Diagnostic Work-up of Renal Insufficiency in Solid Organ Transplant Recipients

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Objectives

• To differentiate Acute Kidney Injury (AKI) from Chronic Kidney Disease (CKD)
• To enumerate common causes of AKI in solid organ transplant (SOT) recipients
• To understand the role of different diagnostic tests in the work-up of causes of AKI in SOT recipients
• To enumerate common causes of CKD in SOT recipients
• To understand the utility of different diagnostic tests in SOT recipients with CKD
CASE 1: In your office

• 65/M with a history of kidney transplant in 2012, HTN and DM, just moved to Nashville, complaining of fatigue, nausea and vomiting.
• Lab check: BUN 75, Creatinine 3.8
THE DIAGNOSTIC APPROACH

• Acute, subacute or chronic ???
  • Baseline creatinine
  • Clinical elements of the case
    • Onset of symptoms
    • Urine output
    • Rate of rise of creatinine
  • Renal ultrasound: size and echogenicity of kidneys *
  • Anemia *
  • Hypocalcemia and hyperphosphatemia
CASE 1: In your office

• 65/M with a history of kidney transplant in 2012, HTN and DM, just moved to Nashville, complaining of fatigue, nausea and vomiting.

• Lab check: BUN 75, Creatinine 3.8

• Sudden decrease in urine output

• Hgb 13.1, Phos 3.5, Ca 10.2, iPTH 30

• Renal ultrasound: normal sized-kidneys with normal echogenicity

• Additional records: creatinine 1 month ago was 1.2
ACUTE KIDNEY INJURY

• Abrupt loss of kidney function
• Retention of urea and other nitrogenous waste products
• Dysregulation of extracellular volume and electrolytes
• Easily detected by measurement of the serum creatinine which is used to estimate the glomerular filtration rate (GFR) *
Defining AKI: RIFLE criteria

- RIFLE criteria

CLASSIFICATION OF AKI

Acute Kidney Injury

- Prerenal
- Intrinsic
- Postrenal
In formulating AKI differentials, remember, a **kidney transplant** is...

- **A TRANSPLANT.**
  - Rejection: Cellular, Antibody-mediated
  - Infection: Pyelonephritis, BK nephropathy
  - Med side effects: CNI toxicity, thrombotic microangiopathy

- **SOLITARY.**
  - Obstruction
  - Renal Artery Stenosis
  - Renal Vein Thrombosis

- **A KIDNEY.**
  - Disease Recurrence
  - Everything else!
Case 2: In the ER

- 75/M with a liver transplant and h/o prostate CA, complaining of decreased urine output x 3 days.
- Lab check: BUN 65, Creatinine 6.8 (baseline 1.2 a year ago)
- UA: pH 5.5, sg 1.010, 1 RBC, no protein
CLASSIFICATION OF AKI

- Prerenal
  - Obstruction from renal pelvis to urethra
  - Bilateral obstruction or unilateral with solitary functioning kidney
  - Increased pressure leads nephron destruction
  - Oliguria/anuria common
  - UA generally not helpful
  - Hydronephrosis on imaging

- Intrinsic

- Postrenal
CLASSIFICATION OF AKI

Acute Kidney Injury

- Prerenal
  - Prostate hypertrophy
  - Neurogenic bladder
  - Intraureteral obstruction – crystals (uric acid, acyclovir, indinavir), stones, clots, tumor
- Intrinsic
- Postrenal
  - Extraureteral obstruction – tumor (cervical, prostate), retroperitoneal fibrosis*
Make sure it’s not post-renal!

• Ask about...
  • Urine output?
  • Symptoms of obstruction?

• Then...
  • Insert Foley catheter
  • Get a renal ultrasound to assess for hydrenephrosis
Case 2: In the ER

- 75/M with h/o prostate CA, complaining of decreased urine output x 3 days.
- Lab check: BUN 65, Creatinine 6.8 (baseline 1.2 a year ago)
- UA: pH 5.5, sg 1.010, 1 RBC, no protein
- Foley catheter inserted
- Urine output of 5 liters in next 24 hours
- Creatinine down to 4.5 the next morning
Case 3: In the MICU

• 45/F with a lung transplant, complaining of fever and chills
• Lab check: BUN 80, Creatinine 3.3 (baseline 0.8 ten days ago)
• Given boluses of 0.9 normal saline, BUN/creatinine down to 60/2.5 the next morning
CLASSIFICATION OF AKI

Acute Kidney Injury

- Prerenal
- Intrinsic
- Postrenal

- Result of physiologic responses that lead to decreased kidney function
- Reduced renal perfusion
- Maximized renal compensation
- No tubular, interstitial or glomerular damage
- Bland UA
- Low urine Na, FE Na < 1%
CLASSIFICATION OF AKI

- **Acute Kidney Injury**
  - **Prerenal**
    - Volume depletion
      - Renal
      - Extrarenal
    - Hypotension
    - Cardiovascular
      - CHF
      - Arrhythmias
      - Acute MI
  - **Intrinsic**
  - **Postrenal**
    - Hemodynamic
      - IV dye
      - NSAIDs
      - Cyclosporine/tacrolimus
      - ACE-I/ARB
      - Amphotericin B
    - Hypercalcemia
    - Hepatorenal syndrome*
Case 5: In the Transplant Unit

- 75/F s/p Kidney Transplant (2002), HTN and DM, admitted with abdominal pain, diarrhea, vomiting x 3 days
- Meds include: prograf, prednisone, lisinopril
- Took Ibuprofen x 3 doses for pain
- BP 90/60, HR 65, RR 18
- Lab check: BUN 65, Creat 3.5 (baseline 2.3 two months ago)
- Prograf trough level=18
PRE-RENAL AZOTEMIA

PRE-RENAL AZOTEMIA

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 5: In the Transplant Unit

- Given 2 liters normal saline for volume depletion
- Lisinopril and prograf held
- Educated about avoidance of NSAIDS!
- Creatinine improved to 2.5 after 2 days
CLASSIFICATION OF AKI

Acute Kidney Injury

- Prerenal
- Intrinsic
- Postrenal

- Kidney itself is site of abnormality leading to decreased GFR
- Categorized anatomically by the area of the kidney parenchyma involved
- UA abnormal
CLASSIFICATION OF AKI

Acute Kidney Injury

- Prerenal
- Intrinsic
  - Glomerular
  - Vascular
  - Interstitial
  - Tubular
- Postrenal
INTRINSIC AKI

Glomerular

• Acute glomerulonephritis (IgA nephropathy, Post-Strep GN, MPGN, Lupus nephritis)
• Vasculitis (Wegener’s, microscopic polyangitis, Churg-Strauss)
• Goodpasture’s syndrome, anti-GBM disease
• Clinically...
  • nephritic syndrome → azotemia, hematuria, hypertension
  • active urine sediment → RBC casts
  • check C3, C4, ANA, ANCA, anti-GBM, cryoglobulins
  • kidney biopsy to confirm
INTRINSIC AKI

Vascular

- Renal infarction, renal artery stenosis, renal vein thrombosis
  - bilateral involvement
  - imaging to confirm
- Malignant hypertension, scleroderma renal crisis
- Atheroembolic disease
  - history of catheterization
  - livedo reticularis, Hollenhorst plaques in retina
  - eosinophiluria
- Thrombotic microangiopathy (TTP, HUS)
INTRINSIC AKI

• Interstitial
  • Acute Interstitial Nephritis – penicillins, cephalosporins, sulfonamides, ciprofloxacin, phenytoin, PPI’s, NSAIDS
  • Clinically...
    • fever, rash, arthralgia, eosinophilia
    • WBC’s and WBC casts, eosinophiluria
INTRINSIC AKI

- Tubular → Acute tubular necrosis (ATN)
  - ISCHEMIC – prolonged prerenal state, sepsis, systemic hypotension
  - NEPHROTOXIC – aminoglycosides, methotrexate, amphoterecin, cisplatin, myoglobin, hemoglobin, IV contrast
- Clinically...
  - renal tubular epithelial cells and granular muddy brown casts
  - bland urinary sediment
  - Fe Na > 2%
IT’S ALL IN THE UA!!!

• pH
• Specific gravity
• Blood
• RBC
• WBC
• Protein
• Granular casts
• Eosinophils
THE FeNa...

• Most accurate diagnostic test to differentiate prerenal disease from ATN
• Fe Na is high in ATN because of...
  • inappropriate sodium wasting due to tubular damage
  • appropriate response to volume expansion
• Difficult to interpret when patient is on diuretics
• Fe Urea < 35 % (prerenal), >50 % (ATN)
• Exceptions to the rule
  • Less severe post-ischemic ATN or ischemic with established ATN
  • ATN superimposed on chronic prerenal disease (cirrhosis, heart failure)
  • ATN due to radiocontrast media or heme pigments (myoglobinuria or hemoglobinuria)
  • Acute glomerulonephritis or vasculitis
  • Less severe acute interstitial nephritis, particularly if nonoliguric
  • Acute urinary tract obstruction (rare)
Causes of AKI in SOT (Kidney) Recipients

• POST-RENAL
  • Transplant ureteral stenosis
  • Bladder outlet obstruction (e.g. neurogenic bladder, urethral stricture)

• PRE-RENAL
  • CNI toxicity
  • Volume depletion
  • Hepatorenal syndrome
  • Cardiorenal syndrome
Causes of AKI in SOT (Kidney) Recipients

• INTRINSIC/”RENAL”
  • Acute rejection
  • BK nephropathy
  • Other viral infections: CMV, adenovirus
  • Prolonged CNI toxicity leading to ATN
  • Renal arterial/venous thrombosis
  • Thrombotic microangiopathy due to CNI’s
  • Recurrent GN (e.g. FSGS, MPGN, IgA nephropathy)
CASE 6

• 55/AA/M, DDKtx (3/2010), complicated by DGF.
• Also with history of failed transplant and history of a high PRA.
• Nadir creatinine 1.3 mg/dL.
• On follow-up 2 months after transplant, creatinine 1.8 mg/dL. UA with 2+ protein, neg blood, 5 WBC’s.
Case 6: Acute Rejection of a Kidney Transplant

- Acute Cellular Rejection
- Acute Humoral Rejection
- Both
T Cell-Mediated Rejection

- Stages:
  - Tubulointerstitial
  - Vascular
    - Intimal
    - Transmural

- Treatment:
  - High-dose steroids
  - +/- Biologic agents
  - Increasing maintenance immunosuppression
Antibody-Mediated Rejection

• Diagnosis:
  • Allograft Dysfunction
  • C4d positivity
  • Donor-specific Ab’s

• Treatment:
  • IVIG
  • Plasmapheresis
  • Rituximab
  • Thymoglobulin
  • Splenectomy
The Usual AKI Work-up:

1. Rule out anything anatomic.
   - Renal US with Doppler: hydronephrosis, RAS

2. Assess urinary sediment.
   - Pyuria: Pyelonephritis, BK nephropathy, Acute rejection, AIN
   - Hematuria: GN, BK nephropathy, AIN
   - Proteinuria: tubular, GN, Acute rejection, transplant glomerulopathy*

3. Check drug levels.
   - CNI toxicity.

4. Assess and optimize volume status.
   - Urine Na/FeNa may not be as helpful

5. Biopsy if diagnosis is unclear.
CKD in SOT Recipients

• Acute versus Chronic
  • Does the patient need a dual-organ transplant?
  • Should the patient be referred for kidney transplantation?

• Measurement of GFR
  • Cut-off values for lung, heart or liver transplants
  • Cut-off values for eligibility for kidney transplantation

• Etiology

• Management
How do you know it’s CKD?

- There is a good reason for CKD (e.g. longstanding DM/HTN).
- Sustained reduction in GFR (3 months)
- Urine sodium NOT low
- Proteinuria
- Ultrasound findings
  - Small kidneys
  - Echogenic kidneys
  - Cortical thinning
- Biopsy findings
  - Glomerulosclerosis
  - Tubular atrophy and interstitial fibrosis
Measurements of GFR

• Estimated GFR
  • Cockroft-Gault
  • MDRD
  • CKD-EPI

• Measured GFR
  • Creatinine clearance
    • 24-hour urine collection (24-hour creatinine to ensure adequate collection)
  • DTPA
Etiology of CKD in SOT recipients

• Diabetes
• Hypertension
• CNI toxicity
• Prolonged ATN
• Others:
  • Glomerular disease
  • ADPKD
Chronic Allograft Nephropathy

- Chronic rejection
  - Transplant glomerulopathy
- CNI toxicity
- BK nephropathy
- Diabetes
- Hypertension
- Others:
  - Recurrent Disease
  - De novo glomerulonephritis
  - Nephrocalcinosis
Management of CKD

• Treat underlying cause if possible.
• Blood pressure control, goal of at least <130/80
• Reduction in proteinuria with RAAS blockade
• Avoidance of nephrotoxic agents
• Avoidance of volume depletion and hypotension