Minding the Gap: Transplant Transitions

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November 3, 2011

Disclosures

- Advisory board (Astellas)

Objectives

- Summarize transplant pharmacotherapy
- Review changes in common renal health issues after transplantation (e.g. anemia, blood pressure and mineral metabolism)
- Describe the process for tapering immunosuppression after loss of graft (transplanted kidney) function
- Discuss the role of the transplant pharmacist in the care of the kidney transplant recipient

Why kidney transplantation?

Transplantation vs. dialysis

- Survival benefit
  - Age 60 to 64: +4 years
  - Age 40 to 59: +11 years
  - Age 20 to 39: +17 years
  - Children: +13 years

Source: Transplant Manitoba

Transplantation vs. dialysis

- Potential Cost Savings (yearly, per patient)
  - hemodialysis treatment
    - $60,000
  - kidney transplant
    - $23,000 (surgery)
    - $10,000 (medication)
  - cost savings
    - $50,000

Source: CORR/CIHI data

The numbers

- Duration of dialysis before transplantation (time spent on wait list), Manitoba 2010
  - Deceased donor: ~ 4.3 years
  - Living donor: ~ 1.5 years
- ~3,300 people on the wait list for a kidney transplant in Canada [2010]
  - ~160 in Manitoba (+ ~450 in work-up process)

Source: Transplant Manitoba; CORR/CIHI 2010 data

Recipient/Donor Evaluation and Immunology basics

Recipient Evaluation

- Transplant nephrologist visit
- Blood group, HLA typing, HLA antibody screening
- Infection screening: TB, HBV, HCV, HIV, CMV, EBV, BK…
- Imaging: CXR, U/S
- Cardiac evaluation
- Vascular disease screen
- Psychiatry assessment
- Other: Specialist consults…

Complete evaluation requires approx. 6-9 months in MB

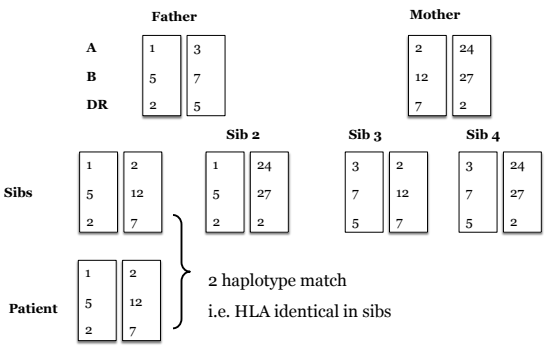
Different types of 'matching'

- Blood type
  - ABO system
- HLA match
  - 3 types of HLA: A, B, DR
- Cross match
  - Looks for donor-specific HLA antibodies
- Sensitization
  - Looks for antibodies to a pool of potential donors or a local population

HLA: human leukocyte antigens

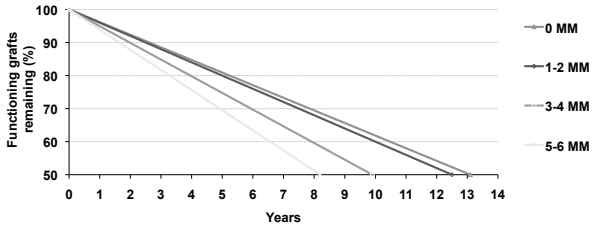
- HLA are markers on most cells
  - Help to identify "self" from "foreign"
- Many types of HLA
  - Class I: A, B, C
    - Stimulate T-killer cells
  - Class II: DR, DP, DQ
    - Stimulate T-helper cells, macrophages, B-cells
- Typical matching between A, B and DR types

HLA matching – In family



HLA Matching

Degree of HLA disparity = Degree of immunologic risk



Cross-matching
(i.e. HLA antibody screening)

- A test between donor and recipient
- HLA antibodies can cause severe rejection and graft loss
- Positive cross-match is bad
  - The recipient's cells are able to recognize and attack the donor cells
  - Increased risk of rejection

Sensitization

- PRA: percent reactive antibodies
  - Amount of HLA antibody
  - Many more than just A, B and DR antibodies
- "Sensitizing events" can lead to anti-HLA antibody
  - Pregnancy, blood transfusions, previous transplant
- PRA (panel reactive antibody) screening
  - Degree of "transplantability"
  - 60% PRA = incompatibility for transplant with about 60 out of 100 potential donors (of same blood group)

Kidney graft survival (percent)

	1995		1999		2003	
	Deceased Donor	Living Donor	Deceased Donor	Living Donor	Deceased Donor	Living Donor
3 month	91.2	99	94.2	98.2	96.2	98.6
1 year	87.4	97.9	91.2	96.6	93.3	98
3 year	82.4	95.8	87	94.5		
5 year	76.1	90.9	78.5	91.6		

Why is survival improving?

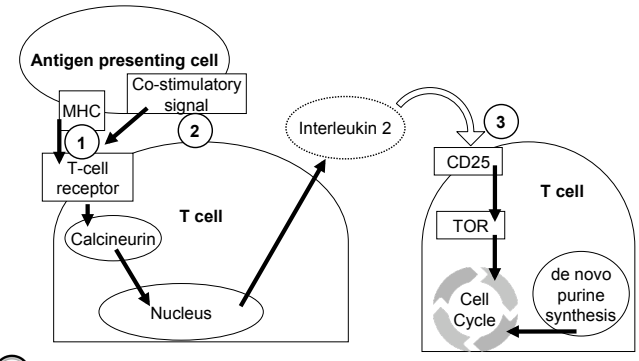
Source: CORR/CIHI data

Immunosuppressants

History of transplant immunosuppressants

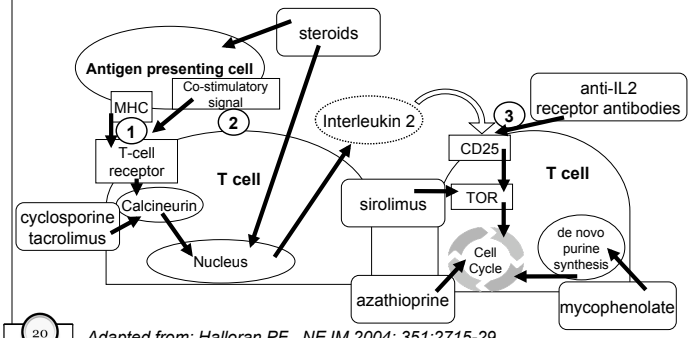
- 1960's
  - Azathioprine
  - Steroids
- 1980's
  - Cyclosporine
  - OKT3
- Early 1990's
  - Tacrolimus
- Late 1990's
  - Mycophenolate
  - ATGAM/ Thymoglobulin
  - Daclizumab
  - Basiliximab
  - Sirolimus

T-cell activation: 3-signal model



Adapted from: Halloran PF. NEJM 2004; 351:2715-29

T-cell activation: 3-signal model



Adapted from: Halloran PF. NEJM 2004; 351:2715-29

T-cell activation: 3-signal model

- Signal 1: Antigen recognition
  - Foreign antigen on antigen presenting cell (APC)
  - T-cell recongizes as foreign
  - Complex is formed between MHC and CD3
  - Activation of the calcineurin pathway

T-cell activation: 3-signal model

- Signal 2: Costimulatory pathway
  - APC meets the T-cell
  - Binding of APC's CD80/86 (B7) with CD28 on T-cell
  - Synergy with Signal 1
    - Strengthens immune signal through CD3 complex

T-cell activation: 3-signal model

- Signal 1 and 2
  - Genes are induced to make IL-2 and other cytokines
  - IL-2 receptor (CD25) is expressed on the T-cell

T-cell activation: 3-signal model

- Signal 3: Cytokine induction of T-cell proliferation
  - IL-2 from the activated T-cell binds to the new IL-2 receptors
  - Binding of IL-2 activates mTOR
    - Stimulates cell cycling
    - Stimulates proliferation of T-cells

How to achieve immunosuppression

- Depletion of lymphocytes
  - Depleting antibodies
- Diversion of lymphocyte traffic
- Blocking of lymphocyte response

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How to achieve immunosuppression

- Depletion of lymphocytes
- Diversion of lymphocyte traffic
- Blocking of lymphocyte response
  - Non-depleting monoclonal antibody IL-2 receptor antagonists (basiliximab)
  - Calcineurin inhibitors (tacrolimus, cyclosporine)
  - Anti-proliferative agents (azathioprine, mycophenolic acid)
  - mTOR inhibitor (sirolimus)

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Immunosuppressants: Induction Therapy

- Depleting antibodies
  - Anti-thymocyte: Thymoglobulin® (rabbit)
  - Alemtuzumab (Campath®)
- Non-Depleting antibodies
  - IL-2 (CD25) receptor: basiliximab (Simulect®)
- Corticosteroids
  - prednisone
  - methylprednisilone (Solu-Medrol®)

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Immunosuppressants: Maintenance therapy

- Calcineurin inhibitors (CNI)
  - cyclosporine [CSA] (Sandoz-cyclosporine®, Neoral®)
  - tacrolimus IR [TAC] (FK-506/Prograf®)
  - tacrolimus ER (Advagraf®)
- Corticosteroids
  - prednisone
  - methylprednisilone (Solu-Medrol®)
- Anti-proliferatives
  - azathioprine [AZA] (Imuran®)
  - Mycophenolate mofetil [MMF] (CellCept®)
  - mycophenolate sodium [MPS] (Myfortic EC®)
- Rapamycin derivatives
  - sirolimus [SIR] (Rapamune®)

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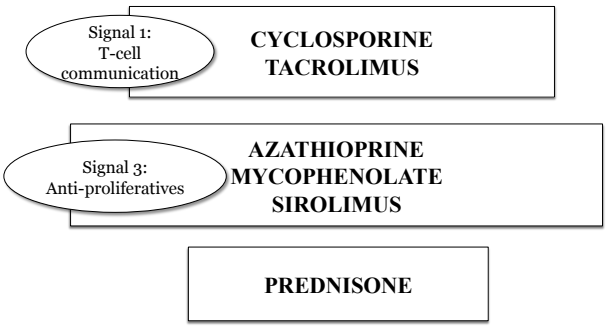
generic [abbreviation] (brand name)

Immunosuppressants: Maintenance therapy



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Usually one from each box

Maintenance Regimens

- Many different combinations
- Combination depends on:
  - Type of transplant
  - Match between donor and recipient (renal)
  - Underlying disease
  - Patient history
  - Medication tolerance
  - Patient age, race

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Corticosteroids
prednisone, methylprednisilone

- Dose
  - tapered to 5-10 mg once daily (or less)
- Action
  - Inhibit antigen presentation, cytokine production and T-cell proliferation
  - Blocks IL-2 transcription
- ADR
  - ↑ lipids, ↑ BG, ↑ BP, ↑ appetite/weight, mood swings, osteoporosis, acne, fluid retention

Calcineurin Inhibitors (CNIs)
cyclosporine, tacrolimus

- Dose: individualized based on blood levels
  - CSA (IV = ⅓ PO dose)
    - Initial: 10-15 mg/kg/day divided q12h (~50-100mg q12h)
  - TAC
    - Initial: 0.1-0.3 mg/kg/day
      - Tacrolimus IR (Prograf®) divided q12h (~1-5mg q12h)
      - Tacrolimus ER (Advagraf®) once daily (~2-10mg daily)
- ADR
  - ↑ BG (TAC), ↑ BP, ↑ lipids, ↑ K+, ↓ Mg+
  - Tremor, nephro- & hepatotoxicity, gingival hyperplasia (CSA), hirsutism (CSA)

cyclosporine [CSA] (Neoral); tacrolimus [TAC] (FK-506/Prograf [IR] & Advagraf [ER])

Calcineurin Inhibitors (CNIs)
cyclosporine, tacrolimus

- Additive nephrotoxicity
  - NSAIDS: afferent vasoconstriction
  - ACEi/ARB: efferent vasodilation
  - Aminoglycosides, amphotericin B
- Renal sparing effect
  - CCB's: afferent vasodilation

Calcineurin Inhibitors (CNIs)
cyclosporine, tacrolimus

CYP-3A4 substrates

- Inhibitors: increase CSA/TAC concentrations
  - Azoles
  - Macrolides
  - Non-DHP CCB's
  - Grapefruit juice
- Inducers: decrease CSA/TAC concentrations
  - Rifampin
  - Phenytoin
  - Carbamazepine
  - St. John's Wort

Calcineurin Inhibitors (CNIs)
cyclosporine, tacrolimus

- CYP-3A4 inhibitor (CSA > TAC)
  - Statins
- CSA/TAC: potassium sparing diuretics
- CSA: colchicine
- TAC: metoclopramide

Calcineurin Inhibitors (CNIs)
cyclosporine, tacrolimus

- Renal dysfunction
  - Tacrolimus: may require decreased dose
  - Neither removed by hemodialysis
- Hepatic dysfunction
  - Cyclosporine: monitor levels closely
  - Tacrolimus: may require decreased dose

cyclosporine [CSA] (Neoral); tacrolimus [TAC] (FK-506/Prograf [IR] & Advagraf [ER])

Anti-proliferatives:
azathioprine, mycophenolate

- Dose: fixed dosing
  - AZA: once daily
  - MMF/MPS: bid (TID/QID for GI tolerability)
  - MMF 500mg = MPS 360mg
    - (MMF 1g BID / MPS 720mg BID)
- ADR
  - AZA: bone marrow suppression, hepatoxicity
  - MMF/MPS: leukopenia, GI intolerance

azathioprine [AZA] (Imuran); mycophenolate (CellCept [MMF], Myfortic EC [MPS])

Anti-proliferatives:
azathioprine, mycophenolate

- AZA common interactions:
  - Allopurinol (increased AZA exposure)
  - Warfarin (decreased INR)
  - ACEi (anemia, leukopenia)
- MMF/MPS common interactions:
  - Antibiotics may change enterohepatic recirculation (may change trough level but not necessarily overall exposure)
  - Binding: Al or Mg antacids, cholestyramine

azathioprine [AZA] (Imuran); mycophenolate (CellCept [MMF], Myfortic EC [MPS])

Anti-proliferatives:
azathioprine, mycophenolate

- Renal dysfunction
  - Mycophenolate: no dose adjustment required
  - Azathioprine: partially removed by hemodialysis, supplemental dose may be required
- Hepatic dysfunction
  - No dose adjustment required

azathioprine [AZA] (Imuran); mycophenolate (CellCept [MMF], Myfortic EC [MPS])

Rapamycin derivatives
sirolimus

- Dose: individualized based on blood levels
  - 2-5 mg once daily
  - Schedule 4 hours after cyclosporine (co-metabolized) – or monitor closely
- ADR
  - ↑ lipids, delayed wound healing, anemia, hypertension
  - Caution in liver and lung transplant
    - Hepatic artery stenosis, bronchial anastomotic dehiscence

sirolimus [SIR] (Rapamune)

Rapamycin derivatives
sirolimus

CYP-3A4 substrate

- Inhibitors: increase SIR concentrations
  - Azoles
  - Macrolides
  - Non-DHP CCB's
- Inducers: decrease SIR concentrations
  - Rifampin
  - Phenytoin
  - Carbamazepine
  - St. John's Wort

Rapamycin derivatives
sirolimus

- Renal dysfunction
  - No dose adjustment required
- Hepatic dysfunction
  - Decrease dose by one-third

sirolimus [SIR] (Rapamune)

Other interactions

- p-glycoprotein is linked to CYP 3A
  - Similarly influenced medications
  - Cyclosporine, tacrolimus, sirolimus, prednisone
- Diarrhea (depletes p-glycoprotein)
  - Increased drug levels/exposure (also it's own cause of GI disturbances)

Drug monitoring

Drug monitoring

- Managing drug levels of a transplant patient is like balancing a scale
  - Rejection vs. toxicity
  - Each person … and each target level … is unique
  - Never a text book case
- Within each "reference range", the appropriate drug level (tighter range) is influenced by:
  - Time post-transplant
  - Organ type
  - Use of induction agents
  - Other immunosuppression
  - Presence of rejection or toxicity

Cyclosporine: monitoring

- Trough level (within 30 min pre-dose)
  - High variability of cyclosporine trough (C0) levels
  - Target level depends on time since transplant and is individual to each patient
- 2-hour post dose correlates to AUC/drug exposure and clinical outcomes
  - Sample time is very important: 2 hours +/- 10 minutes post-dose
  - C2 can be difficult to coordinate with patients and labs
  - 2-hour level not routinely done in Manitoba

Tacrolimus: monitoring

- Trough level (within 30 min pre-dose)
  - Correlates well to AUC/drug exposure
  - Target level depends on time since transplant and is individual to each patient

Mycophenolate: monitoring

- Trough level (within 30 min pre-dose)
- Controversial: MMF/MPS drug levels not routinely done
  - Occasionally done if toxicity or absorption concerns
  - Dose not necessarily adjusted based on level
    - e.g., 'low' level but persistent GI upset

Sirolimus: monitoring

- Trough level (within 30 min pre-dose)
  - Correlates well to AUC/drug exposure
  - Target level depends on time since transplant and is individual to each patient

Adjunct Therapy: Anti-Infectives

Infections:
Pneumocystis jiroveci (formerly PCP)

- PJP has significant morbidity and mortality in solid organ transplant patients (mortality up to 50%)
- Associated with periods of higher immunosuppression (e.g. first six months post-transplant)
- Prophylaxis
  (Winnipeg kidney: 3 months; other centres: 6-12+ months)
  - Co-trimoxazole 400/80mg daily or EOD
  - Sulfa allergy: Dapsone 100mg daily
  - Pentamidine inhalation every four weeks
- Treatment (three weeks)
  - Co-trimoxazole (Oral/IV) 15-20 mg TMP/kg/day
    - ~1600/320mg (2 DS tabs) q8h
  - Pentamidine infusion (IV) daily
  - Atovaquone (Mepron®) 750mg po bid

Infections:
Viral (CMV)

- Cytomegalovirus
- Risk
  - Use of induction agents
  - D+R- > D+R+ > D-R+ > D-R-
- Prophylaxis*
  - valganciclovir 900mg daily for 3-6 months
- Treatment*
  - ganciclovir IV
  - Valganciclovir po
- *Adjust dose for renal function
- Do NOT adjust for WBC/platelets: risk of antiviral resistance; effect may be due to CVM disease

Infection:
Immunization

- Inactivated vaccine only
  - Diptheria
  - Hemophilus
  - Hepatitis A and B
  - Influenza (not live nasal vaccine)
  - Meningococcal
  - Pertussis
  - Polio (Salk)
  - Tetanus
- Controversies
  - Trigger for subclinical rejection?
  - Adjuvants?

Post-transplant Complications

Complications

A. anemia

B. bone density (decrease)
- steroid use
- renal bone disease

B. blood pressure (increase)

C. cholesterol (increase)
- especially sirolimus, also cyclosporine/tacrolimus

C. cancer risk
- skin cancer most common
- PTLD (post-transplant lymphoproliferative disorder): lymphoma, leukemia

D. diabetes
- new onset after transplantation (steroids, tacrolimus)
- difficult to control with steroid use

D. depression
- steroid use
- change in chronic disease status

E. eyes (cataracts)
- steroid use

Transitions Between RRT and Transplantation

Times of increased mortality

- Length of time on dialysis before dialysis
  - Accumulated risk persists after transplantation
    - <3 years » 3.1/100 patient years
    - >3 years » 4.3/100 patient years
- First 90-days after being removed from the waitlist
  - 34/100 patient years
- The first 12 months after kidney transplantation
  - 0-3 months » 8.2/100 patient years
  - Throughout transplant » 2.7/100 patient years
- Loss of transplanted kidney function and return to dialysis
  - Duration of transplant function not predictive of risk
    - 17.9/100 patient years
    - During first 2 years back on dialysis, 18% mortality (spike at 3 months)
  - ~25% of patients with a failed transplant die within 2 years of returning to dialysis
    - ~20% for incident dialysis patients
    - ~6% for recipients of a deceased donor kidney

The importance of transitions between dialysis and transplantation in the care of end-stage renal disease patients. Kid Int. 2007; 71: 442-7.
Managing patients with a failed kidney transplant: how can we do better? Curr Opin Nephrol Hypertens. 2011; 20: 616-21.

What do those stats mean?

- Something happens during the transitions between ESRD/RRT and transplantation
- Transplantation lowers the mortality risk (vs. ESRD/RRT) but doesn't eliminate it
  - Mortality is still higher than in the general population (3-10x)
- Higher mortality risk on return to dialysis (vs. never receiving a transplant)

Mortality risk factors in dialysis patients waiting for transplant

Higher mortality

- Renal disease
  - Diabetes mellitus
- Medical history
  - COPD
  - Non-ambulatory
  - Coronary artery disease
  - Peripheral vascular disease
  - Congestive heart failure
  - Diabetes requiring insulin
  - Cerebrovascular disease
  - Smoker

Reduced mortality

- Renal disease
  - Hypertension
  - Glomerulonephritis
  - Polycystic kidney disease
- Medical history
  - Hypertension
  - Currently employed
- Non-caucasian ethnicity (e.g., Asian, Latin American, Black or Aboriginal)

CMAJ. 2010; 182(7): 666-72.

Differences in the transitions: Cardiovascular Disease

Characteristics of CVD

- CAD/MI
  - ALERT trial: fluvastatin reduced MI by 35%
    - No studies on specific targets (KDIGO = LDL <2.6)
  - ? Change immunosuppressants
  - DM (↑ risk if DM develops after transplant)
- LVH
  - CNI » sirolimus
  - ? BP
  - ? Anemia management
  - ? Ca/PO4 balance
- Stroke
  - ? BP

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Characteristics of CVD

- General ↑ CVD risk
  - Anemia
  - Hypertension
    - KDIGO goal <130/80
  - Proteinuria
    - ? ACEi/ARB
  - Obesity
  - Smoking
    - ? Smoking cessation

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Cardiovascular disease in kidney transplant recipients

- Different risk factors and CVD course than the general population
  - Framingham underestimates risk
    - Only adding renal function improved risk prediction
  - Smoking, ↑ BP, ↑ lipids: not independently associated with ↑ CVE
    - Does predict CVD history
- Disease burden is carried on from dialysis

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Cardiovascular disease in kidney transplant recipients

- Different risk factors and CVD course than the general population
  - CVE risk factors:
    - pre-existing cerebrovascular, peripheral-vascular and coronary heart disease;
    - male;
    - history of cancer;
    - DM;
    - BMI >35;
    - receiving a deceased donor kidney;
    - time on dialysis before transplant

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Cardiac Risk in Renal Transplant

Pre-transplant

- Age
- Diabetes
- Time on dialysis
- Smoking
- Pre-existing CVD

Post-transplant

- Immunosuppression
- Renal function
- LVH/anemia
- BP
- Lipids
- New diabetes (NODAT)

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Lancet. 2011; 378(9800): 1419-27. / Transplant International. 2010; 23(12): 1191-1204.

Dyslipidemia

- Total cholesterol may increase by more than 25% after transplant
  - Steroids
  - CNI (CSA>TAC)
  - Sirolimus!
- Diagnosis
  - Chol > 5.2 mmol/L
  - LDL > 2.6 mmol/L » KDIGO target < 2.6
  - TG > 1.7 mmol/L » KDIGO target <5.65
  - HDL < 1 mmol/L

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Current Diabetes Reports. 2009; 9:305-311.

Dyslipidemia

- ALERT trial: fluvastatin 80mg daily x2 years
  - Reduction of MACE but not overall mortality
  - Supported early introduction of statins
  - No increase in ADE (LFTs/CK/myopathies)
- Statin metabolism decreased by cyclosporine and ?tacrolimus (statin levels increase 5-10x)
  - Start low and monitor

67 Current Diabetes Reports. 2009; 9:305-311. / Am J Transplant. 2005 Dec;5(12):2929-36. Current Pharm Design. 2006; 12: 4771-4783. / Cochrane Database Syst Rev. 2009 Apr 15;(2):CD005019.

Hypertension

- Pervasive
  - >90% kidney transplant recipients (>130/80)
- Immunosuppressant related
  - Steroids: sodium retention
  - CSA>TAC:
    - Vasoconstriction
- Other causes
  - Nephropathy (decreased GFR / RAAS)
  - Transplant renal artery stenosis

68 AJKD. 2011;57(2):331-41.

Hypertension

- Treatment
  - ? Lifestyle
  - CCBs
    - 154 hypertensive patients, studying LVH
      - Lisinopril vs. nifedipine: both equally effective for BP/LVH
      - Possible nifedipine benefit on GFR (counters CNI vasoconstriction)
    - Non-DHP CCB: interaction with CSA/TAC
      - Often used intentionally for CSA/TAC dosage reductions
  - ACEi/ARB
    - Potential to worsen GFR, exacerbate ↑ K+, potentiate anemia
    - Reduces proteinuria and BP
    - Quinapril vs. atenolol: improved LVH
    - Valsartan: ↓ SBP by 12 mmHg (at 8 weeks)
- Outcomes
  - Observational database study (N=24,404)
    - SBP reduced to <140 = ↑ transplant survival
    - SBP lowering = ↑ patient survival (if <50 yr old)

69 AJKD. 2011;57(2):331-41. / Transplant. 2001;72(1):107-11.

Differences in the transitions: Anemia

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Post-transplant Anemia

- Renal anemia should resolve with a new kidney, but…
  - Immunosuppressants (direct bone effects)
    - Azathioprine, mycophenolate, sirolimus
  - Frequently of blood draws in the first 1-2 months
  - ACEi/ARB
  - Renal dysfunction
  - Cotrimoxazole
  - Valganciclovir
  - CMV infection

71 Transpl Rev. 2010; 24: 89-98.

Post-transplant Anemia

- No Hgb targets or treatment preferences in the literature
- KDOQI/KDIGO recommendations (CKD)

72 Transpl Rev. 2010; 24: 89-98.

Post-transplant Erythrocytosis

- Hct > 51%
  - ~ Hgb 170 g/L
  - Occurs in ~10% of patients (2-25%)
- Newly transplanted kidney
  - EPO production peaks ~ day 3
  - New reticulocytes form ~ day 7
  - Anemia correction in ~ 3 months
- Proposed mechanism
  - Native kidneys don't respond to normal feedback
  - Continued EPO production
    - "Tertiary hypererythropoietinemia"
- Treatment
  - ACEi/ARB
  - Phlebotomy

Kid Int. 2003; 63: 1187-1194.

Differences in the transitions: Bone Metabolism

Bone disease after transplant

- Calcium-phosphate balance and PTH often normalize within 1 year after transplant
  - Occasional failure of parathyroid gland size to resolve
  - PTH may remain elevated in ~25% of recipients after 1 year
- Increased fracture rates after transplant
  - Increase in fractures vs. dialysis patients
  - 2 - 20% of transplant recipients experience a fracture in the first 3 years
    - Increased mortality after hip fracture
- Hypercalcemic hyperparathyroidism bone disease
  - Potential for either increased and decreased bone turnover
    - ↓ing Ca/PTH could worsen low-turnover disease

1) Transplant Proc. 2010; 42: 1148-55. / 2) AJT. 2007; 7: 2515-21. / 3) Nephrol. 2009; 14:437-442.

Bone metabolism

- Primary hyperparathyroidism
  - Often related to adenomas
- Secondary hyperparathyroidism
  - Common in CKD/ESRD
  - Response to ↑ PO_4, ↓ Ca or ↓ vitamin D
- Tertiary hyperparathyroidism can occur
  - Hyperplasia/hypertrophy of parathroid glands
  - Autonomous PTH production (exacerbates ↑ Ca)
  - Despite normal renal function

Risk factors

Pre-transplant Risk Factors

- Tertiary HPT
  - Prolonged dialysis
  - High PTH, Ca, P, Alk Phos
  - Large glands on U/S
- Transplant bone disease
  - Adynamic bone disease
  - Malnutrition
  - Hypogonadism

Post-transplant Risk Factors

- Tertiary HPT
  - Level of graft function
  - Steroids
  - Low vitamin D3 and calcitriol levels
  - Decreased expression of vitamin D and calcium sensing receptors in PTH glands
- Transplant bone disease
  - Persistent HPT
  - ↑ Ca, ↓ PO_4
  - Immunosuppressants
  - Renal function/metabolism acidosis

Transplant Proc. 2010; 42: 1148-55.

Treatment of bone disease

- Vitamin D and bisphosphonates improve BMD
  - No data for changing fracture rates or mortality
- Risk for low-turnover bone disease
  - Targeted bisphosphonate therapy
    - Osteoporosis on BMD
    - Vertebral fractures
- KDIGO
  - Follow recommendations for CKD
    - Correct Ca / PO_4 abnormalities
    - BMD in CKD1-3
- KDOQI
  - BMD at month 0-3, 1 year, 2 year
  - Use bisphosphonate if BMD T-score < -2

Immunosuppressants Before and After Transplant

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Pre-transplant Immunosuppression

- Tacrolimus IR (Prograf®)
  - Started ~1 week prior to living donor transplant
  - Allows for dose titration and achieving therapeutic drug levels
    - Some immunosuppression is achieved prior to transplant surgery

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Post-transplant Immunosuppression

- Goal to avoid antibody development and rejection
  - Non-functioning kidney tissue can remain immunogenic
  - 'Rejection' symptoms ('graft intolerance syndrome')
    - Pain/tenderness at transplant graft site
    - Systemic reactions (fever, malaise)
  - Potential to preserve residual renal function
  - Minimize antibody formation

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Post-transplant Immunosuppression

- Tapering is usually outlined in the nephrologist's transfer case summary
  1. Stop mycophenolate / azathioprine in ~2-4 weeks
  2. Then, taper CSA/TAC over ~2 months
  3. Then, taper steroid last

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Sem Dial. 2011; 24(3): 307-313.

Renal Transplant Clinic

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The numbers

- Manitoba kidney transplant recipients
  - ~50 new adult kidney recipients each year
  - ~2,000 hospital bed days
- Post-transplant clinic visits
  - 550 – 600 actively followed patients
  - ~5,000 clinic visits annually
  - Monday – Friday mornings (~25-30 patients/clinic)
    - Bloodwork reviewed for that day's clinic each afternoon
    - Medication changes: prescriptions sent/patient's phoned

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Renal transplant pharmacist

- Meet with scheduled transplant recipients prior to transplant
  - Review of immunosuppressants, typical post-transplant course and complications
  - Review medication coverage (with social worker)
- Discharge medication reconciliation
  - Minimal inpatient involvement
- Meet with selected patients in follow-up clinic
  - Nurse identified issues (often non-transplant – DM, BP, cholesterol, ED, bone health, depression, HRT, smoking cessation, herbal use, pain management…)
- Liaise with consultants about drug therapy
- Organize prescription refills and narcotics

Renal transplant pharmacist

- Teaching
  - Pharmacists
  - Students and residents
  - Nurses
- Research
  - Personal (e.g., survey of Canadian transplant pharmacist roles and practices)
  - Program (e.g., Simulect®/Advagraf®)
- Maintain knowledge
  - Keep up on current practice trends, medications and innovations
  - Be knowledgeable about media health reports

Transplant Clinic Team

- A dedicated team follows kidney transplant recipients for as long as their kidney lasts
  - Physician, nurses, pharmacist, dietitian, social worker
  - You should never need to adjust immunosuppressant doses or interpret blood level results on your own
- Please call the transplant care provider/team if you have questions about a mutual patient or plan to start/stop any medications

Questions?

Please contact me:

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