

Introduction to Kidney  
Transplantation-2  
Evaluation of graft dysfunction

R. John Crew

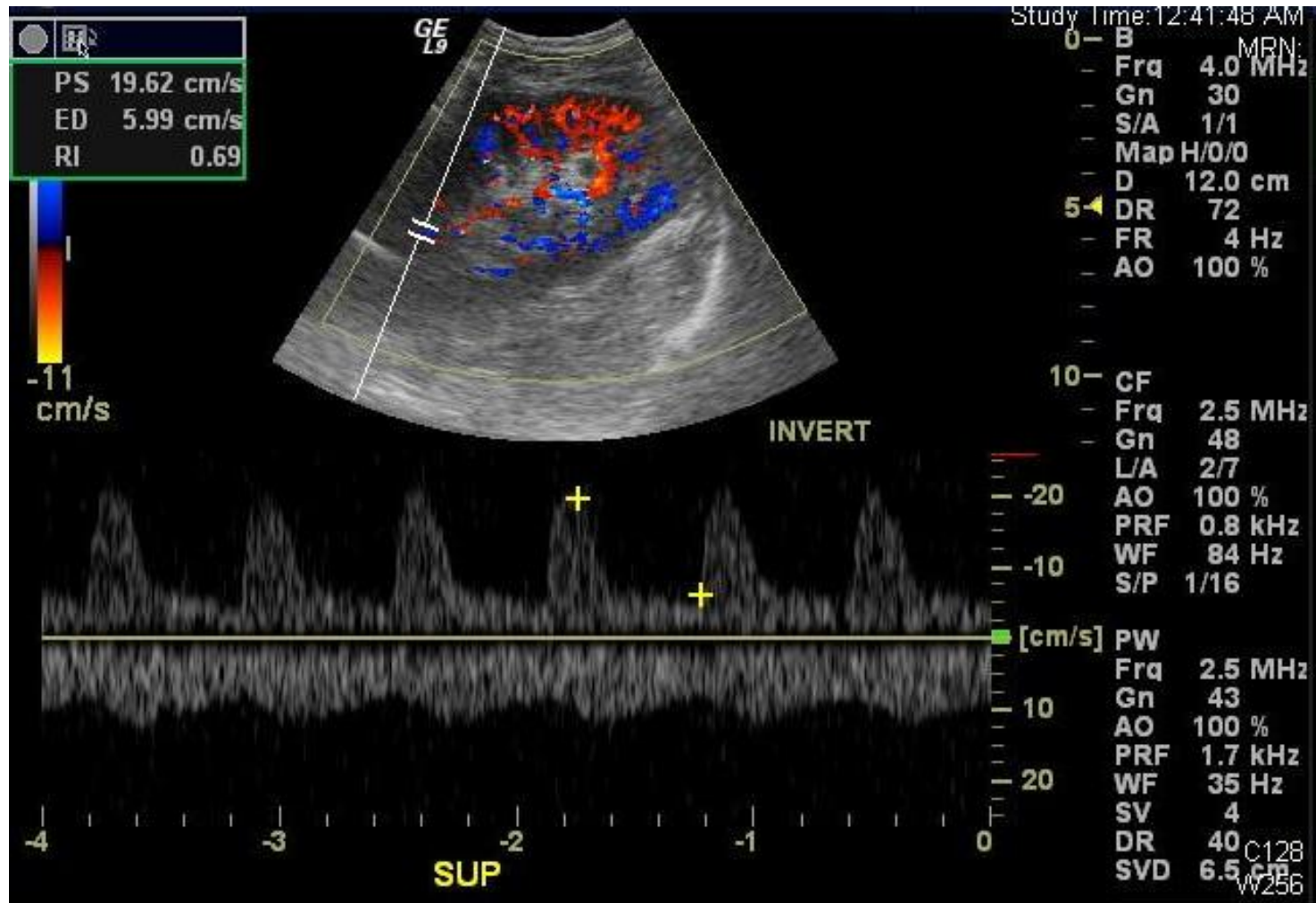
# Evaluation of Graft Dysfunction

- Differential dependent on time after transplant
  - Immediate (during hospital stay)
  - Short term (up to ~6 months)
  - Long term (beyond 6 months)
- Delayed graft function
  - Need for dialysis within 7 days of transplant for any cause (hyperkalemia, CHF, uremia)
  - Essentially ATN (ischemic injury, perfusion damage, reperfusion injury)
  - Long term impact debated

# Case 1

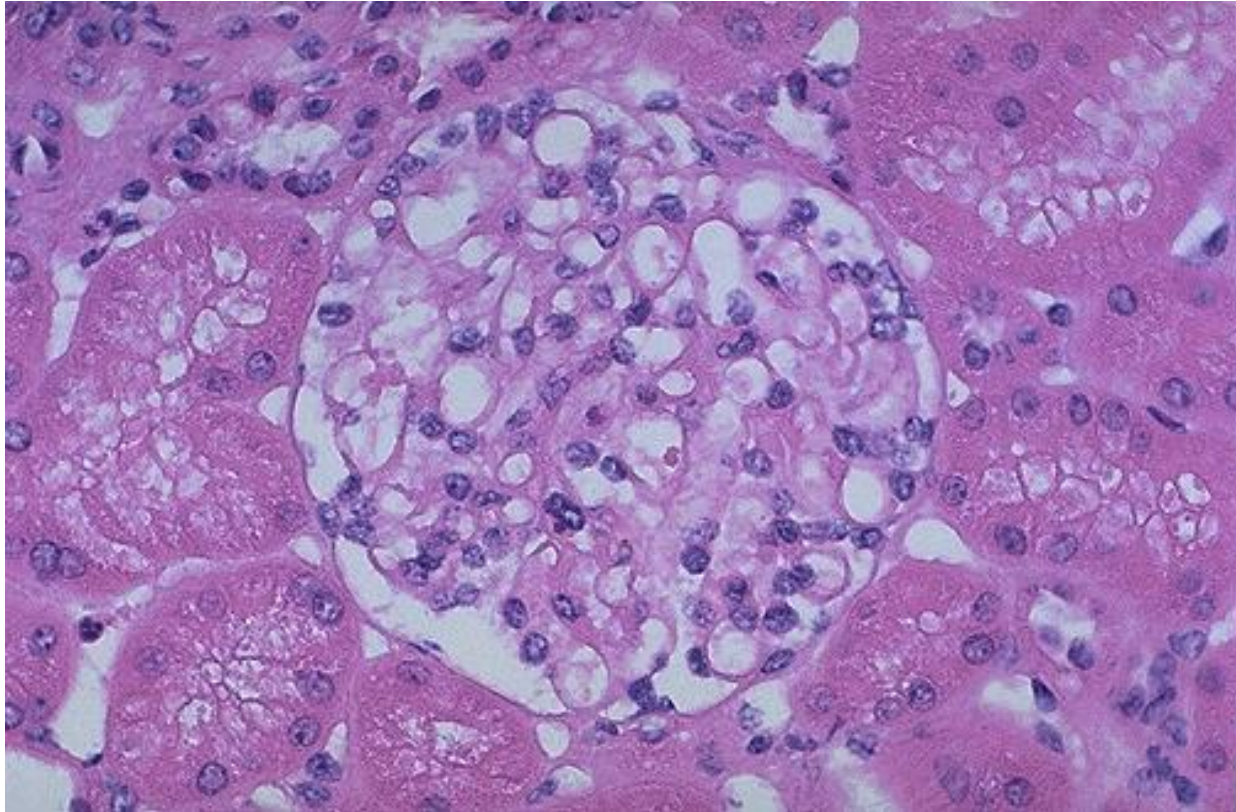
- 44 Caucasian with ESRD from IgAN
- 1<sup>st</sup> transplant 1993- failed due to chronic allograft nephropathy
- Pre-emptive 2<sup>nd</sup> transplant from brother
- Basiliximab induction, Rapamycin/Mycophenolate
- Moderate post-op pain and ileus but on IVF
- Creat 6.7 → 2.7 → 3.1 → 3.7
- UOP preserved, Rapamycin level 7
- What's wrong and what testing?

# Case 1: Renal Ultrasound



Excellent perfusion, no hydronephrosis, very small peritransplant collection

# Case 1: Renal biopsy



## Normal Kidney

N.B. Began oozing fluid through biopsy needle skin insertion point immediately after biopsy

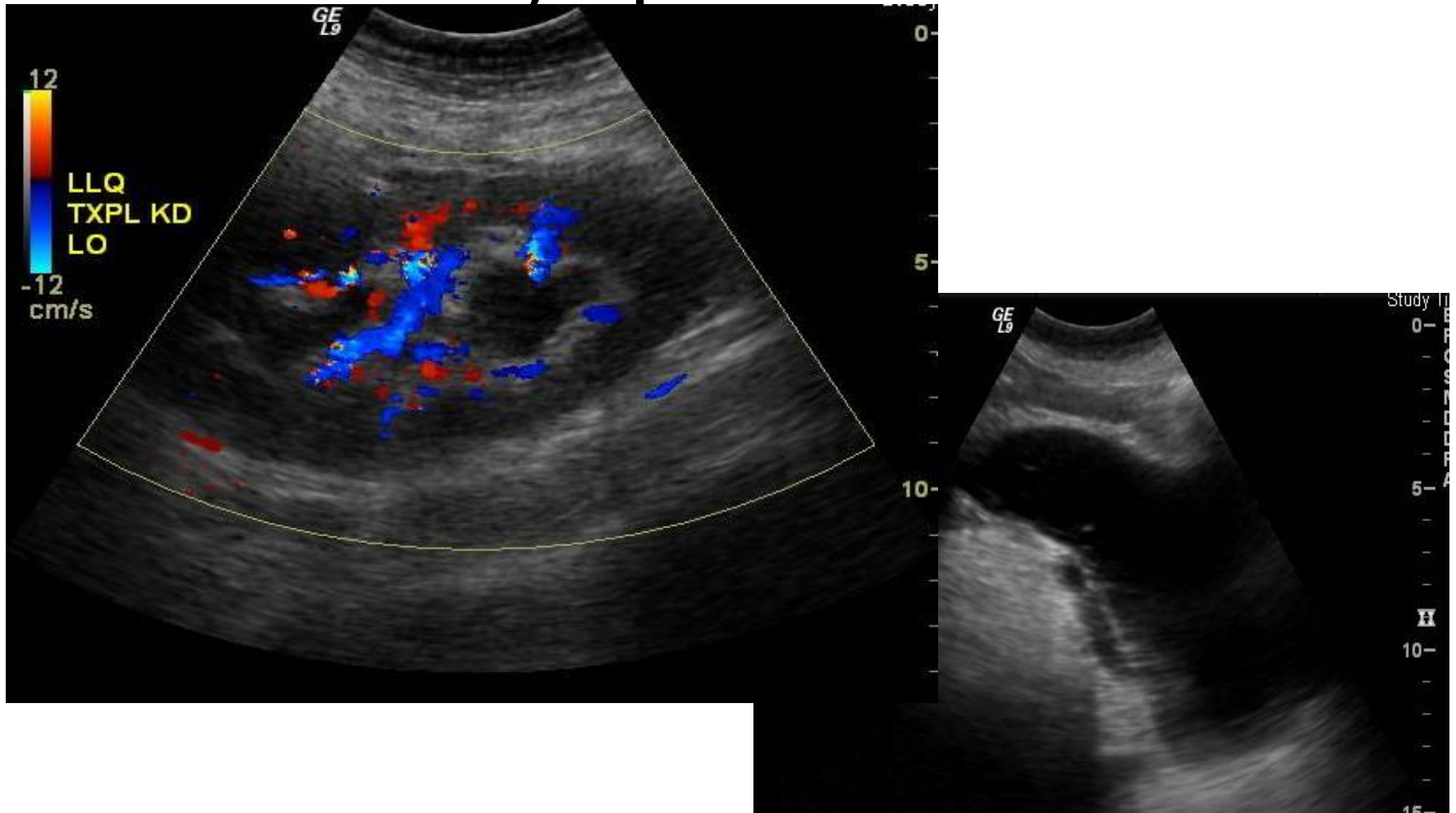
# Urine leaks and Ureteral Stents

- Urine Leak
  - filtered urine and creatinine reabsorbed leading to high serum creatinine with normal biopsy and ultrasound
  - Chemical peritonitis leads to pain, ileus
- Site of leak
  - Pelvis (trauma of surgery)
  - Ureter (trauma)
  - Anastomosis to bladder
  - Diagnosis- send fluid creatinine, potassium
- Ureteral Stents
  - Reduce incidence of leaks
  - Reduce obstruction (clots or strictures)
  - Increase incidence of UTI
  - Increased cost due to removal (GU)
    - Overall reduction in GU complications is small but each event is costly

# Urologic Complications

- Occur in 1-3% of transplants
- Ureteral strictures (usually further out)
  - Ischemic ( ureter supplied by lower pole artery)
  - Viral (BK virus infection)
  - Rejection of ureteral/vasculature
  - Managed with stent placement → surgical repair
- Bladder outlet obstruction
  - BPH in men after foley removal
  - Neurogenic bladder in men/women (DM)
- Ureteral Obstruction
  - Blood clots
  - Kidney stones
  - “Lymphocoeles”
  - Fungus balls

# Ureteral obstruction due to lymphocoele

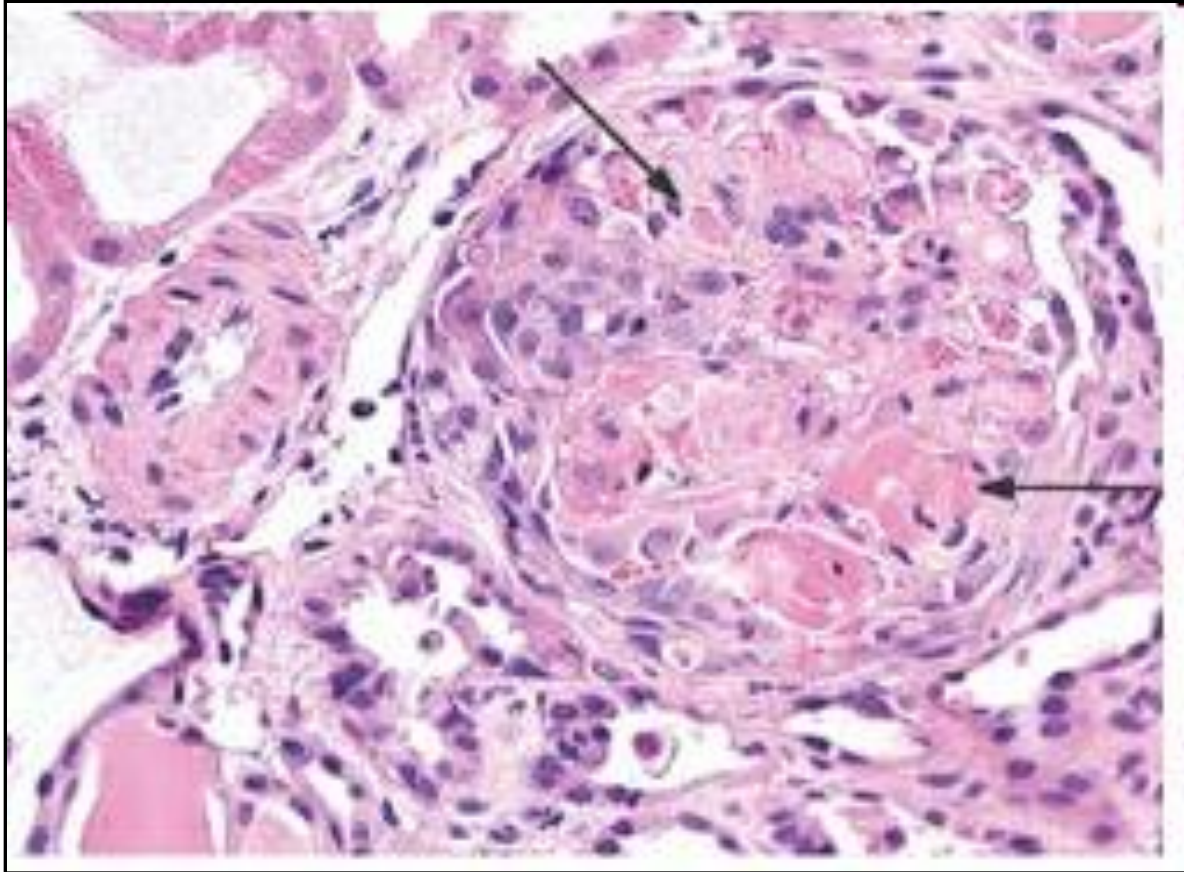




# Case 2

- 41 year old with CRF ?etiology- +proteinuria, negative serologies except +ACL
- LURTx (boyfriend) 10 days ago
- No antibodies detected against donor pre-Txp
- Thymoglobulin → Prograf/Cellcept
- Creat 1.3 → 1.8, Prograf level- 6.7-8.3
- Hct 32, Plat 140 (<130 <- 61), LDH 337, Haptoglobin 308
- Renal U/S unremarkable
- Diagnosis?

# Case 2- Pathology



Liptak, P. and I Bela *Nature Clinical Practice Nephrology* (2006) 2, 398-404

# Case 2- Thrombotic Microangiopathy

- Differential diagnosis
  - Calcineurin inhibitor nephrotoxicity
  - Antibody mediated rejection
  - Antiphospholipid antibody syndrome
  - Recurrent disease (i.e. familial HUS)
  - Reperfusion injury (deceased donors)
- ESRD due to HUS- 29% recurrence rate
- *de novo* rate- 0.8%; 4.6/1000 patient years
- Increased relative risk of combine sirolimus with calcineurin inhibitor

# Case 2- Thrombotic Microangiopathy

- Endothelial damage/ activation of clotting cascade
  - Localized thrombus formation
  - Micro-circulatory abnormality
  - Organ dysfunction
  - ADAMTS 13 levels normal
- Systemic form ~50-60%
  - Hemolysis, thrombocytopenia, +/- mental status changes/fevers
  - Graft loss ~20-40%
  - Rx- Controversial!! Plasmapheresis, stopping CNI, steroids, rituximab (anti-CD20)
- Localized form ~30-40% (graft loss very rare)
  - Renal only disease
  - Stopping CNI temporarily is usually sufficient
  - Can switch to another CNI (Tacrolimus → Cyclosporine) or to rapamune
- Renal limited form may be seen in kidneys of other solid organ recipients (up to 40% of lung transplant patients biopsied for CKD)

Schwimmer J. *Am J Kid Dis* 2003; 41(2): 471-9

Lefaucheur, C. *Am J Transplantation* 2008;8 1901-1910

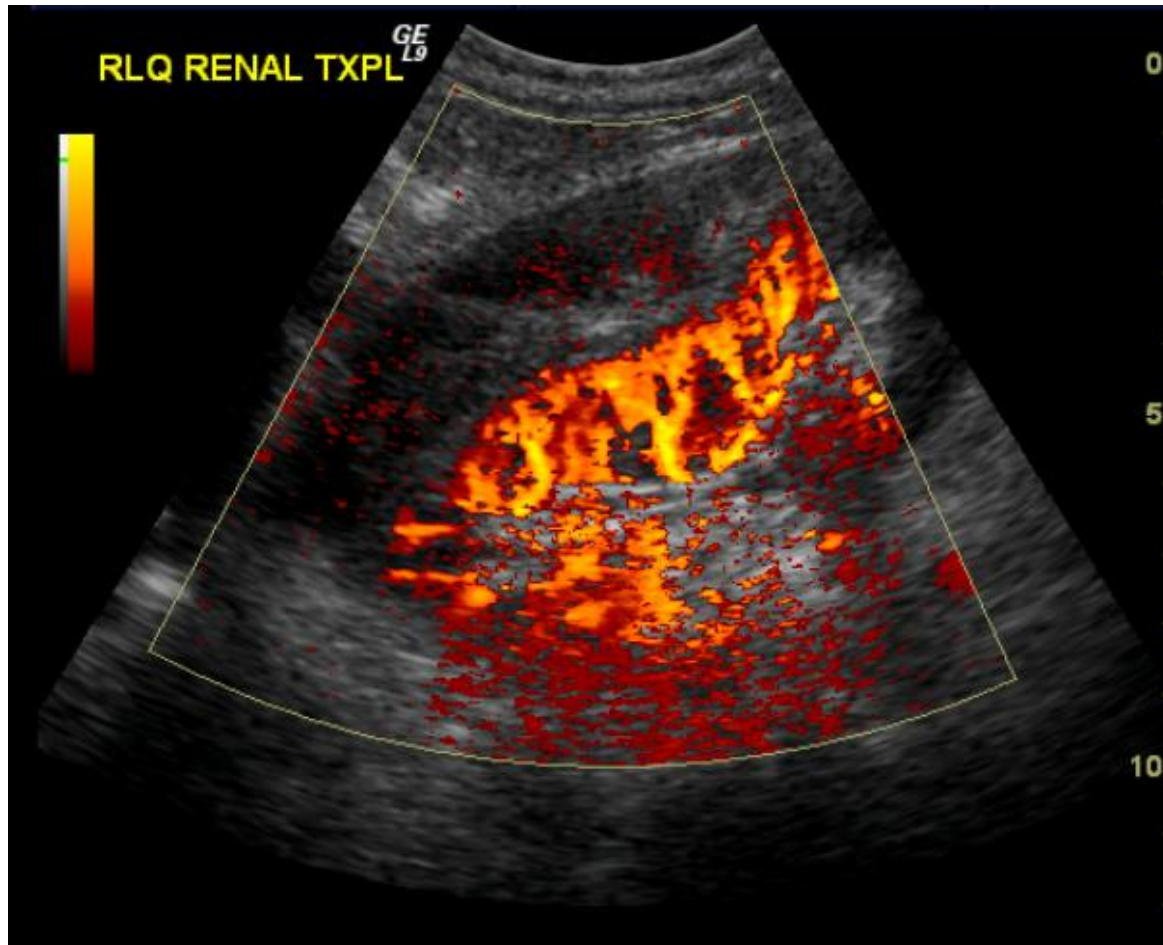
# Case 2- Other features of CNI toxicity

- Acute
  - Reduced renal blood flow (vasoconstriction)
  - Tubular toxicity (vacuolization)
  - Association with genes controlling intracellular concentration of CNI in kidney
    - ABCB1 gene of DONOR associated with 9 fold RR of dx of CNI toxicity
- Chronic
  - Stripe like Interstitial fibrosis
    - >90% of patients have 25% or more fibrosis after 2y
  - Secondary FSGS glomerular lesions
- Renal failure after non-renal solid organ txp
  - 20% with GFR <30 after 10 years, ~8-10% on HD

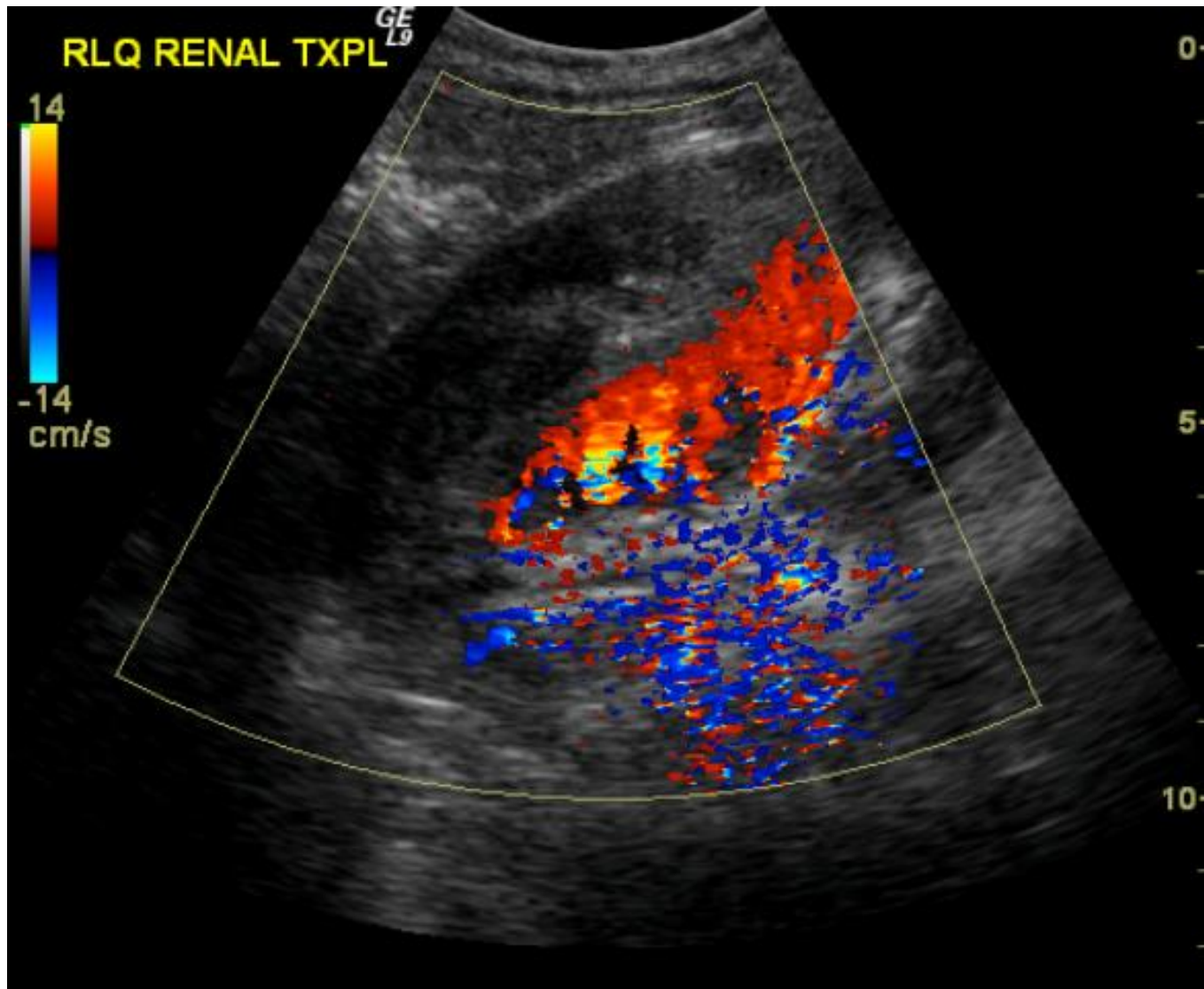
# Case 3

- 70 year old man with CRF from hypertension
- Pre-emptive renal transplant with thymoglobulin induction, Prograf/Mycophenolate
- Creat 6 → 3.5-4 after 4 days without improvement despite good oral intake and normal tacrolimus levels
- No improvement with hydration
- Renal U/S- increased “RI”, no hydronephrosis

# Case 3

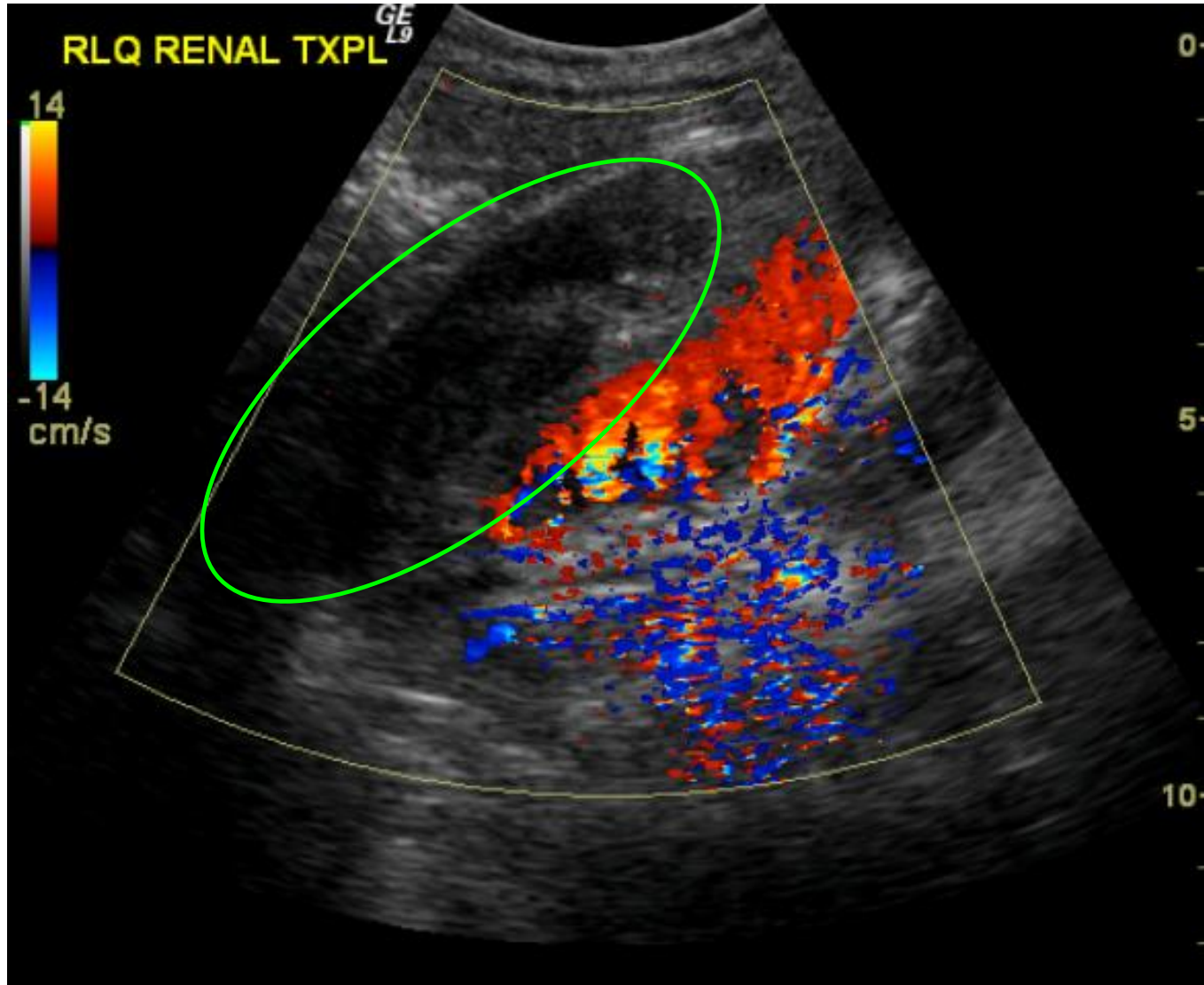


# Case 3





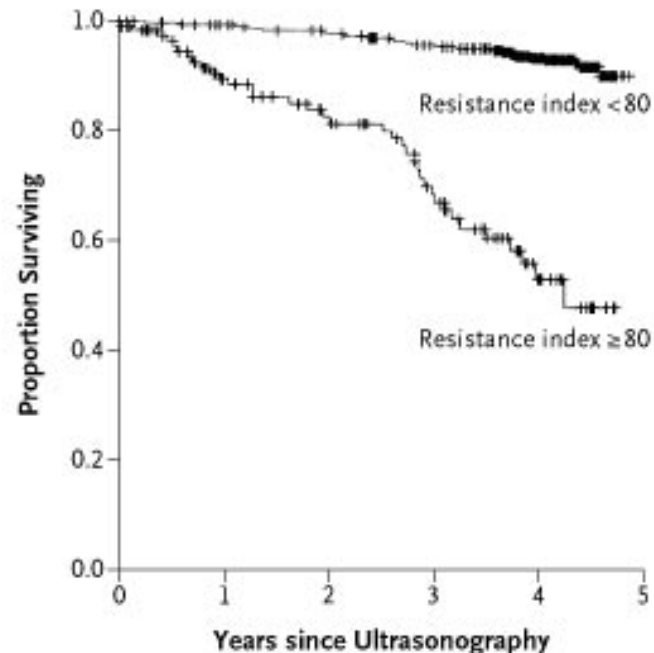
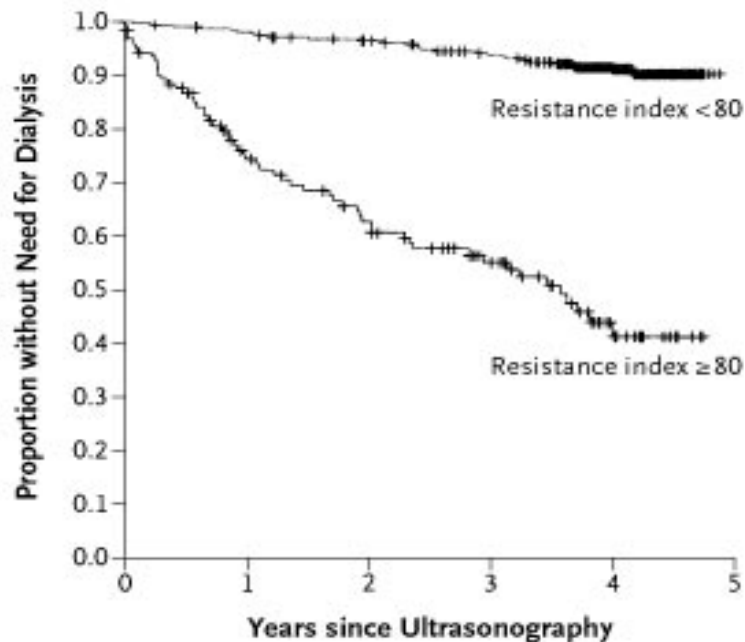
# Case 3-Subcapsular hematoma



# Elevated Resistive Index (Resistance Index)

- (Systolic-Diastolic)/ systolic flow
  - Assumes reduction in diastolic flow due to increase vascular resistance
  - Other contributors- pulse pressure (aortic stiffness, using beta-blockers), intraparenchymal pressure
- More important (and specific) is complete absence of diastolic flow
- DDX for RI  $\sim 1$ 
  - Hyperacute rejection/severe antibody mediate rejection
  - Renal vein thrombosis
  - Subcapsular hematoma
  - VERY elevated Prograf levels
  - ?severe thrombotic microangiopathy/reperfusion injury

# In chronic setting, increased RI predicts worse renal outcomes



601 renal transplant recipients imaged with calculated RIs followed for 3 or more years

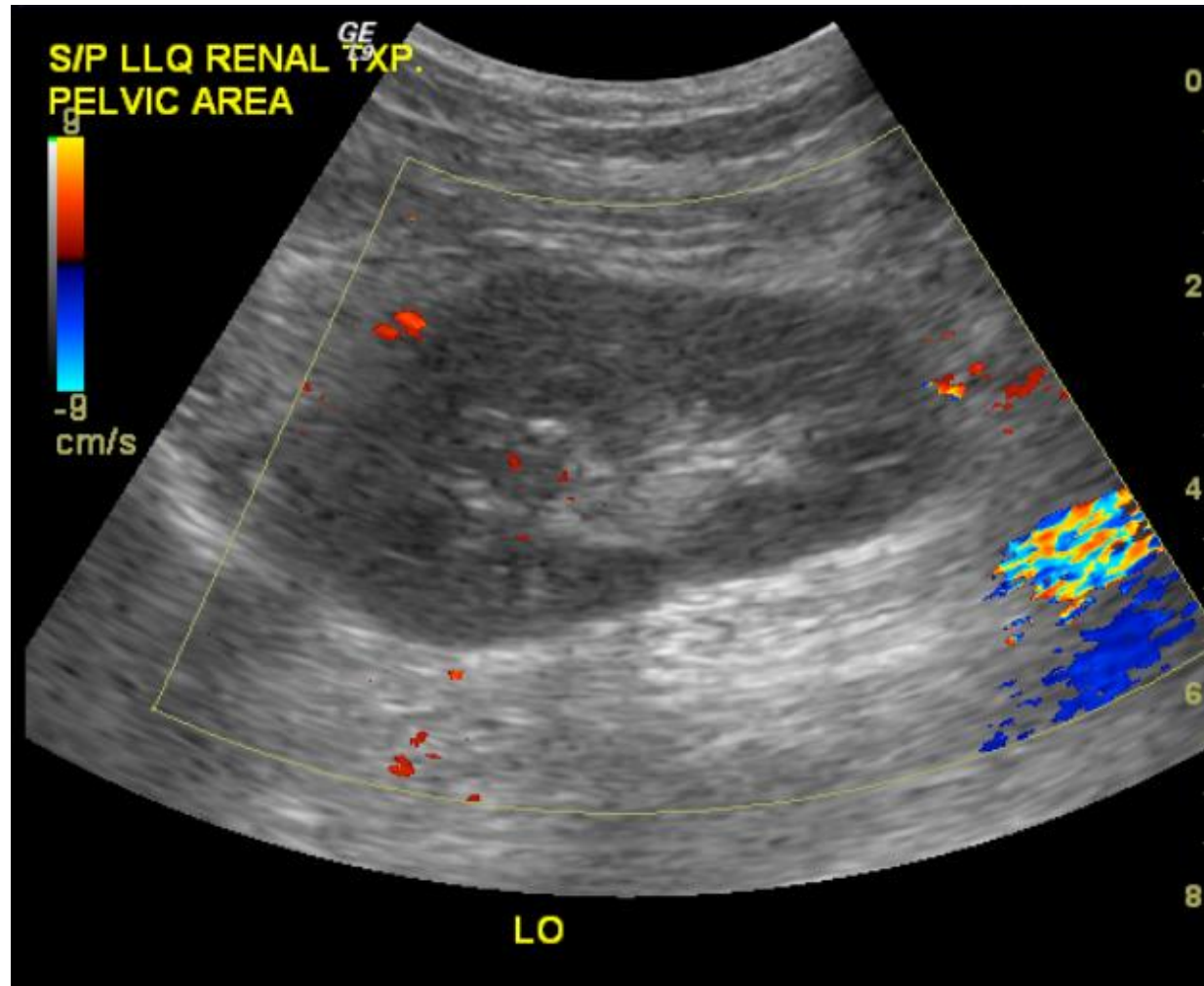
RI >0.8 best predictor of 50% decline in renal function or death (better than proteinuria, BP, donor type, second transplants)

Radermacher et al. *NEJM* 2003, 349;115-24

# Other vascular complications

- Transplant renal artery stenosis
  - Early- due to kink, edema, surgical error
  - Late- fibrosis, atherosclerosis, rejection
  - Pseudo-TRAS– iliac artery stenosis
- Renal artery thrombosis
- Iliac artery dissection
  - Before or after anastamosis
- Renal vein thrombosis
  - Iliac vein thrombosis
  - Increase risk with pediatric donors
- Renal vein stenosis

# Renal Vein Thrombosis

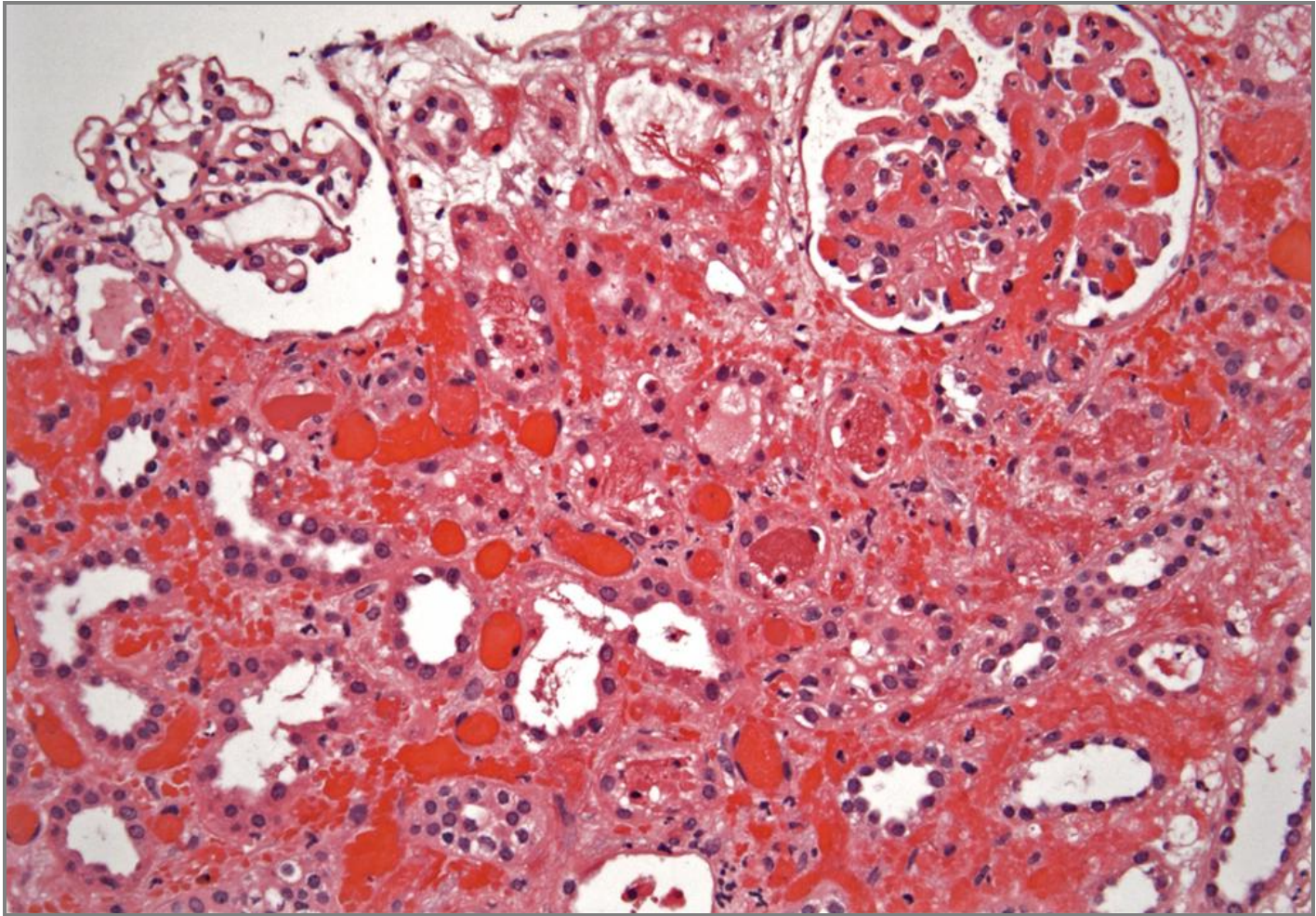


# Case 4

- 28 yo woman with ESRD from reflux
- 1<sup>st</sup> txp failed in 2 years from rejection
- Panel reactive antibodies- 90%
- Received ABO incompatible txp from HLA identical brother
- Zenapax/Prograf/Cellcept/Prednisone/Rituximab
- Creat 1.0 → 6 with anuria on POD #8
- U/S- absent diastolic flow



# Case 4



# Antibody Mediated Rejection(AMR)

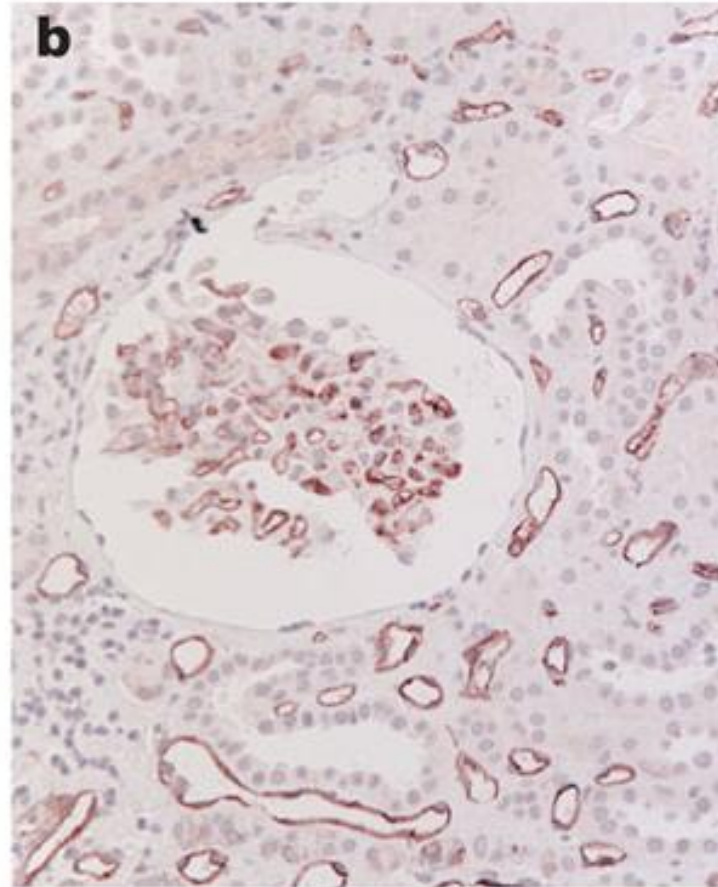
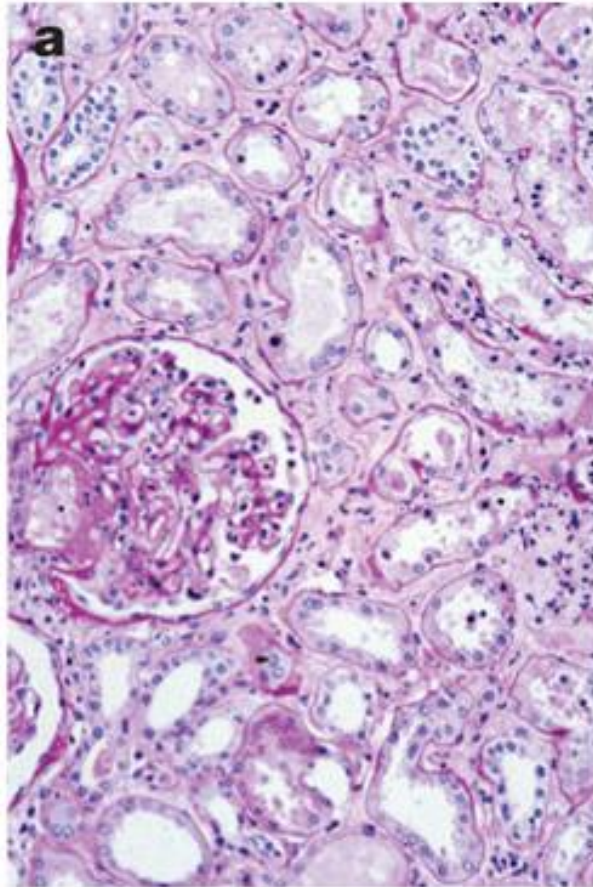
- Antibody types
  - HLA antibodies
  - ABO antibodies (isohemagglutinins)
  - Anti- MICA, Anti MICB, Anti- angiotensin receptor Ab
- Early AMR
  - risk ~0% if no prior sensitizing events
  - ~5-10% of all rejections
  - In 140 transplants at CPMC, AMR occurred only patients with prior DSA, pregnancy, txp, or PRBC
  - excellent prognosis with recurrence rate ~20% or less and 98% 1 year graft survival
- Late AMR- worse prognosis
  - Patients have developed donor specific antibodies despite immunosuppression regimen



# Antibody Mediated Rejection

- Diagnosis/Assessment
  - Measure DSA titer
  - Detection of C4d deposition on biopsy
  - Graft dysfunction and severity of injury
- Treatment
  - Steroids +/- anti-T cell therapy
    - 30-50% of AMR has concomitant cellular rejection
  - Plasmapheresis/IVIG (100 mg/kg)
  - High dose IVIG alone (effective for low titers)
  - Rituximab?
  - Anti-C5 Ab (eculizumab)
  - Anti-C1 Ab

# AMR and C4d staining



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# Cellular rejection

- T cell mediated
- Banff 97 criteria
  - Borderline: tubulitis without interstitial inflammation
  - 1A/B: tubulitis (5-10 or >10 cells per tubule)
    - >25% interstitial inflammation
  - 2A/B: endopheliitis/endovasculitis
    - Lymphocytes in vessel wall (B if occludes 25% of lumen)
    - Interstitial inflammation not necessary
  - 3: transmural infarction

# Treatment of Cellular Rejections

- Depends on:
  - Severity of rejection, interstitial disease, prior drug levels/compliance,
    - 2A or worse: Thymoglobulin or OKT3
    - Borderline/1A: Steroid boost alone
    - 1B: steroids or thymoglobulin depending on degree of renal dysfunction, prior immunosuppression levels, degree of interstitial fibrosis (i.e. is it worth accepting to toxicity of potent meds to make this kidney work)

# Impact of Cellular Rejection on Outcomes

- Early

- If creatinine returns to normal → no impact
- If creatinine not to baseline → worse outcome
  - Reflects degree of fibrosis
  - May reflect incomplete treatment of rejection

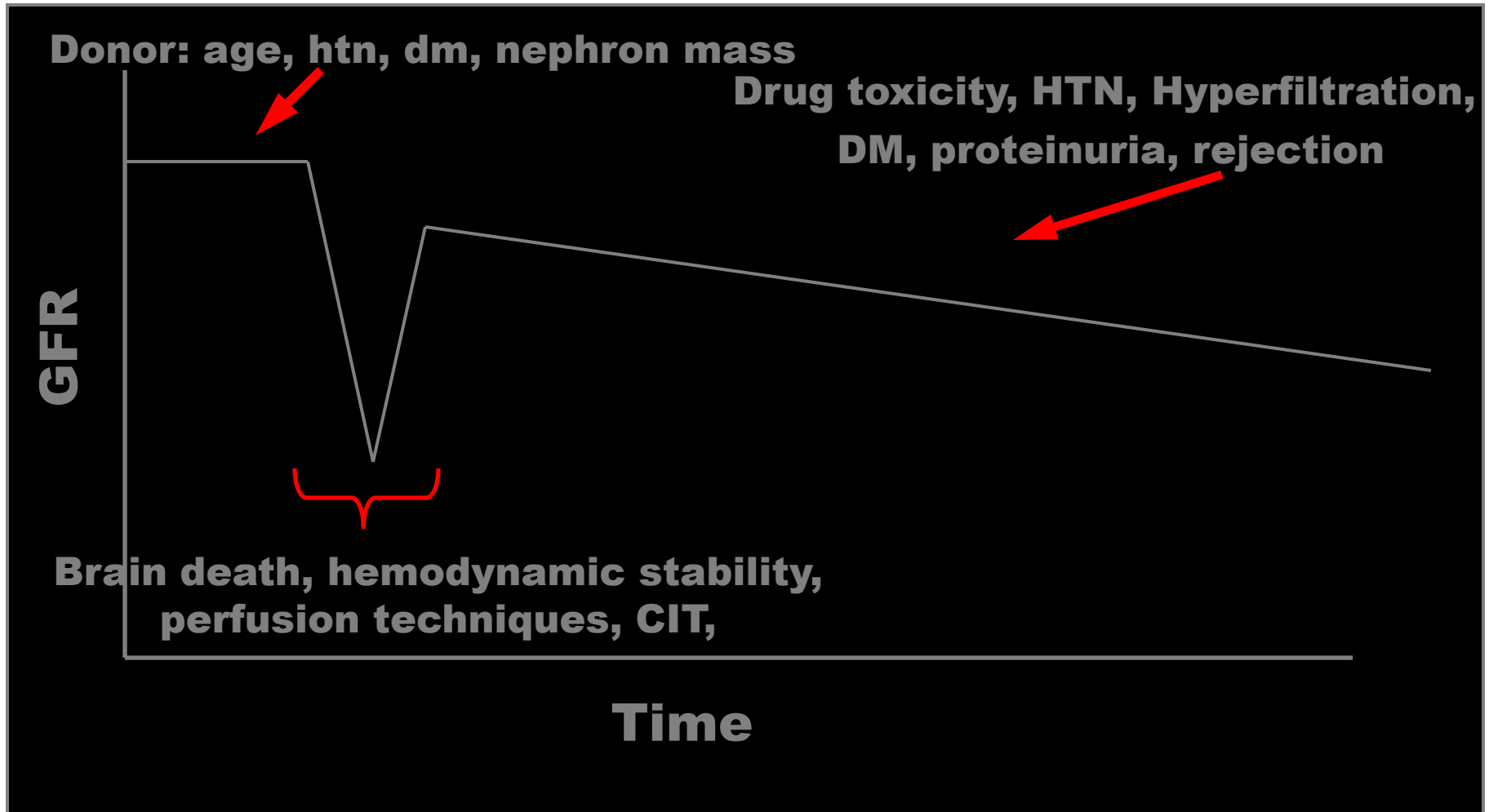
- Late

- Tends to have worse outcomes
- Labs checked less often → more advanced fibrosis
- Immunologically different in compliant patients who reject late
- Non-compliant patients may not have recurrent rejection but have recurrent non-compliance

# Allograft Dysfunction- Late

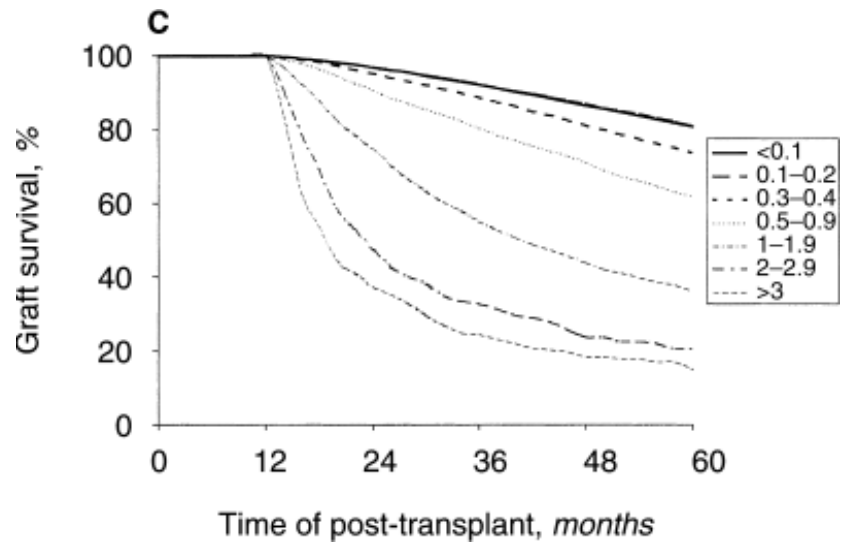
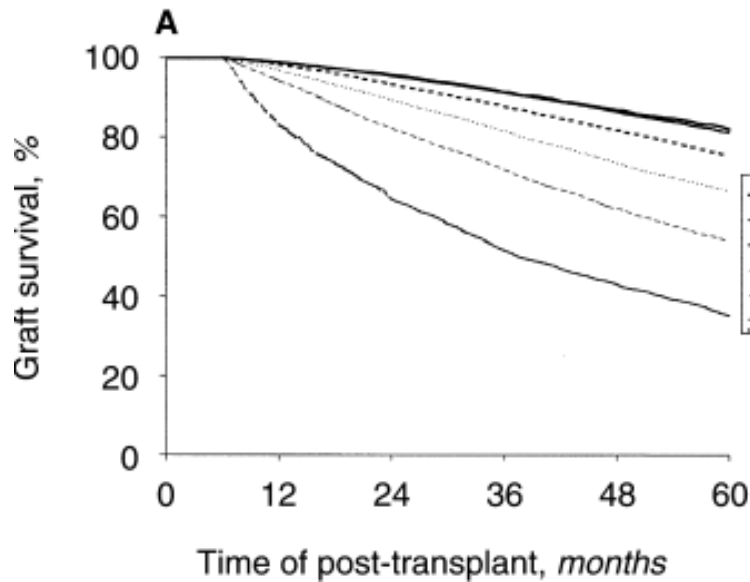
- Chronic rejection/acute rejection
- Chronic drug toxicity
- Recurrent glomerular disease
- BK virus interstitial nephritis
- All the diseases that everyone else gets  
(to be covered in separate lectures in future)

# Simplified model of CAN



# Post transplant renal function and change in creatinine from month 6 -12 predict graft survival

Hariharan, S. *Kidney International*, Vol. 62 (2002), pp. 311–318



A: Creatinine at 6 months

C:  $\Delta$  creatinine b/w 6 and 12 months

>100,000 transplants performed 1988-1998 among survivors >1 yr

Donor/recip characteristics, creatinine, and graft loss at follow up

Does not account for causation, but excellent at predicting