

# Acute Renal Allograft Rejection

Hatem Moussa, MD

Transplant service

SUNY Downstate Medical Centre.

## Pathologic Categories of Acute Rejection of Renal Allografts

### Banff 97

Suspicious for acute rejection, borderline

Type IA

Type IB

Type IIA

Type IIB

Type III

### Banff 93 – 95

Borderline

Grade I

Grade IIA

Grade IIB

Grade III

Grade III

### CCTT

Type I\*

Type I\*

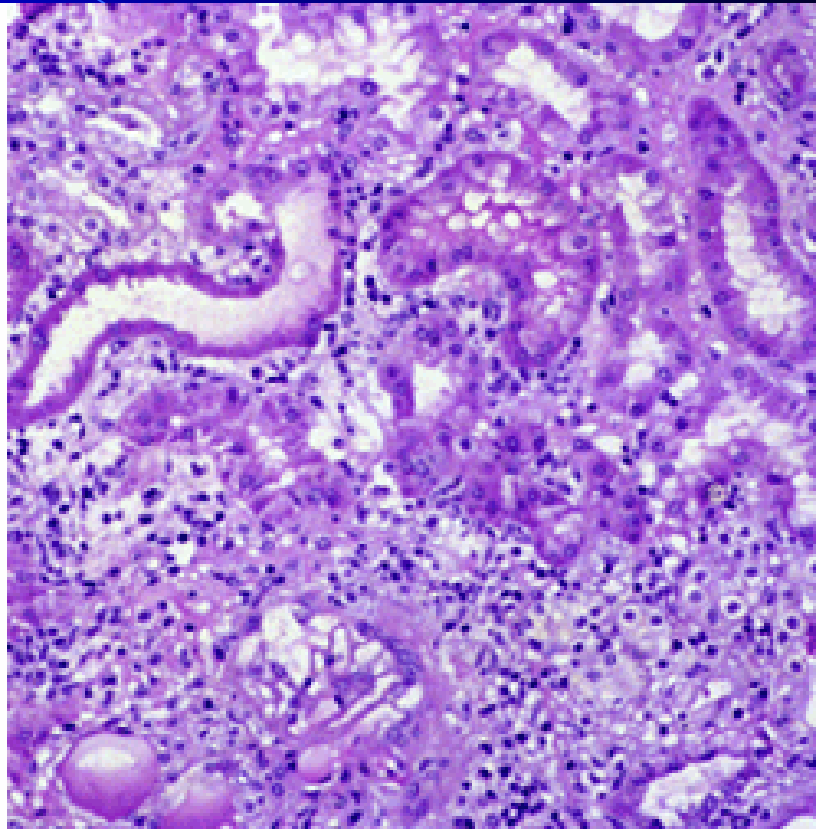
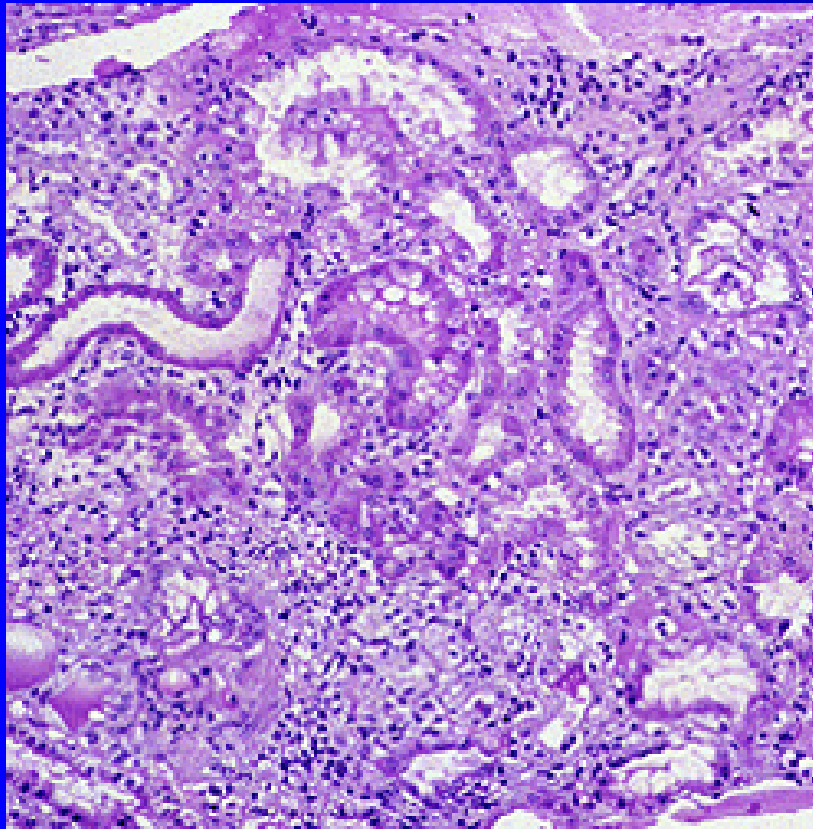
Type I\*

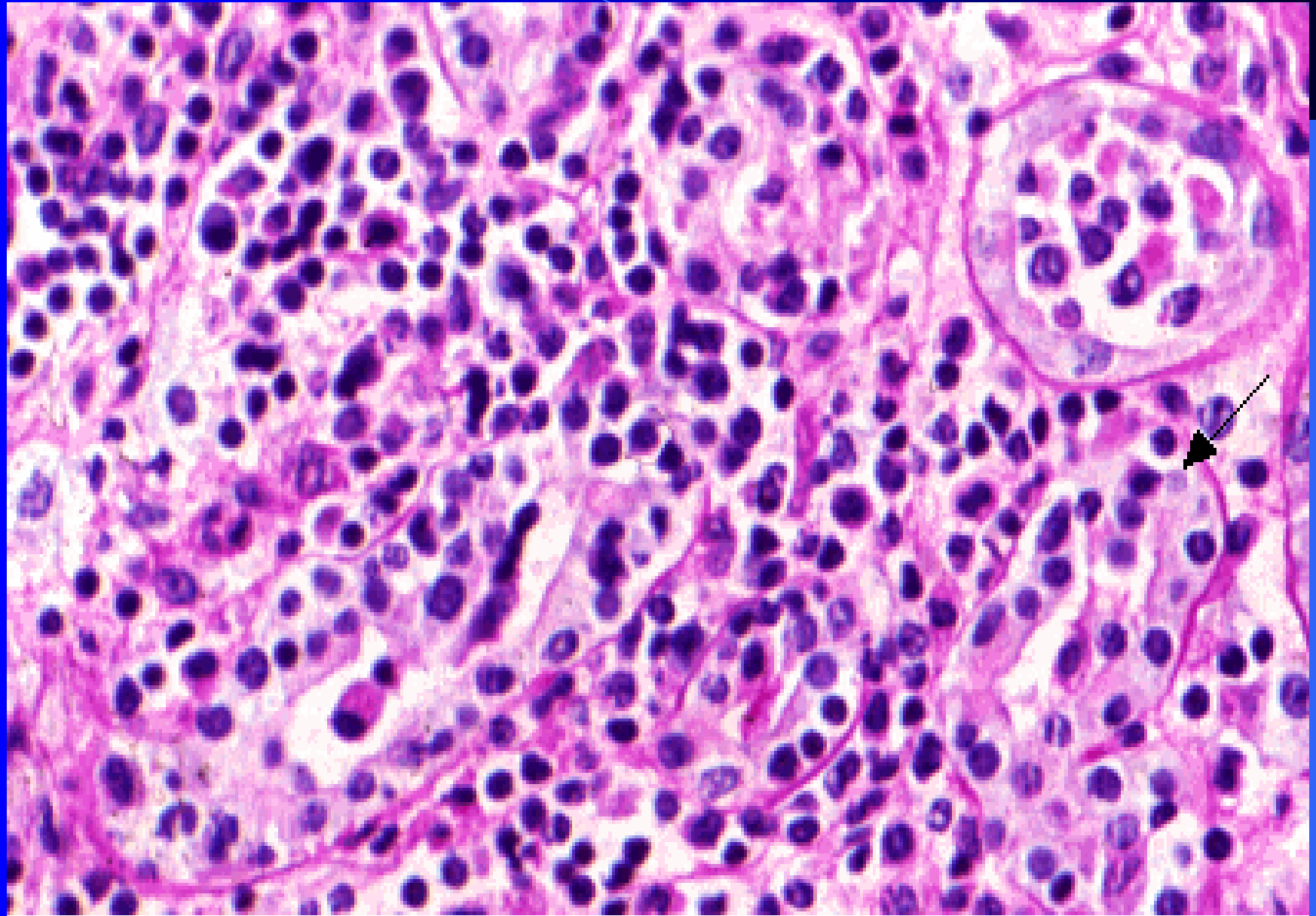
Type II

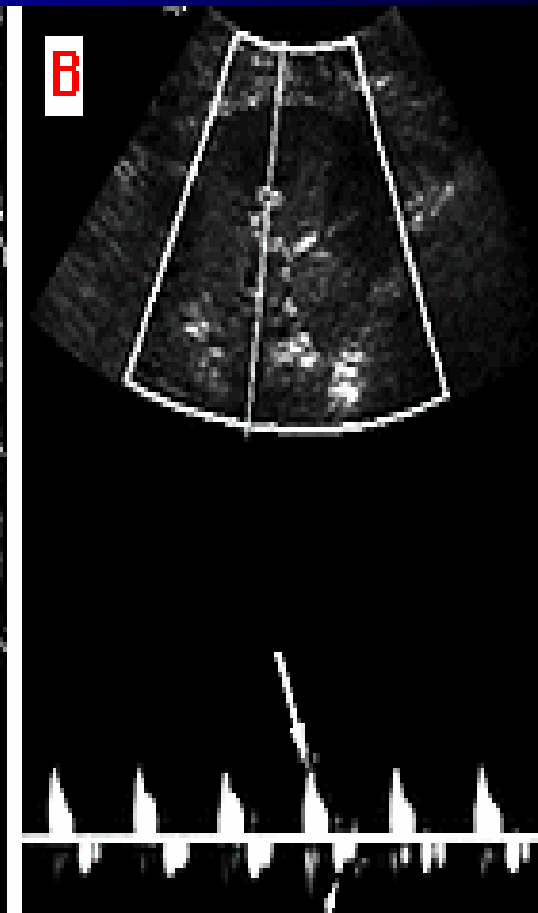
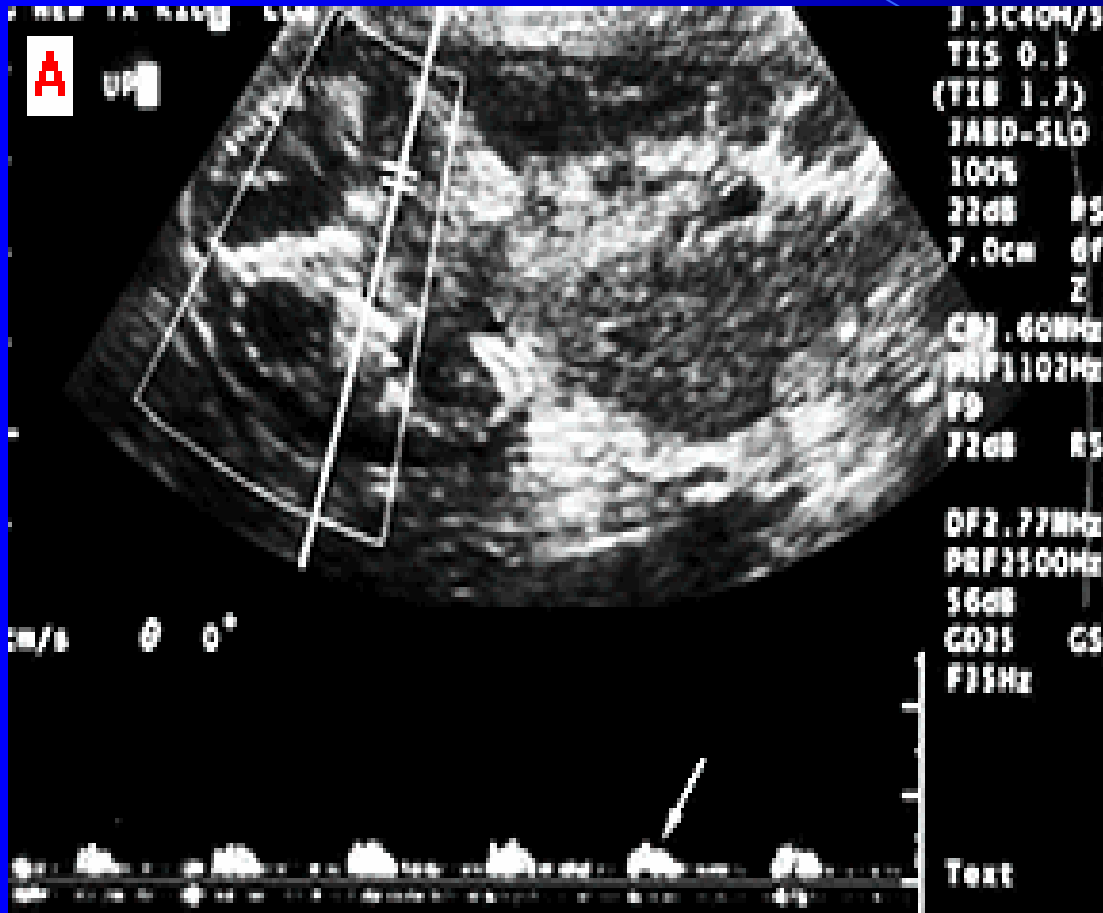
Type III

\*This requires that at least 10 to 25 percent of interstitium is involved with mononuclear cells, and at least 2 of the following 3 features are present: edema, activated lymphocytes, and tubular injury.

Data from Racusen, LC, Solez, K, Colvin, RB, et al. *Kidney Int* 1999; 55:713.







# Acute Renal Allograft Rejection

- **Definiton:**

acute deterioration in allograft function that is associated with specific pathologic changes in the graft.

# Acute Renal Allograft Rejection

- Incidence:
  - vary with the therapy used for immunosuppression.
  - more potent immunosuppressive regimens has lowered the rate of acute rejection

# Acute Renal Allograft Rejection

- \* Previously,  
one in 50 to 60 % of renal allograft recipients.
- \* In the second half of the 1990s,  
30 % of first cadaver transplants,  
27 % of living related transplants,  
37 % of second transplants.
- \* Today, below 15 %.



# Acute Renal Allograft Rejection

- Early acute rejection episodes have a major effect on allograft survival, which is decreased at one year by 18 and 27 % in living and cadaver recipients, respectively.

Transplantation 1993 Apr;55(4):752-6; discussion 756-7.

# Acute Renal Allograft Rejection

- Kidneys which recover function still have a 10 % decrease in one-year survival when compared to rejection-free kidneys.

Transplantation 1993 May;55(5):993-5.

# Acute Renal Allograft Rejection/ DIAGNOSIS

- Should be suspected in every transplant patient with a rising serum Cr.
- Fever, graft pain &/or tenderness, and graft swelling are uncommon in the cyclosporine era.
- Most episodes occur within the first 6 months after transplantation, with many such episodes occurring early after surgery.

# Acute Renal Allograft Rejection/ DIAGNOSIS

- \* Approximately 8 % of patients with functioning grafts have a first episode of rejection after one year.
- \* Noncompliance with medical therapy or low cyclosporine levels are often associated with this complication.

N Engl J Med 1994 Aug 11; 331(6):358-63.

# Acute Renal Allograft Rejection/ DD

- ongoing ischemic acute tubular necrosis (ATN).
- Cyclosporine Nephrotoxicity.
- urinary tract obstruction.
- Rarely, acute arterial or venous thrombosis.
- interstitial nephritis due to drugs or infection.

- If the ultrasonogram does not show hydronephrosis and cyclosporine levels are not elevated, we routinely perform a renal biopsy in patients with delayed allograft function that persists for one week post transplantation and even earlier (day three to five) to rule out occult rejection in "high risk" patients who are highly sensitized or who have received a second transplant.

# Acute Renal Allograft Rejection/ DIAGNOSIS

- Renal sonogram.
- Drug level.
- Renal biopsy.
- Duplex Doppler Scanning Ultrasound.
- Renal scan

# Acute Renal Allograft Rejection/ DIAGNOSIS

- Fine needle aspiration biopsy with subsequent cytological examination of infiltrating cells of the allograft.
- > 90 % sensitivity and specificity for the diagnosis of acute cellular rejection
- low morbidity, so can be performed repeatedly to follow the response to therapy.

Kidney Int 1988 Sep;34(3):376-81.



# Acute Renal Allograft Rejection

- **Subclinical rejection**

- \*histologic evidence of rejection but no elevation in the S Cr. concentration,

- \*significance is unclear.

- \*common within the first 3 months.

- \*30 % of patients with stable allograft function on a cyclosporine-based regimen.

# Acute Renal Allograft Rejection/ Treatment

- Should be started when the diagnosis is suspected
- Inadequate immunosuppression.
- Failure to recognize may eventually lead to graft failure.

Transplantation 2003 Jun 27;75(12):2058-63.

# Acute Renal Allograft Rejection/ Treatment

- **PULSE CORTICOSTEROIDS**

- The first-line therapy for acute rejection in most centers.
- The mechanism of action is incompletely understood.
- The expected reversal rate for the first episode of acute cellular rejection is 60 to 70 % with this regimen.

Am J Kidney Dis 1999 Aug; 34(2):304-7.

# Acute Renal Allograft Rejection/ Treatment

- Some evidence suggests that success with pulse corticosteroids may be enhanced by switching to TACROLIMUS among those being administered cyclosporine.

Transplantation 2003 Jun 27; 75(12):2058-63.

# Acute Renal Allograft Rejection/ Treatment

- **POLYCLONAL ANTI-T CELL ANTIBODIES**

- ALS has been used both for prophylaxis against and for the primary treatment of acute rejection.
- The reversal rate has been (75 –100%) different series.
- The efficacy of ALS in treating acute rejection appears to vary according to the animal source of globulin.

# Acute Renal Allograft Rejection/ Treatment

- **Complications:**

- \* Fever and chills develop in a majority of patients during the initial ALS infusion.
- \* Anaphylactic reactions are exceedingly rare.

# Acute Renal Allograft Rejection/ Treatment

- **OKT3**

- Rescue therapy for resistant rejection
- Directed against the CD3 antigen
- Reversal rate 70-90 % for steroid and/or ALS resistant rejection.
- rebound rejection in 50 % of cases
- primary therapy in vascular rejection.
- Infection, lymphoproliferative disease pulmonary edema hemolytic-uremic syndrome.

# ADDITIONAL RESCUE THERAPY

- **Tacrolimus**

- The overall response rate was 74%.
- Dialysis-dependent patients had a 50% response rate.
- A more recent trial demonstrated long-term graft survival following rescue therapy .
- Reversal is significantly slower than with either pulse corticosteroids or anti-lymphocyte antibody therapy.

- Transplantation 1997 Jan 27;63(2):223-8.



# ADDITIONAL RESCUE THERAPY

- Mycophenolate mofetil.
- Sirolimus.
- Intravenous immune globulin.
- Allograft irradiation.

Clin Transplant 1996 Feb;10(1 Pt 2):131-5.

Transplantation 2001 Jun 15;71(11):1579-84.

Transplantation 2001 Aug 15;72(3):419-22.

# Acute Renal Allograft Rejection/ Treatment

## ● RECOMMENDATIONS

\*steroid pulse.

\*if there is partial clinical and histological response, a second pulse may be given before resorting to antilymphocyte therapy.

# Cessation of therapy

- The patient is infected.
- The patient has received two to three courses of OKT3,
- Renal biopsy shows nonviable kidney tissue.
- the rejection episode is more than 90 days post transplantation.

# Induction therapy

- The optimal prophylactic induction therapy remains controversial.
- induction strategies utilized by transplant centers fall into one of two categories
- include perioperative antilymphocyte serum (ALS) or antithymocyte globulin and humanized anti-IL-2 receptor antibodies.

Ann Intern Med 1998 May 15;128(10):817-26.

# Induction therapy

- Non immunosuppressive component of induction of therapy:
  - \* CMV testing
  - \* Trimethoprim-Sulfamethoxazole to prevent *Pneumocystis carinii* pneumonia, sepsis, and urinary tract infection.

# Induction therapy

- Thymoglobulin: a polyclonal immunosuppressive agent derived from the rabbit
- reverse acute rejection, thereby reducing the risks of developing chronic allograft nephropathy
- acute rejection occurred in only 4.2% of those receiving thymoglobulin compared to 25% with ATGAM

- Transplantation 1998 Jul 15;66(1):29-37.

# Induction therapy

- No consensus for induction therapy.
- Recommendation:
  - In one regimen, cyclosporine, mycophenolate mofetil, and prednisone
  - In a sequential regimen, IV prednisolone and thymoglobulin are administered intraoperatively, followed by thymoglobulin/day for 3 to 6 days
- Maintenance therapy : cyclosporine azathioprine or mycophenolate mofetil , and prednisone.

# Maintenance Therapy

- Triple immunosuppression:
  - Prednisone (usually 5 to 15 mg/day).
  - An antimetabolite.
    - cyclosporine(3 to 5 mg/kg per day)  
or tacrolimus(1 to 4 mg BID)

These dose levels are attained by 6 to 12 months post-transplantation.



# Indications for nephrectomy

- The most common indications for transplant nephrectomy are the onset of symptoms and/or complications related to rejection after withdrawal of immunosuppression, and a history of early graft failure (with or without symptoms and/or complications):
- Symptoms resulting from rejection and necrosis include graft tenderness, fever, hematuria, localized edema, and occasionally infection. Less fulminant rejection may present with unusual symptoms, such as weight loss, anemia, fatigue, gastrointestinal complaints, and neurologic disturbances
- Patients who have early graft failure (defined as a return to dialysis within one year of transplantation) are much more likely to develop a graft-related complication requiring nephrectomy than are those with late allograft failure, independent of whether immunosuppressive medications are withdrawn.

- Most centers have adopted a policy of immediate withdrawal of immunosuppression combined with preemptive nephrectomy for patients with early allograft failure (ie, less than one year after surgery)

J Am Coll Surg 1994 Jan;178(1):59-64.  
Urol 1994 Apr;151(4):855-8.

## ● **REASONS FOR WITHDRAWAL OF IMMUNOSUPPRESSIVE AGENTS**

- \* Increased risk of infection.
- \* Infection is the second leading cause of death in this setting.
- \* Dosing is difficult in patients with renal failure.

Kidney Int 2002 Nov;62(5):1875-83

## COMPLICATIONS OF WITHDRAWAL OF IMMUNOSUPPRESSION —

- \* Precipitation of rejection, possibly requiring transplant nephrectomy
- \* Secondary adrenal insufficiency.
- \* Loss of residual renal function.
- \* Potentially adverse immunologic effects among those pursuing another transplantation.