

Long-Term Management of Kidney Transplant Recipient

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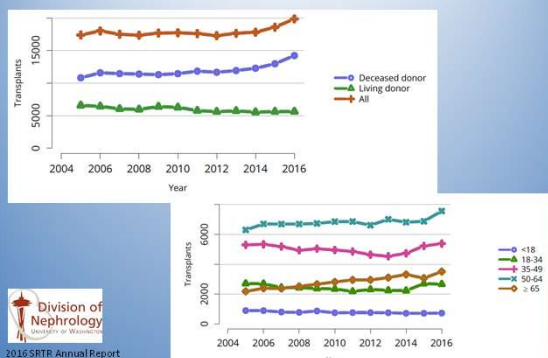
Disclosures

- Nothing Relevant to Disclose

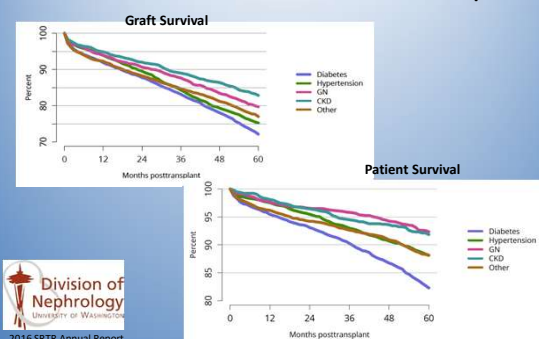
Objectives

- Describe common late post-transplant complications and how to respond to each.
- Identify common transplant-related drug interactions.
- Understand and apply cancer surveillance and prevention in kidney transplant recipients.

Increasing Kidney Transplant/Yr & Age



Graft & Recipient Survival after 2011 Deceased Donor Transplant



Long term management of transplant recipient

- Graft function
- Side effects Medications
 - Infection
 - Cancer
- Cardiovascular
 - HTN
 - Hyperlipidemia
- Diabetes
- Metabolic
 - Ca, PTH
 - Hyperuricemia
 - Obesity
- Hematologic
 - Anemia
 - Cytopenia
 - Erythrocytosis
- Bone Mineral Metabolism
- Reproductive health
- Neuropsychiatric

Case #1

- Mr H is a 67yo man with type 2 DM, HTN and CAD who developed ESRD 2 years ago. He required CABG and had a prolonged recovery. Finally, he is strong enough to be evaluated for kidney transplant.
- What information does the transplant center need to initiate a transplant evaluation?

Pre-Transplant Evaluation

Guided by Pre-Transplant Coordinators

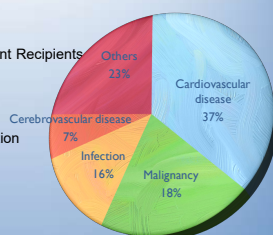
- Cardiovascular Health & Screening
 - Cardiac stress test/Cardiac Catheterization
 - Echocardiogram
- Health Maintenance Screening
 - Age-appropriate cancer screening
 - Dental evaluation/care
 - PPD, Labs

• In Person Evaluation

- Nephrologist
- Surgeon
- Psychologist
- Social Worker
- Dietitian
- Financial Counselor

Contemporary Background

- > Risk of CVD & Cancer in Transplant Recipients
- > CVD & Cancer in CKD and ESRD
- > CVD & Cancer in General Population
- > Aging population



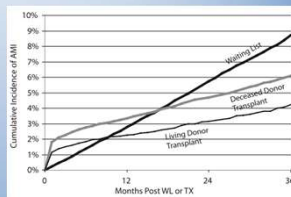
Cause of Death after Renal Transplantation



Adapted from Reza Abdi
Neph Dial Transplant. 2001;16

Cardiovascular Disease

- Most common cause of renal graft loss is death with a functioning graft
 - CV events: CHF, MI, CVA, Arrhythmias
 - CV events 3-5%/year (fatal and non-fatal), 20x general population, and 30% of all deaths
 - Cancer (18% of deaths)
 - Infections (16% of deaths)



Kasiske B, et al. JASN 2005

Post-Transplant Care

- Mr. H receives a living donor transplant from his wife, does well post-op and is discharged on POD4.
- Meds: Tacrolimus, Mycophenolate, prednisone, lantus insulin, atorvastatin, ASA, metoprolol, TMP-SMX, clotrimazole and Valganciclovir
- He has clinic appts 2x/week, and returns to transplant clinic 2 weeks post-transplant.

Transplant Medications

- Immunosuppression Options
 - Induction
 - Antithymocyte globulin (ATG)
 - Basiliximab (IL-2r antagonist)
 - Solu-medrol
 - Maintenance
 - Tacrolimus (Prograf;CNI)
 - Cyclosporine (Neoral;CNI)
 - Mycophenolic acid (Myfortic; MPA)
 - Mycophenolate mofetil (Cellcept; MMF)
 - Prednisone (Or Steroid-Sparing)
 - Sirolimus or Everolimus
 - Belatacept (CNI-Sparing)
- Infectious Prophylaxis Options
 - PCP Prevention (x6 mos)
 - TMP-SMX (Bactrim SS)
 - Dapsone
 - Pentamidine
 - CMV Prevention (3-6 mos)
 - Valganciclovir
 - Acyclovir
 - Mucocutaneous Candida Prevention (3 mos)
 - Nystatin
 - Clotrimazole

Lab results

- Scr 1.4 mg/dl (declining)
 - Hgb 12.2 g/dl
 - K 6.1 meq/L
 - Glucose 324mg/dl
 - All other labs normal
- What are the potential causes of the hyperkalemia?
 - A. Tacrolimus
 - B. TMP-SMX
 - C. Hyperglycemia
 - D. Mycophenolate

Lab results

- What are the potential causes of the hyperkalemia?
 - A. Tacrolimus
 - B. TMP-SMX
 - C. Hyperglycemia
 - D. Mycophenolate
- What are the potential treatment options?
 - A. Decrease Tacrolimus, based on level
 - B. Discontinue TMP-SMX (*ONLY short-term*)
 - C. Insulin
 - D. Kayexelate
 - E. Lasix (Try to avoid)

Clinic Evaluation

- He returns to clinic at 3 weeks feeling well.
- His BP is 176/98.
- Serum Creatinine 1.2mg/dl;
- K 5.1, Hgb 12.8, Glucose 121

What medication would you initiate for hypertension?

Transplant team maximized his metoprolol, but his BP remains 160s/80s. What medication would you start next? What would be a good second choice?

- A. Amlodipine
- B. Lisinopril
- C. Verapamil
- D. Diltiazem
- E. Furosemide

What medication would you initiate for hypertension?

- A. Amlodipine:** Minimal drug interaction (P-450), possible LE edema
- ~~B. Lisinopril:~~ Avoid early (<30days) use 2/2 K/Scr
- ~~C. Verapamil:~~ Inhibits P-450, raises CNI levels
- ~~D. Diltiazem:~~ Inhibits P-450, raises CNI levels
- ~~E. Furosemide:~~ Risks volume depletion

Continued Care...

- His BP improves with amlodipine, though requires maximized dose. Next medication of choice is lisinopril based on comorbidities, though his K is persistently 5.0-5.5. What can be done?

Continued care...

- Please call Transplant team to discuss options
 - Use of low-dose ACEi with strict low K diet
 - Change Bactrim to Dapsone/Pentamidine or early D/C
 - Use of alternative antihypertensives, including thiazide or alpha antagonists

Cardiovascular risk (CHF>AMI)

- Increased in ESRD
 - 'Framingham risk factors' (HTN, smoking, age)
 - HTN, lipids, ECV excess, oxidative state, hyperPTH
- Evidence of decreased CVD after transplant?
 - Role of HTN, lipid treatment
 - Drug interactions with statins etc.

Mechanisms of HTN post transplant

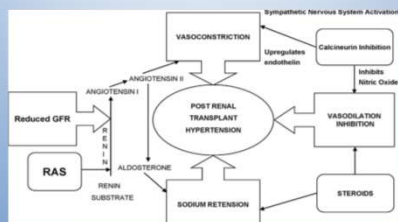


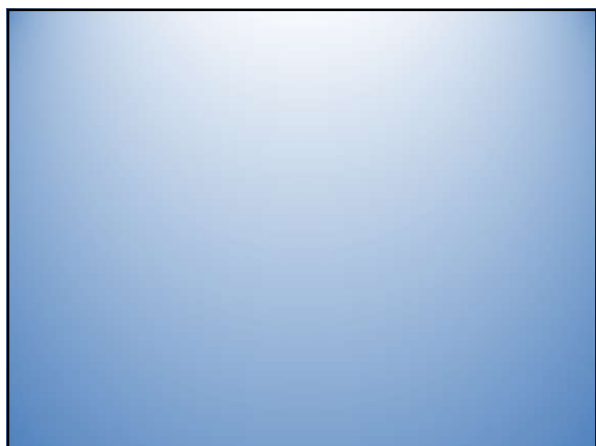
Figure 16. Mechanisms by which hypertension after kidney transplant is mediated. A complex interplay exists resulting from decreased GFR, vasoconstriction, and sodium retention that are variably adversely affected by immunosuppressive agents. RAS, Renin-angiotensin system. Reprinted with permission from Mangray M, Vella JP. Hypertension after kidney transplant. Am J Kidney Dis 57: 331–341, 2011.

HTN treatment in transplant patients

- **Goals** extrapolated from CKD literature; tighter control in those with proteinuria or DM.
- **Calcium channel blockers:** Pros: may mitigate CNI vasoconstriction; Cons: edema, reflex tachycardia
- **ACE-I, ARB:** Pros: benefit proteinuria, DM; may downregulate TGF- β ; Cons: hyperkalemia, elevation of creatinine
- **Diuretics:** Cons: may exacerbate electrolyte abnormalities, hyperuricemia, metabolic syndrome, volume depletion.

Metabolic issues contributing to CV risk

- **Obesity**
 - Weight gain common after transplant, not only 2/2 steroids
 - Effect on outcomes not clear; waist/hip ratio may be more important than BMI
- **Diabetes (CVD equivalent):** CNI (Tacro>CsA), steroids cause insulin resistance
 - Risk groups: older >50, BMI>25, AA or Hispanic, FH, HCV
 - Hyperglycemia early post transplant with high dose steroids
 - NODAT in 4% without, 18% with but not needing insulin, 30% of those requiring insulin.



Case #2

- Mrs. D is a 62yo woman with history of IgA nephropathy and underwent a deceased donor kidney transplant in July 2012.
- Meds: Tacrolimus, MMF, prednisone, atorvastatin, metoprolol, amlodipine

Case #2 cont...

- She returns to your clinic in January reporting bilateral proximal muscle aches and weakness.
- She tells you that she's really enjoying the Grapefruit (2x/day) from Texas that her friends brought back.

Case #2, cont...

- What is the likely diagnosis?
 - A. Musculoskeletal spasm
 - B. Polymyalgia rheumatica
 - C. Rhabdomyolysis
 - D. Viral myopathy

Case #2, cont...

- What is the likely diagnosis?

A. Musculoskeletal spasm

B. Polymyalgia rheumatica

C. Rhabdomyolysis

D. Viral myopathy

Grapefruit impairs P450 metabolism of atorvastatin and tacrolimus leading to risk of rhabdomyolysis.

Case #2, cont...

- What labs should you consider checking now?

A. Liver function tests (LFTs)

B. Basic metabolic panel (BMP)

C. Complete blood count

D. LFTs and BMP

Case #2, cont...

- What labs would you consider checking now?

A. Liver function tests (LFTs)

B. Basic metabolic panel (BMP)

C. Complete blood count

D. BMP and LFTs

Case #2, THP

- Grapefruit juice inhibits tacrolimus metabolism, leading to increased risk of AKI.
- Atorvastatin (especially with MMF) has increased risk of hepatitis

Case #2, cont...

- ALT/AST in 400s.
- BMP revealed a Serum Creatinine 4.3mg/dl, tacrolimus trough level is 19ng/ml.
- You discontinue the atorvastatin and consider what to do about the AKI and rhabdomyolysis treatment.

Case #2, cont...

- What are the best next steps?
- A. Admit the patient to local hospital and initiate IVF
- B. Send the patient home, and instruct them to call the transplant center
- C. Call the transplant center and discuss care plan
- D. Discontinue tacrolimus, and prescribe 4L H2O over next 24hrs

Case #2, cont...

- What is the best next step?
- A. Admit the patient to the hospital and initiate IVF or
- B. Send the patient home, and instruct them to call the transplant center
- C. Call the oncall transplant nephrologist to discuss care plan
- D. Discontinue tacrolimus, and prescribe 4L H₂O over next 24hrs

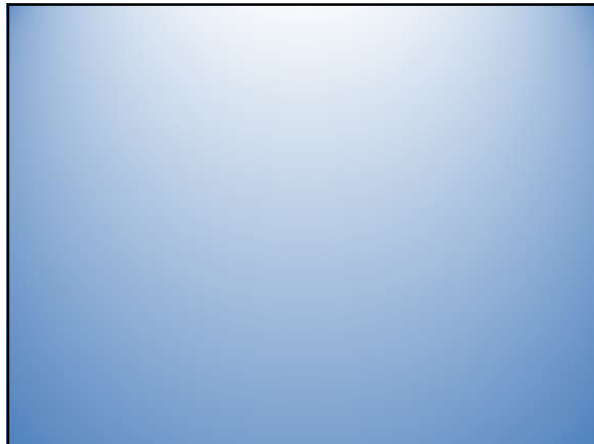
Case #2, THP

- We always welcome your phone call
- Low-dose statins (5-20mg) are commonly tolerated when used without other strong P450 inhibitors:
 - Gemfibrozil
 - Diltiazem, verapamil
 - Ketoconazole, other azoles
 - Grapefruit/Grapefruit Juice
- Pravastatin is a choice statin for new need

Table 6. Effect of Selected Drugs on Calcineurin Inhibitor Concentrations

Concentrations increased by ¹⁸⁵	Concentrations decreased by ^{155,188}
Macrolide antibiotics	Anticonvulsants (phenobarbital, phenytoin, carbamazepine)
Calcium channel blockers (Diltiazem, verapamil)	Rifampicin
Triazole antifungals	Dexamethasone
Protease inhibitors	St John's Wort (used for depression)
Amlodarone	Marijuana
Metoclopramide	Orlistat
Grapefruit juice	Octreotide
Ciprofloxacin	
Selective serotonin reuptake inhibitors (SSRIs)	

Gupta G, et al. JGIM 2010



Case #3

- Mr. S is a 52 yo man with history of Autosomal Dominant Polycystic Disease who underwent a deceased donor kidney transplant 5 years ago, baseline Scr 1.3mg/dl.
- He presents to your clinic with unilateral flank pain and hematuria lasting 5 days.
- He has been taking Ibuprofen 600mg every 4 hours without improvement

Case #3, cont...

- Which of the following would you order as part of his evaluation?
- A. CT-abdomen/pelvis with/without contrast
- B. Urinalysis with microscopy
- C. Basic Metabolic Panel & CBC
- D. Tacrolimus 12hr trough level
- E. Urine Culture
- F. CT-abdomen, stone protocol (without contrast)

Case #3, cont...

- Which of the following would you order as part of his evaluation?

- A. ~~CT-abdomen/pelvis with/without contrast~~
- B. Urinalysis with microscopy
- C. Basic Metabolic Panel & CBC
- D. Tacrolimus 12hr trough level
- E. Urine Culture
- F. CT-abdomen, stone protocol (without contrast)

Case #3, THP

- A. ~~CT-abdomen/pelvis with/without contrast~~
Please contact Transplant Center/Assigned Transplant Nephrologist when considering use of IV contrast

Case #3, cont...

- You find that he has a UTI: >100k cfu *Enterococcus faecalis*, and stone-protocol CT only shows multiple bilateral native kidney cysts without evidence of stone.
- Serum creatinine is 2.5mg/dl (baseline 1.3mg/dl)

Case #3, cont...

- What are your best next steps?
- A. Treat UTI with Bactrim x3 days
- B. Treat UTI with Erythromycin x12 days
- C. Discontinue NSAIDs
- D. Treat UTI with Ciprofloxacin x 14 days
- E. Recheck BMP at end of UTI treatment

Case #3, cont...

- What are your best next steps?
- ~~A. Treat UTI with Bactrim x3 days~~
- ~~B. Treat UTI with Erythromycin x12 days~~
- C. Discontinue NSAIDs
- D. Treat UTI with Ciprofloxacin x7-14 days
- E. Recheck BMP at end of UTI treatment

Case #3, THP

- Avoid NSAIDs, with potential use upon discussion with transplant center
- Erythromycin (macrolide) inhibits P-450, raises CNI (cyclosporine/tacrolimus) levels

Case #3, THP

- While good for UTI/pyelonephritis, Bactrim can raise Scr through impaired tubular secretion and/or AIN, so would choose to avoid if able
- Urinary Tract Infections are always complicated UTIs in transplant recipients, so treat for at least 7-14 days

Case #3, cont...

- Mr. S returns to clinic 2 weeks later feeling well, with resolved hematuria and flank pain.
- Repeat Urine Culture is negative & Scr 1.2mg/dl
- He asks whether he should be on long-term suppressive antibiotics AND
- His daughter has chicken pox and wonders if he should receive the VZV vaccination and annual influenza vaccination

Case #3, THP

- First time UTI/pyelo episodes can be treated in isolation
- Repeat UTI/transplant pyelonephritis should be evaluated by urology or transplant ID
 - Urodynamics
 - Imaging
- Long-term suppressive antibiotics are avoided unless patient has clinically significant recurrent infections, including discussion with Transplant Center

Case #3, THP

- Transplant Recipients vaccine advice
 - Yearly flu vaccines for patient, family members and close contacts
 - Tetanus (Td) every 10 years after Tdap administration
 - Pneumococcal 5 years after last dose and at the age of 65
- **All Live vaccines (including Zostavax, MMR and Flumist) are contraindicated after a transplant.**
- **Avoid Shingrix in OTRs because of increased rejection**
- Prior to traveling outside of the United States, please have the patient call Transplant Program, and possibly see Transplant ID to be assessed for appropriate vaccinations and prophylactic antibiotics.

Post-Transplant Vaccine Guide

SAFE VACCINES

COMMON

- Hepatitis A
- Hepatitis B
- Combined Hepatitis A & B: (Twinrix)
- Influenza (Injection)
- Pneumococcal: Pneumovax 23, Prevnar13
- Tetanus with Pertussis: Tdap
- Tetanus & Diphtheria: Td

UNCOMMON

- Haemophilus (Hib)
- Human Papillomavirus (HPV)
- Japanese Encephalitis
- Meningococcal: Menactra, Menveo, Bexsero, Trumenba
- Polio (Injection)
- Rabies
- Typhoid (Injection)

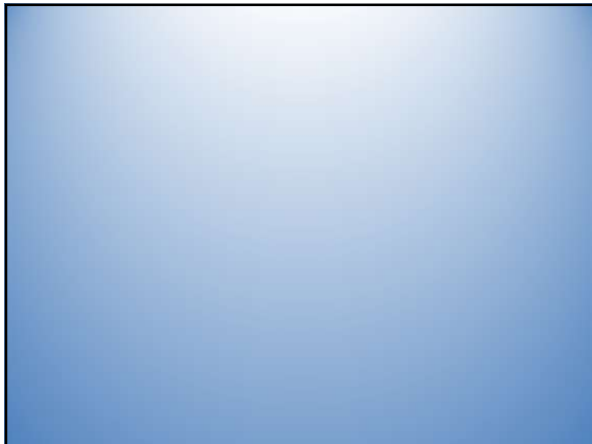
NOT SAFE VACCINES

COMMON

- Measles, Mumps, Rubella: MMR
- Shingles: Zostavax, Shingrix
- Varicella: Varivax
- Influenza as **Nasal Spray: LAIV**

UNCOMMON

- Typhoid (Oral)
- Yellow Fever



Case #4

- Mr Z is a 72yo male who received a living donor kidney transplant 28 years ago for Membranous Nephropathy.
- He has stable, excellent allograft function (Scr 1.2mg/dl) on cyclosporine, azathioprine and prednisone
- He presents to your clinic with multiple actinic keratoses, basal cell and squamous cell carcinomas of the skin

Case #4, cont...

- Your best next steps are:
 - A. Treat the AKs, SCC and BCC yourself
 - B. Refer to dermatology for evaluation and treatment
 - C. Provide sun-exposure education in light of his increased skin cancer risk
 - D. Change the patient's immunosuppression to decrease his future risks

Case #4, cont...

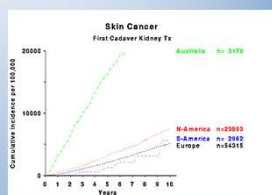
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 - D. Change the patient's immunosuppression to decrease his future risks

Case #4, THP

- Kidney transplant recipients are at 10-20x higher risk of skin cancer than general population
- Azathioprine/mycophenolate increases risk
- Sirolimus can decrease risk of SCC/BCC
- Sun protection and avoidance is critical
- Annual dermatologic evaluation is recommended

Skin cancer

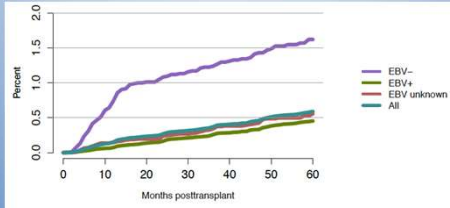
- Squamous cell CA: 100x gen pop
 - Don't forget about lip/vulvar/cervical CA
- Basal cell CA
- Risk factors: age, prior skin CA, caucasian, red hair
- SUNSCREEN, hats etc.
 - Don't forget about the lips/scalp/ears
- Regular (q6-12mos) dermatology screening
- Treat aggressively; ?immuno reduction



Cancer risk

- 10 year incidence of all de novo cancers in transplant recipients 2-4x general population
- “Move up” age related cancer risk by 10 years
- Risk related to immunosuppression, disruption antitumor, antiviral immune surveillance, and oncogenic viruses
- Skin cancer: SCC>BCC
- Lymphoma (PTLD) 1-3%
 - R EBV neg/D EBV pos higher risk

Incidence of PTLD in Adult Recipients, 2009-2013



Division of Nephrology

2015 SRTR Annual Report

Table 4. Risk of Selected Cancers in Subgroups of Transplant Recipients

	Cancer Site			
	Non-Hodgkin Lymphoma	Lung Cancer	Liver Cancer	Kidney Cancer
	Standardized Incidence Ratio (95% CI)			
Sex				
Male	7.11 (6.66-7.57)	1.92 (1.71-1.95)	10.78 (10.02-11.58)	4.39 (4.03-4.77)
Female	8.54 (7.62-9.32)	2.33 (2.12-2.56)	16.06 (13.89-18.50)	5.50 (4.77-6.30)
Age at transplant, y				
0-34	45.86 (41.54-50.51)	2.62 (1.26-4.63)	27.55 (18.16-40.09)	16.63 (12.60-21.55)
35-49	8.87 (8.02-9.79)	2.74 (2.41-3.11)	12.09 (10.53-13.81)	8.39 (7.45-9.41)
≥50	4.78 (4.43-5.15)	1.85 (1.74-1.96)	11.15 (10.35-12.02)	3.28 (2.97-3.62)
Transplanted organ				
Kidney	6.05 (5.59-6.54)	1.48 (1.34-1.59)	1.08 (0.80-1.43)	6.66 (6.12-7.23)
Liver	7.77 (6.99-8.61)	1.95 (1.74-2.19)	43.83 (40.90-46.91)	1.80 (1.40-2.29)
Heart	7.79 (6.89-8.79)	2.67 (2.40-2.95)	1.02 (0.54-1.74)	2.30 (2.32-3.59)
Lung	18.73 (15.99-22.32)	6.13 (5.18-7.21)	2.04 (0.66-5.22)	1.49 (0.64-2.94)

*Test of heterogeneity based on Poisson regression yielded P values of less than .001 for all of the comparisons in the category (eg, P < .001 for the comparison between male and female for non-Hodgkin lymphoma and cancers of the lung, liver, and kidney).

JAMA. 2011 Nov 2;306(17):1891-901.

Hematologic issues

- Anemia (up to 30% pts)
 - Bone marrow suppression due to immuno meds
- Inadequate endogenous Epo
- Hemolysis (CNI, dapsone, IVIg)
- Iron deficiency/GI blood loss
- Use of ESAs in transplant pts not well studied

Table 7. Hematologic complications of transplantation

Complication	Relationship
Anemia	Antibody induction therapy anticoagulation immunosuppression wTAR ACU/ARI Iron deficiency Dapsone IVIg (high dose/11) CNI/IVIg
Hemolysis	Absolute or relative endogenous erythropoietin causes Antibody-mediated antibody infection RBC anticoagulation immunosuppression Antifolate antibodies CNI
Posttransplant erythrocytosis	TPMS/MZ
Leucopenia	Cytoreductive therapy Antibody-mediated antibody infection RBC anticoagulation immunosuppression Antifolate antibodies CNI
Thrombotic microangiopathy	Cytoreductive therapy Antibody-mediated antibody infection RBC anticoagulation immunosuppression Antifolate antibodies CNI Pregnancy post transplantation

Hematologic issues

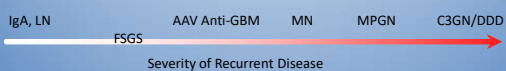
- Post transplant erythrocytosis (HCT>50)
 - Up to 15% of pts (SPK>KTR)
 - Rule out 3 causes: RCC, RAS, Jak mutation
 - Inappropriately high erythropoietin levels; higher AT1 receptors on RBCs
 - Risk of thrombosis (10-30%); HA, malaise
 - ACEI/ARB vs Phlebotomy

CKD in the renal allograft

- 'Chronic rejection' and Transplant Glomerulopathy (TG)
 - HTN, proteinuria, slowly increasing creatinine
 - Donor specific antibodies (DSA), Prior AR, subclinical rejection
- HTN, hyperlipidemia
- CNI nephrotoxicity
- Polyoma (BK) nephropathy
- Recurrent or de novo GN

Recurrent GN

- Four most common Recurrent GNs are
 - IgA Nephropathy
 - FSGS
 - Membranous Nephropathy
 - MPGN/C3GN



Bone disease

- Preexisting metabolic bone disease 2 ESRD:
- Low turnover, high turnover, mixed
- Can be up to 20-30% loss of bone density post transplant (first 6 months ?steroids)
- Higher fracture rate: hip, spinal
- Vitamin D, PTH, calcium intake, exercise
- Avascular necrosis: steroids

Reproductive issues - Women

- Sexual dysfunction can improve (women: menstruation, fertility)
- Pregnancy possible but wait for the right time:
 - Recommended wait >1-2 yrs, good graft function, no rejection
 - Need to take off teratogenic meds: MMF/MPA, ACEI, Leflunomide
 - High risk OB monitoring

Reproductive issues - Men

- Erectile dysfunction
 - Decreased testosterone
 - DM, PVD
 - BP meds, antidepressants
 - Role of sildenafil
- Adverse effect of mTOR inhibitors on sperm production

Neuropsychiatric Issues

- Depression and anxiety is common
 - Transition from dialysis is a true stressor
 - Carry-over mental illness, especially when transplant doesn't meet expectations
 - Need to remember about drug interactions CNI and antidepressants
- Can effect adherence

Adherence

- Daily challenge for ALL
- Greater challenge for:
 - Adolescents/Young Adults
 - Elderly
 - Pts with chronic illness
 - Pts on multiple medications

Long term management of transplant recipient

- | | |
|----------------------------|------------------------|
| • Graft function | • Hematologic |
| • Side effects Medications | – Anemia |
| • Infection | – Cytopenia |
| • Cancer | • Bones |
| • Cardiovascular | • Reproductive health |
| • HTN | • Neuropsych |
| • Hyperlipidemia | • Adherence/Compliance |
| • Diabetes | |
| • Metabolic | |
| • Ca, PTH | |
| • Hyperuricemia | |
| • Obesity | |

Resources

- My cell phone 734-972-4101
- University of Washington Medical Center Transplant Program
– 206-598-3882



Comments & Questions?