Caring for the Acutely Ill Kidney Transplant Recipient

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Disclosures

I HAVE NOTHING TO DISCLOSE.

Objectives

- Review immunosuppressive medications and common drug interactions and side effects related to these
- Discuss the evaluation and management of acute kidney injury in kidney transplant recipients
- Discuss the evaluation and management of common signs/symptoms and diseases in kidney transplant recipients that require hospital admission

Richard and Ronald Herrick

MAN'S LIFE SAVED BY TWIN'S KIDNEY

Identical Brother Furnishes Organ in First Successful Transplanting Surgery

December 23, 1954

Immunosuppression

- Induction Agents
  - Lymphocyte-depleting
  - Non-Lymphocyte depleting
- Maintenance Agents
  - Calcineurin Inhibitors
  - Purine Antagonists/Anti-metabolites
  - mTOR inhibitors
  - Co-stimulation blockers
- Adjunctive Agents

Induction Agents

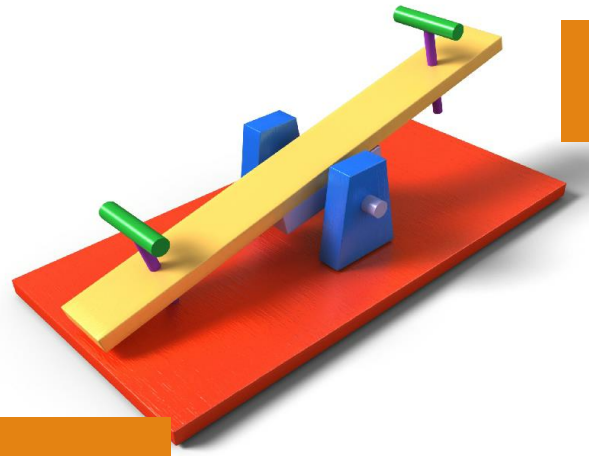
- Polyclonal Antibodies
  - Rabbit anti-thymocyte globulin (Thymoglobulin®)
  - Horse anti-thymocyte Globulin (Atgam®)
- Monoclonal Antibodies
  - Anti-CD3: Murumonab (OKT3®)*
  - Anti-CD52: Alemtuzomab (Campath®)
  - Anti-CD25/IL-2 Receptor: Basiliximab (Simulect®), Dacluzimab (Zenapak®)*

*no longer available

Maintenance Agents

- Calcineurin Inhibitors
  - Cyclosporine (Neoral®, Gengraf®, Sandimmune®)
  - Tacrolimus (Prograf®)
- Purine antagonists/Anti-metabolites
  - Azathioprine (Imuran®)
  - Mycophenolate Mofetil (CellCept®) or Mycophenolic Acid (Myfortic®)
- mTOr Inhibitors
  - Sirolimus (Rapamune®)
  - Everolimus (Zortress®)
- Prednisone
- Co-stimulation blocker
  - Belatacept (Nudjolix®)

Immunosuppression:
A balancing Act



Rejection

TOO LITTLE DRUG

Infection/Malignancy

TOO MUCH DRUG

NET STATE OF IMMUNO-SUPPRESSION

Target Levels

Time post-tx	Tacrolimus	CSA	Sirolimus
0-6 months	8-10	200-250	8-10
6-12 months	6-8	125-175	6-8
>12 months	4-6	75-100	4-6

Common side effects

- Calcineurin Inhibitors
  - Nephrotoxic
    - Acute: afferent arteriole constriction → “pre-renal”
    - Chronic: interstitial fibrosis and tubular atrophy
  - Non-Nephrotoxic
    - Cyclosporine: HTN, Hyperlipidemia, Hirsutism, Hyperuricemia, Gingival Hypertrophy
    - Tacrolimus: Neurotoxicity, Post-transplant DM, Alopecia, GI symptoms

Common side effects

- Mycophenolate
  - Bone marrow suppression (leukopenia)
  - GI symptoms: diarrhea, nausea/vomiting
- Azathioprine
  - Bone marrow suppression
  - Hepatotoxicity
- mTORs
  - Hyperlipidemia
  - Impaired wound healing, oral ulcers
  - Proteinuria
  - Pneumonitis
  - Bone Marrow suppression (thrombocytopenia, anemia)

Drug Interactions: CNI's and mTOR's

Will INCREASE levels	Will DECREASE levels
Diltiazem, Verapamil (not Amlodipine, Nifedipine)	Rifampin
Erythromycin, Clarithromycin (not Azithromycin)	Anti-convulsants (not levetiracetam)
Azoles (Ketoconazole > voriconazole > itraconazole > fluconazole)	St. John's Wort
Protease inhibitors	
Cimetidine (not Famotidine, Ranitidine)	
Amiodarone	
Grapefruit juice	

Other Drug Interactions to Remember

- CNI's + Statins, Fibrates → ↑ Rhabdomyolysis
- CNI's + NSAID's, ACE/ARB's → ↑ hemodynamic effects
- Azathioprine + Allopurinol → Bone Marrow Suppression (Azathioprine toxicity)

Key Points

- There are no fixed rules.
- Every patient is unique.
  - High-risk versus Low-risk: Race, HLA matching, History of rejection, Quality of Kidney
- Hepatic Metabolism. GI absorption.
- Lower dose if sick.
- FREQUENT CHANGES. FREQUENT MONITORING.

What causes AKI in a kidney transplant?

- PRERENAL → reduced kidney perfusion
- INTRA-RENAL → something going on inside the kidney
- POST-RENAL → obstruction

In formulating AKI differentials, remember, a kidney transplant is…

- A TRANSPLANT.
  - Rejection: Cellular, Antibody-mediated
  - Infection: BK nephropathy
  - Med side effects: CNI toxicity, thrombotic microangiopathy
- SOLITARY.
  - Obstruction
  - Renal Artery Stenosis
  - Renal Vein Thrombosis
  - Pyelonephritis
- A KIDNEY.
  - Disease Recurrence
  - Everything else!

Pre-renal AKI

- Cause is reduced kidney perfusion/blood flow
- Some examples
  - Volume depletion: diarrhea, bleeding, infection/sepsis, overdiuresis
  - Volume overload: heart failure, liver failure
  - Drugs: calcineurin inhibitors (FK, CsA), NSAIDs, IV contrast
  - Renal artery stenosis
- Work-up/intervention:
  - If dry: Hydration (not just water but also salt) or hold/reduce diuretics
  - If wet: diuresis
  - Adjust FK/CsA dose
  - Avoid nephrotoxic agents
  - Ultrasound (examining blood flow)

Post-renal AKI

- Cause is obstruction (site can be anywhere from bladder to kidney)
- Some examples
  - BPH
  - Neurogenic bladder
  - Stone
  - Ureteral stricture
- Work-up/intervention:
  - Ultrasound or CT scan → hydronephrosis
  - Foley catheter, percutaneous nephrostomy tube, ureteral reimplantation

Intra-renal AKI

- The problem is in the kidney (different parts of the nephron include the tubules, interstitium, small blood vessels, glomerulus)
- Some examples
  - Tubules: acute tubular necrosis (ATN)
  - Interstitium: pyelonephritis, acute rejection, BK nephropathy, interstitial nephritis from drug reaction/allergy
  - Small blood vessels: TMA
  - Glomerulus: glomerulonephritis, recurrent FSGS, etc
- Work-up/intervention:
  - Urinalysis
  - Serum BK
  - Donor specific antibodies (DSA)
  - Kidney biopsy

Key points

- Need to know what the baseline creatinine is. If the creatinine is higher than baseline → work-up for AKI.
- All hydration leads to a better creatinine, so need high index of suspicion for other non-prerenal causes.
  - Low threshold for additional testing
- Need to follow patients closely
  - Repeat creatinine
  - Repeat FK/CsA levels
  - Re-assess volume status

CASE 1

75/F s/p DDKT (2018), HTN and DM, admitted with abdominal pain, diarrhea, vomiting x 3 days

Meds include: tacrolimus, prednisone, lisinopril

Took Ibuprofen x 3 doses for pain

BP 90/60, HR 65, RR 18

Lab check: BUN 65 mg/dl, Creatinine 3.5 mg/dl (baseline 2.3 mg/dl two months ago)

Tacrolimus trough level= 18 (high)

CASE 1: Acute CNI Toxicity

- Afferent arteriole constriction leading to pre-renal picture and if prolonged, ischemic ATN
- Exacerbated by other hemodynamic factors:
  - Volume depletion, NSAID's, Amphoterecin, Hypercalcemia, ACE's/ARB's
- Usually reversed by decreasing drug levels

CASE 2

35/F with LRDKT (2019), baseline creatinine 1.3 mg/dL.

Recurrent UTI's

3 days of allograft pain, fever/chills, nausea/vomiting

UA: 100 WBC's, 1+ protein, 10 RBC's, numerous bacteria

Creatinine: 1.8 mg/dL

CASE 2: Pyelonephritis

- Can cause elevation in creatinine
- Empiric antibiotics based on previous cultures and sensitivities
- Imaging to look for abscess if persistently febrile or bacteremic
- 10-14 day course of antibiotics with repeat cultures after treatment
- Consider urologic work-up and additional imaging if recurrent

CASE 3

55/M, DDKT (3/2021), complicated by delayed graft function

Also with a history of a failed transplant and history of a high PRA.

Nadir creatinine 1.3 mg/dL.

On follow-up 4 months after transplant, creatinine 1.8 mg/dL.

UA with 2+ protein, negative blood, 5 WBC’s.

Case 3: Acute Rejection

- Acute Cellular Rejection
  - Treatment: high dose steroids ± anti-thymocyte globulin
- Acute Humoral (Antibody-mediated) Rejection
  - Treatment: IVIG ± plasmapheresis; some centers may add other agents such as rituximab, bortezomib, eculizumab
- Both

The Usual AKI Work-up:

1. Rule out anything anatomic.
   - Transplant Renal US with Doppler: hydronephrosis, RAS
2. Assess urinary sediment
   - Pyuria: Pyelonephritis, BK nephropathy, acute rejection, interstitial nephritis
   - Hematuria: GN, BK nephropathy, interstitial nephritis
   - Proteinuria: tubular, GN, acute rejection, transplant glomerulopathy*
3. Check CNI drug levels.
4. Check other markers.
   - Serum BK and donor specific antibodies
5. Assess and optimize volume status
   - Urine Na and FeNa may not be as helpful
6. Biopsy if diagnosis is unclear.

The Transplant Recipient: “Early” versus “Late” Phase

- “Early”: First 3 months
  - Peri-operative Risks and Complications
  - High Risk of Rejection → Increased Immunosuppression
  - High Risk of Infection → Prophylaxis
- “Late”: > 3 months onwards
  - Reduced Immunosuppression
  - Long-term effects of Immunosuppression

The Transplant Recipient…

…is immunocompromised.

- Med side effects, Infection and CA risk

…has Chronic Kidney Disease.

- CV risk, Bone Disease, Anemia, Metabolic and Volume abnormalities

…is a patient.

- Health Maintenance

Case 4: SOB, cough, pulmonary infiltrates

38/M, DDKT (2019), ADPKD, no issues posttransplant

Presents with worsening dry cough and SOB x 1 week, with associated temp of 101 at home

On presentation, BP 90/60, HR 120s, RR 24, Temp 99.4, O2 sat 94% on RA

Bilateral crackles without wheezing, no JVD or lower extremity edema

CXR with bilateral interstitial infiltrates

Case 4: SOB, cough, pulmonary infiltrates

- Differentials?
  - Bacterial and atypical pneumonia
  - Opportunistic Infections: PJP, CMV, Fungal
  - mTOR-induced pneumonitis
- Work-up?
  - If concern for atypical infection: obtain fungal serologies, CMV PCR
  - Consider CT Chest to look for loculated fluid collections, lymphadenopathy
  - Low threshold for bronchoscopy/BAL/biopsy

COVID-19

- Higher risk of death in transplant recipients thought to be due to comorbidities not immunosuppression per se
- Vaccine not as effective as in the general population (3rd dose of mRNA vaccine is recommended)
- Treatment
  - Monoclonal antibody for mild to moderate disease (usually outpatient)
  - Reduction in immunosuppression (usually the anti-metabolite) in hospitalized patients
  - Same indications for dexamethasone, remdesivir, tocilizumab as in the general population

Case 5: Diarrhea, Fatigue

68/F, LURD KT (2020), DM

Presents with on and off watery diarrhea x 3 months

Associated 20 lb weight loss and anorexia

Some improvement with reduction in mycophenolate dose

Afebrile, cachectic appearing, no abdominal tenderness

Creatinine 1.5 mg/dl (at baseline)

CBC normal

Case 5: Diarrhea, Fatigue

- Differentials?
  - Mycophenolate toxicity
  - Norovirus diarrhea
  - CMV Disease
  - Other opportunistic pathogens
- Work-up?
  - Empiric reduction of mycophenolate
  - Stool studies (norovirus PCR, GI pathogen panel, C. diff)
  - CMV PCR
  - Low threshold for Colonoscopy/EGD

Norovirus diarrhea

- Underrecognized cause of severe chronic diarrhea in transplant recipients
- Highly contagious
- Commonly associated with nausea/vomiting, abdominal pain and wasting
- Mean duration of symptoms prior to diagnosis: 4 months
- Relapses common
- Treatment
  - Nitazoxamide
  - Reduction in immunosuppression

Mycophenolate-related diarrhea

- Commonly associated with nausea and vomiting
- Esophagitis, colitis can be seen on EGD with very similar appearance to IBD
- Dose dependent
  - May respond to dose reduction

Case 6: Fever of Unknown Origin

68/M, DDKT (2019), complicated by acute rejection (2020), treated with steroids and anti-thymocyte globulin.

Presents with on and off fevers as high as 101 for the last 2-3 weeks

Associated anorexia, mild diarrhea, dry cough

On presentation, ill but non-toxic appearing

BP 110/60, HR 110s, RR 20, Temp 101, O2 sat 98% on RA

Lungs clear, abdomen soft/non-tender

WBC 2.5, Hgb 9, platelet 120; creatinine 1.9 mg/dl (baseline); AST and ALT 3 times upper limit of normal

CXR clear

Case 7: Fever of Unknown Origin

- A fever usually means something. Even a “low-grade temp”.
- Differentials?
  - Occult infection: bacterial, viral, fungal
  - Post-transplant Lymphoproliferative Disorder
  - Rejection rarely causes fever but can happen
- Work-up?
  - Low threshold for procedures and imaging
  - Low threshold for broad-spectrum antibiotics

Disseminated Histoplasmosis

- Infection with *Histoplasma capsulatum*
- Most common in the Midwestern states (Ohio and Mississippi River valleys)
- Symptoms: fever, fatigue, weight loss
- Signs: lymphadenopathy, altered mental status, skin lesions, diffuse interstitial infiltrates on CXR, elevated LFTs, splenomegaly/hepatomegaly, lesions on EGD/colonoscopy
- Diagnosis: urine histoplasma antigen ± serum histoplasma antigen; CT imaging to look for lymphadenopathy, infiltrates/nodules, etc.; lumbar puncture if with CNS symptoms
- Treatment:
  - Liposomal Amphotericin B (severe disease, CNS disease)
  - Itraconazole

Cytomegalovirus (CMV)

- Most common opportunistic Infection
- Increased in CMV IgG D+/R- transplants
- Mixed bag of ‘organ’-itis
  - Gastroenteritis/colitis, hepatitis, pneumonitis, nephritis
  - Leukopenia
  - Undifferentiated fever
- Diagnosis: CMV DNA Quantification (CMV PCR); at times, pathology (biopsy)
- Prophylaxis: Valganciclovir x first 4-6 months posttransplant
- Treatment: induction dose valganciclovir/IV ganciclovir for 3 weeks and negative PCR x 2, then maintenance valganciclovir dose (duration is variable)

Key Points

- High index of suspicion
- Atypical presentations are common
- Several disease processes may be going on
- Low threshold for additional imaging
- Low threshold for procedure (EGD, bronchoscopy, biopsy)

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Thank you!

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