Heart, Liver, and Kidneys – Oh My!
Solid Organ Transplantation: What the PNP needs to know
Kelci LaPorte, MSN, CPNP-AC, CCTC
Heart Transplant/Heart Failure
Pediatric Nurse Practitioner
Children’s Healthcare of Atlanta

Disclosures
• No disclosures or conflicts to report

Learning Objectives
• Discuss the common indications for pediatric heart, liver, and kidney transplantation
• Discuss common early and late post-transplant complications
• Discuss the overall primary management of pediatric solid organ recipients
• Review the basic transplant pharmacology and drug use, along with immunization recommendations for solid organ recipients

Pediatric Solid Organ Transplantation

Pediatric solid organ transplantation (SOT) is a remarkable, life-saving procedure that allows survival for the majority of children with diseases that would otherwise likely be fatal.

The risks of pediatric SOT are considerable and the pre- and post-transplant care requires multi-disciplinary care and coordination.

There are currently 1810 pediatric patients either waiting for a heart, liver, or kidney transplant in the United States.*


Common Pediatric Diagnoses Requiring Transplant

<table>
<thead>
<tr>
<th>Disease</th>
<th>Liver</th>
<th>Kidney</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital Heart Disease</td>
<td>Cholestatic Disease (Biliary Atresia)</td>
<td>Aplastic, hypoplastic, or dysplastic kidney</td>
</tr>
<tr>
<td>Cardiomyopathies (Dilated, Restrictive, Hypertrophic)</td>
<td>Metabolic Disease</td>
<td>Obstructive Uropathy</td>
</tr>
<tr>
<td>Maligancy (hepatoblastoma, hepatocellular carcinoma)</td>
<td>Focal Segmental Glomerulosclerosis (FSGS)</td>
<td>Acute liver failure (drug-induced hepatitis, viral hepatitis)</td>
</tr>
</tbody>
</table>

For each organ group, there are absolute and relative contraindications which may exclude a patient from being a suitable transplant recipient.

Consideration for Transplant

Heart
• Advanced symptoms of heart failure
• Inoperable heart disease
• Requiring mechanical assistance/circulatory support
• Abnormal hemodynamics or increasing pulmonary vascular resistance
• Symptomatic arrhythmias not amenable to medication or device therapy

Liver
• Emergent referral: acute liver failure or acute decompensation of an established liver disease with encephalopathy and/or coagulopathy
• Urgent referral: those with liver-based metabolic crises refractory to medical/surgical therapy; unresectable hepatoblastoma; unresectable hepatocellular carcinoma meeting certain criteria; those with chronic liver disease and decompensating function

Kidney
• Seriously considered when Glomerular Filtration Rate (GFR) ≤ 30mL/min per 1.73m²
• Children with bladder problems require additional evaluation prior to transplant

For each organ group, there are absolute and relative contraindications which may exclude a patient from being a suitable transplant recipient.
Management While Waiting for Transplant

- Nutrition
- Immunizations
- Serologies
- Psychosocial concerns
- Minimize infection
- Therapies (PT/OT/ST)
- Palliative Care Team

Organ specific care

- Heart: may require Ventricular Assist Device (VAD) support
- Liver: evaluate for portal hypertension, encephalopathy
- Kidney: dialysis, growth

Early Post-Transplant Complications

- Heart: graft dysfunction, hyperacute rejection, pulmonary hypertension
- Kidney: graft dysfunction, acute tubular necrosis, thrombus
- Liver: graft dysfunction, hepatic artery thrombosis, hemorrhage, bile leak

Rejection

- Screening for cellular rejection is organ specific and is based on:
  - the time from transplant
  - certain signs or symptoms which are concerning for rejection
- Monitoring for rejection:
  - Heart: endomyocardial biopsies, ECHO, BNP (brain natriuretic peptide)
  - Kidney: urine protein levels, serum creatinine levels
  - Liver: transaminase, bilirubin, GGT (gamma glutamyl transferase)

Late Post-Transplant Complications

Cardiovascular Risks

- Hypertension
- Diabetes Mellitus
- Hyperlipidemia
- Obesity

Chronic Kidney Disease

Infections

Biliary Obstruction & Portal Vein Complications

Complications in liver transplant patients

Hypertension

Defined as blood pressure > 90% for age, height and gender

Occurs in up to:

- 75% of renal transplant patients
- 28% of liver transplant patients
- 65% of heart transplant patients

The choice of antihypertensive therapy depends on one’s comorbidities, type of transplant, and immunosuppression regimen.

Diabetes Mellitus

Occurrence: Highest in first 3 months post-transplant

Seen in up to 13% of liver and kidney transplant patients, only 2% of heart transplant patients

Risk factors

- Older age at transplant
- Family history of DM
- Obesity
- Tacrolimus use
- Sedentary lifestyle
- Steroid use

Post-transplant screening

Goal to keep A1C <7%

Treatment options

- Insulin per endocrine team
- Oral hypoglycemic agents
- Kidney patients: may require aspirin for primary prevention of CVD
### Hyperlipidemia

**Treatment options**
- Statins are preferred agent for transplant patients (start with initial doses lower than general population due to potential interactions with CNIs)
- Some literature suggests benefit to fish oil supplementation in liver transplant patients

### Obesity

- Defined as Body Mass Index greater than 30 kg per m²
- Occurs in 20-30% of adult liver and kidney recipients who were not obese pre-transplant
- Increased appetite after transplant and medication adverse effects are likely contributing factors
- Bariatric surgery is not contraindicated

### Osteopenia/Osteoporosis

**Common pre- and post-transplant**
- Long term diuretic requirements
- Chronic kidney disease
- Corticosteroid therapy
- Immobility with chronic illness

**Post-transplant screening**
- Lab work: Calcium, Vitamin D, phosphorus, parathyroid hormone in kidney patients
- Biphosphonate therapy can be used, usually in the first year post-transplant

### Chronic Kidney Disease

**Risk factors**
- CNI use can cause both acute nephrotoxicity and chronic kidney disease
- Pre-transplant dialysis (heart patients)
- Hypertension

**Post-transplant screening**
- Glomerular filtration rate
- Urine protein-to-Cr ratio

**Strategies to reduce disease progression**
- Appropriate blood pressure and glucose control
- Transplant team may elect to decrease CNI or switch to CNI free regimen to preserve renal function

### Post-Transplant Infections

**First 30 days Post-Transplant**
- Bacterial (pneumonia, pyelonephritis, surgical wound infections)
- Nosocomial viral infections (influenza, RSV)

**Infections >6 months Post-Transplant**
- Can include many infections listed above, along with pneumonias, urinary tract infections, and hepatitis.
- Community-acquired infections

**Two to six months Post-Transplant**
- Viral (EBV, CMV, HSV, VZV, hepatitis infections
- Opportunistic (Pneumocystis jiroveci (PPD), aspergillus fumigates, listeria)

### Cytomegalovirus (CMV)

**Signs/symptoms**
- fever, hematologic abnormalities, visceral organ involvement, +CMV-PCR

**Types**
- Primary infection: acquired from infected organ
- Secondary infection: reactivation of infection or superinfection with different strain

**Prophylaxis**
- valganciclovir (may cause bone marrow suppression)

**Treatment**
- reduction of immunosuppression
- valganciclovir
- ganciclovir
CMV Resistance

Risk factors for resistance
- Donor + / Recipient –
- Prolonged exposure to CMV antivirals
- High levels of immunosuppression
- Congenital immunodeficiency

Treatment strategies
- Mutation testing
- Low level of resistance -> consider dose escalation
- High level of resistance -> change therapy
  - Foscarnet
  - Cidofovir
- Consider adjunctive therapy

Other Common Viral Infections

- Herpes Simplex Virus: some patients receive prophylaxis based on their serologies; can be treated with acyclovir or valganciclovir
- Varicella: very important to know about any exposure to varicella -> may consider prophylaxis, can also receive treatment with acyclovir
- Polyomavirus hominis (BK virus) – significant cause of graft failure in the kidney transplant population

Respiratory Infections

- Influenza
- Respiratory Syncytial Virus (RSV)
- Human metapneumovirus (hMPV)
- Pneumocystis Jiroveci Pneumonia (PJP)
- Fungal (Candida)
- Bacterial infections (MRSA, VRE, pseudomonas)

Epstein Barr Virus (EBV)

- Epstein-Barr Virus is a human oncovirus from the gamma herpes virus group (mononucleosis)
- Highest risk is with EBV – recipient / EBV + donor
- Usually manifests through unexplained fevers and/or rapidly enlarging lymph nodes; many patients are asymptomatic with positive EBV PCRs
- There is no truly effective prophylaxis or treatment options other than reduction in immunosuppression

Post-Transplant Lymphoproliferative Disease (PTLD)

- Can range from mild EBV disease to lymphoma
- Any lymphoma malignancy arising after transplant is classified as PTLD; usually caused by proliferation of EBV infected B cells
- Typically occurs in the first two years post-transplant
- Incidence of PTLD for SOT recipients ranges from 2.2% to 15% depending on the organ group
  - At five years post-transplant the incidence of PTLD in pediatrics is:
    - 2-3% for kidney recipients
    - 6% for heart recipients
    - 5-10% for liver recipients

Risk factors
- Type of organ transplanted
- Age of recipient
- EBV seronegativity at time of transplant
- Intensity of immunosuppression

Monitoring
- EBV PCR (quantitative)
- MRI, Ultrasounds, PET scans

Non-specific signs/symptoms
- Malaise
- Recurrent unknown fevers
- GI symptoms
- Weight loss
- Adenopathy


Post-Transplant Lymphoproliferative Disease (PTLD)

Treatment strategies:
• Reduction of immunosuppressant medication
• Antineoplastic drugs:
  - Rituximab: standard treatment for many types of PTLD
  - Cytotoxic drugs
  - Some centers use anti-viral drugs as PTLD prophylaxis in high risk patients

Prognosis: Recovery from PTLD is greater in children than adults


Post-Transplant Medications

Induction
• Thymoglobulin
• Steroids
• Basiliximab

Maintenance
• Calcineurin Inhibitors (tacrolimus, cyclosporine)
• Purine Synthesis Inhibitors (cellept, myfortic, azathioiprine)
• Steroids
• Mammalian Target of Rapamycin (sirolimus, everolimus)

Rejection
• T-cell rejection:
  - steroids
  - thymoglobulin
• B-cell rejection:
  - IVIG
  - Rituximab
  - Bortezomib (Velcade®)
  - Eculizumab (Soliris®)

Calcineurin Inhibitors (CNI)
• Tacrolimus (Prograf®)
  - Increased risk for diabetes mellitus
• Cyclosporine
  - Increased risk of gingival hyperplasia, dyslipidemia, hirsutism
• All CNIs have potential adverse effects of: hyperkalemia, hypertension, nephrotoxicity, neurotoxicity

Purine Synthesis Inhibitors
• Mycophenolate (Cellcept®, Myfortic®)
  - Potential adverse effects: bone marrow suppression, GI upset
  - Myfortic® is an enteric coated pill that has less GI upset than Cellcept®
• Azathioiprine (Imuran®)
  - Potential adverse effects: bone marrow suppression, cholestatic hepatitis

Medication Interactions
• Common drugs that increase Tac/CSA concentrations:
  - amiodarone
  - allopurinol
  - certain antifungals
  - certain Ca channel blockers
  - fluoroquinolones
  - macrodides
  - metronidazole
  - NSAIDs
  - warfarin

• Common drugs that decrease Tac/CSA concentrations:
  - antacids
  - antibiotics (naftolin, rifampin)
  - barbiturates
  - certain anticonvulsants
  - loperamide (modium*)
  - certain supplements (Echinacea, St John’s wort)
  - valproic acid (Depakote®)

Please note that this list is not fully inclusive.

Pre-transplant Vaccination Recommendations
• All age-appropriate vaccinations should be up to date before transplant listing, including Prevenar 13 and Pneumovax if applicable
• Live vaccines are allowed up to 4 weeks before transplant
• Patient may require accelerated schedule
• Don’t forget about siblings and guardians

Potential barriers to vaccines not being up to date:
• may be overlooked due to the demands of the chronic illness
• inconsistent visits with the PCP
• lack of structure in subspecialty practices to administer vaccines
• uncertainty from providers on when and what to order

Feldman, A.G., Kempe, A., Beaty, B.L., & Sundaram, S.S. (2016)
Post-transplant Vaccination Recommendations

- Live vaccines are contraindicated post-transplant
- Vaccines to be held during intensive periods of immunosuppression (usually restarted 2-6 months post-transplant)
- Influenza vaccine can be given after one month post-transplant
- Palivizumab (Synagis®): consideration for SOT recipients <24 months of age
- Again, don’t forget about herd immunity: siblings, guardians, health care workers…..even pets!

Growth and Development Post-Transplant

Nutrition
- many require catch-up growth
- dietary restrictions
- consider drug side effects
- follow food safety guidelines

Cognitive/Emotional
- pre-transplant factors: disease onset and severity, duration of disease, age at time of diagnosis
- anxiety and depression

School Function
- Risk for poor academic performance
- Patients should return to school as soon as possible
- Patients may benefit from neurodevelopmental assessments

Quality of Life (QOL) After Transplant

Kidney: >95% 5 year survival
- common complaints: headaches, fatigue, short stature, weight gain
- 93% of patients returned to school and participated in recreational activities/school sports
- 78% had improved psychological functioning after transplant

Liver: 85% 5 year survival
- pre-transplant factors associated with increased QOL: primary diagnosis of biliary atresia, Caucasian race, maternal education level
- pre-transplant factor associated with decreased QOL: older age at time of transplant

Heart: 75% 5 year survival
- 93% of patients returned to school and participated in recreational activities/school sports
- 78% had improved psychological functioning after transplant

Primary Care Role with QOL

How can primary care practitioners help with transplant patients’ quality of life?
- Inquire about medication side effects
- Screen for early signs of anxiety or emotional distress
- Monitor neurocognitive development
- Mobilize community resources to aid patient and family
- Work with transplant team – bidirectional communication!

Adolescent Population

Contraceptives
- Oral contraceptives:
  - some interact with transplant meds (thios with estrogen)
  - IUD (no increased risk of infection)
  - Subdermal implants
  - Medroxyprogesterone (Provera®) may decrease bone mineral density
- Condom use is recommended as a 2nd form of birth control to help prevent sexually transmitted infections

Sexual Health
- Transplant centers ideally work with patients before planning to conceive
  - Avoid mycophenolic acid and mTORs
  - Patients should be counseled on potential adverse maternal and fetal outcomes and potential risks to the graft

High Risk Behaviors
- Tobacco Use
- Alcohol
- Marijuana
- Illicit drug use

Tattoo/Body Piercings
- Increased risk of infections
- Licensed facilities only

Nonadherence
- Medication nonadherence is a major issue in adolescents
- At risk for severe rejection and/or graft loss
- May become ineligible for another transplant

Image from: https://www.papermasters.com/adolescence.html
Transition to Adulthood

- All pediatric transplant centers should have a multidisciplinary program in place to transition transplant recipients to adult facility.
- Should be individually and developmentally appropriate.
- Should begin well before time of transfer (as early as 10 years of age).

References

References