Transplant 101

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Considerations for the Front Line Pharmacist

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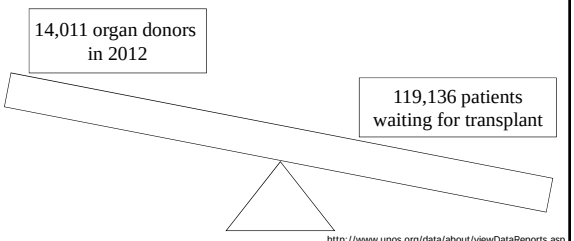
Epidemiology

28,051 transplants performed in 2012



http://www.unos.org/data/about/viewDataReports.asp

Epidemiology

Organ	5-year patient survival rate
Lung	44-50%
Heart	67-74%
Liver	71-74%
Kidney	84-86%

http://www.optn.org/latestData/rptStrat.asp

Terminology

- Rejection
  - **Hyperacute**
    - Minutes to hours after transplant
    - Mediated by alloantibodies and complement
  - **Acute**
    - Days to months after transplant
    - T-Cell and/or antibody mediated
  - **Chronic**
    - Months to years after transplant
    - T-Cell and/or antibody mediated

Terminology

- **Panel reactive antibody (PRA):** represents the percent of lymphocytes on a panel representative of the U.S. population to which the anti-human antibody in a recipient's blood will react
- **Crossmatch:** Process of comparing recipient and donor tissue reactivity for purposes of compatibility
- **Donor specific antibody (DSA):** Anti-HLA antibodies found within the recipient against the donor

Induction Immunosuppression

Induction Immunosuppression

Definition

Intense, prophylactic therapy used at the time of transplantation based on the empiric observation that more powerful immunosuppression is required to prevent early acute rejection

Transplantation 2006; 82(5): 593-602

Induction Agents

- Anti-lymphocyte globulin (ATGAM® and Thymoglobulin®)
- Alemtuzumab (Campath®)
- IL-2 receptor antagonists
  - Basiliximab (Simulect®)
- Corticosteroids

Anti-lymphocyte globulin

- Mechanism of action
  - Complement mediated cell lysis of circulating T-cells

Crit Rev Oncol Hematol. 2005 Oct;56(1):23-46.
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Anti-lymphocyte globulin

- Dosing
  - ATGAM®
    - 10-15 mg/kg/day
  - Thymoglobulin®
    - 1.5-5 mg/kg/day
  - Duration of therapy depends on indication and patient tolerance of medication
- Adverse effects
  - Fever, rash, pruritis, thrombocytopenia
  - Serum sickness
  - Pre-medication is given before each dose

Crit Rev Oncol Hematol. 2005 Oct;56(1):23-46.
www.micromedex.com

Alemtuzumab

- Mechanism of action
  - Binds to CD52 on B and T lymphocytes, macrophages and natural killer cells which causes antibody-dependent lysis of these cells

Crit Rev Oncol Hematol. 2005 Oct;56(1):23-46.
www.micromedex.com
Drugs 2003; 63(12): 1229-1243

Alemtuzumab

- Dosing
  - Two doses of 20 mg IV/subcutaneous
  - One dose of 30 mg IV/subcutaneous
- Adverse effects
  - Rigors, fever, nausea, vomiting, skin rash, dyspnea, hypotension
  - Pre-medication given before each dose

Crit Rev Oncol Hematol. 2005 Oct;56(1):23-46.
www.micromedex.com
Drugs 2003; 63(12): 1229-1243

Basiliximab (Simulect®)

- Mechanism of action
  - Binds to the alpha unit of the IL-2 receptor and inhibits IL-2 binding thereby preventing the activation of lymphocytes

Crit Rev Oncol Hematol. 2005 Oct;56(1):23-46.
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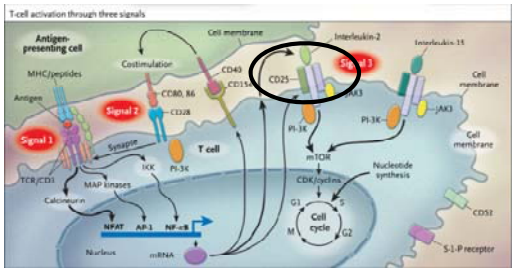
Basiliximab –Mechanism of action



N Engl J Med 2004; 351: 2715-29
Crit Rev Oncol Hematol. 2005 Oct;56(1):23-46

Basiliximab (Simulect®)

- Dosing
  - 20 mg IV on day 0 and day 4
- Adverse effects
  - Abdominal pain, dizziness, insomnia

Crit Rev Oncol Hematol. 2005 Oct;56(1):23-46.
www.micromedex.com

Corticosteroids

- Mechanism of action
  - Anti-inflammatory response
    - Reduced production of cytokines (IL-1, IL-2, IL-6, IFN-γ and TNF-α)
  - Impair monocyte/macrophage function
  - Decrease the number of circulating $CD4^+$ T cells

Crit Rev Oncol Hematol. 2005 Oct;56(1):23-46
www.micromedex.com

Corticosteroids

- Dosing
  - Methylprednisolone 250-1000 mg IV prior to transplant and tapered per protocol
- Adverse effects
  - Hypertension, hyperglycemia, impaired wound healing, fluid retention, electrolyte abnormalities, increased risk for infection

Crit Rev Oncol Hematol. 2005 Oct;56(1):23-46
www.micromedex.com

Comparison of Induction Agents

	ATGAM®	Thymoglobulin®	Basiliximab	Corticosteroids
Mechanism of action	Complement mediated cell lysis of T-cells	Complement mediated cell lysis of T-cells	Prevents activation of lymphocytes by blocking IL-2 receptor	Decrease in inflammatory response
Dosing	10-15 mg/kg/day for 3-5 doses	1-5 mg/kg/day for 3-5 doses	20 mg Day 0 and day 4	500-1000 mg pre-op then rapid steroid taper
Adverse effects	Serum sickness Infusion-related reaction	Serum sickness Infusion-related reaction	Well-tolerated by most patients	Hypertension, hyperglycemia, impaired wound healing, fluid retention

N Engl J Med 2004:351:2715-29
Crit Rev Oncol Hematol. 2005 Oct;56(1):23-46.
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Factors influencing what induction agent(s) to use

- Patient specific factors
  - Immunologic risk
  - Gender
  - Age
- Hospital specific factors
  - Drug availability
  - Ease of administration
  - Cost
- Physician specific factors
  - Clinical experience

Maintenance Immunosuppression

Maintenance Immunosuppression

Definition

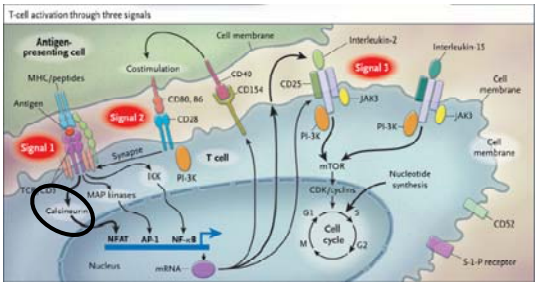
Less potent prophylactic therapy used throughout the life of the transplanted organ to prevent late acute rejection and improve graft survival

Transplantation 2006; 82(5): 593-602

Maintenance Agents

- Calcineurin Inhibitors
  - Cyclosporine, Tacrolimus
- Antimetabolites
  - Azathioprine, Mycophenolate mofetil
- mTOR Inhibitors
  - Sirolimus, Everolimus
- Corticosteroids

Mechanism of action



N Engl J Med 2004; 351: 2715-29
Crit Rev Oncol Hematol. 2005 Oct;56(1):23-46

Calcineurin Inhibitors–Kinetics

- Absorption
  - Very poor (CSA ~30%; TAC ~ 25%)
  - Cyclosporine extremely variable (less variable with modified formulation)
- Metabolism
  - Majority through CYP450-3A4 and p-glycoprotein
- Elimination
  - Urine and bile
  - Half-life is approximately 19 hours (CSA) and 11 hours (TAC)

N Engl J Med 2004:351:2715-29
Crit Rev Oncol Hematol. 2005 Oct;56(1):23-46.
www.micromedex.com

Calcineurin Inhibitors–Dosing

- Cyclosporine
  - 10-15 mg/kg/day in 2 divided doses
  - Adjust to target trough of 150-400 ng/mL
  - To convert from PO to IV, give 30% of oral dose IV twice daily
- Tacrolimus
  - 0.1-0.2 mg/kg/day in 2 divided doses
  - Adjust to target trough of 5-12 ng/mL
  - To convert from PO to IV, give 25% of TOTAL oral daily dose via 24h continuous IV infusion

N Engl J Med 2004:351:2715-29
Crit Rev Oncol Hematol. 2005 Oct;56(1):23-46.
www.micromedex.com

Calcineurin Inhibitors–Adverse Effects

- Class effects
  - Nephrotoxicity, hypertension, hyperlipidemia, hyperglycemia
- Cyclosporine
  - Gingival hyperplasia, hirsutism
- Tacrolimus
  - Alopecia, hyperglycemia, hyperkalemia, neurologic toxicity

N Engl J Med 2004:351:2715-29
Crit Rev Oncol Hematol. 2005 Oct;56(1):23-46.
www.micromedex.com

Calcineurin Inhibitors–Drug Interactions

Drug Interactions

- CYP450 inhibitors
  - Azole antifungals
  - Diltiazem and verapamil
  - Erythromycin
  - Protease inhibitors
- CYP450 inhibitors
  - Antiepileptics
  - Rifampin
  - Rifabutin
  - St. John's Wart

N Engl J Med 2004:351:2715-29
Crit Rev Oncol Hematol. 2005 Oct;56(1):23-46.
www.micromedex.com

Calcineurin Inhibitors–Monitoring

- Cyclosporine
  - 12 hour trough levels
  - 2 hour peak levels
- Tacrolimus
  - 12 hour trough levels

N Engl J Med 2004:351:2715-29
Crit Rev Oncol Hematol. 2005 Oct;56(1):23-46.
www.micromedex.com

Comparison of Calcineurin Inhibitors

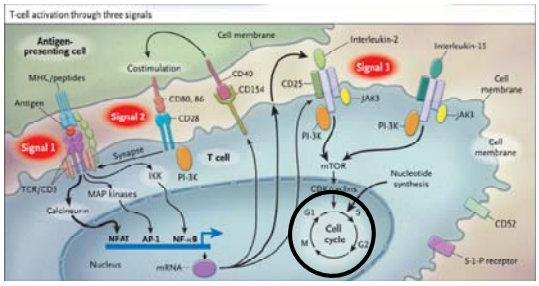
	Cyclosporine	Tacrolimus
Mechanism of action	Binds to cycophilin	Binds to FKBP-12
Potency	+++	+++±
Dosing	10-15 mg/kg/day	0.1-0.2 mg/kg/day
Nephrotoxicity	++	++
Neurotoxicity	+	++
Hirsutism	++	---
Hyperglycemia	+	++
Monitoring	2-hour peak level 12-hour trough level	12-hour trough level

Adapted from *Crit Rev Oncol Hematol.* 2005 Oct;56(1):23-46.

Maintenance Agents

- Calcineurin Inhibitors
  - Cyclosporine, Tacrolimus
- Antimetabolites
  - Azathioprine, Mycophenolate mofetil
- mTOR Inhibitors
  - Sirolimus, Everolimus
- Corticosteroids

Mechanism of action



N Engl J Med 2004; 351: 2715-29
Crit Rev Oncol Hematol. 2005 Oct;56(1):23-46

Azathioprine

- Mechanism of action
  - Inhibits proliferation of T and B cells by preventing RNA and DNA synthesis

N Engl J Med 2004:351:2715-29
Crit Rev Oncol Hematol. 2005 Oct;56(1):23-46.
www.micromedex.com

Azathioprine

- Absorption
  - Bioavailability: 40-45%
- Metabolism
  - Via oxidation or methylation to active metabolite 6-mercaptopurine
- Elimination
  - Majority of drug excreted in the urine
  - Half-life: 3-5 hours
  - Partially dialyzed by hemodialysis

N Engl J Med 2004:351:2715-29
Crit Rev Oncol Hematol. 2005 Oct;56(1):23-46.
www.micromedex.com

Azathioprine

- Dosing
  - 3-5 mg/kg/day initially, then decreased to 1-3 mg/kg/day
  - To convert PO to IV, give 50% of oral dose IV
- Adverse effects
  - Bone marrow suppression, GI intolerance, elevated liver transaminases

N Engl J Med 2004:351:2715-29
Crit Rev Oncol Hematol. 2005 Oct;56(1):23-46.
www.micromedex.com

Azathioprine

- Drug Interactions
  - Allopurinol: decrease AZA dose by 30-50% if given concomitantly
  - Aminosalicylates (mesalamine, olsalazine, sulfasalazine)
  - Warfarin
- Monitoring
  - Signs/symptoms of adverse drug reactions

N Engl J Med 2004:351:2715-29
Crit Rev Oncol Hematol. 2005 Oct;56(1):23-46.
www.micromedex.com

Mycophenolate mofetil

- Mechanism of action
  - Selectively inhibits proliferation of B and T cells by inhibiting *de novo* purine synthesis within the cells; may also inhibit recruitment of leukocytes to areas of inflammation and graft rejection

N Engl J Med 2004:351:2715-29
Crit Rev Oncol Hematol. 2005 Oct;56(1):23-46.
www.micromedex.com

Mycophenolate mofetil

- Absorption
  - Rapid and extensive
  - Bioavailability: 95%
- Metabolism
  - Rapidly metabolized to active form mycophenolic acid by esterases in the liver
- Elimination
  - Majority excreted in the urine
  - Half-life 8-16 hours

N Engl J Med 2004:351:2715-29
Crit Rev Oncol Hematol. 2005 Oct;56(1):23-46.
www.micromedex.com

Mycophenolate mofetil

- Dosing
  - Mycophenolate mofetil: 500-1500 mg PO BID
  - Mycophenolic acid: 360-720 mg PO BID
  - Mycophenolic acid 180mg = Mycophenolate mofetil 250mg
  - PO to IV conversion 1:1 for mycophenolate mofetil
- Adverse effects
  - GI intolerance, myelosuppression, higher incidence of opportunistic infections

N Engl J Med 2004:351:2715-29
Crit Rev Oncol Hematol. 2005 Oct;56(1):23-46.
www.micromedex.com

Mycophenolate mofetil

- Drug Interactions
  - Aluminum and magnesium-containing antacids
  - Cholestyramine
- Monitoring
  - Drug levels may be drawn
  - Signs/symptoms of adverse drug effects

N Engl J Med 2004:351:2715-29
Crit Rev Oncol Hematol. 2005 Oct;56(1):23-46.
www.micromedex.com

Comparison of antimetabolites

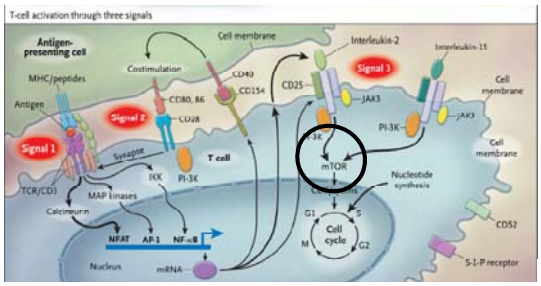
	Azathioprine	Mycophenolate
Mechanism of action	Inhibition of DNA and RNA synthesis	Inhibition of DNA and RNA synthesis
Potency	+	++
Dosing	1-3 mg/kg/day	500-1500 mg PO BID
Diarrhea	---	++
Hepatotoxicity	+	---
Marrow suppression	+	+
Monitoring	Signs/symptoms of ADRS	Blood concentration levels may be drawn

Adapted from *Crit Rev Oncol Hematol.* 2005 Oct;56(1):23-46.

Maintenance Agents

- Calcineurin Inhibitors
  - Cyclosporine, Tacrolimus
- Antimetabolites
  - Azathioprine, Mycophenolate mofetil
- mTOR Inhibitors
  - Sirolimus, Everolimus
- Corticosteroids

Mechanism of action



N Engl J Med 2004; 351: 2715-29
Crit Rev Oncol Hematol. 2005 Oct;56(1):23-46

mTOR Inhibitors–Kinetics

- Absorption
  - Rapidly absorbed
  - Poor bioavailability
  - Reduced when taken with high-fat meal
- Metabolism
  - Extensive metabolism by CYP450-3A4 and p-glycoprotein
- Elimination
  - Majority excreted in feces
  - Half-life: 57-63 hours (SIRO) and 30 hours (EVER)

N Engl J Med 2004:351:2715-29
Crit Rev Oncol Hematol. 2005 Oct;56(1):23-46.
www.micromedex.com

mTOR Inhibitors–Dosing

- Sirolimus
  - 6 mg PO daily for 1-3 doses then 2 mg PO daily (loading dose controversial)
  - Target trough 10-15 ng/mL
  - No IV formulation
- Everolimus
  - 0.75mg PO every 12 hours
  - Target trough 3-8 ng/mL
  - No IV formulation

N Engl J Med 2004:351:2715-29
Crit Rev Oncol Hematol. 2005 Oct;56(1):23-46.
www.micromedex.com

mTOR Inhibitors–Adverse Effects

- Class effects
  - Anemia, hyperlipidemia, impaired wound healing, proteinuria, mouth ulcers, elevated liver function tests
- Sirolimus
  - Hepatic artery thrombosis (BBW), acne, diarrhea
- Everolimus
  - Renal artery thrombosis (BBW), constipation, rash

N Engl J Med 2004:351:2715-29
Crit Rev Oncol Hematol. 2005 Oct;56(1):23-46.
www.micromedex.com

mTOR Inhibitors–Drug Interactions

Drug Interactions

- CYP450 inhibitors
  - Azole antifungals
  - Diltiazem and verapamil
  - Erythromycin
  - Protease inhibitors
- CYP450 inhibitors
  - Antiepileptics
  - Rifampin
  - Rifabutin
  - St. John's Wart

N Engl J Med 2004:351:2715-29
Crit Rev Oncol Hematol. 2005 Oct;56(1):23-46.
www.micromedex.com

mTOR Inhibitors–Monitoring

Drug Interactions

- Sirolimus
  - 24 hour trough levels
- Everolimus
  - 12 hours trough levels

N Engl J Med 2004:351:2715-29
Crit Rev Oncol Hematol. 2005 Oct;56(1):23-46.
www.micromedex.com

When would you use a mTOR inhibitor?

- Delayed graft function (kidney transplant)
- Underlying renal insufficiency (heart or lung transplant)
- Drug intolerance (all transplants)
- Calcineurin toxicity (all transplants, especially kidney)
- Pancreas transplant

Maintenance Agents

- Calcineurin Inhibitors
  - Cyclosporine, Tacrolimus
- Antimetabolites
  - Azathioprine, Mycophenolate mofetil
- mTOR Inhibitors
  - Sirolimus, Everolimus
- Corticosteroids

Prednisone

- Mechanism of action
  - Anti-inflammatory response
    - Reduced production of cytokines (IL-1, IL-2, IL-6, IFN-γ and TNF-α)
  - Impair monocyte/macrophage function
  - Decrease the number of circulating $CD4^+$ T cells

N Engl J Med 2004:351:2715-29
Crit Rev Oncol Hematol. 2005 Oct;56(1):23-46.
www.micromedex.com

Prednisone

- Absorption
  - Bioavailability: 92%
- Metabolism
  - Extensive metabolism by the liver
- Elimination
  - 2.5 to 3 hours

N Engl J Med 2004:351:2715-29
Crit Rev Oncol Hematol. 2005 Oct;56(1):23-46.
www.micromedex.com

Prednisone

- Dosing
  - Steroid taper immediately following transplant
  - Maintenance dose of 5-10 mg PO daily
- Adverse effects
  - Chronic adrenal insufficiency, GERD, hyperglycemia, hypertension, osteoporosis

N Engl J Med 2004:351:2715-29
Crit Rev Oncol Hematol. 2005 Oct;56(1):23-46.
www.micromedex.com

Prednisone

- Drug interactions
  - Tacrolimus and cyclosporine
- Monitoring
  - Signs/symptoms of adverse drug effects

N Engl J Med 2004:351:2715-29
Crit Rev Oncol Hematol. 2005 Oct;56(1):23-46.
www.micromedex.com

	Calcineurin Inhibitors	Antimetabolites	mTOR Inhibitors	Corticosteroids
Mechanism of action	Block production of cytokines (i.e. IL-2)	Inhibition of DNA and RNA synthesis	Prevents progression of the cell cycle	Decrease inflammatory response
Potency	+++ / ++++	+ / ++	++±	+
Nephrotoxicity	++	---	---	---
Neurotoxicity	+ / ++	---	---	---
Hirsutism/ hypertrichosis	++ / --	---	---	++
Hyperglycemia	+ / ++	---	---	++
Diarrhea	---	--- / ++	+	---
Hepatotoxicity	±	+ / -	+	---
Marrow suppression	---	+	+	---
Monitoring	Drug levels	ADRs/drug levels	Drug levels	ADRs

Adapted from *Crit Rev Oncol Hematol*. 2005 Oct;56(1):23-46.

Factors influencing what maintenance regimen to use

- Patient specific factors
  - Comorbid disease states
  - Medication intolerance
  - Compliance history
  - Insurance coverage
- Physician specific factors
  - Clinical experience
  - Clinical trial data

Maintenance Regimens

- Most frequently used regimen
  - Tacrolimus + mycophenolate ± prednisone
- Other therapeutic options
  - Tacrolimus + azathioprine ± prednisone
  - Cyclosporine + mycophenolate ± prednisone
  - Sirolimus + mycophenolate + prednisone
  - Everolimus + tacrolimus/cyclosporine ± prednisone

Case Study

WM is a 60M with ESRD secondary to diabetes mellitus II and hypertension admitted for a cadaveric renal transplant.

1. What are his therapeutic options for induction immunosuppression?
2. What maintenance immunosuppression should be started for WM?

Case Study

WM is started on tacrolimus 2mg PO BID and mycophenolic acid 720mg PO BID. He develops a post-operative ileus and is now unable to take PO medications. The resident asks you how to convert his immunosuppression to IV.

Case Study

- Tacrolimus
  - Total daily dose = 4mg
  - Give 25% of this dose (1mg) as a continuous IV infusion over 24 hours
  - Start tacrolimus infusion at 0.04 mg/hr
- Mycophenolic acid
  - 720mg mycophenolic acid= 1000mg mycophenolate mofetil
  - 1000mg mycophenolate mofetil PO = 1000mg mycophenolate mofetil IV

Future Directions

- New drugs with novel mechanisms
  - Sequestering of circulating lymphocytes
  - Prevention of graft vasculopathy
  - Blockade of T-cell co-stimulation
- Perfecting use of current immunosuppressants
- Genetic testing

Summary

- Imbalance between number of patients waiting for transplant and number of organs available
- Optimizing use of immunosuppressive medications will increase longevity of transplanted organs
- Pharmacists play a vital role in helping ensure the safe and effective use of these medications

Considerations for the Front Line Pharmacist

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It Can Get Complicated: Common Post-Op Complications

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Allograft Rejection

- Immune response injuring the transplanted tissue
  - Inflammation and direct tissue destruction
  - Ultimately can lead to loss of graft function
- Acute cellular rejection (ACR)
  - Infiltration of the allograft by lymphocytes and other inflammatory cells

Allograft Rejection

- Antibody mediated rejection (AMR)
  - Morphologic evidence of acute tissue injury
  - Circulating donor-specific antibodies
  - Immunological evidence of an antibody-mediated process
- Cellular and antibody-mediated processes may coexist

Rejection Pathophysiology

- Hyperacute rejection
  - Occurs within hours to days after transplant
  - Mediated by preformed circulating antibodies
- Acute rejection
  - Occurs within days to months after transplant
  - Mediated by host T-lymphocytes
    - Less commonly due to humoral-mediated rejection
- Chronic rejection
  - Occurs over months to years after transplant

Rejection Clinical Manifestations

- Kidney transplant
  - Fever, oliguria, and graft pain and/or tenderness
  - Elevated serum creatinine (SCr), pyuria, worsening proteinuria

Rejection Clinical Manifestations

- Liver transplant
  - Fever, abdominal pain, hepatosplenomegaly, increasing ascites
  - Elevated serum aminotransferases, alkaline phosphatase, gamma-glutamyl transpeptidase (GGT), bilirubin levels

Rejection Clinical Manifestations

- Pancreas transplant
  - Fever, graft pain and/or tenderness, vomiting, flu-like symptoms
  - Elevated serum glucose
  - Elevated serum amylase and lipase, urinary amylase (bladder drained allografts)

Douzdjian V, et al. Clin Transplant 1994; 8:246.

Acute Cellular Rejection: Treatment Options

Corticosteroids

- Pulse methylprednisolone
  - First line therapy
- 250-500mg IV for 3-5 days
  - Transition to oral steroids (prednisone) and taper off over weeks to months

Increase Immunosuppression

- Calcineurin inhibitor (CNI) if levels were previously subtherapeutic
- Mycophenolic acid if dose was already reduced from baseline or if CNI dosing was not changed
- Add another agent (i.e. corticosteroid) if not already part of the regimen

Anti-T-cell Therapy

- Antithymocyte globulin (Thymoglobulin®, Atgam®)
  - 1-1.5mg/kg (Thymoglobulin®) IV Q24H for 7-14 days
  - 10-15 mg/kg (Atgam®) IV Q24H x 7-14 days
- Alemtuzumab
  - 30mg IV x 1 or 2 doses (optimal dose is not defined)
  - Limited studies

Puttarajappav C, et al. J of Transplant, vol. 2012, 1-9, 2012.

Antibody-Mediated Rejection: Treatment Options

Antibody Removal/Neutralization

- Plasmapharesis (PP)
  - Blood purification procedure that removes antibodies from circulation
  - Used in conjunction with other therapies
  - Donor specific antibodies (DSAs) are measured for effectiveness

Puttarajappav C, et al. J of Transplant, vol. 2012, 1-9, 2012.
Shah A, et al. Transplantation. 2004;77(9):1399.
Lefaucheur C. et al. Am J Transplant. 2009;9(5):1099.

Antibody Removal/Neutralization

- Intravenous immunoglobulin (IVIG)
  - Derived from the pooled human plasma of thousands of donors
  - Mechanism is poorly understood
  - High dose (2gm/kg) when used alone
  - Low dose (100mg/kg) following each PP session

Puttarajappav C, et al. J of Transplant, vol. 2012, 1-9, 2012.
Rocha PN, et al. Transplantation. 2003;75(9):1490.

Anti B-Cell Therapies

- Anti B-Cell therapies
- Rituximab
  - Anti-CD20 chimeric (murine/human) monoclonal antibody
  - 375 mg/m^2/week for 2-4 weeks
  - First dose "infusion reaction complex"
- Mycophenolic acid
  - If not already part of the maintenance regimen

Puttarajappav C, et al. J of Transplant, vol. 2012, 1-9, 2012.
Faguer S, et al. Transplantation. 2007;83(9):1277.

Terminal-complement Pathway Inhibitor

- Eculizumab
  - Humanized monoclonal IgG antibody that binds to complement protein C5
  - 900-1200mg/week x 4-8 weeks (possibly longer)
  - Black Box Warning for meningococcal infections
  - Extremely high cost (Approx $18,000-$24,000 per dose)

Puttarajappav C, et al. J of Transplant, vol. 2012, 1-9, 2012.
Locke JE, et al. Am J Transplant. 2009;9(1):231.

Antiplasma Cell Therapy

- Bortezomib
  - Inhibits proteasomes, enzyme complexes which regulate protein homeostasis within the cell
  - 1.3 mg/m^2 x 4 doses (given over 2 weeks)
  - Lacks strong evidence from randomized studies
  - Not recommended for primary therapy
  - May be beneficial after standard therapies have failed

Puttarajappav C, et al. J of Transplant, vol. 2012, 1-9, 2012.
Everly MJ, et al. Transplantation. 2008;86(12):1754.

Antibody Removal/Neutralization

- Splenectomy
  - Resistant AMR
  - Not commonly used due to both the surgical risk and long term risk of infections
  - Important to immunize against encapsulated organisms
    - *S. pneumoniae*, *N. meningitidis*, *H. influenzae* type B

Puttarajappav C, et al. J of Transplant, vol. 2012, 1-9, 2012.

Primary Non-Function

- Transplanted organ never starts working
  - Rare
  - Organ typically requires removal
  - Does not prevent re-transplant
  - Reinstatement of original wait time

Delayed Graft Funtion (DGF): Kidney

- Use of dialysis within 7 days of the transplant
- Incidence is >20%
- Risk factors include
  - Prolonged ischemia
  - Expanded criteria donors (ECD)
  - Donation after cardiac death (DCD)
- Negative impact on both graft life and patient survival

Siedlecki, A, et al. *Am J of Transplant* 2011; 11: 2279–2296.
Ojo AO, et al. *Transplantation* 1997; 63: 968–974.

Graft Thrombosis

- Clot formation in artery or vein of the transplanted organ
  - Often leads to graft loss
- Thrombectomy
- Fibrinolysis
  - Recombinant tissue-type plasminogen activator
- Aspirin (81mg or 325mg) for prevention

Garcia A, et al. *Am J Transplant* 2010 Aug;10(8):1931-3.

Infection Risk

- Overall level of immunosuppression
  - Induction therapy
  - High dose maintenance immunosuppression
  - Neutropenia
  - Changes over time

Fishman JA. N Engl J Med 2007; 357:2601.

Infection Risk

- Epidemiological exposures
  - Donor-derived infections
  - Recipient-derived infections
  - Nosocomial infections
  - Community infections

Fishman JA. N Engl J Med 2007; 357:2601.

Infection

- Early post-transplant period (< 1 month)
  - Donor or recipient derived
    - May included antimicrobial resistant organisms (i.e. MRSA, VRE)
  - Surgical site infections
  - Catheter infection
  - *Clostridium difficile* colitis
  - Opportunistic infections are not typical

Fishman JA. N Engl J Med 2007; 357:2601.

Infection

- Intermediate post-transplant period (1-6 months)
  - *Pneumocystis jirovecii* (formerly *carinii*) pneumonia (PCP)
  - Herpes simplex virus (HSV), varicella- zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV)
  - Polyoma BK virus
  - Hepatitis B virus (HBV), hepatitis C virus (HCV)
  - *Clostridium difficile* colitis
  - *Cryptococcus neoformans*, *mycobacterium tuberculosis*
  - Listeria, nocardia, toxoplasma

Fishman JA. N Engl J Med 2007; 357:2601.

Infection

- Late post-transplant period (>6 months)
  - Community acquired pneumonia
  - Urinary tract infections
  - *Aspergillus*, atypical molds, mucor
  - CMV (colitis, retinitis), HBV, HCV, HSV (encephalitis)
  - JC polyoma virus
  - West nile virus

Fishman JA. N Engl J Med 2007; 357:2601.

Cytomegalovirus Treatment

- Ganciclovir (5mg/kg IV Q12H)
- Valganciclovir (900mg PO BID)
  - Mild to moderate disease
- Foscarnet (60 mg/kg every 8 hours (or 90 mg/kg every 12 hours)
  - Drug resistant strains; nephrotoxic
- CMV hyper immune globulin
  - Adjunctive therapy

Kotton, C. N. Am J Transplant, 2013: 24–40.

Cytomegalovirus Prevention

- Donor or recipient IgG anti-CMV antibody positive
  - Highest risk is Donor (+) and Recipient (-)
- Prophylactic approach
  - Valganciclovir 450 or 900mg PO daily for 3-6 months
- Pre-emptive approach
  - Periodic CMV viral load monitoring

Kotton, C. N. Am J Transplant, 2013: 24–40.

Pneumocystis Treatment

- Trimethoprim-sulfamethoxazole (TMP-SMX)
  - 5mg/kg (IV or PO) every 6-8 hours
- Pentamadine isethionate IV
  - 4 mg/kg/day
  - Renal dysfunction, dysglycemias, pancreatitis, and Torsades de pointes
  - Aerosolized form is not effective for acute therapy

Martin S.I., et al. Am J Transplant, 2013; 13: 272–279.

Pneumocystis Treatment

- Combination clindamycin and primaquine
  - Clindamycin 300mg-450mg PO Q6-8 hrs, 600-900mg IV Q8hrs (and
  - Primaquine (30mg/day)
  - Check patients for G-6-PD deficiency
- Atovaquone
  - 750mg PO BID

Pneumocystis Treatment

- Trimethoprim-dapsone
  - Trimethoprim 15 mg/kg/day PO divided TID
  - Dapsone 100mg PO daily
- Adjunctive corticosteroids
  - Prednisone 40-60mg PO BID
    - Taper after 5 days over 1-2 weeks
    - Administer within 72 hours in the setting of hypoxia (pAO_2 <70 mmHg)

Pneumocystis Prevention

- Trimethoprim-sulfamethoxazole (TMP-SMX)
  - 1 SS or DS tab daily or 1 DS tab three times weekly
  - Also protects against toxoplasmosis and enteric pathogens
- Dapsone
  - 50-100mg daily
  - Glucose-6-phosphate dehydrogenase (G-6-PD) deficiency testing recommended

Martin S.I., et al. Am J Transplant, 2013; 13: 272–279.

Pneumocystis Prevention

- Atovaquone
  - 1500mg PO daily
- Pentamidine isethionate inhaled (aerosolized nebulizer)
  - 300mg inhaled monthly
- Clindamycin and pyrimethamine
  - 300mg clindamycin with 15mg pyrimethamine daily

Other Infection Prophylaxis

- HSV
  - Valacyclovir
    - Only if donor and recipient are CMV serostatus negative
  - Typical duration is 3-6 months
- Oral thrush (yeast)
  - Clotrimazole troche, nystatin swish/swallow
  - Typical duration ~3 moths

Neutropenia

Absolute Neutrophil Count (ANC)	Infection Risk
>1500/uL (>1.5 x 109/liter)	None
1000 to 1500/uL	No significant risk of infection
500 to 1000/uL	Some risk of infection
<500/uL	Significant risk of infection

ANC = WBC (cells/microL) x percent (PMNs + bands) ÷ 100

Adapted from www.uptodate.com/overview-of-neutropenia. Accessed August 17, 2013.

Drug Induced Neutropenia

- Anti T-cell therapy
- Antimetabolites
- Ganciclovir, valganciclovir
- Trimethoprim-sulfamethoxazole
- Rituximab

Neutropenia Management

- Decrease or discontinue offending medication
  - Stop valganciclovir and use the pre-emptive approach
  - Change TMP-SMX to alternative agent (i.e. atovaquone)
  - Antimetabolite in immunosuppression regimen
  - Consider filgrastim administration
    - ANC <1000/uL

Post Transplant Lymphoproliferative Disorder (PTLD)

- Lymphoid proliferations that occur in the setting of immunosuppression
- Associated with EBV infection
  - EBV infected B-cells proliferate without the surveillance and subsequent elimination by activated T-cells
  - Highest risk in EBV-positive donor and EBV-negative recipient

Jagadeesh D, et al. Curr Treat Options Oncol. 2012 Mar;13(1):122-36.

Post Transplant Lymphoproliferative Disorder (PTLD)

- Incidence is ~1-5% in liver and kidney transplants
  - ~10-25% in heart, lung or multi-organ transplants
    - Higher level of immunosuppression
- Potentially fatal complication
  - Mortality rates of approximately 50–70%

Jagadeesh D, et al. Curr Treat Options Oncol. 2012 Mar;13(1):122-36.

PTLD Treatment

- Reduction of immunosuppression
  - Initial treatment strategy
- Rituximab
  - Earlier initiation may improve survival
- Chemotherapy
  - CHOP is most commonly used regimen

Jagadeesh D, et al. Curr Treat Options Oncol. 2012 Mar;13(1):122-36.

Case Study

NW is a 40 year old African American female with a history of end-stage renal disease secondary to lupus nephritis. She underwent a living unrelated kidney transplant 6 weeks ago and returns to the clinic with fever, graft pain and an elevated SCr of 3.8. Her current medications include: tacrolimus 2mg POD BID, mycophenolic sodium 720mg BID, TMP-SMX SS daily, valganciclovir 450mg daily, nystatin 5ml swish/swallow QID.

- What type of rejection pathophysiology would this be considered?
  - a. Hyperacute
  - b. Acute
  - c. Chronic
  - d. Acute on chronic

Case Study

The kidney biopsy is showing moderate acute cellular rejection.

- What is a potential treatment option for NW's kidney rejection?
  - a. Plasmapharesis
  - b. Intravenous immunoglobulin (IVIG)
  - c. Bortezomib
  - d. Antithymocyte globulin

Case Study

Two weeks after being treated with a 10 day course of antithymocyte globulin her absolute neutrophil count has decreased to 1.1/uL

- What would be the best strategy to manage her neutropenia?
  - a. Discontinue her immunosuppression
  - b. Stop valganciclovir and start pre-emptive approach
  - c. Administer filgrastim
  - d. Discontinue her nystatin swish and swallow

Summary

- Transplant patients are at risk for multiple complications which can occur early or late post-transplant
- Despite advances in immunosuppression, allograft rejection continues to be a significant problem
- Immunosuppressed patient are at risk for opportunistic infections and prophylaxis can help prevent infection
- Immunosuppression should be decreased when appropriate to limit toxicity and long term consequences

It Can Get Complicated: Common Post-Op Complications

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Comparison of Induction Agents

	ATGAM®	Thymoglobulin®	Basiliximab	Corticosteroids
Mechanism of action	Complement mediated cell lysis of T-cells	Complement mediated cell lysis of T-cells	Prevents activation of lymphocytes by blocking IL-2 receptor	Decrease in inflammatory response
Dosing	10-15 mg/kg/day for 3-5 doses	2.5-5 mg/kg/day for 3-5 doses	20 mg Day 0 and day 4	500-1000 mg pre-op then rapid steroid taper
Adverse effects	Serum sickness Infusion-related reaction	Serum sickness Infusion-related reaction	Well-tolerated by most patients	Hypertension, hyperglycemia, impaired wound healing, fluid retention

Comparison of Calcineurin Inhibitors

	Cyclosporine	Tacrolimus
Mechanism of action	Binds to cycophilin	Binds to FKBP-12
Potency	+++	+++±
Dosing	10-15 mg/kg/day	0.1-0.2 mg/kg/day
Nephrotoxicity	++	++
Neurotoxicity	+	++
Hirsutism/hypertrichosis	++	---
Hyperglycemia	+	++
Monitoring	2-hour peak level 12-hour trough level	12-hour trough level

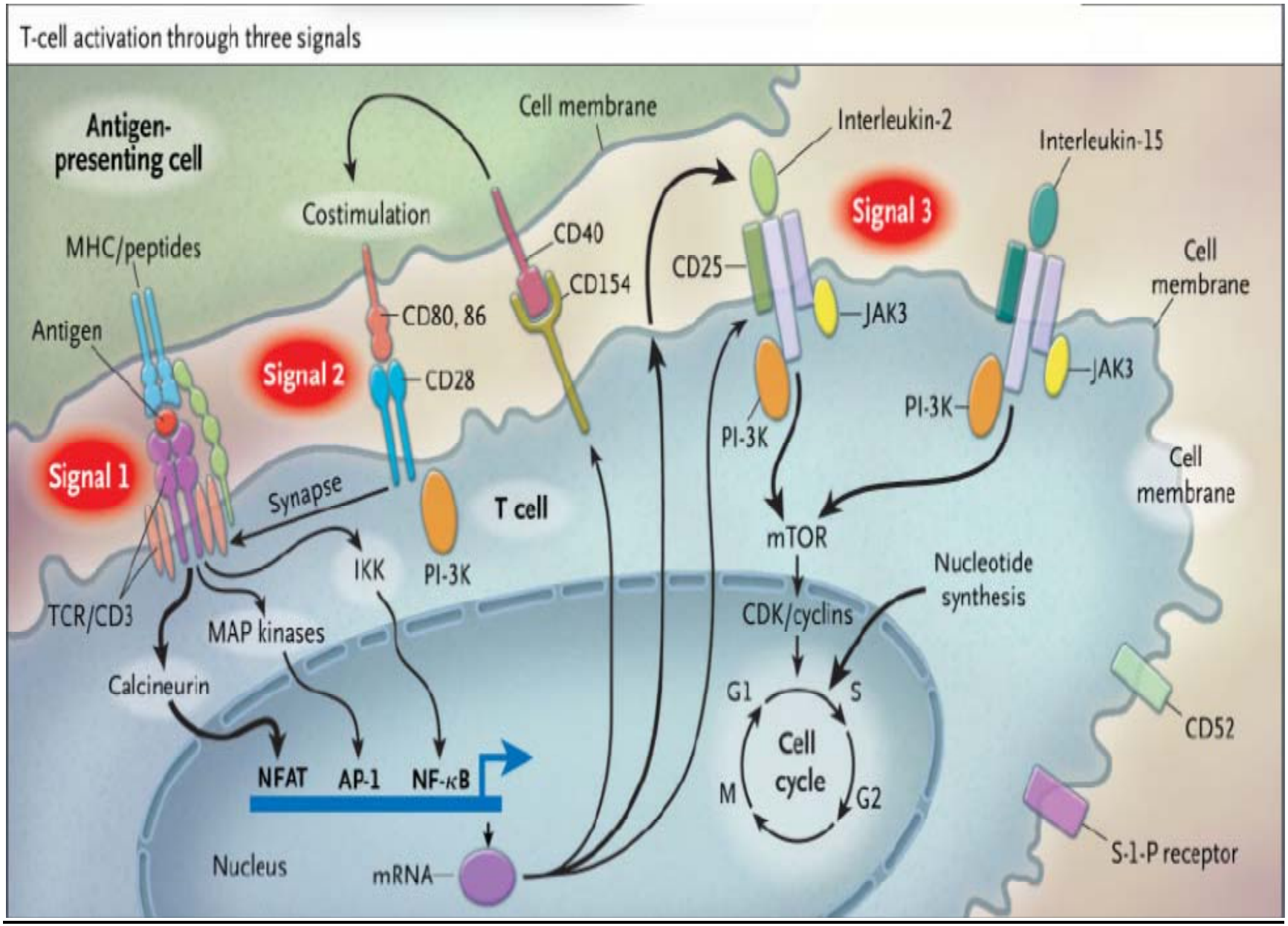
Comparison of Antimetabolites

	Azathioprine	MMF/MPA
Mechanism of action	Inhibition of DNA and RNA synthesis	Inhibition of DNA and RNA synthesis
Potency	+	++
Dosing	1-3 mg/kg/day	500-1500 mg PO BID 360-720mg PO BID
Diarrhea	---	++
Hepatotoxicity	+	---
Marrow suppression	+	+
Monitoring	Signs/symptoms of ADRS	Blood concentration levels may be drawn

Comparison of Drug Classes

	Calcineurin Inhibitors	Antimetabolites	TOR Inhibitors	Corticosteroids
Mechanism of action	Block production of cytokines (i.e. IL-2)	Inhibition of DNA and RNA synthesis	Prevents progression of the cell cycle	Decrease inflammatory response
Potency	+++ / ++++	+ / ++	++±	+
Nephrotoxicity	++	---	---	---
Neurotoxicity	+ / ++	---	---	---
Hirsutism/ hypertrichosis	++ / --	---	---	++
Hyperglycemia	+ / ++	---	---	++
Diarrhea	---	--- / ++	+	---
Hepatotoxicity	±	+ / -	+	---
Marrow suppression	---	+	+	---
Monitoring	Drug levels	ADRs/drug levels	Drug levels	ADRs

T-Cell Activation and Drug Mechanism



N Engl J Med 2004; 351: 2715-29

Chad Richardson

References:

1. Douzdjian V., Abecassis M.M., Corry R.J., Hunsicker L.G. Simultaneous pancreas-kidney versus kidney-alone transplants in diabetics: increased risk of early cardiac death and acute rejection following pancreas transplants. *Clin Transpl*. 1994; 8:246–251.
2. Puttarajappa C., Shapiro R., Henkie T.P., Antibody-Mediated Rejection in Kidney Transplantation: A Review. *Journal of Transplantation*, vol. 2012, Article ID 193724, 9 pages, 2012.
3. Shah A., Nadasdy T., Arend L., Brennan J., Leong N., Coppage M., et al. Treatment of C4d-positive acute humoral rejection with plasmapheresis and rabbit polyclonal antithymocyte globulin. *Transplantation*. 2004 May 15;77(9):1399-405.
4. Lefaucheur C., Nochy D., Andrade J., Verine J., Gautreau C., Charron D., et al. Comparison of combination Plasmapheresis/IVIg/anti-CD20 versus high-dose IVIg in the treatment of antibody-mediated rejection. *Am J Transplant*. 2009 May;9(5):1099-107.
5. Rocha P.N., Butterly D., Greenberg A., Reddan D.N., Tuttle-Newhall J., Collins B.H., Kuo P.C., et al. Beneficial effect of plasmapheresis and intravenous immunoglobulin on renal allograft survival of patients with acute humoral rejection. *Transplantation* 75.9 (2003): 1490-1495.
6. Faguer S., Kamar N., Guilbeaud-Frugier C., Fort M., Modesto A., Mari A., et al. Rituximab therapy for acute humoral rejection after kidney transplantation. *Transplantation* 83, no. 9 (2007): 1277-1280.
7. Locke, J.E., Magro C.M., Singer A.L., Segev D.L., Haas M., Hillel A.T., et al. The Use of Antibody to Complement Protein C5 for Salvage Treatment of Severe Antibody-Mediated Rejection. *American Journal of Transplantation* 9, no. 1 (2009): 231-235.
8. Everly, M.J., Everly J.J., Susskind B., Brailey P., Arend L.J., Alloway R.R., et al. Bortezomib provides effective therapy for antibody-and cell-mediated acute rejection. *Transplantation* 86, no. 12 (2008): 1754-1761.
9. Siedlecki A., Irish W., Brennan D.C. Delayed graft function in the kidney transplant. *American Journal of Transplantation* 11, no. 11 (2011): 2279-2296.
10. Ojo A.O., Wolfe R.A., Held P.J., Port F.K., Schmouder R.S. Delayed Graft Function: Risk Factors and Implications for Renal Allograft Survival. *Transplantation* 63, no. 7 (1997): 968-974.
11. Garcia A., Vedula G., Nowygrod R., Ratner L.E., Goldstein M.J. Recombinant tissue-type plasminogen activator in the treatment of acute renal artery thrombosis after kidney transplantation. *Am J Transplant*. 2010 Aug;10(8):1931-3.
12. Fishman J. A. Infection in solid-organ transplant recipients. *New England Journal of Medicine*, 2007. 357(25), 2601-2614.
13. Fishman J.A. Infection in solid-organ transplant recipients. *New England Journal of Medicine* 357, no. 25 (2007): 2601-2614.
14. Kotton, C. N. CMV: Prevention, Diagnosis and Therapy. *American Journal of Transplantation*. 2013. 13: 24–40.

15. Martin S. I., Fishman J. A. and the AST Infectious Diseases Community of Practice. *Pneumocystis* Pneumonia in Solid Organ Transplantation. *American Journal of Transplantation*. 2013. 13: 272–279.
16. UpToDate. Overview of Neutropenia. Available at: http://www. uptodate.com/overview-of-neutropenia. Accessed August 17, 2013.
17. Jagadeesh D., Woda B.A., Draper J., Evens A.M. Post transplant lymphoproliferative disorders: risk, classification, and therapeutic recommendations. *Curr Treat Options Oncol*. 2012 Mar;13(1):122-36.

Transplant 101
0121-0000-13-051-L01-P
0121-0000-13-051-L01-T
Nicole Alvey, PharmD, BCPS & Chad Richardson, PharmD

Post Test Questions:

1. True/False: Induction immunosuppression is defined as the intense, prophylactic therapy used at the time of transplantation based on the empiric observation that more powerful immunosuppression is required to prevent early acute rejection.

2. What is the time course for the development of hyperacute rejection post-transplant?
    a. Months to years
    b. Minutes to hours
    c. Days to months
    d. Greater than 5 years

3. Which of the following is a common adverse effect of tacrolimus?
    a. Hyperglycemia
    b. Hirsutism
    c. Gingival hyperplasia
    d. None of the above

4. DB is a 65M with a history of end stage liver disease secondary to hepatitis C status-post liver transplant in 2011. He is taking tacrolimus 5mg PO BID and mycophenolic acid 720mg PO BID. He is admitted for pancreatitis and is now strict NPO. The resident would like help converting his immunosuppression medications to IV. Which of the following would be the correct IV dosing for his IV medications?
    a. Tacrolimus 5mg IV q12h and mycophenolate mofetil 500mg IV q12h
    b. Tacrolimus 2.5mg IV q24h and mycophenolate mofetil 1000mg IV q12h
    c. Tacrolimus 0.1mg/hr and mycophenolate mofetil 1000mg IV q12h
    d. Tacrolimus 0.1mg/hr and mycophenolate mofetil 500mg IV q12h

5. Which of the following should be considered when deciding on a patient's maintenance immunosuppresion regimen?
    1. Patient's comorbid conditions
    2. Prescription insurance coverage
    3. Physician experience
    4. All of the above

6. Which of the following best describes acute cellular rejection?
    1. Infiltration of the allograft by lymphocytes and other inflammatory cells
    2. Morphologic evidence of acute tissue injury
    3. Immunological evidence of an antibody-mediated process
    4. Circulating donor-specific antibodies

7. Which of the following best describes delayed graft function?
    a. Kidney never starts working
    b. Blood clot formation in the renal artery
    c. Use of dialysis within 7 days of the kidney transplant
    d. Infiltration of the allograft by lymphocytes

8. Which of the following is an anti B-cell medication used to treat antibody mediated rejection?
    a. Rituximab
    b. Antithymocyte globulin
    c. Eculizumab
    d. Bortezomib

9. Which of the following infections typically occur late post transplant (>6 months)
    a. *Clostridium difficile* colitis
    b. Surgical site infection
    c. Hepatitis C virus
    d. Aspergillus

10. Trimethoprim-sulfamethoxazole can be used as prophylaxis against which infection?
    a. *Clostridium difficile* colitis
    b. Pneumocystis pneumonia (PCP)
    c. Cytomegalovirus (CMV)
    d. *Mycobacterium tuberculosis*