Transplant Medicine and Immunosuppression

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Overview

- History of Transplant
- Brain Death
- Organ Specific Transplant
- Immunology of Rejection
- Pharmacology of Immunosuppression
History

• First successful transplant was a living related kidney transplant in 1954 between identical twins by Joseph Murray
• First attempt at liver transplant in 1963 by Thomas Starzl ended in early mortality but 1-yr survival was attained in 1967
• 1967 also marked the first heart transplant by Barnard in South Africa
• Significant progress followed the introduction of cyclosporine in 1981 by Sir Roy Calne of Cambridge
• Further advances in the 1980’s such a UW solution allowed the field to progress further
Brain Death

• Prior to 1950’s, death was solely the cessation of cardiac activity

• A Harvard Medical School committee in published a pivotal report in 1968 outlining the features of brain death as cessation of brain stem reflexes including apnea

• Uniform Determination of Death Act in 1981 legally defined death as cessation of cardiopulmonary or brain activity

• This legislation in conjunction with improved ICU care paved the way for organ donation
Number of Transplants Performed in the USA 2000*

- Lung Transplant 956
- Liver Transplant 4,954
- Kidney Transplant 13,327
- Kidney and Pancreas Transplant 911
- Pancreas Transplant 435
- Heart Transplant 2,198
- Heart and Lung Transplant 48
- Intestine Transplant 79

In the year 2000, there were 5,984 cadaverous donors and 5,700 living donors that yielded usable organs.

*Source UNOS
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USA National Patient Waiting List Statistics*

- Lung Transplant 3,612
- Heart Transplant 50,898
- Heart and Lung Transplant 2,451
- Kidney Transplant 18,752
- Kidney and Pancreas Transplant 1,217
- Pancreas Transplant 183
- Liver Transplant 4,139

An average of 1 person are added to the organ transplant waiting list every day.
5,794 people died in the year 2000 because they did not receive a transplant in time.

*Source UNOS January 2002. Patients can be listed with more than one organ transplant center, and some patients are waiting for more than one organ.
Heart Transplant

Dick Cheney
Indications

• End stage heart failure

• Ischemic cardiomyopathy (39.5%)

• Non-ischemic cardiomyopathy (49.5%)

• congenital disease, valvular disease, amyloidosis, sarcoidosis and re-transplantation represent the remaining indications

• Note: 40% were on inotropic support and 30% had mechanical circulatory support; 70% were outpatients
Work up

- **VO$_2 < 10$ mL/kg/min** with adequate β blockade and RER > 1.05
  - ability to tolerate β blockade is a (+) prognostic marker

- Right-heart catheterization is mandatory
  - PVR > 5 Woods, iPVR > 6 or TPG > 16-20 mmHg
  - more important is **response of LV to unloading** with nitroprusside

- Cardiac-Renal Limit
  - defined by systemic hypotension, renal dysfct, hyperkalemia mediated by RAAS
  - intolerance of aggressive medical therapy (e.g. ACE-I, β-bl) identifies a high-risk pop’l

- Heart Failure Survival Score
  - composed of HR, SBP, LVEF, Na, VO$_2$, QRS, ischemia stratifying pts into high, medium, low risk
  - 1 yr survival with med mgmt 35% in high risk group- relative indication for transplant
Operation

A. Recipient aorta and pulmonary arteries remain. Heart is cut so diseased heart can be removed.

B. Recipient aorta and pulmonary arteries remain. Donor (transplanted) heart is in place. Sutures used to attach donor heart.
Postconditioning reperfusion has been successful in decreasing repercussion injury.
Postop Management

- **RV dysfct**: hypokinetic, distended RV; underfilled LV; absence of tamponade
  - Rx with iNO, iloprost, epoprostenol; may require RVAD
  - Milrinone can be used as an adjunct for RV dysfct with nl PVR
- Diastolic dysfct 2/2 dennervation
- Atrial pacing for **bradycardia** (sinus & AV block)
  - atropine has no effect on dennervated heart
- **Epinephrine** is first line pressor followed by NE if needed
- 7-14d postop- **cardiac biopsy** to r/o acute rejection
Outcomes

- HD requirement, female gender, donor death 2/2 CVA, CAD as reason for transplant and HLA-DR mismatches increase risk for early mortality

- Presence of a VAD, mechanical ventilation, inotrope dependence and hospitalization at time of transplant do NOT predict 5-yr mortality

- 50% survival of cardiac allografts is currently 10 years however, 56% of pts have coronary artery vasculopathy at that time

- 10% have Cr > 2.5 by 8 yrs and 35% have developed malignancy at 10 yrs
Lung Transplant

Charity Tillemann-Dick,
Opera singer
Indications

- COPD and α-1 anti-trypsin deficiency in 50%
  - FEV1 < 25% predicted post bronchodilator
- IPF and CF account for 19% and 16% respectively
  - VC < 65% predicted or new oxygen requirement
  - FEV1 < 30% or PaCO2 > 50, freq severe exacerbations
- patients referred when projected 2-yr survival approaches 50%; intolerable quality of life important but secondary
Epidemiology

- Historically, lung procurement was poor (15-20%), has improved with optimized mgmt to 35-40%.

- Since 2004, number of pts on wait list has decreased, number of transplants has increased to almost 1300/yr and deaths on wait list have decreased.

- SLT was traditionally the most common procedure but slightly improved survival with BLT has shifted - BLT now about 60% of transplants.

- Transplantation for COPD is stable while transplantation for IPF has increased significantly.
Double Lung Transplant

- CF absolute indication
- small but significant survival advantage @ 5 yrs vs SLT
Single Lung Transplant

COPD most common indication
Combined Heart Lung Transplant

- ESLD + CAD
- pHTN + CHD (ToF, VSD)
- pHTN + LV dysfct
Bilateral Lobar Transplant is uncommon, used in patients who cannot survive 12-14 months on the wait list.
Postop Management

- 50% extubated POD 1, 75% extubated POD 2
- leading causes of 30-day mortality post transplant are primary allograft failure and pneumonia
- pneumonia immediately postop is bacterial from the donor lungs
  - assoc with aspiration, pre-donation ventilation
  - decreased PNA rate with pre-procurement abx (24-48hr)
- allograft failure = severe hypoxia, pulmonary edema, +/- HoTN
  - treated with judicious fluid resuscitation and pressors
- Anastomotic stenosis, bronchomalacia are most common airway complications
Outcomes

• 1-, 3-, 5-, 10- year survival are 78%, 61%, 49% and 25%

• higher survival is seen in centers with more experience

• survival advantage is seen with CF and IPF

• no clear advantage is seen with COPD

• Obliterative bronchiolitis most common cause of death after one year
  • lymphocytic-mediated cytotoxicity of bronchiolar epithelial cells creating necrosis and inflammatory cascade
  • results in formation of granulation tissue -> progressive obliteration
  • median survival after diagnosis 2 years
Liver Transplant

Steve Jobs
<table>
<thead>
<tr>
<th>Indications</th>
<th>Contraindications</th>
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<tbody>
<tr>
<td>• HCV (30%), HBV (6%)</td>
<td>• extrahepatic malignancy</td>
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<tr>
<td>• EtOH (18%)</td>
<td>• &gt; UCSF criteria</td>
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<tr>
<td>• HCC (≤6.5cm, ≤3 nodules ≤4.5cm,</td>
<td>• AIDS, active Hep B</td>
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<tr>
<td>total size ≤8cm, no vasc invasion)</td>
<td>• HIV</td>
</tr>
<tr>
<td>• FHF (King’s College criteria)</td>
<td>• sustained CPP &lt; 40</td>
</tr>
<tr>
<td>• PBC, PSC</td>
<td>• CPP &lt; 60</td>
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<tr>
<td>• autoimmune liver disease</td>
<td>• pHTN &gt; 45</td>
</tr>
<tr>
<td>• stratified on wait list with MELD (INR, Cr, bilirubin)</td>
<td>• Hepatopulmonary syndrome (PaO2 &lt;100 on FiO2 = 1)</td>
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Preop Workup

- decision to transplant is complex based on degree of co-morbidities and potential benefit from transplant
  - average MELD at transplant 20, average time on waiting list 12-36 mo
  - MELD > 30 associated with 50% 3mo mortality
  - extrahepatic disease unrelated to liver failure equivalent to 50% 5-year mortality considered a contraindication
  - irreversible neurologic damage and degree of cardiopulmonary support NOT due to liver failure also preclude transplant
Orthotopic Liver Transplant

Technique

- Suprhepatic vena cava anastomosis
- Donor liver
- Hepatic artery anastomosis
- Portal vein anastomosis
- T-tube
- End-to-end anastomosis of common bile duct
- Intrahepatic vena cava anastomosis
- Choledochoduodenostomy
- Roux-en-Y

Donor-recipient sites for vascular and biliary anastomoses

Choledochoduodenostomy with Roux-en-Y avoids use of recipient common bile duct in primary sclerosing cholangitis
Piggyback technique

Preserves IVC flow in the face of marked hemodynamic instability

*Liver Transpl* 2005; 11(8):861-71
Living Related Recipient
Periop Management

- minimize versed and fentanyl (<20mcg/kg); isoflurane maintains splanchnic flow, cisatracurium paralytic of choice (Hoffman elimination)

- liver pts have decreased factors and plts (preserved vWF)- TEG based algorithm: plts if <50k, MA <45; FFP if R > 20; cryo if fibrinogen <100; antifibrinolytic if LY30 > 7.5%

- aprotinin has been shown to decrease RBC trfs, be anti-inflammatory (NO, TNF inhib); use is limited by thrombotic risk (PE)

- factor VII has also been used though its efficacy and ideal dosing are not known

- postop complications include primary non-fct, thrombosis, rejection, biliary dysfct
Outcomes

- Increased graft failure associated with donor age > 40, DCD, split liver donation, AA race, height < 170cm (5’7”)

- Cold ischemia time <6 hours is preferred

- Pts with higher APACHE II scores, are mech vent or on HD have worse survival after liver transplant

- Transplantation for FHF increases 1-yr survival from 25% to 75%
Kidney Transplant

Tracy Morgan
Epidemiology/ Work-up

- **$27B** spent on ESRD- trspl most cost effective treatment

- **16,477 pts** received transplants while >70K on wait list in ’05; ~10K were cadaveric vs ~6K were living donor transplants

- indications include DM, HTN nephrosclerosis, polycystic dz, glomerular dz, interstitial dz, renovascular dz, neoplasm

- contraindications include active malignancy, advanced cardiopulmonary disease, active infection, substance abuse and non-compliance

- work up includes screening for hepatitis, HIV, may include stress test,
Renal Transplant
Periop Care

• Brisk diuresis is expected after transplant and is multifactorial (diuretics, proximal tubule damage, hyperglycemia)
  
  • **UOP < 100-200/hr** is concerning

  • **DDx:: arterial or venous thrombosis, ATN, rejection, urinoma, clots in bladder**

• Postop HTN is assoc with delayed graft fct so control of HTN is important; Ca channel blockers are first line Rx for HTN assoc with cyclosporine- induced renal damage

• Postop course can also be marred by respiratory failure, CV events (6%), wound infection, DVT/PE, bleeding, etc
Kidney Pancreas

A. Pancreatic duct drains into small intestine

B. Pancreatic duct drains into bladder
Kidney Pancreas

- Main indication is **ESRD 2/2 DM**

- Pancreas is rarely transplanted alone as risks of immunosuppression are not overcome by insulin independence

- **Bladder drainage** has lower infx rate and ability to monitor urinary amylase levels for rejection; higher bicarb losses cause meta acidosis, cystitis, stricture and hematuria

- **Enteric drainage** is more common and better tolerated but harder to monitor for rejection- kidney becomes the “canary”

- **Hyperglycemia** is a late sign of rejection
Transplant Immunosuppression
Hyperacute Rejection

- complement mediated due to recipient preformed antibodies against donor graft
- presents with intraop thrombosis requiring explant, frequently precludes subsequent transplant
Acute Rejection

mediated by T-cells in response to Ag processed by APCs and carried on MHC molecule to T-cells
Acute Rejection (cont)

- T-cell receptor (TCR) determines antigen specificity
- Presentation of Ag by APC/MHC activates the T-cell
- This complex, plus CD3, CD4 or CD8 generates clonal expansion against that antigen, mediated by IL-2 and IL-2R production
- IL-2 is a potent growth hormone for T-cells and attracts various other cell types and cytokines leading to inflammation
- Hence acute rejection histologically shows invasion of lymphocytes
- The treatment and prevention of acute rejection are focused on T-cells, their receptors and the IL-2 cascade
Immunosuppression

- Corticosteroids
- Calcineurin inhibitors
  - cyclosporine
  - tacrolimus
- mTOR inhibitors
- Antiproliferatives
  - azathioprine
  - mycophenolate
- Biologics
  - monoclonal vs polyclonal Ab
Corticosteroids

• Produce multiple effects on cells including:
  • blocking of production of IL-1 and IL-2 thus decreasing T-cell activation
  • inhibition of histamine release and kinin activation
  • reduction in circulating immunoglobulin, neutrophil, and eosinophil levels
  • inhibition of leukocyte adhesion to endothelium

• Adverse effects are many including infections, impaired healing, osteoporosis and impaired glucose tolerance
Cyclosporin

- Isolated from a fungus found in soil samples from Norway

- Binds cyclophilin which inhibits calcineurin thus preventing the transcription of many cytokines including IL-2 (T-cell growth factor)

- Adverse effects are many, including HTN, renal and liver dysfct, tremors/sz, GI complaints and gingival hyperplasia

- metabolized by P450

- oral bioavailability varies btw 10-60% (30%)
Tacrolimus (ProGraf)

- Also isolated from a fungus
- Classified as a macrolide abx
- Binds FK-BP12 which also inhibits calcineurin
- Effect on TNF-β differs; TNF-β may play a role in chronic rejection
- Metabolized by P450, CYP3A4
- Oral bioavail is inconsistent and therapeutic monitoring is vital
- Plasma levels shld be 0.5-2 ng/mL
- Toxicity profile similar but less HTN, more neurotoxicity
Azathioprine (Imuran)

- thio analog of adenine, acts to inhibit purine metabolism preventing DNA synthesis
- useful in maintenance, no utility in acute rejection
- long half life of metabolites allows daily dosing
- adverse effects primarily myelosuppresion (1-2wks); WBC < 3K shld have ↓ dosing
- hepatotoxicity and pancreatitis have limited its used
- allopurinol increases toxicity
Mycophenolate Mofetil (CellCept)

- MPA inhibits IMPDH, a key enzyme regulating the purine nucleotide de novo synthesis pathway

- T & B cells require purine synthesis via de novo path for proliferation

- other cells can utilize salvage

- rapid oral absorption but undergoes first-pass metabolism

- action can be affected by albumin levels

- most common adverse effects are GI, including perforation; myelosuppression is uncommon
Sirolimus and Everolimus (Rapamune)

- structurally similar to tacrolimus
- binds FK-BP12 but inhibits mTOR inhibiting the cells response to IL-2 preventing progression of the cell cycle
- highly lipophilic thus it readily enters cells and produces a large volume of distribution
- metabolized by CYP3A4; half life 60hrs
- has synergy with cyclosporine
- levels should be followed and checked q5-7d until steady state
- adverse reactions include myelosuppression, HL/HChI (peaks at 3 months, normalize by 1yr), mouth ulcers
- Everolimus has same mechanism but shorter half life, is used in heart transplants
Antibodies

• Anti-lymphocyte globulin is derived from immunized animals creating polyclonal antibodies which were pooled

• These Ab interfere with lymphocyte function and tags them for removal

• Atgam is derived from equine serum and targets a broader array of cell types; more likely to cause serum sickness

• Thymoglobulin is derived from rabbit serum and is more specific for T-cells and has a longer duration of suppression

• Should be given with an antihistamine, antipyretic and steroids

• Useful in induction and rejection
Monoclonal Antibodies

- OKT3 is directed at the CD3 receptor, found on all mature T-cells
- Binding of OKT3 to CD3 receptor opsonizes the cell and causes removal from circulation
- Initial administration can cause a “first-dose effect” with release of pro-inflammatory cytokines mimicking septic picture
- Daclizumab and basiliximab are anti-IL-2R Ab which to activated T-cells
- Both have smaller murine portion of the molecule, thus decreasing production of anti-drug Ab
- Prevents but does not treat acute rejection
## Regiments

<table>
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<tr>
<th>Induction</th>
<th>Maintenance</th>
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<tr>
<td>methylprednisolone</td>
<td>tacrolimus*/cyclosporine</td>
</tr>
<tr>
<td>tacrolimus OR</td>
<td>MMF*/ azathioprine</td>
</tr>
<tr>
<td>mono- or polyclonal Ab if kidney disease ~50%</td>
<td>prednisone-taper to off</td>
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<tr>
<td>MMF’</td>
<td>Rejection:</td>
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<td></td>
<td>high dose steroids</td>
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<td>biologics</td>
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