American College of Surgeons
Critical Care Review Course 2012: Transplant

Overview:
I. Transplant Immunology
II. Immunosuppression
III. Organ Specific Issues
IV. Bibliography

I. Transplant Immunology
Main function of immune system: Distinguish self from non-self
Innate versus Adaptive immunity:
   Innate response
      - Neutrophils, macrophages, natural killer cells, cytokines, complements
      - Rapid response to infection
   Adaptive response
      - B and T lymphocytes
      - Foreign antigen recognized; memory developed

Cellular response:
MHC Cell types:
Major Histocompatibility complex (MHC) is the coding region on DNA.
Human Leukocytes Antigen (HLA) is the name of the MHC in humans
   Cells that code for MHC class I (HLA-A, B, C)
      - All nucleated cells
      - MHC I binds mostly self-peptides following intracellular processing
      - MHC/Peptide complex is processed to cell surface
      - Cytotoxic (CD8+) T-Cells Respond
   Cells that code for MHC class II (HLA-D)
      - B lymphocytes, macrophages, dendritic cells
      - MHC II binds foreign peptides following intracellular processing
      - MHC/Peptide complex is processed to cell surface
      - Helper (CD4+) T-Cells Respond
   Cells that code for MHC class III
      - Codes for components of the complement system, cytokines, etc.

Accessory molecules:
   T Cell receptors (TCR) recognize the MHC/Peptide Complex
   Accessory molecules stabilize response
      Ex: CD4 (complex of differentiation) binds class II MHC
      Ex: CD8 binds class I MHC

Co-stimulatory molecules:
   Other ligands and receptors bind between Antigen Presenting Cells (APCs) and T cells to potentiate activation.
   Ex: CD-28 (receptor) on T cells and B7 (ligand) on APCs
      - Regulates cellular expansion, differentiation, inhibition
   Ex: CD-40 on T-cells (ligand) and CD-40 (receptor) on APCs
-Activation of B cells (Antibody production), dendritic cells, monocytes, B7 up-regulation

**Activation:**
T Cells (Both Cytotoxic (CD8+) and Helper (CD4+)) are “activated” upon binding MHC. Upon activation, T Cells can proliferate, recruit other cells in the response, or induce cytotoxic processes. B Cells produce antibodies when activated

**Rejection:**
Direct alloreognition:
Recipient MHCs activated by Donor APCs within graft
Indirect alloreognition:
Recipient MHCs process donor proteins and present as MHC peptide complexes

Types:
- **Hyperacute**
  - Recipient antibodies versus cellular components of graft
  - Evident in operating room (cardiac/kidney)
  - Dx: Thrombosis of organ in OR
  - Rx: Retransplant

- **Acute**
  - T cells recognize foreign antigen with MHC protein on surface. Helper T cells can produce cytokines (i.e. IL-2) upon activation which will stimulate increased cytotoxic T Cell responses, T cell and B Cell proliferation, and ongoing inflammatory responses leading to organ dysfunction.
  - Evident in days to months
  - Dx: Clinical evidence of organ dysfunction, biopsy
  - Rx: Increase immunosuppression, pulse dose steroids, antilymphocyte antibodies

- **Chronic**
  - Results in fibrosis and eventual organ dysfunction
  - Evident in months
  - Dx: Clinical evidence of organ dysfunction, Biopsy
  - Rx: Possible retransplant depending on organ

**Donor-recipient pairing:**

**HLA Typing**
- Number of HLA matches can correlate with improved graft survival
- Limitations of HLA mismatch depend on organ being transplanted
- MHC class I and II matching

**ABO compatibility**
- Incompatibility can lead to hyperacute rejection (depending on organ)
- Some techniques (i.e. plasmaphoresis) may overcome ABO incompatibility

**Cross matching**
- Assessment for recipient cytotoxic antibodies against donor lymphocytes
II. Immunosuppressive Agents

Types:

Calcineurin inhibitors
Examples: Cyclosporine, tacrolimus
Mechanism of Action:
Binds immunophilins; complex then binds calcineurin and prevents translocation of nuclear factor in activated T cells; IL-2 production is subsequently blocked; Ultimately prohibits T cell activation and proliferation
Metabolism:
Cytochrome p450; variable bioavailability
Side Effects:
Cyclosporine: Hirsutism, hepatotoxicity, renal toxicity, HTN, hyperkalemia, hyperlipidemia, neurotoxicity
Tacrolimus: Nephrotoxicity, neurotoxicity, Diabetes, diarrhea, hyperkalemia, hypomagnesemia

Proliferation signal inhibitors
Examples: Sirolimus, Everolimus
Mechanism of Action:
Interacts with “mammalian Target of Rapamycin” (mTOR) inhibitor; Can arrests cell in G0 and S phases; Can block cytokine associated cell progression (anti-proliferation of T Cells)
Metabolism:
Cytochrome p450
Side Effects:
Hyperlipidemia, myelosuppression, impaired wound healing, diarrhea, arthralgia, oral ulcers, interstitial pneumonitis,
*antineoplastic, antiviral, antiarthrogenic

Anti-proliferation agents
Examples: Azathiaprine, Mycophenolate mofetil
Mechanism of Action:
Azathiaprine: Converted to 6-Mercaptopurine (6-mp), blocks purine synthesis
Mycophenolate Mofetil: Inhibits inosine monophosphate dehydrogenase which inhibits DNA/RNA synthesis
Metabolism:
Cytochrome p450
Xanthine oxidase allows for metabolism of 6-mp
(If admin allopurinol, 6-mp levels can elevate)
Side Effects:
Leukopenia, thrombocytopenia, anemia, hepatotoxicity, pancreatitis

Anti-lymphocyte antibodies:
Examples: Antithymocyte antibodies (polyclonal), OKT-3 (monoclonal)
Mechanism of Action:
T Lymphocyte depletion - Apoptosis, Antibody cytotoxicity, complement lysis

Metabolism:
Cytochrome p450

Side Effects:
Antithymocyte antibodies: leukopenia, thrombocytopenia (due to non-specificity of antibody), serum sickness, cytokine release syndrome (Pulmonary edema, fevers, rigors, bronchospasm)
OKT-3: Diarrhea, CMV, lymphoproliferative disorder, cytokine release syndrome

Humanized antibodies:
Examples: Basiliximab, Alemtuzumab
Mechanism of Action:
IL-2 Receptor targets:
Basiliximab: Antibody that targets CD-25 on activated T cells; Inhibits proliferation of T cells. T cell non-depleting.
Alemtuzumab: Antibody to CD-52 on B-cells, T-Cells, Monocytes and other cell lines. T cell depleting.

Metabolism:
Cytochrome p450
Side effects:
Hypersensitivity reactions, cytokine release syndrome (Pulmonary edema, fevers, rigors, bronchospasm)

Corticosteroids:
Examples: Prednisone, Methylprednisolone
Mechanism of Action:
Blocks IL-2, IL-1β, TNF-α, IL-6 synthesis by inhibiting NF-κβ; Ultimately inhibits T cell proliferation

Metabolism:
Cytochrome p450
Side Effects:
Hyperglycemia, osteoporosis, impaired healing, Cushing’s-related features, Addisonian crisis with withdrawal

Drug interactions:
Given the metabolism of immunosuppressants by Cytochrome P450 (CYP3A4), any medication that induces or inhibit CYP3A4 activity may affect drug levels of immunosuppressants.
Examples: CYP3A4 inhibitors (can lead to immunosuppressant toxicity)
Diltiazem, Verapamil, Amiodarone, Erythromycin, Azole antifungals, Micafungin, protease inhibitors
Examples: CYP3A4 inducers (can lead to decreased immunosuppressant levels)
Phenobarbital, Phenytoin, Carbamazepine, Rifampin
III. Organ Specific Issues

Kidney:

Background:
- Over 320,000 individual kidney transplants in US since January 1st 1988*
- Graft Survival*:
  - 1 Year: 89% (Cadaveric Donor); 95% (Living Donor)
  - 5 Year: 66.5% (Cadaveric Donor); 79.7% (Living Donor)
*(OPTN data as of May 10, 2012)

Indications for transplant:
Chronic renal failure secondary to:
  - Diabetes Mellitus
  - Glomerular diseases
  - Hypertensive nephrosclerosis
  - Re-transplant/Graft failure
  - Polycystic kidney disease
  - Tubular/interstitial diseases
  - Renovascular diseases
  - Congenital metabolic disorders
  - Neoplasm

Surgical Issues:
Living donors:
  - Laparoscopic Donor Nephrectomy: Decreased morbidity;
    Improved HLA matching; Mortality 0.03%
Deceased Donors:
  - Limited supply
Prophylactic antibiotics given
Induction agents given
  - T Lymphocyte Depleting vs. Non-Depleting agents
  - Corticosteroids

Post-Operative Management Issues:
Immediate diuresis if kidney functioning
- Secondary to ischemic injury to tubules, uremia, fluid/electrolyte disturbances, hyperglycemia
- Urine output/Creatinine decreases as graft function improves
- Rx: Ongoing hypotonic fluid replacement

Unique Complications:
  Early:
  Oliguria/Anuria:
    - Assessment: Foley working, volume status
- Work-up: Ultrasound
- Ddx: Urine leak, obstructing lymphocele, arterial or venous thrombosis, vascular anastomosis dehiscence
- Rx: Vascular thrombosis: reoperation; Urine leak: Drainage, stenting, and/or reoperation; Lymphocele: Potential drainage

Hypertension:
- Emergency: Rx: Labetolol or nicardipine
- Non-Emergent: Rx: Dihydropyridine calcium channel blockers, clonidine, beta-blockers

Electrolyte abnormalities:
Hyperkalemia:
- Kidney dysfunction, immunosuppression related
- Rx: Calcium, insulin/glucose, albuterol, bicarbonate, dialysis

Hypophosphatemia/Hypercalcemia:
- Tertiary hyperparathyroidism
- Rx: Usually resolves in 6-12 months; may need parathyroidectomy

**Early to Late:**

Infections:

Cytomegalovirus:
- Presentation: Fever, leukopenia, gastroenteritis, pneumonitis, thrombocytopenia
- Dx: Antigenemia by immunofluorescence; PCR
- Rx: Valganciclovir or Ganciclovir, supportive care

Pneumocystis jirovecii Pneumonia:
- Presentation: Fever, cough, severe dyspnea, leukopenia, bilateral infiltrate on CXR
- Dx: Sputum or Bronchoalveolar lavage with Wright-Giemsa Stain (trophozoite detection)
- Rx: Bactrim

BK Virus
- Presentation: Elevating creatinine, Graft dysfunction to loss
- Dx: Blood and urine viral screening, Biopsy
- Rx: Staged reduction in immunosuppression (Calcineurin inhibitors and/or MMF)

Rejection:
- Presentation: Kidney dysfunction (elevated creatinine, decreased urine output)
- Dx: Biopsy
- Please see “Transplant immunology” for Dx/Rx

Ureteral obstruction:
- Presentation: Decreased urine output, pyelonephritis
- Dx: Ultrasound, urine culture
- Rx: Stenting
Pancreas:

**Background:**
- Over 7200 individual pancreas transplants in US since January 1st 1988*
- Graft Survival*:
  - 1 Year: 75-79%
  - 5 Year: 49-54%
- Simultaneous pancreas and kidney transplants are more frequent
- Research is ongoing for islet cell transplant *(OPTN data as of May 10, 2012)*

**Indications for transplant:**
- Refractory diabetes with complications
  - with end stage renal failure
  - s/p kidney transplant
  - s/p total pancreatectomy

**Surgical Issues:**
- Donor “Y” graft to superior mesenteric artery and splenic artery on donor pancreas
- Anastomoses:
  - Arterial: Common iliac
  - Venous: Portal, SMV, iliac, inferior vena cava
  - Exocrine drainage: Bladder or bowel
- Prophylactic antibiotics given
- Induction agents given
  - T Lymphocyte Depleting vs. Non-Depleting agents
  - Corticosteroids

**Post-Operative Management Issues:**
- Blood glucose monitoring:
  - Sudden hyperglycemia/insulin requirement may indicate graft problem
- Bladder drained pancreas:
  - The development of hematuria or decreases in urinary amylase might indicate graft dysfunction

**Unique Complications:**

**Early:**
- Portal venous thrombosis
  - Prevention: Low dose anti-coagulation(?)
  - Presentation: Graft tenderness, hyperglycemia, hematuria, decreased urinary amylase
  - Dx: Ultrasound
  - Rx: Pancreatectomy
Wound infection
- Higher rates in pancreas transplant
- Dx: Physical exam, CT
- Rx: Drainage, antibiotics

Anastomotic leak:
- Bladder: Rx: Foley catheterization
- Enteric: Rx: Surgery

Early to Late:
Pancreatitis:
- Secondary to reflux in bladder drained patients
- May occur due to prolonged ischemia post-op
- Presentation: Cystitis, urinary retention
- Dx: Urinary retention, elevated amylase/lipase
- Rx: Foley drainage, may require eventual conversion to enteric drainage

Recurrent urinary tract infections:
- Secondary to changes in bladder pH
- Presentation: Cystitis, urinary retention, dysuria
- Dx: Urinary retention, sepsis
- Rx: Drainage, antibiotics, may require conversion to enteric drainage

Infections:
- See “Kidney Transplant: Infections” for Dx/Rx

Rejection:
- Presentation: Hyperglycemia, decreased urinary amylase, hematuria, kidney dysfunction if transplanted kidney
- Dx: Biopsy of pancreas: Bleeding risks
  May biopsy transplanted kidney for Dx
- Please see “Transplant immunology” for Dx/Rx

Liver:

Background:
- Over 114,000 liver transplants in US since January 1st 1988*
- Graft Survival*
  - 1 Year: 81.9% (Cadaveric Donor); 82.5% (Living Donor)
  - 5 Year: 65.0% (Cadaveric Donor); 65.9% (Living Donor)
*(OPTN data as of May 10, 2012)

Indications for transplant:
  Malignant disorders (specific criteria)
End stage liver disease due to:
- Autoimmune hepatitis
- Viral Hepatitis
- Metabolic diseases
- Overdose
- Cirrhosis
- Cystic liver disorders
- Cholestatic liver disorders
- Trauma

**Surgical Issues:**

Living donors: Split-liver transplants; Mortality: 0.5-1%
Deceased Donors: Most common means of donation

Hemodynamic management:
- Pulmonary artery catheter
- IV fluid and blood used to replete losses.

Prophylactic antibiotics given

Induction agents given
- T lymphocyte depleting vs. Non-depleting agents
- Corticosteroids

Anastomoses:
- Venous: Vena cava and portal vein
- Arterial: Hepatic artery
- Biliary: Bile duct

Drains left

**Post-Operative Management Issues:**

Third space losses: Replaced with intravenous fluids and albumin
Regular assessments of liver function tests, blood counts, coagulation function, and chemistries are performed

**Unique Complications:**

*Early:*

Post-op bleeding:
- Presentation: shock refractory to transfusion
- Ddx: Surgical bleeding, hypocalcemia, dilution, coagulopathy
- Dx: Clinical, Laboratory values, TEG may be helpful
- Rx: Resuscitation, Reoperation

Hepatic artery thrombosis:
- Presentation: Sudden LFT elevation
- Dx: Ultrasound
- Rx: Reoperation with thrombectomy

Prolonged respiratory failure:
- Ddx: Massive transfusion, ventilator-associated pneumonia, immunosuppression, reperfusion, blood loss, ARDS
- Dx: Inability to wean, CXR, Chest CT
- Rx: Treat underlying cause, vent support

Abdominal infections:
- Ddx: Cholangitis, Clostridium Difficile colitis, liver abscess, bowel or bile duct leaks
- Dx: CT scan, Ultrasound, Candida from peritoneal drain: upper GI perforation
- Rx: Antibiotics, drainage, ERCP, possible operation

Primary Graft Failure:
- Presentation: Encephalopathy, coagulopathy, oliguria, hypoglycemia
- Dx: LFT abnormalities, INR abnormalities, acidemia, no vascular or rejection related cause
- Rx: Relist, supportive care, avoid potassium

Early to Late:
Infections:
Cytomegalovirus:
  - Presentation: Fever, leukopenia, gastroenteritis, pneumonia, thrombocytopenia
  - Dx: Antigenemia by immunofluorescence; PCR
  - Rx: Valganciclovir or ganciclovir, supportive care

Hepatitis C Recurrence
- Presentation: Fever, jaundice, elevated LFTs, elevated viral load
- Dx: Liver biopsy with trichrome staining
- Rx: Interfuron +/- ribavirin, immunosuppression adjustment, retransplant

Biliary obstruction:
- Presentation: Jaundice, elevated bilirubins
- Dx: Ultrasound, ERCP
- Rx: ERCP, PTC, reoperation

Rejection:
- Presentation: Fever, elevated LFTs, encephalopathy
- Dx: Biopsy
- Please see “Transplant immunology” for Dx/Rx

Lung:

Background:
- Over 23,000 lung transplants in US since January 1st 1988*
- Graft Survival*:
  - 1 Year: 82.5% (Cadaveric Donor); 83.7% (Living Donor)
  - 5 Year: 46.0% (Cadaveric Donor); 34.0% (Living Donor)
*(OPTN data as of May 10, 2012)

Indications for transplant:
  - Idiopathic pulmonary fibrosis
  - Chronic Obstructing Pulmonary Fibrosis
  - Cystic fibrosis

Surgical Issues:
  - Single lung versus bilateral lung decision based on disease process and comorbid disease
Heart with simultaneous lung transplant is an option

Post-Operative Management Issues:
- Ventilator support
- Maintenance of volume status

Unique Complications:

Early:
Primary graft dysfunction:
- Ischemia/reperfusion versus inflammatory mechanism
- Presentation: Worsening hypoxemia due to non-cardiogenic pulmonary edema within 72 hours
- Dx: CXR with bilateral opacities, hypoxemia, no cardiac or volume related explanation
- Rx: Supportive, lung-protective ventilation, nitric oxide, ECMO

Airway Dehiscence:
- Presentation: Pneumomediastinum, Pneumothorax
- Dx: CXR, Bronchoscopy
- Rx: Tube thoracostomy, stents

Early to Late:

Infectious:
- Pneumonia:
  - Bacterial: P. aeruginosa, Staphylococcus aureus
  - Viral: Cytomegalovirus
  - Fungal: Aspergillus
- Dx: CXR, hypoxemia, sepsis, airway necrosis (fungal)
- Rx: Targeted antibiotic for bacteria; Ganciclovir vs. valganciclovir for CMV; Voriconazole in Aspergillus; Decrease immunosuppression

Airway stenosis:
- Presentation: Can be silent, wheezing, recurrent PNA
- Dx: Bronchoscopy
- Rx: Dilation, debridement, stenting

Rejection:
- Presentation: Fever, infiltrate, cough
- Dx: Bronchoscopy with multiple biopsies (patchy process)
- Please see “Transplant immunology” for Dx/Rx
- Chronic rejection: Bronchiolitis obliterans syndrome

Heart:

Background:
- Over 52,000 individual heart transplants in US since January 1st 1988*
- Graft Survival*:
  - 1 year: 86-88%
  - 5 year: 67-72%
*(OPTN data as of May 10, 2012)*

**Indications for transplant:**
End-Stage Heart Failure

**Surgical Issues:**
- Central access-Avoid right internal jugular (biopsy tract)
- Close attention to hemostasis through monitoring (TEG, Coags, ACT)
- and treatment (Aprotinin, blood component therapy)
- Prophylactic antibiotics given

**Post-Operative Management Issues:**
- Post-op respiratory failure: MI, heart failure, hypervolemia, aspiration, pulmonary embolism, ARDS
- Right or left heart failure may be graft failure: Pressors vs. VAD vs. ECMO
  - Monitor with echo, assess by CVP, hemodynamics

**Unique Complications:**

*Early:*
- Tricuspid regurgitation:
  - Presentation: Can be asymptomatic; possible dyspnea, edema, need for diuretic, renal dysfunction, develops following endocardial biopsy
  - Dx: Echo
  - Rx: Diuretics, surgical correction

*Post-op bleeding:*
- Presentation: Bleeding refractory to transfusion
- Ddx: Surgical bleeding, hypocalcemia, dilution, coagulopathy
- Dx: Clinical, laboratory values, TEG may be helpful
- Rx: Resuscitation, reoperation

*Right Heart Failure:*
- Presentation: Ongoing hemodynamic instability
- Dx: Echo, CVP, hemodynamics
- Rx: Dobutamine, milrinone, nitric oxide, avoid hypoxia/acidemia, balloon pump

*Early-Late:*

**Infections:**
- Bacterial: Staphylococcus aureus, Gram neg bacilli, Listeria, Nocardia, mycobacteria
- Viral: Cytomegalovirus, Herpes
- Fungal: Aspergillus, Candida
- Dx: Sepsis criteria, culture data
- Rx: Targeted antibiotic for bacteria; Ganciclovir vs. valganciclovir for CMV; Voriconazole in Aspergillus;
Decomment

Decrease immunosuppression
Left atrial thrombosis:
- Presentation: Systemic emboli, incidental
- Dx: Echo, CT angiogram evidence for emboli
- Rx: Anticoagulation

Rejection:
- Presentation: Arrhythmias, fevers, hypotension
- Dx: Endomyocardial biopsy
- Please see “Transplant immunology” for Dx/Rx
- Chronic rejection: Chronic allograft vasculopathy

Complications affecting all transplants:
Calcineurin inhibitor toxicity
- Presentation: Nephrotoxicity, neurotoxicity, hepatotoxicity
- Dx: Elevated blood levels
- Rx: Hold immunosuppression, follow blood markers of organ function, supportive care

Posterior Reversible Encephalopathy Syndrome (PRES)
- Calcineurin related neurotoxicity
- Presentation: Altered mental status, headache, HTN, focal neuro deficits, visual changes, seizures
- Dx: Cortical or subcortical areas of edema on MRI
- Rx: Reduce or discontinue calcineurin inhibitors, avoid hypomagnesemia, control HTN

Other:
Lymphoproliferative disorders
Skin Cancers

IV. Bibliography:


