

Transplant Cases for the Boards

Edgar L. Milford, MD

Director, BWH Tissue Typing HLA Laboratory
Senior Physician, Renal Division, Department of Medicine
Associate Professor of Medicine, Harvard Medical School
John P. Merrill & Charles B. Carpenter Chair

Melissa Yeung, MD, FRCPC, FAST

Medical Director, BWH Tissue Typing Laboratory
Associate Physician, Renal Division, Department of Medicine
Assistant Professor of Medicine, Harvard Medical School

BRIGHAM HEALTH



BRIGHAM AND WOMEN'S
Department of Medicine



HARVARD
MEDICAL SCHOOL

Global and Continuing
Education

Disclosures

ELM:

Scientific Advisory Board, New England Donor Services

MY Y:

Consultant, One Lambda Inc.

Case 1.

A 53 y/o Caucasian man with DN who underwent a DDRT 6 months ago comes for routine follow-up to your clinic. He received rATG for immunosuppression induction followed by maintenance therapy with tacrolimus, mycophenolate, and prednisone. His posttransplant course was complicated with acute cellular rejection (Banff 1B) 8 weeks after transplant that was treated with rATG and high dose steroids. Patient's allograft function eventually stabilized at SCr of 1.5 mg/dl. Today, he feels overall well and physical exam is unremarkable. Labs show an elevated SCr of 2.0 mg/dl, CBC WNL, and tacrolimus trough level of 8 ng/ml. Serum PCR for BK polyoma virus is positive for the first time at 80,000 copies/ml.

Which one of the following statements is MOST CORRECT regarding management of his case?

- A. Start another course of rATG and high dose steroid for suspected acute cellular rejection.
- B. Allograft biopsy followed by decrease in maintenance immunosuppression if there is no evidence of acute rejection.
- C. Start IV cidofovir.
- D. Switch from tacrolimus to sirolimus.
- E. Addition of leflunomide

Answer B. Allograft biopsy followed by decrease in basal immunosuppression if there is no evidence of acute rejection

- With the positive BK viral load, one needs to consider the possibility of BK nephropathy as the cause of his elevated serum creatinine (B)
- Definitive diagnosis of BK nephropathy requires a renal allograft biopsy, also to rule out the possibility of concurrent acute rejection which occurs in >50% of patients with BK nephropathy, and has similar histologic features (A, B).
- Histological features distinguishing BK from acute cellular rejection: presence of BK viral inclusion bodies, evidence of virally infected cells (typically TECs), positive staining for SV40.
- There is a lack of good evidence for any treatment strategy other than reduction in immunosuppression for treatment of BK nephropathy (B-E).

Case 2.

A 45 y/o Asian man with ESRD from PKD who underwent a second DDRT 6 weeks ago (1st transplant failed due to chronic rejection) comes for routine follow-up to your clinic. His allograft function has been excellent with stable SCr at 1.2 mg/dl. His last routine laboratory testing one week ago revealed SCr of 1.2 mg/dl and tacrolimus level of 10 ng/ml. CBC was WNL. Five days ago, he underwent EGD for ongoing odynophagia and was diagnosed with candida esophagitis so that he was started on fluconazole 200 mg PO daily. Today, he reports that his odynophagia has resolved. He feels overall well and physical examination is unremarkable. He takes tacrolimus and mycophenolate for maintenance immunosuppression. His standard lab tests from today indicate that his CBC is WNL, but his SCr is elevated to 1.6 mg/dl.

Which one of the following statements is MOST CORRECT regarding further evaluation and management of his case ?

- A. Start pulse steroids since he is at high immunological risk for acute rejection.
- B. Wait for tacrolimus level to come back since fluconazole can significantly increase tacrolimus metabolism
- C. Wait for tacrolimus level to come back since fluconazole can significantly decrease tacrolimus metabolism
- D. Switch tacrolimus to cyclosporine since the latter has no interaction with fluconazole.
- E. Arrange for urgent biopsy to rule out rejection and/or CNI-induced thrombotic microangiopathy (TMA).

Answer C. Wait for tacrolimus level to come back since fluconazole can significantly decrease tacrolimus metabolism.

- Both cyclosporine and tacrolimus are metabolized by the cytochrome P-450III_A (CYP3A) in GI and liver (D)
- Antifungal agents (fluconazole, ketoconazole, itraconazole, voriconazole) can markedly increase CNI level by inhibition of CYP3A (B, C, D). Therefore, great care must be taken when starting and stopping these antifungal agents
- Although one should consider the possibility of acute rejection, preemptive anti-rejection treatment or biopsy would be premature, since a markedly elevated tacrolimus level would explain the rise in serum creatinine (A, E)
- Both cyclosporin and tacrolimus have been associated with the development of TMA (E). The usual extrarenal manifestations of TTP may not be present because the condition can be limited to the allograft with no decrease in the platelet count, schistocytes, or elevation in LDH levels.

Case 3.

A 52 y/o Hispanic woman with ESRD from diabetic nephropathy underwent a LRRT from her sister 18 weeks ago (CMV D+/R+; EBV D-/R-). She received rATG for immunosuppression induction followed by maintenance therapy with tacrolimus, mycophenolate and prednisone. She presents to your clinic today for routine follow-up. She reports of ongoing diarrhea, nausea, and bloating. Her BP is 118/70 mmHg and HR is 90/min, afebrile. Her physical examination is overall unremarkable. Standard lab tests indicate Hb 8, WBC of 1,400/ μ l, and platelets of 90,000/ μ l. Renal allograft function is stable with a SCr level of 1.2 mg/dl, and the tacrolimus level is 8 ng/ml. She takes tacrolimus 3 mg bid, MMF 1g bid, and prednisone 5 mg daily for immunosuppression. Prophylaxis includes valgancyclovir 450 mg daily and co-trimoxazole SS daily.

Which one of the following statements is MOST CORRECT regarding further evaluation and management of her case ?

- A. Decrease MMF dose and send serum CMV PCR.
- B. Decrease tacrolimus dose and send serum CMV PCR.
- C. Continue MMF at current dose since diarrhea and nausea are rare side effects of MMF.
- D. Stop valgancyclovir since she has leukopenia and is at low risk for CMV infection (CMV D+/R+).
- E. Increase valgancyclovir to 900 mg bid to start empiric treatment for CMV disease.

Answer A. Decrease MMF dose and send serum CMV PCR.

- Most common adverse events of MMF are related to the GI tract (A,C).
 - Diarrhea occurring in up to one third of patients.
 - Varying degrees of nausea, bloating, dyspepsia, and vomiting in up to 20% of patients.
 - Most symptoms respond to reduction of drug dosage or splitting the total daily dose into 3 or 4 doses.
 - The GI side effect profile of the enteric-coated formulation of mycophenolic acid (MPA) is not significantly different from the original MMF, but anecdotally has improved symptoms in some patients.
- MMF can cause leukopenia, anemia, and thrombocytopenia -usually responds to reduction in dose.
- Leukopenia is a rare side effect of tacrolimus (B)
- Valgancyclovir can cause leukopenia but stopping it would be premature since she is at risk (CMV D+/R+) for both reactivation of latent CMV and superinfection with a new viral strain (D)
- CMV infection can also cause leukopenia, but starting empiric treatment, before confirming CMV viremia, is premature since she has been on prophylaxis (E)

Case 4.

A 45 y/o woman comes to your clinic complaining of fatigue, weight loss, and abdominal pain. She underwent a DDRT in 2008 due to FSGS. Her graft function is stable (SCr of 1.3 mg/dl) on tacrolimus, MMF, and prednisone. MRI reveals a circumferential mass involving an approximately 4 cm segment of jejunal loop in the LUQ without evidence of obstruction.

Which one of the following statements regarding PTLD after kidney transplantation is CORRECT ?

- A. EBV seronegative status of the recipient at time of transplant and induction with T cell-depleting antibodies have been associated with increased risk for the development of PTLD.
- B. PTLD only occurs in the first year after transplantation, when patients are most immunosuppressed.
- C. While the majority of cases are not caused by EBV, EBV-associated PTLD does occur.
- D. Rituximab is not an effective treatment option since most PTLD is of T-cell origin.
- E. Treatment includes increase in basal immunosuppression.

Answer A. EBV seronegative status of the recipient at the time of transplant and induction with T cell-depleting antibodies have been associated with increased risk for the development of PTLD

- The principal risk factors for development of PTLD are the EBV serostatus of the recipient and the degree of T cell immunosuppression (A).
- While the incidence of PTLD appears to be highest in the first year after transplantation, the time of most intense immunosuppression, the cumulative incidence over 5 years ranges from 1 to 3 % (B).
- Most cases are induced by EBV infection causing uncontrolled proliferation of B cells (EBV+ disease). However EBV negative disease does occur (C).
- Most are NHL, are of B-cell origin, and are CD20-positive (D).
- Restoration of host immunity is the most important therapy for the control of lymphoid proliferation.
- Therapeutic options include reduction of basal immunosuppression, rituximab in the case of CD20-positive lymphomas, CHOP alone or in combination with rituximab (E).

Case 5.

A 65 y/o Asian man with ESRD from PKD presents to your clinic 8 months after a LRRT from his nephew (CMV D+/R-; EBV D+/R-). His course was complicated by an episode of acute cellular rejection (Banff 1B) 5 months after transplant, which was treated with rATG and high dose steroids. Today, he reports fever, chills, and malaise since last week. His vital signs are: BP 115/65 mmHg, HR 101/min, T 103° F. Physical examination is overall unremarkable. Laboratory tests show Hb 7.5, WBC of 1,200/ml, and platelets of 95,000/ml. His SCr level is at 1.4 mg/dl, and tacrolimus level is at 7 ng/ml. AST and ALT are 150 and 188 U/ml, respectively. UA is unremarkable, and CXR is pending. His maintenance immunosuppression includes tacrolimus, MMF, and prednisone. He is on co-trimoxazole prophylaxis.

Which one of the following statements is MOST CORRECT regarding his case ?

- A. Arrange for renal allograft biopsy to rule out BK nephropathy.
- B. Send serum BK polyoma virus PCR and start IV cidofovir while waiting the result.
- C. CMV disease is unlikely since the patient is CMV-seronegative, and therefore at low risk.
- D. PTLD is unlikely since the patient is EBV-seronegative, and therefore at low risk.
- E. The initial work-up should include serum CMV PCR.

Answer E. The initial work-up should include serum CMV PCR.

- The patient is at highest risk for CMV infection and disease (CMV-positive donor to CMV-negative recipient). He also received anti-rejection treatment with rATG and high dose steroids 3 months ago, putting him at further risk for CMV disease (C). The serum CMV PCR is the test of choice to diagnose CMV viremia and disease, and to monitor response to antiviral therapy (E).
- Among kidney transplant recipients, BK virus causes tubulointerstitial nephritis which most commonly presents with an asymptomatic acute or slowly progressive rise in serum creatinine level, and rarely ureteral stenosis. Systemic symptoms such as fever, chills and malaise are uncommon (A, B).
- There is an increased risk of PTLD among EBV-negative recipients of EBV-positive donor organs. Also, the recent anti-rejection treatment with rATG puts him at higher risk for PTLD

Case 6.

A 48 y/o AA woman with ESRD from lupus nephritis underwent a second DDRT 3 weeks ago (CMV D+/R+; EBV D+/R-). Her first transplant failed due to chronic antibody-mediated rejection (CAMR). Her current posttransplant course has been complicated by delayed graft function (DGF) with ongoing need for intermittent hemodialysis. Allograft biopsy on POD#7 showed severe ATN. Now POD#21, the patient remains oliguric and dialysis-dependent, and you decide to perform a repeat allograft biopsy which reveals ongoing ATN and neutrophils in the peritubular capillaries (PTC). C4d-staining is diffusely positive in the PTC. Duplex ultrasonography during the biopsy was unremarkable. She takes tacrolimus and MMF for maintenance immunosuppression.

Which one of the following statements is MOST CORRECT regarding her case ?

- A. Arrange for renal allograft biopsy to rule out BK nephropathy.
- B. Check for donor-specific anti-HLA antibody and arrange for plasmapheresis and IVIG.
- C. Start treatment for T cell-mediated rejection with rATG and pulse steroids.
- D. Send serum BK PCR and decrease MMF dose.
- E. Switch tacrolimus to belatacept since CNI is delaying recovery from ATN.

Answer B. Check for donor-specific anti-HLA antibody (DSA) and arrange for plasmapheresis and IVIG.

- The histologic appearance of acute ABMR may appear as ATN, neutrophil margination in the glomerular capillaries and PTC, thrombotic microangiopathy, and/or arterial fibrinoid necrosis. It frequently, but not invariably, occurs in the setting of preexisting sensitization. Therefore, it is important to stain for C4d positivity, and useful to repeat the crossmatch if possible and to measure DSA in the recipient (A, B).
- Acute ABMR does not respond to the usual treatments for T cell-mediated rejection (C).
- Switching tacrolimus to belatacept would not help in acute ABMR. Also, belatacept is contraindicated in this patient who is EBV seronegative since the risk of PTLD is particularly increased in patients who are EBV seronegative (E).

Case 7.

A 58 y/o AA man with ESRD from reflux nephropathy underwent a DDRT 4 years ago. He was found to have biopsy-proven ABMR one year posttransplant that was treated with 5 sessions of plasmapheresis and IVIG. He has been maintained on tacrolimus, MMF, and prednisone for maintenance immunosuppression since then. Over the past year, patient's SCr has been slowly rising from 1.5 to 3.0 mg/dl. A biopsy was therefore performed which revealed glomerular capillary wall thickening with a double contour appearance, arterial intimal fibrosis with intimal mononuclear cell infiltration, and interstitial fibrosis and tubular atrophy. C4d staining in the peritubular capillaries was positive.

Which one of the following statements is MOST CORRECT regarding his biopsy findings ?

- A. The presence of anti-HLA donor-specific Ab (DSA) has been associated with chronic ABMR.
- B. The absence of anti-HLA antibodies rules out the diagnosis of ABMR.
- C. Since introduction of more potent immunosuppressants, chronic ABMR has become a rare cause for chronic allograft failure.
- D. It usually responds well to treatment with plasmapheresis, IVIG and pulse steroids.
- E. It usually responds well to treatment with rituximab.

Answer A. The presence of anti-HLA donor-specific Ab (DSA) has been associated with chronic ABMR.

- The presence of DSA has been associated with a significantly lower long-term graft survival. Chronic ABMR has been associated with anti-HLA Abs, specifically with those against MHC class II antigens (A).
- Non-HLA antibodies such as antiendothelial antibodies and MHC class I chain-related antigens (MICA) have also been implicated as potential cause of ABMR (B).
 - MICA are expressed on endothelial cells and are polymorphic. They have been identified as targets of ABMR, and sensitization against MICA has been associated with poorer allograft survival.
- Despite current IS regimens, a high percentage of chronic allograft loss remains due to chronic ABMR (C).
 - In some studies, up to 60% of patients with chronic allograft failure show evidence of antibody-mediated injury.
- Treatment for chronic ABMR is problematic and not well defined.
 - Treatment protocols for acute ABMR, such as the use of plasmapheresis, IVIG, and rituximab/bortezomib remains of unclear benefit at this time (D, E).

Case 8.

A 52 y/o AA woman with ESRD from lupus nephritis underwent a DDRT 4 months ago. She received basiliximab for immunosuppression induction followed by maintenance therapy with tacrolimus, mycophenolate, and prednisone. She has been doing overall well since then and her renal allograft function stabilized at SCr level of 1.1 mg/dl. On her routine follow-up visit yesterday, however, her SCr was found to be elevated at 1.8 mg/dl. Her tacrolimus level at the same time was 5 ng/ml. A bedside US was done which revealed kidney allograft size of 10.2 cm, and no hydronephrosis. A renal allograft biopsy was performed which showed “prominent interstitial inflammation and moderate focal tubulitis, mild-to-moderate intimal arteritis; negative staining for C4d”.

Which one of the following statements is MOST CORRECT regarding her case ?

- A. The patient has acute ABMR. A treatment with plasmapheresis, IVIG, and pulse steroids should be initiated.
- B. The patient has acute T cell-mediated rejection (TCMR). Treatment with belatacept and pulse steroids should be initiated.
- C. The patient has acute T cell-mediated rejection. Treatment with rATG and pulse steroids should be initiated.
- D. BK nephropathy is ruled out since the patient has an acute rejection.

Answer C. The patient has acute T cell-mediated rejection. A treatment with rATG and pulse steroids should be initiated.

- The standard definition of acute TCMR relies on the Banff criteria, which defines and classifies TCMR depending on the presence and extent of tubulitis, interstitial inflammation, and arteritis. The presence of endarteritis in acute renal allograft rejection is classified as TCMR type II according to the Banff classification.
- Thymoglobulin and pulse steroids are considered the first-line treatment option for severe acute TCMR. Plasmapheresis and IVIg are used in the treatment of ABMR (A, B, C). Belatacept is not appropriate for treatment of acute rejection
- BK nephropathy and acute cellular rejection can occur concurrently where BK nephropathy can have similar histologic features as acute cellular rejection (tubulitis, interstitial inflammation). The diagnosis of BK nephropathy relies on demonstration of the virus in tubular epithelium using immunohistochemical stain and/or in situ hybridization (D).

Case 9.

A 69 y/o man with ESRD from DN who has been on HD x1 year received a kidney from a 61 y/o deceased donor with a cold ischemia time (CIT) of 28 hours. He remained oliguric after transplantation and was dialyzed on POD#2 for hyperkalemia and volume overload. Allograft biopsy performed on POD#10 revealed diffuse tubular injury with negative staining for C4d. He received basiliximab for induction and is currently treated with tacrolimus, mycophenolate, and prednisone. He presents for routine follow-up 3 weeks after transplantation. His 24h urine output is ~300 ml. He remains dialysis-dependent 3x a week. His vital signs are: BP 140/90 mmHg, HR 90/min, no fever. He has bilateral moderate LE edema, but the rest of physical examination is unremarkable. Laboratory tests show normal CBC, SCr of 8.4 mg/dl, and tacrolimus level of 8 ng/ml.

Which one of the following statements is MOST CORRECT regarding delayed graft function (DGF) and its prevention ?

- A. The most common cause of DGF is acute rejection.
- B. Risk for DGF is nearly the same for kidneys procured from donors after cardiac death.
- C. This patient's risk factors for DGF include CIT and CNI therapy.
- D. Compared with storage in cold solution, machine perfusion has never been shown to reduce the risk of DGF.
- E. While DGF greatly impacts 1-yr graft survival, it has no impact on long-term graft function or patient survival.

Answer C. This patient's risk factors for DGF include CIT and CNI therapy.

- The incidence of DGF increases with higher donor age, donor hypertension and hypotension, CIT exceeding 24h, and with CNI therapy (C).
- The leading cause of DGF is ATN related to the events surrounding organ procurement and ischemia/reperfusion (A).
- incidence of DGF: ~5% in recipients of live donor kidneys, up to 70% for donor after cardiac death (DCD) kidneys, and 20-50% in non-DCD kidneys
 - DD kidneys from donors with KDPI 0-50 = 20%, KDPI 51-85 = 32%, KDPI >85 = 40%
 - KDPI: kidney donor profile index –combines 10 donor factors to provide an estimate of the likelihood of graft failure after deceased donor transplant
- Machine perfusion has been shown to reduce the risk for DGF and graft failure compared to static cold storage (D).
- Both graft and patient survival rates are adversely impacted by the kidney source and the development of DGF (E)

Case 10.

A 50 y/o woman with ESRD from ADPKD who is on maintenance HD is referred to your clinic for evaluation for kidney transplantation. Her medical history includes HTN and dyslipidemia. The patient has heard that kidney transplantation can cause diabetes, and worsen dyslipidemia and asks you for more information regarding this. She is very interested in kidney transplantation, but is concerned about the impact it may have on her long-term health.

Which one of the following statements is MOST CORRECT regarding cardiovascular disease and kidney transplantation?

- A. The annual rate of fatal or non-fatal cardiovascular disease (CVD) events in kidney transplant recipients is nearly similar to the general population.
- B. Kidney transplantation is known to reduce mortality compared to dialysis despite significant increase in cardiovascular risk after kidney transplantation.
- C. CMV seronegativity has been associated with increased risk for cardiovascular death in kidney transplant recipients.
- D. New onset diabetes mellitus after transplantation (NODAT) may occur as a result of insulin resistance, increased insulin metabolism, and/or diminished insulin secretion.
- E. Hyperlipidemia and hyperglycemia are less marked with cyclosporine than with tacrolimus.

Answer D. New onset diabetes mellitus after transplantation (NODAT) may occur as a result of insulin resistance, increased insulin metabolism, and/or diminished insulin secretion.

- The mechanisms responsible for the development of NODAT appear to be mixed: insulin resistance (secondary to weight gain, steroids, or sirolimus), increased insulin metabolism (due to restored kidney insulin metabolism), and/or diminished insulin secretion and pancreatic b cell toxicity (due to tacrolimus) (D).
- Transplant recipients have a lower risk of fatal and non-fatal CV events compared with wait-listed patients on dialysis, but a much higher risk compared with the general population. CVD is the leading cause of morbidity, mortality and death-censored graft loss after kidney transplantation (A).
- Reduced mortality after kidney transplantation compared to dialysis may be largely due to the reduction in CV risk associated with the improved kidney function that a successful transplant provides (B).
- CMV seropositivity has been associated with increased risk for death as a result of cardiovascular causes (C).
- Hyperlipidemia is less marked with tacrolimus so that lipid levels may decrease when patients are switched from cyclosporine to tacrolimus. Hyperglycemia is more common with tacrolimus (E).

Case 11.

A 27 y/o Caucasian woman with ESRD from primary FSGS, recently started on maintenance hemodialysis, is referred to you for pre-transplant evaluation. She would like to know about possibility of pregnancy after transplantation.

Which one of the following statements is MOST CORRECT regarding pregnancy after transplantation and immunosuppression ?

- A. The pregnancy rate after kidney transplantation is nearly similar compared with the general population.
- B. She can attempt to become pregnant as soon as her SCr starts to decline, since her risk of graft dysfunction will be low.
- C. Pregnancy has a significant unfavorable effect on long-term graft function regardless of the baseline allograft function.
- D. Mycophenolate is associated with an increased risk of congenital malformations, and therefore it is absolutely contraindicated during pregnancy.
- E. The use of cyclosporine in pregnancy increases the incidence of hypertension, and therefore it is absolutely contraindicated during pregnancy.

Answer D. Mycophenolate is associated with an increased risk of congenital malformations, and therefore it is absolutely contraindicated during pregnancy.

- Mycophenolate is associated with an increased risk of congenital fetal abnormalities and is therefore contraindicated in pregnancy. US FDA mandates that all female patients of childbearing potential acknowledge that they have been informed about the risks of mycophenolate during pregnancy (D).
- Fertility is usually improved within a few months after kidney transplantation. The pregnancy rate remains, however, significantly lower after kidney transplantation compared with the general population (A).
- It is recommended to wait at least 1 year after transplantation before becoming pregnant, and only to attempt to become pregnant when allograft function is stable ($\text{SCr} < 1.5 \text{ mg/dl}$) with no or minimal proteinuria ($< 500 \text{ mg/24h}$) (B). A 90% incidence of successful pregnancies has been reported for women with a baseline $\text{SCr} < 1.5 \text{ mg/dl}$
- Most studies suggest that pregnancy does not have an unfavorable effect on long-term graft function as long as baseline allograft function is excellent ($\text{SCr} < 1.5 \text{ mg/dl}$) (C).
- Although cyclosporine has the potential to cause or exacerbate maternal hypertension, it does not appear to be a major teratogen and is not absolutely contraindicated. Intrauterine growth retardation and small-for-gestational-age neonates have been reported with cyclosporine use and may reflect chronic vasoconstriction (E).

Case 12.

Which statement is MOST CORRECT about side effects of maintenance immunosuppressants after kidney transplant?

- A. Both cyclosporine and tacrolimus can cause hypokalemia and hypomagnesemia.
- B. Hirsutism and gum hypertrophy are more common with tacrolimus than with cyclosporine.
- C. Hypertension and hyperuricemia are more common with tacrolimus than with cyclosporine.
- D. Sirolimus is associated with de novo proteinuria and exaggeration of preexisting proteinuria.
- E. Since the introduction of enteric-coated formulation of mycophenolic acid (MPA), GI side effects are very rare now.

Answer D. Sirolimus is associated with de novo proteinuria and exaggeration of preexisting proteinuria.

- De novo proteinuria, nephrotic syndrome, and exaggeration of preexisting proteinuria have been reported with mTOR inhibitors (sirolimus, everolimus). Therefore, periodic quantitative monitoring of urinary protein excretion is recommended while on these drugs. Administration of mTOR inhibitors in proteinuric patients should be avoided (D).
- Both cyclosporine and tacrolimus can cause hyperkalemia and hypomagnesemia (A). Cyclosporine is associated with hirsutism and gum hypertrophy while tacrolimus can cause alopecia (B). Hypertension, hyperuricemia, and hyperlipidemia are more common with cyclosporine while hyperglycemia and neurotoxicity is more common with tacrolimus (C). The GI side effect profile (e.g. diarrhea, nausea, vomiting, dyspepsia) of the enteric-coated formulation of MPA is not significantly different from the original MMF, but anecdotally has improved symptoms in some patients (E).

Case 13.

A 55 year old patient with ESRD on dialysis receives his third renal transplant from a 68 y/o donor after cardiac death, with a cold ischemia time (CIT) of 30 hours. The transplant is placed in the R iliac fossa where a failed transplant was removed. There is good initial function with SCr falling from 4.9 pre-transplant to 2.1 mg/dl on POD#2. On POD#5, the urine output falls to 400 ml/day. A modest sized (10x8x10 cm) perinephric collection is seen on ultrasound. There is a good blood flow to the transplant kidney, and no hydronephrosis. Allograft biopsy shows 20% glomerulosclerosis and moderate vascular disease thought to be donor-related. Trough tacrolimus level was 9 ng/ml. One week later, the patient remains oliguric, BUN is 30 mg/dl and SCr is 12.5 mg/dl. Repeat ultrasound shows similar sized collection, and repeat biopsy findings are similar. Tacrolimus level is 5 ng/ml.

What would the BEST course of action be?

- A. Switch the tacrolimus to rapamycin because CNI-related renal vasoconstriction is the cause of his allograft dysfunction.
- B. Decrease tacrolimus dose further and repeat a biopsy in another week if there is no improvement in allograft function.
- C. Continue current management; the patient likely has ATN from the prolonged CIT, and allograft function will likely improve over the next week.
- D. Sample the perinephric fluid to rule out a urinoma and do a nuclear scan.
- E. Continue current management; the patient has no pain, and the collection likely represents a lymphocele.

Answer D. Sample the perinephric fluid to rule out a urinoma and do a nuclear scan.

- The possibility of a urinary leak/urinoma should be excluded (D).
 - SCr is disproportionately high, reflecting the re-absorption of urine (and therefore creatinine) by the peritoneum.
 - Presence of vascular disease in the allograft raises the possibility of vascular compromise of a number of vessels, including the vessels supplying the ureter. This is a risk factor for distal ureteric necrosis at the ureterovesical junction and urine leak.
 - A nuclear scan (or an antegrade pyelogram) may show extravasation of urine into the perinephric space and peritoneum. But demonstration of elevated fluid creatinine (>serum levels) is sufficient to diagnose urinoma
- It is less likely that tacrolimus toxicity would explain the worsening graft function, particularly after significant reduction in the dosage (A, B).
- ATN is less likely given the absence of tubular injury (either from ischemia or toxic nephropathy) on two biopsies (C).
- It is possible that the fluid collection represents a lymphocele, but unlikely to cause such significant graft dysfunction unless it was causing hydronephrosis or compression of the allograft (E).
 - Sampling the perinephric fluid and measuring creatinine levels from the fluid would allow one to distinguish between a lymphocele and a urinoma: urinomas would have markedly elevated levels of creatinine.
 - Absence of pain does not rule out a urinoma.

Case 14.

A 27 y/o AA man with ESRD from primary idiopathic FSGS who underwent a DDRT 6 weeks ago comes to your clinic for routine follow-up. He received rATG for immunosuppression induction followed by maintenance therapy with sirolimus, mycophenolate, and prednisone. His allograft function has been stable (SCr of 1.2 mg/dl). He reports to you today that he has noticed worsening b/l lower extremity edema. His BP is 128/78 mmHg. His physical exam is otherwise normal except for 2+ pitting edema of b/l lower extremities. Laboratory testing reveals SCr of 1.6 mg/dl, and a spot urine protein-to-creatinine ratio of 8. CBC is WNL, and sirolimus trough level is 7 ng/ml.

Which one of the following statements is MOST CORRECT regarding his case ?

- A. Predictors of recurrence for FSGS include rapid progression of initial disease to ESRD and adult-onset of disease.
- B. This is unlikely recurrent FSGS since the patient is currently treated with mycophenolate and steroids.
- C. Use of mTOR inhibitors have been shown to cause FSGS.
- D. This is unlikely recurrent FSGS since recurrence of primary FSGS is very rare.
- E. Recurrence of primary FSGS is unlikely to occur so quickly posttransplant.

Answer C. Use of mTOR inhibitors have been shown to cause FSGS.

- Sirolimus has been associated with the development of proteinuria, and FSGS (C).
 - In one study, of patients converted to sirolimus from CNI, 64% developed proteinuria. Of these, 30% were found to have FSGS.
 - Also associated with the collapsing form of FSGS.
 - Proteinuria was reversible in ~1/3 of patients after discontinuation of sirolimus.
- Major risk factors for recurrence of primary FSGS include childhood onset of initial disease, rapid progression of initial disease, white race, and a history of recurrence in a prior allograft (A).
- There is no association between maintenance immunosuppressive regimen and the risk of recurrent glomerular disease after transplantation (B).
- Risk for recurrent primary idiopathic FSGS vary from 30-50% (D). It can recur virtually immediately after transplantation and is likely due to a circulating permeability factor (E). However, the effectiveness of pre-transplant plasmapheresis and rituximab remains uncertain.

Case 15.

A 51 y/o Caucasian man with ESRD from IgA nephropathy underwent a DDRT (CMV D-/R+; EBV D-/R+). His posttransplant course was complicated by DGF with ongoing need for hemodialysis. An allograft biopsy was performed on POD#10 which showed severe ATN with no evidence of acute rejection upon which his tacrolimus dose was reduced to a trough level of 8 ng/ml. Patient, however, remained oliguric and dialysis-dependent so that a second allograft biopsy was performed on POD#20 which again revealed ATN with no evidence of acute rejection. He currently takes tacrolimus, mycophenolate, and prednisone. He has read about belatacept in internet and would like to know if changing his immunosuppressive regimen to include belatacept will help.

Which one of the following statements is MOST CORRECT regarding a regimen of belatacept, mycophenolate mofetile, and prednisone compared to a maintenance regimen of cyclosporin, mycophenolate mofetile, and prednisone ?

- A. Maintenance belatacept regimen may help to improve renal allograft function compared to cyclosporine-treated patients.
- B. He is at high risk for developing PTLD involving CNS (EBV D-/R+), and therefore belatacept is contraindicated in this patient.
- C. He is at high risk for developing CMV disease (CMV D-/R+), and therefore belatacept is contraindicated in this patient.
- D. Seven-year patient and graft survival rates are inferior in the belatacept regimen due to the higher likelihood of developing acute rejection.
- E. Switching to the belatacept regimen increases his risk for cardiovascular disease.

Answer A. Maintenance belatacept regimen may help to improve renal allograft function compared to cyclosporine-treated patients.

- Belatacept is a selective T cell costimulation blocker.
- In the BENEFIT trial, patients who received belatacept had better renal allograft function in terms of serum creatinine levels. Rates of death or graft loss were also significantly lower at seven years in patients who received maintenance belatacept compared with cyclosporine despite a higher incidence of early acute rejection (A, D).
- BP, lipid levels, and the incidence of new onset diabetes mellitus after transplantation (NODAT) were lower in the belatacept group (E).
- Higher incidence of PTLN involving CNS was seen in the belatacept group which was largely in EBV seronegative patients receiving EBV seropositive kidneys (EBV D+/R-). Thus, belatacept is used only in EBV-seropositive patients (B, C).

Case 16.

A 57 y/o Caucasian woman who underwent a LRRTx 10 years ago comes for routine follow-up to your clinic. Her creatinine remains at baseline ~1.2. She had an acute episode of gout 2 wks ago, which resolved after her PCP started her on a course of prednisone, which is now tapered down to her usual dose of 5 mg daily. She remains on tacrolimus and azathioprine for immunosuppression.

Which one of the following statements is MOST CORRECT regarding her management?

- A. Switch to cyclosporine, as this is associated with a decreased incidence of gout compared with tacrolimus
- B. Increase her prednisone to 10 mg daily, to prevent another attack
- C. Start her on allopurinol, to prevent another attack
- D. Reassure her that short-term NSAIDs can be used during an attack since her GFR is relatively intact

Answer D. Reassure her that short-term NSAIDs can be used during an attack since her GFR is relatively intact

- CSA is associated with higher risk of gout and hyperuricemia (A)
- A short course of pulse steroids is a reasonable option for treating acute gout attacks, but increasing maintenance dose of prednisone is not warranted for prevention of gout (B)
- Azathioprine is an antimetabolite and derivative of 6-mercaptopurine. It is converted to inactive 6-thiouric acid by xanthine oxidase. Thus, initiation of allopurinol or febuxostat (which inhibits this enzyme) should be avoided or must be monitored closely and azathioprine dose reduced by 25-50%. WBC and platelet counts should be followed closely (C).

Case 17.

A 44 yo female presents with fever, malaise and nausea for the past 5 days. She has no other localizing symptoms. She has had recent contact with her grandson, who is PPD+ and on INH. She herself has had no recent travel. Her medical history includes ESRD due to IgA nephritis, and she underwent DDRTx 8 months ago with no complications. Her donor had a positive CMV IgG level. At the time of transplant, her CMV IgG was negative. Her current medications include: MMF 1000 mg bid and rapamycin. She has been off steroids since 2 wks post-transplant, and her TMP-SMX and valgancyclovir were stopped 6 months post-transplant. On exam, her T= 102F, HR 90, BP 130/82. 98% RA. Lungs are clear auscultation, and rest of her exam is unremarkable. CXR shows diffuse, patchy infiltrates bilaterally. WBC 3.0, Hb 9.5, plt 175. SCr stable at 1.2, rapamycin level 6.7.

Which of the following would be the LEAST appropriate next step?

- A. Switch from rapamycin to tacrolimus
- B. Check an induced sputum for PCP and TB
- C. Obtain blood cultures
- D. Check CMV viral load
- E. Placement of a PPD

Answer A. Switch from rapamycin to tacrolimus

- While rapamycin (sirolimus) is associated with pneumonitis, it does not explain the constellation of symptoms and switching to tacrolimus would be premature
- With her fever and pulmonary infiltrates, full work-up of infectious causes must be entertained

Case 17 (cont'd).

Induced sputum was negative for PCP, TB and other organisms. Blood cultures were negative. CMV VL was 18,000 copies/ml. The diagnosis of CMV infection (with CMV pneumonitis) was made, and the patient was started on valgancyclovir 900 mg po bid, and her MMF was reduced to 500 mg bid. One week later, she felt better. She was no longer febrile, HR 70, BP 120/70. Lab results showed a creatinine of 1.2, rapamycin level of 6.2, WBC 1.2, Hb 9.2, and platelets 155. A repeat CMV VL is pending.

Which of the following is the MOST appropriate next step?

- A. Leukopenia likely represents worsening CMV infection, and foscarnet should be added to her treatment regimen
- B. Leukopenia likely represents a resistant strain of CMV, and she should be switched from valgancyclovir to foscarnet
- C. Leukopenia likely represents a marrow-suppressive effect of valgancyclovir, and her dose should be reduced
- D. Leukopenia likely represents a marrow-suppressive effect of valgancyclovir, and she should be switch to foscarnet
- E. Leukopenia likely represents a marrow-suppressive effect of valgancyclovir, and she should be started on G-CSF

Answer E. Leukopenia likely represents a marrow-suppressive effect of valgancyclovir, and she should be started on G-CSF

- CMV infection can cause BM suppression and leukopenia, but assuming resistance or worsening viremia would be premature (A,B). There is no evidence to support the addition of foscarnet (with valgancyclovir). Foscarnet is nephrotoxic (causes ATN) and is avoided unless there is resistance or worsening viremia despite valgancyclovir treatment (D)
- Lowering valgancyclovir dose would be inappropriate and place the patient at high risk for developing CMV resistance (C)

Case 18.

Which statement is INCORRECT regarding the evaluation of a potential renal transplant recipient?

- A. Donor and recipient EBV IgG negative status increases the risk of PTLD
- B. Recent diagnosis of breast ductal carcinoma in situ is not a contraindication to transplant
- C. High panel reactive antibody is associated with longer waiting time on the deceased donor list
- D. ABO-O blood group is associated with longer waiting time on the deceased donor list compared with ABO-AB
- E. CMV serology is performed to match CMV negative recipients to CMV negative donors

Answer E. CMV serology is performed to match CMV negative recipients to CMV negative donors

- CMV serology is performed to determine the risk of CMV infection, superinfection or reactivation in recipients. Both donor and recipient CMV IgG status is used to guide decisions regarding prophylaxis.
- PTLD risk is highest among EBV-negative recipients (no prior exposure) of EBV-positive donor organs (24-fold increase risk)
- Absolute contraindications to transplant: active infection, active malignancy, active substance abuse, reversible renal failure, uncontrolled psychiatric disease, treatment non-adherence, life expectancy <1yr. Typically, a five-year cancer-free interval is recommended prior to transplant. In the case of breast DCIS, a 2-yr wait may be appropriate.
- Median waitlist time:
 - blood type O = 1851 days; A = 1207; B = 1935; AB = 853

Case 19.

45yo male with ESRD 2/2 Type I DM presents 2 wks after undergoing DDRTx. He complains of fevers to 101 F, malaise and vague pain over the allograft. His current medications include: tacrolimus 3 mg bid, MMF 1g bid, TMP-SMX daily, and valgancyclovir 450 mg daily. On examination: T 100 F, HR 110, BO 130/80, with mild tenderness over the allograft in the RLQ. His JP drain has drained 200ml of serous fluid in the last 24h, up from 40-50 cc/d last week. Labs show his creatinine is elevated to 2.7 (from a nadir of 1.2 last week), WBC 15. UA shows 1+ blood, 1+ protein, 1+ WBC, with trace bacteria. Ultrasound shows a small fluid collection (3x3x5 cm) medial to the graft, and a stent going from the renal pelvis to the bladder. Blood flow is seen throughout, and there is no evidence of hydronephrosis. Urine culture is pending, and JP fluid creatinine is measured at 90 mg/dL.

Which of the following is the MOST appropriate next step?

- A. Obtain a renal allograft biopsy
- B. Obtain a renal allograft biopsy, and start empiric pulse IV solumedrol 500 mg daily x3 days while awaiting biopsy results
- C. Remove the urinary stent
- D. Arrange for IR to sample the fluid collection around the allograft.
- E. Insert a foley catheter

Answer E. Insert a Foley catheter

- The elevated JP fluid creatinine level is diagnostic of a urinary leak/urinoma. Treatment is to insert a foley catheter and monitor the patient for improvement in creatinine levels and resolution of the fluid collection by ultrasound. A nuclear scan can be performed to evaluate for and follow the urinary leak.
- A renal allograft biopsy is not necessary, as the elevated creatinine can be explained by the presence of the urinoma
- The urinary stent reduces the risk of urinary leak, so its removal is not warranted
- There is no need to sample the abdominal fluid collection, as the diagnoses has already been made.

Questions?

Melissa Yeung, MD, FRCPC, FAST

myeung@rics.bwh.harvard.edu



Edgar Milford, MD

Harvard Medical School

Internal Medicine Residency, Columbia P&S

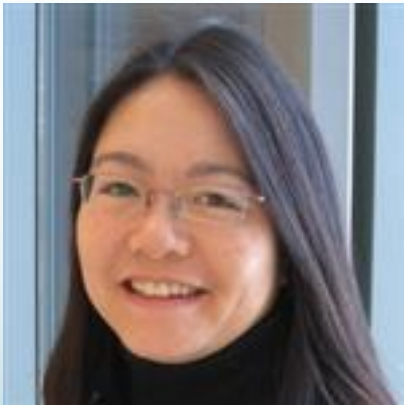
Nephrology Fellowship, Columbia P&S

Nephrology Fellowship, Brigham & Women's Hospital

Associate Professor of Medicine, Harvard Medical School

Clinical focus: kidney transplant, HLA

Research focus: immunogenetics



Melissa Yeung, MD

University of Ottawa Medical School

Internal Medicine Residency, Maine Medical Center

Nephrology Fellowship, MGH/Brigham & Women's Hospital

Assistant Professor of Medicine, Harvard Medical School

Clinical focus: kidney transplant, HLA

Research focus: regulatory B cells, alloantibody