- Hypersensitivity
- Anaphylaxis

---

### Maintenance

- Depending on the Organ system and transplant team.
- No set immunosuppression regiments
- Could have every patient on a different regiment.
- Some experiments with some patients who can not tolerate certain classes of medications.
**Maintance**

- Common maintenance immunosuppression:
  - Calcineurin Inhibitors
    - Cyclosporin (Gengraf®, Neoral®)
    - Tacrolimus (Prograf®, FK506)
  - Antiproliferative Drugs
    - Mycophenolate Mofetil (Cellcept®)
    - Mycophenolic Acid (Myfortic®)
    - Azathioprine (Imuran®)
  - mTOR Inhibitors
    - Sirolimus (Rapamune®)
    - Everolimus (Afinitor®, Zortress®)

**Calcinurin Inhibitors**

**Mechanism of Action**
- Exact mechanism of action unknown; inhibits T-lymphocyte activation

**Side Effects**
- TAC
  - Hyperglycemia
  - Tremor
  - Alopecia
- CSA
  - Hypertrichosis
  - Gingivitis
  - HTN

**Antiproliferative Drugs**

**Mechanism of Action**
- Inhibits B- and T-lymphocyte proliferation

**Side Effects**
- Myelosuppression
- Leucopenia
- GI distress
- Increase risk for skin cancers
mTOR Inhibitors

Mechanism of Action
- inhibits mammalian target of rapamycin (mTOR) kinase activity, resulting in cell death.

Side effects
- Delayed wound healing
- Hyperlipidemia
- Bone marrow suppression
- Pneumonitis

Steroids

Mechanism of Action
- Exact mechanism of anti-inflammatory action unknown; inhibits multiple inflammatory cytokines; produces multiple glucocorticoid and mineralocorticoid effects

Side Effects
- Hypertension
- Diabetes
- Osteopenia
- Hyperlipidemia
- Cushingoid
- Acne
- Growth retardation

Acute Rejection Treatment

High dose steroids
- 250 to 1000 mg IV for 3 to 5 days
- Hyperglycemia
- Insomnia
- Hyperactivity

Some new approaches on the horizon!
Cytochrome p450 In Transplant

- CYP450 Inhibitors:
  - Increase levels of the drug by inhibiting metabolism of antirejection drug.
- CYP450 Inducers:
  - Decrease levels of the drug by inducing metabolism of antirejection drug.

Common Cytochrome p450 Inducers

- Antiepileptics
  - Phenobarbitone
  - Phenytoin
  - Fosphenytoin
  - Carbamazepine
  - Oxcarbazepine
- Antibiotics
  - Caspofungin
  - Nafcilin
  - Rigabutin
  - Rifampicine
  - Rifapentine
Common Cytochrome p450 Inducers

- **Antivirals**
  - Efavirenz
  - Etravirine
  - Nevirapine

- **Others**
  - Antacids (containing mag, ca, or al)
  - Dererazirox
  - Modafinil
  - St John’s wort
  - Thalidomide
  - Ticlopidine
  - Troglitazone

Common Cytochrome p450 Inhibitors

- **Antibiotics**
  - Clarithromycin
  - Erythromycin (Not azithromycin)
  - Metronidazole
  - Tinidazole
  - Levofloxacin

- **Antivirals**
  - Indinavir
  - Nelfinavir
  - Ritonavir

- **Antifungals**
  - Clotrimazole
  - Fluconazole
  - Ketoconazole
  - Itraconazole
  - Voriconazole

Common Cytochrome p450 Inhibitors

- **Cardiovascular**
  - Amiodarone
  - Lidocaine
  - Diltiazem
  - Verapamil

- **Others**
  - Grapefruit juice
  - Nefazodone

Charles O. Strickler Transplant Center
Opportunistic infection Prophylaxis

- To prevent opportunistic infections that we are putting these patients at risk for.
  - Prime example:
    - I live in Virginia, if I leave cardboard outside for a few days in the summer it will grow mold on it. Just imagine what a human lung can grow in it.

Opportunistic infection Prophylaxis

- PJP (PCP)
  - Bactrim DS
  - Dapsone
- Antifungal
  - Mycelex
  - Nystatin
  - Itraconazole
  - Voriconazole
- Antiviral
  - Acyclovir
  - Valacyclovir
  - Ganciclovir
  - Valgancyclovir
Care of the transplant recipient

END OF LIFE

Charles O. Strickler Transplant Center

End of Life Care

- Transplant patient need to have the same end of life considerations as everyone else.
- Some transplant patients feel cheated when they get a terminal diagnosis after a transplant.
- Remember solid organ transplant patients trade one set of problems for another!
  - Transplanted for ESRD, die of metastatic skin cancer.

Charles O. Strickler Transplant Center

End of Life Care

- What are the goals of care?
- Are we going to disable devices?
- Are we going to stop immunosuppression?
- Are organ transplant patients able to donate their organs?
Abbreviations

- UNOS, United Network for Organ Sharing
- CMV, cytomegalovirus
- EBV, Epstein-Barr virus
- Gastroesophageal reflux disease
- CMV, cytomegalovirus
- Gastroesophageal reflux disease
- HBV, hepatitis B virus
- HCV, hepatitis C virus
- HSV, herpes simplex virus
- VZV, varicella-zoster virus
- MALT, mucosa-associated lymphoid tissue
- NSAID, nonsteroidal anti-inflammatory drug

Charles O. Strickler Transplant Center

References


References


