Management of Post Heart Transplant Patients

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AGENDA
• History of heart transplantation
• Indications
• Selection
• Immunosuppression
• Surveillance
• Complications

OBJECTIVES
• Refer patients appropriately for evaluation for cardiac transplantation
• Avoid cultural and socioeconomic biases in referral patterns
• Identify any racial/ethnic disparities in post-transplant outcomes

History
• 1905: Alexis Carrel and Charles Guthrie demonstrated that a heart could be transplanted and resume functioning in the new host (canine model)
• 1944: Medawar: Tx immunology (Nobel prize in physiology, 1960)
• 1959: The current most commonly used surgical technique for transplantation originated with the work of Lower and Shumway (canine heart transplant)
• 1967: First human heart transplant performed by Christiaan Barnard in Capetown, South Africa
**History**

- 170 transplants were performed by 65 surgical teams between December 1967 and March 1971
  - The 1-year survival was only 15%, and because of this, enthusiasm rapidly waned by the end of 1971

- Cyclosporine discovered as immunosuppressant in the late 1970s
- Early 1980s: Established as an accepted treatment for end-stage heart disease

- The International Society for Heart & Lung Transplantation figures in 2010:
  - One-year survival: 85% (LVAD 68%)
  - Five-year survival: 75%
  - Ten-year survival: 50%
  - Survival has improved over the past 30 years due to improvements in immunosuppression and in the prevention and treatment of infection

- 2007: cumulative total of 75,000 transplant procedures performed
- Currently ~ 4000 patients/year are suitable candidates for transplantation in the U.S.; however, only 2300 donor hearts per year are available in the U.S.

**CASE STUDY**

- 68 yo AAM with h/o MI x 2, CABG x 3 2002, HTN, chol, DM c/o progressive DOE for past 6 months
- DOE 1 block (worsening), 2 pillow orthopnea, no PND, LOC, CP.
- AICD placed 3 months ago
- TTE: EF 20%, LVEDd 6.5, PAP 55
CASE STUDY

• Meds: lisinopril 20 mg qd
  – Carvedilol 12.5 mg bid
  – Spironolactone 25 mg qd
  – Asa 81 mg qd
  – Atorvastatin 40 mg qd
  – Lasix 40 mg bid
  – Digoxin 0.125 mg qd

CASE STUDY

• HRB: 20 pk-yrs, quit 20 yrs ago, no ETOH or illicit drugs
  • Social Hx: retired, lives with wife, adult children in area
  • PE: BP 90/60, HR 60. BMI 33
    – JVD 7 cm, no rales or S3, trace edema
    – ECG: NSR, IVCD with QRS 125 ms
    – Labs: Cr 1.3, Na 137, CBC nl, BNP 352

CASE STUDY

• Important questions:
  1. Salt/fluid/med compliance
  2. On maximum tolerated doses of medicines?
     Add hydralazine/isordil?
  3. CRT candidate?
  4. Integrity of grafts?

CASE STUDY

• 1. Compliant: dig level 0.8, no “no shows”
  • 2. Can BP support hydral/isordil?
    Further Hx: lisinopril 40 mg caused inc Cr and K+; carvedilol 25 bid caused lower BP and dizziness
  • 3. Not CRT candidate: no LBBB, QRS<130
  • 4. Grafts?

TRANSPANT INDICATIONS

Recipient Selection

• Medical screening for severe coexisting diseases
• Comprehensive psychosocial evaluation
  – ability to follow a complex medical regimen
  – family support
**INDICATIONS**

- Functional class III or IV
- Not correctable by medical/surgical means
- \( VO_2 < 12-14 \) or \( VE/VCO_2 > 35 \)
- CI < 2 L/min/m²
- Unable to wean from mechanical or inotropic support

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**CASE STUDY**

- Pt undergoes CPET: VO2=9 ml/kg/min
- What’s the next step?

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**CONTRAINDICATIONS**

- Significant PVD
- Pulmonary HTN (PVR>4-6 Woods units or TPG>15, irreversible, PASP > 60)
- Severe COPD after Rx for CHF: FEV1< 1 sec, FVC < 50% predicted
- Cr Cl < 40
- Major CVA

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**CONTRAINDICATIONS**

- BMI < 19, > 35
- DM with severe end-organ damage
- CA (except non-melanoma skin CA or no recurrence for > 5 yrs)
- Autoimmune disease with multi-organ involvement
- Severe symptomatic osteoporosis
- Active infection/GIB/PUD

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**INDICATIONS**

- Peak VO2
  - provides the most objective assessment of functional capacity
  - may be the best predictor of when to list a patient for transplant
  - peak VO2 < 12 ml/kg/min on beta blocker, or <14 if intolerant to BB should be strongly considered for listing for transplantation
  - peak VO2 of less than 10 ml/kg/min portends a very poor 1-year survival rate* and warrants listing in nearly all contraindication-free cases


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**CONTRAINDICATIONS**

- Psychosocial behavioral/support issues
  - Substance abuse: must document complete abstinence for 6 months
  - Nicotine use
  - Lack of adequate support system
  - Major psychiatric problem
  - Lack of compliance
CASE STUDY

- CATH:
  - LHC: grafts patent
  - RHC: PAP 55/20/35
  - PCWP 25
  - TPG 10

Diurese: repeat RHC: PAP 40/15/23, W 18

LIST!

- Patients are categorized on the basis of size, ABO blood group, time on the waiting list, and clinical status
- Patients are "delisted" if they improve or if they suffer complications or superimposed illnesses
- Time accumulated on the waiting list can be held forever by a patient and can be accrued if the patient is delisted and reactivated

Average Days from List to Transplant

Maximum Days from Listing to Transplant

ETHNICITY MIX

CASE STUDY

- Pt listed for heart transplant
- Receives new heart after waiting 6 months at home
- Feels great, except gets winded with short bursts of activity
- PE: BP 140/90, HR 107.
  - Well-healed median sternotomy, rest wnl
PHYSIOLOGY OF THE TRANSPLANTED HEART

- New heart is denervated
  - partial reinnervation of the transplanted heart begins within 1 year
  - cardiac response to exercise or stress is less than normal but adequate for almost all activities (delayed hormonal response)

PHYSIOLOGY

- resting heart rate is generally higher due to absence of vagal tone
- increase in beta-adrenergic receptor density - increased responsiveness to noradrenaline and isoproterenol
- blunts systemic responses to volume changes

ARRHYTHMIAS

- Atrial arrhythmias—particularly atrial flutter—may signal rejection and are a sufficient indication for heart biopsy.
- Ventricular arrhythmias are uncommon except with ischemic disease or severe rejection

CASE STUDY

- New medical regimen:
  - Tacrolimus 2 mg bid
  - Mycophenolate 1500 mg bid
  - Prednisone 12 mg daily
  - Asa 81 mg
  - Pravastatin 20 mg daily
  - Sulfamethoxazole-trimethoprim for 1 yr, ganciclovir for 6 months (d+/r+), Ca++/D

Immunosuppression

- Corticosteroids
  - immunosuppressive and anti-inflammatory
  - steroids affect the number, distribution, and function of ALL types of leukocytes as well as endothelial cells
  - >50% of patients weaned off by 5 years nationally

- Cyclosporine
  - Blocks calcium-activated calcineurin by binding to cyclophilin, which inhibits IL-2 expression (and other cytokines)
  - limits the differentiation into and proliferation of cytotoxic T lymphocytes
Immunosuppression

- **Tacrolimus (FK-506)**
  - Also inhibits calcineurin but by forming a complex with FK-binding protein 12, an immunophilin distinct from cyclophilin
  - Studies indicate that tacrolimus is comparable to cyclosporine in terms of survival but associated with lower rate of rejection and probably graft vasculopathy

- **Azathioprine**
  - Prodrug that is converted into a purine analog which is incorporated into DNA, inhibiting its synthesis
  - Blocks proliferation of replicating cells, including lymphocytes
  - Was an effective component of triple-drug therapy together with cyclosporine and steroids

- **MMF (mycophenolate mofetil)**
  - Non-competitively inhibits inosine monophosphate dehydrogenase and guanylate synthetase, key enzymes in the de novo pathway of purine synthesis.
  - Specifically targets proliferating B and T lymphocytes, since they lack salvage pathways for purine synthesis

- **Sirolimus (Rapamycin)**
  - Isolated from soil samples from Rapa-Nui (Easter Island)
  - A macrolide antibiotic
  - Binds to FKBP like tacrolimus, but doesn’t block calcineurin-dependent T-cell activation
  - Used in CNI-minimization protocols

- **Everolimus**
  - A derivate of sirolimus
  - Better tolerated than sirolimus, including wound healing
  - No direct comparison to MMF, but probably less progression of TCAD but more side effects
  - Reduces risk of malignancies
  - Everolimus/Rapamune use in 20% of pts at 5 yrs nationally
Immunosuppression

• Run CNI 25% less (synergistic nephrotoxicity)
• Don’t use if 24 hour urine protein >400-500 mg
• Check echo for effusions

CASE STUDY

• Pt goes for first biopsy after repatriating back
  Result: 1A

REJECTION

HYPERACUTE: vigorous immune response within minutes to hours due to preformed donor-specific antibodies (DSAs)
ACUTE CELLULAR: most common, well-defined, incidence decreases with time (don’t usually biopsy after 1st year), easy to treat
ANTIBODY-MEDIATED: less common, less well-defined, harder to treat

Hyperacute Rejection

• Therapy usually occurs in OR
• High-dose IV steroids, plasmapharesis, IV Ig, cytolytic agent, IV CNI, MMF, inotropes/vasopressors, the kitchen sink
• May need to list urgently for re-transplantation

Acute Cellular Rejection

• Risk peaks during 1st month after transplant
• 1.25 episodes of rejection/patient during the first year, 0.18 episodes/patient in the second year, and 0.13 and 0.02 episodes/patient in the third and fourth years, respectively (Cardiac Transplant Research Database)

Acute Cellular Rejection

• Risk factors for recurrent rejection:
  – female gender of recipient or donor, black race, recipient positive CMV serology and CMV infection, shorter time since previous rejection, more prior rejection episodes, more HLA mismatches between the donor and recipient
• Accounts for 45% of deaths in the first 30 days after transplant, and 20% of deaths during the first year
Acute Cellular Rejection

• In most cases, acute rejection is diagnosed by endomyocardial biopsy at a time when the patient is asymptomatic.
• Symptoms occur infrequently.
  – The most common symptoms of rejection are manifestations of left ventricular dysfunction such as dyspnea on exertion or at rest, PND, orthopnea, palpitations, and syncope or near-syncope.

Acute Cellular Rejection

• Echocardiography can detect presence of left ventricular dysfunction.
  – May reveal an acute decrement in systolic function.
• Infrequently, acute rejection presents with atrial arrhythmias.

Post-transplant Biopsy Schedule

<table>
<thead>
<tr>
<th>TIME AFTER TRANSPLANT</th>
<th>INTERVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 14</td>
<td>First biopsy</td>
</tr>
<tr>
<td>1–4 wk</td>
<td>Every week</td>
</tr>
<tr>
<td>5–12 wk</td>
<td>Every 2 wk</td>
</tr>
<tr>
<td>12-20 wk</td>
<td>Every mo</td>
</tr>
<tr>
<td>20-32 wk</td>
<td>Every 6 wks</td>
</tr>
<tr>
<td>32-52 wk</td>
<td>Every 8 wks</td>
</tr>
<tr>
<td>Subsequent years</td>
<td>No biopsy — Allomap in 2nd year</td>
</tr>
</tbody>
</table>

*Rebiopsy if indeterminate and 10 d after conclusion of rejection treatment.

Acute Cellular Rejection - Treatment

• **Mild** (grades 1A or 1B/1R) or focal moderate (grade 2/1R) rejection are generally not treated unless there is concomitant hemodynamic compromise since corticosteroid therapy does not increase the likelihood of resolution.

• **Moderate** (grades 3A/2R or 3B/3R) rejection NOT associated with hemodynamic compromise or LV dysfunction consists of a transient increase in the corticosteroid dose.
  – 80 to 85% of these rejection episodes respond to steroids.

• **Severe rejection** (grade 3A or 3B) associated with LV dysfunction
  – Anti-thymocyte Globulin + heparin
  – This regimen reverses 80 to 95 percent of rejection episodes.
• **Severe rejection** (3A, 3B, 4) associated with hemodynamic compromise
  – Plasmapheresis in addition to ATG, steroids.
Antibody-Mediated Rejection

Predisposing factors:
• Pre-sensitization to HLA  
  – Prior OHT
  – h/o transfusion
  – Pregnancy
  – Use of LVAD
  – +donor/recipient crossmatch

Antibody-Mediated Rejection

Predisposing factors, continued
• De novo post-transplant antibodies  
  (DSA vs non-DSA)
• Infection or CMV seropositivity?

Antibody-Mediated Rejection

Diagnosis: somewhat controversial, evolving
• Clinical evidence of graft dysfunction
• Histologic findings: acute capillary injury  
  (EC swelling, macrophage infiltration, interstitial edema/hemorrhage)

Antibody-Mediated Rejection

• Immunopathologic evidence for Ab-mediated injury: tissue  
  immunofluorescence + for C4d, C3d, C1q or CD68+macrophages in  
  endothelium
• Serologic evidence of DSAs (anti-HLA class I or II Abs)

Antibody-Mediated Rejection

Treatment (also controversial)
• Removal of circulating anti-HLA Abs  
  (plasmapheresis)
• Reduction of anti-HLA Ab production: IV Ig, ATG, rituximab, bortezomib, photopheresis
• Anti-complement Rx: eculizumab, anti-C5 Ab
• High-dose steroids

CASE STUDY

• Pt returns for f/u and c/o tremors (has difficulty writing); his blood sugars are difficult to control and his blood pressure is up
• He also notices some hair loss
Complications of Immunosuppression

• CYCLOSPORINE TOXICITY
  – Causes decreased creatinine clearance, an increase in serum creatinine level, hypertension
  – May act by increasing urinary thromboxane B2 levels in a dose-dependent manner, with local vasoconstriction, platelet aggregation, and release of platelet-produced thromboxane

Complications of Immunosuppression

• CSA toxicity (continued)
  – Hepatotoxicity - uncommon, usually acute and secondary to exceptionally high levels of cyclosporine, reverts to normal after the dose of cyclosporine is lowered or eliminated

Complications of Immunosuppression

• CSA toxicity
  – Neurotoxicity - fine tremor, paresthesias, and occasionally seizures. Most of these events are dose related and reversible
  – Hirsutism, hypertrichosis, gingival hyperplasia (increased with nifedipine + csa)

Complications of Immunosuppression

• Drug interactions:
  – Bile acid sequestrants interfere with enterohepatic circulation, reducing MPA
  – Antacids containing magnesium and aluminum reduces absorption
  – Co-administration with valcyte in pts with CKD will increase both serum levels (both compete for tubular excretion)

Complications of Immunosuppression

• Drugs that increase CSA levels:
  – Mycins and azoles
  – the calcium channel blockers diltiazem, verapamil, nifedipine, and nicardipine
  – warfarin and amiodarone
  – Diltiazem and ketoconazole have been used adjunctively to lower the dose and cost of cyclosporine maintenance

Complications of Immunosuppression

• CYCLOSPORINE (CSA)
  • Metabolized almost exclusively by the liver (P450 cytochrome system) → so hepatic dysfunction can cause abrupt elevations of blood levels of cyclosporine, precipitating renal dysfunction
Complications of Immunosuppression

CYCLOSPORINE (CSA)
- Certain medicines can cause a decline in circulating CSA levels → danger of causing rejection
  - Omeprazole
  - Antibiotics rifampin and nafcillin
  - Anticonvulsants phenytoin, carbamazepine, valproic acid, primidone, and methsuximide

Complications of Immunosuppression

- Tacrolimus Toxicity
  - Nephrotoxic → do not use simultaneously with CSA
  - Hyperkalemia
  - Hyperglycemia requiring insulin therapy
  - Neurotoxicity - tremor, headache, coma, and delirium have been associated with high blood levels of tacrolimus

- Tacrolimus vs cyclosporine:
  - Less HTN and dyslipidemia, more hyperglycemia and neurotoxicity, alopecia (not hirsutism), no gingival hyperplasia

Complications of Immunosuppression

- Corticosteroid Toxicity
  - Adrenal cortical atrophy
  - Cushingoid appearance
  - Cataracts
  - Skin fragility
  - Severe osteoporosis
  - Peptic ulcers
  - Aseptic necrosis of bone
  - Weight gain
  - Psychiatric effects
  - Diabetes
  - Elevated serum lipid levels
  - Heightened susceptibility to infection
  - Axial growth may be impaired in children

Complications of Immunosuppression

- Mycophenolate mofetil Toxicity
  - Usually well-tolerated
  - Most common side effects are nausea, diarrhea, and abdominal cramping
  - Increased incidence of opportunistic infections vs. azathioprine

- GI: dyspepsia, diarrhea, ulcerations and hemorrhage
  - Severe neutropenia (in up to 2 percent of patients)
  - Mild to moderate hypertension
  - Lymphoproliferative (~1 percent) and skin malignancies
  - PML (multifocal leukoencephalopathy)
Complications of Immunosuppression

• **AZATHIOPRINE TOXICITY**
  – hepatotoxicity
  – severe myelosuppression, especially in patients deficient in thiopurine methyltransferase, an enzyme important in azathioprine metabolism
    • leukopenia, anemia, thrombocytopenia

Complications of Immunosuppression

• **Rapamicin toxicity**
  – Hyperlipidemia, especially TGs
  – thrombocytopenia, neutropenia, anemia
  – exacerbates renal effects of cyclosporine (dose 4 hours apart)
  – edema

Complications of Immunosuppression

• **Everolimus Toxicity**
  – Hypertriglyceridemia
  – Pericardial and pleural effusions
  – Proteinuria
  – Edema
  – More bacterial and fungal infections, less viral infections vs MMF

CASE STUDY

• We decide to replace tacrolimus with cyclosporine.

The patient later c/o mild fever (101°F), loose stool and abdominal cramping

Complications of Immunosuppression

• Overall incidence of infections ranges from 41 to 71 percent in various series
• Most common cause of death after transplantation
• First postoperative month – infections mostly due to bacterial pathogens, frequently pulmonary
  – Nosocomial organisms - *Legionella, Staph epidermidis, Pseudomonas aeruginosa, Proteus, Klebsiella, and E. coli*

Complications of Immunosuppression

• Infections from 1 to 4 months after surgery usually involve opportunistic pathogens, especially CMV
  – Also herpes, Pneumocystis carinii, Candida, Aspergillus, Toxo
  – prophylactic trimethoprim-sulfamethoxazole (TMP-SMZ) recommended to prevent PCP and Toxoplasma infection
After 4 months, both conventional and opportunistic infections occur
Do not hold immunosuppression!
–Pts can die of massive rejection within 48 hours if immunosuppression is held

Complications of Immunosuppression

• CMV-positive donor almost always transmits infection
• Presentation: leukopenia, pneumonia, gastroenteritis, hepatitis, or retinitis
  • pneumonia is the most lethal (13 percent mortality)
  • retinitis is the most refractory; requires indefinite maintenance therapy
• Most cases are responsive to ganciclovir or foscarnet
  • addition of hyperimmune globulin has decreased mortality

Complications of Immunosuppression

• Viral cultures may be negative in the presence of infection, and serological responses may be diminished due to immunosuppression
• CMV should always be suspected in the event of unexplained fevers, gastroenteritis, or culture-negative interstitial pneumonitis

Complications of Immunosuppression

• Duration of prophylaxis with ganciclovir depends upon the donor/recipient positivity:
  – r+ for 6 mo, d+/r- for 12 mo, d-/r- 3 mo
• Recognition of CMV infection is important because of its relation to the development of late graft arteriosclerosis

Complications of Immunosuppression

• most frequent viral infection in transplant recipients
  – incidence in cardiac recipients of between 73 and 100%
  – minimized in CMV-negative patients by the use of CMV-negative blood products

CASE STUDY

• CMV DNA PCR is sent: negative
• Other family members had similar illness after sharing the same meal
• Symptoms resolve in a few days without drug treatment
CASE STUDY

- The transplant coordinator diligently reminds the patient to check for adenopathy
- He is reminded to wear sunscreen SPF>30, wide-brim hat/long sleeves if out in the sun for more than 10 minutes
- Pt was EBV+ on initial screening

Complications of Imunosuppression

NEOPLASMS
- Transplant recipients have a 3-fold increase in the incidence of cancers
- Most common tumors among transplant recipients:
  - skin and lips
  - non-Hodgkin lymphomas
  - Kaposi sarcomas
  - uterine, cervical, vulval, and perineal neoplasms
- The frequency of breast, lung, prostate, and colon cancers does not exceed that in the general population

CASE STUDY

- The patient has his first annual catheterization
- “Mild distal pruning” is noted, otherwise normal coronary arteries, Vgram, and RHC

Complications of Imunosuppression

NEOPLASMS
- Increased incidence of lymphoproliferative tumors early after transplantation
  - more frequent in younger recipients
  - thought to be the result of Epstein-Barr viral infection
  - consist of B-cell proliferation that is unchecked because of T-cell suppression or depletion
  - arise in extranodal sites, such as lung, gut, or central nervous system

CASE STUDY

- The patient has his first annual catheterization
- “Mild distal pruning” is noted, otherwise normal coronary arteries, Vgram, and RHC

Complications of Transplantation

GRAFT VASCULOPATHY
- Incidence between 20 and 50% at 5 years
- Observed as an incidental finding at autopsy as early as 3 months after transplantation
- Significant CAD may produce arrhythmias, MI, sudden death, or impaired LV function with CHF
- Angina pectoris is rare because the cardiac allograft remains essentially denervated
- CAD tends to be diffuse and concentric

Complications of Transplantation

GRAFT VASCULOPATHY
- Cause remains controversial; likely multifactorial
  - endothelial damage due to immune and non-immune causes and the exaggerated response to that injury
  - possible recognition of alloantigens on EC surface
  - immune-mediated injury is predominant cause (abundance of inflammatory cells)
Histologically: extensive concentric intimal proliferation with hyperplasia of smooth muscle and lipid-laden macrophages

Grossly: vessels show diffuse disease extending symmetrically into distal branches with few collaterals

Risk factors:
- prior episodes of acute rejection
- hyperlipidemia
- older donor age
- CMV infection
- DM

Complications of Transplantation

GRAFT VASCULOPATHY

• Prevention:
  - Aggressively treat lipids
    • Reduced intake of cholesterol and saturated fats, use of statins, regular exercise
    • Smoking cessation
  - Antioxidant vitamins (C and E)
  - Can change antiproliferative therapy to sirolimus/everolimus, which slows the progression of transplant vasculopathy
  - Low-dose aspirin

• Treatment:
  - CBI, CABG: palliative, probably no impact on outcome
  - Re-transplantation: best choice
    • results of re-transplantation are worse than for the primary procedure, with a reported patient survival rate of approximately 81 percent at 1 year

Post-Transplant Follow-Up

• Early monitoring for rejection and infection
• Late monitoring for graft vasculopathy and cancer
• Endomyocardial biopsy is performed at decreasing intervals per institution
• Recommend coronary arteriography on a yearly basis
  - some programs alternate this with noninvasive studies of myocardial function or ischemia

Conclusions

• Heart transplantation has become accepted therapy for patients with end-stage heart disease
• With improved immunosuppression, deaths due to rejection and infection have declined
• Vigilant monitoring and patient compliance are required
• Racial/ethnic differences exist in wait times