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Medical Management of the Kidney Transplant Recipient

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1. Introduction

Once a patient receives kidney transplant, critical attention should be paid to ensure patient's hemodynamic stability, they should be monitored for any side effects of the new medications and prevent infections that may jeopardize the renal allograft and patients' general health. Medical problems such as diabetes and hypertension that may be medical complications of transplant immunosuppression need to be managed appropriately. This chapter will go over the medical management of the kidney transplant recipient.

2. Early post operative management

2.1. Assessing fluid status

There are two broad goals to assess fluid status: the transplanted kidney needs to receive adequate perfusion and make adequate amounts of urine.

When patients' are admitted for kidney transplant, it is preferred to have the patient about 1kg above their dry weight (1). This is to decrease the risk for hypotension intra-operatively, and ensure that the patients are somewhat hypervolemic and there is enough mean arterial pressure to perfuse the new transplanted kidney at the end of the surgery. Post transplant, it is important to assess urine output on hourly basis to ensure that patients are not oliguric, i.e., urine output should at least be greater than 0.5ml/kg/hr or 500ml/24hrs. Patient's pre-transplant urine output should be known and be accounted for when assessing for urine output adequacy post-transplant. Initial blood pressure and volume status on clinical exam should dictate fluid replacement. If the patient is hypovolemic, patient should be given isotonic saline in 500ml to 1L boluses until mean arterial pressure of at least 65 mm hg can be established. Most patients are hypervolemic. In that scenario, it is not necessary to replace all of the urine output.

There are many different protocols for replacement and maintenance fluids. In general, there is no evidence that crystalloids are better than colloids. Replacement fluid should also account for any other body fluid losses such as in nasogastric tube output. Half normal saline can be used for replacement fluid as urinary sodium after kidney transplant initially tends to be between 60 and 80 mEq/L (1). Maintenance fluids should account for insensible losses which can range in from 500cc to 1500cc in a 24 hour period for surgical patients (3). Typically the maintenance fluid used is 5% dextrose in water at the rate of at least 30cc/hr (1). For cases where electrolyte replacement is needed such as in potassium, this should be carefully given monitoring for any risk of hyperkalemia if patient is oliguric and preferably through a separate intravenous line. Electrolytes including potassium, phosphate, calcium and magnesium should be checked at least every 6 hours (1).

2.2. Delayed & slow graft function

The consensus definition of delayed graft function (DGF) is lacking, though, it is generally agreed upon that if dialysis is needed within first 7 days of transplant that constitutes delayed graft function (2). Delayed graft function, in reality, is acute kidney injury in transplanted kidney and should be worked up as any other acute kidney injury with attention paid to the special circumstance that is kidney transplant and differential diagnosis broadened accordingly to include acute rejection as well as acute ischemic tubular necrosis.

The long waiting list of patients awaiting kidney transplant and shortage of donors has necessitated accepting expanded criteria donors (ECD) and donation after cardiac death donors (DCD). Not surprisingly, incidence of DGF has increased to 21% for the years 1998-2008 from 14% during 1985-1992 (6,7,9). DGF increases the risk of graft rejection, transplant glomerulopathy and ultimately, decreases the long-term allograft survival (4,11,12). Long-term patient survival after DGF is not known, but it is likely that patients who suffer graft failure compared to patients with functioning grafts may have decrease survival rates. Besides ECD and DCD kidneys, there are several other risk factors for DGF. Donor specific risk factors include: donor age >60, cold ischemia time >15 hours, warm ischemia time > 45 minutes, Non T-cell antibody induction, female gender and obese donor (5, 7, 8, 9, 10, 13, 14, 15, 16). Recipient risk factors include: maintenance hemodialysis prior to transplantation, obesity, diabetes, male gender, age > 55, African-American race, small-for-size organ and prior immune sensitizing events such as blood transfusions, pregnancy and previous transplant (7, 10, 15, 16, 17). Machine perfusion technique for preservation of organ also seems to decrease the risk for DGF in ECD kidneys (7). The underlying mechanisms including molecular pathways and cytogenetic mechanisms are being established and may aid future prevention as well as treatment measures for DGF. For now, focus remains on prevention with controlling for risk factors as well as trying to avoid intra-operative and post-operative hypovolemic states and hypotensive conditions. If patient does have DGF, patient is supported with preventing further nephrotoxicity from all measures and providing dialysis until allograft kidney function recovers.

Indications for dialysis should be dictated by clinical circumstances but persistent acidosis, hyperkalemia especially with EKG changes suggestive of destabilization of cardiac membrane and volume overload that is resistant to high doses of diuretics. Both intermittent hemodialysis and peritoneal dialysis can be used. When hemodialysis is used, close attention should be paid to patient's blood pressure and unless need for hypervolemic status, ultrafiltration should be avoided. Peritoneal dialysis can be used, though, dwelling volumes may need to be as low as 500ml in order to avoid worsening pain (1). Preferably hemodialysis should be performed, unless peritoneal dialysis catheter is readily available.

There is a subset of transplanted patients that do not require dialysis within the first 7 days, but the serum creatinine is very slow to decrease. This group of patients can be defined as having intermediate graft function or slow graft function (18). The risk factors and the graft outcomes are likely similar to DGF, though less severe (18). This can possibly be explained by lesser severity kidney injury or lesser degree of baseline clinical or subclinical kidney dysfunction in the allograft (18).

2.3. Immunosuppression

Every transplant center has their own immunosuppressive protocol which serves as guides for therapy based on type of transplant (kidney vs. kidney-pancreas) and patient's risk group determined by pre-formed antibodies, sensitization status, age and race (2). Low-risk group patients such as two-haplotype match may require less immunosuppression. African-Americans, on the other hand, have been shown to require higher doses of immunosuppression.

There are two phases to immunosuppression. Acute rejection risk is highest from time zero to first few months after transplantation (2). The immunosuppression induced at time zero is called induction phase. Maintenance immunosuppression is also introduced early-on, however, this therapy is maintained for the rest of the patient's transplant life and constitutes the post-induction phase, the maintenance phase.

Both phases of immunosuppression are described in a separate chapter in this textbook and will not be further discussed here

2.4. Infection prophylaxis

All patients undergoing kidney transplant should received prophylaxis for infection as immunocompromised state post-transplant puts this group of patient at high risk of life-threatening common and uncommon infections. Any infection subsequently also increases risk of allograft failure through primary (e.g. ATN secondary to sepsis) or secondary mechanisms (e.g.. allograft rejection).

The following antimicrobial therapy should be given peri-operatively (1,2):

1. Standard antibiotic pre-operative prophylaxis per center based guidelines should be used. Prophylaxis should be against common skin and urinary tract pathogens. Cefazolin 1 or 2 grams based on body weight, generally, is the preferred agent.

2. Also, bactrim should be introduced as prophylaxis against for UTI, sepsis, nocardia and pneumocystis jiroveci pneumonia (pjp). One single strength tablet daily is the general recommendation. Dosing should be done renally and adjusted to patient's creatinine clearance. For UTI prophylaxis, patients allergic to bactrim can use any other oral quinolone such as levaquin. In that scenario, patients should also get atovaquone 1500mg daily for pneumocystis jiroveci. Pentamidine monthly nebulized is another option if atovaquone cannot be tolerated. Dapsone 100mg daily may be used for same prophylaxis, though G6PD status must be checked. Any such prophylaxis should be continued for one year for pjp prophylaxis.
3. CMV status should be checked for both donor and recipient. CMV negative recipients from CMV positive donors are at highest risk for CMV disease as are patients receiving OKT3 or other t-cell depleting agents. CMV positive recipients are at risk for reactivation. All such patients should receive valganciclovir 900mg daily or three times weekly adjusted to renal function for 6 months. Alternatively, ganciclovir 1000mg three times daily or valacyclovir 2g four times daily can be used. All donor and recipient CMV negative patients should receive Acyclovir 400mg twice daily for 3 months.
4. During induction phase, oral or topical antifungal agents such as clotrimazole or nystatin are used. Systemic antifungal agents are not recommended in uncomplicated renal transplant.

3. Early post-transplant follow-up: First three months

3.1. Immunosuppression

The risk of acute rejection and allograft loss is highest in the first three months, so immunosuppression should be at its highest levels in this time period. The topic of immunosuppression has been reviewed in a separate chapter.

4. Long-term follow-up

4.1. Immunosuppression

All patients should be maintained on 2 or 3 drug regimen as long as the patient has functional graft. Target drug levels may be lowered after the first three months.

4.2. Patient and graft survival

Graft survival (i.e., patient survival with a functioning graft) has steadily improved. Graft survival for deceased donor kidneys in 2009 was 94.4% at 6 months; for transplants in 2008, 92.0% at 1 year; for transplants in 2006, 81.9% at 3 years; for transplants in 2004, 70.0% at 5 years; and for transplants in 1999, 42.7% at 10 years (19). Graft survival for living donor transplants in 2009 was 97.7% at 6 months; for transplants in 2008, 96.5% at 1 year; for transplants in 2006, 90.9% at 3 years; for transplants in 2004, 82.5% at 5 years; and for transplants in 1999, 59.6% at 10 years (19). While one-year graft survival has improved significantly, there is much room for improvement in 10-year graft survival.

The rate of late graft failure is traditionally measured by the graft half-life conditional on 1-year survival, defined as the time to when half of grafts surviving at least 1 year are still functioning. Graft half-lives for deceased and living donor kidneys have increased (19). For deceased donor kidneys, the half-life increased 45%, from 10.1 years for transplants in 1991 to 14.7 years for transplants in 2007 (19). For living donor kidneys, the half-life increased 68.2%, from 15.8 years for transplants in 1991 to 26.6 years for transplants in 2007 (19). Remarkably as per the 2010 Scientific Registry of Transplant Recipients/Organ Procurement and Transplantation Network annual report, the half-life of a deceased donor kidney in 2007 (14.7 years) is less than the half-life of a living donor kidney in 1991 (15.8 years). This suggests there is substantial room to improve the rate of late graft failure, at least for recipients of deceased donor kidneys.

The number of patients with a functioning kidney graft has doubled, from 68,200 in 1998 to 144,180 in 2009 (19).

Besides donor type, DGF and presence of HLA-antibodies also reduces the short-term graft survival. Long-term graft survival is also reduced by DGF, history of known HLA antibodies, HLA mismatching, cold ischemia time and insufficient immunosuppression. Inadequate renal mass for body size, CMV seropositivity, ongoing renal injuries, medical non-compliance, poorly managed hypertension, hyperlipidemia and recurrent or *de novo* glomerular disease are some of the other risk factors portending shorter graft survival.

The most common causes of death in kidney transplant recipients include death from cardiovascular disease followed by infection, malignancy and other miscellaneous causes. The miscellaneous causes, such as pulmonary embolus, brain hemorrhage, colon or peptic ulcer perforation etc. can contribute 1-2% each to annual death rate (20). Death from cardiovascular disease remains the leading cause of mortality. It accounts for 40-55% of all deaths in transplant recipients (20). This includes congestive heart failure, coronary artery disease, cerebrovascular disease, and peripheral vascular disease. Renal transplant recipients have up to 10 times the rate of cardiac death and 50 times the annual rate of fatal or nonfatal cardiovascular events as the general population (21). Nearly 40% of patients have experienced a cardiovascular event at 36 months after renal transplantation, with congestive heart failure and myocardial infarction being the most common events (22, 23)). The prevalence of cerebrovascular events, though less than dialysis patients, is still high in patients who have undergone renal transplantation, and the risk of cerebral hemorrhage is higher than in the general population (24, 25). Finally, incidence of peripheral arterial disease is lower in renal transplant recipients, though *de novo* peripheral arterial disease increases the relative risk for death by almost twofold (26).

There are also other risk factors that impact survival of transplant recipients. Survival is superior with an allograft from a living donor compared to those who receive a kidney from a deceased donor, including both standard criteria and extended criteria donors. Older patients who undergo renal transplantation have a higher mortality rate than younger recipients. The presence of systemic disorders, particularly vascular disease, is associated with poorer long-term patient survival after renal transplantation. Survival of diabetic

patients after renal transplantation (75 to 80 percent at five years) is lower than that reported in nondiabetic patients. It is still better than diabetic patients on dialysis whose 5-year survival is estimated to be 30% (2).

Perhaps, the most important predictor of graft survival is renal function. 1-year creatinine of less than 1.5mg/dl and change of less than 0.3mg/dl portends excellent long-term graft survival (5). Higher creatinine values at one year signal poor long-term graft outcome.

Despite all of these, patient and graft survival has improved significantly in the recent decade, which likely reflects our improved ability to manage patient and graft related risk factors.

5. Management of medical co-morbidities

5.1. Hypertension

Immediate post transplant hypertension is common and most commonly reflects pain, although, could also reflect overzealous volume resuscitation (27). If patient is volume overloaded, he or she should be diuresed. Controlling pain likely needs to be done simultaneously as sometimes early-on it is difficult to determine the causative etiology of hypertension. Moderately elevated blood pressure should be tolerated as it will help to maintain adequate renal perfusion to the transplanted kidney. However, if blood pressure is greater than 180mm hg despite best pain control in euvolemic patient, a dihydropyridine calcium channel blocker such as nifedipine can be used (28). This will allow for dual benefit of ameliorating some of the afferent arteriolar vasoconstriction induced calcineurin inhibitors. Alternatively, an alpha blocker such as clonidine can be used if pain is difficult to control and blood pressure remains high, i.e., there is excessive sympathetic stimulation. Blood pressure should not be lowered below 110 mm hg. If patient is not taking medications orally, labetalol or hydralazine can be used for intravenous administrations.

Chronic hypertension is a risk factor for CVD and affects graft survival in the long-term (27). In the era of CNIs, roughly 60-90% of patients seem to be afflicted with hypertension (29). The etiology of hypertension is likely multifactorial and management needs to be more nuanced. Goal blood pressure as defined by KDOQI guidelines should be <130/80 mm Hg (30). The same medications used for hypertension control in general population may be beneficial in renal transplant population as well.

KDOQI establishes five points for the evaluation and management of hypertension in renal transplant patients (30). First, patients should be evaluated for chronic kidney disease, cardiovascular disease and any cardiovascular risk factors. Second, diet and lifestyle changes should be part of all therapy including sodium intake <2.4g/day, weight loss if BMI is >25kg/m², exercise, moderate alcohol intake and smoking cessation. Third, risk factors for cardiovascular disease should be managed concurrently such as diabetes and hyperlipidemia. Fourth, systolic blood pressure should be managed to less than 130 mm Hg with anti-hypertensive medications. Fifth, for patients with spot urinary protein-to-creatinine ratio >500-1000mg/g a lower blood pressure goal may be advisable, an ACE

inhibitor or ARB should be added or dose should be increased, ACE inhibitor or ARB may need to be used in combination and if still needed another antihypertensive medication should be added as needed to lower proteinuria.

Since calcium channel blockers are used early in transplant, they can be considered first-line therapy (29). ACE inhibitors are second line therapy and have been shown safe to use 6-12 weeks after transplant. For de novo initiation, it is recommended that therapy be started at least 6 weeks post-transplant (29). A recent randomized study comparing nifedipine and lisinopril demonstrated improved kidney outcomes (lower creatinine and improved GFR at 2 years) with the use of nifedipine (28). However, the study had limited follow-up, and it cannot be determined whether the improved GFR with calcium-channel blockers reflects the short-term hemodynamic effects of these agents or a long-term protective effect. Post transplant patients with hypertension and a compelling indication for an ACE inhibitor or an ARB should be restarted on therapy as soon as the graft is functional, the serum creatinine level is <2.5 mg/dL, and the potassium level is <5.5 mEq/L. If the patient has proteinuria, ACE inhibitor or ARB can be used as long as the reduction in GFR is less than 30% over 4 months. Since ACE inhibitor or ARB can potentiate hyperkalemia caused by CNIs, close attention should be paid to patient's potassium. Finally, tailoring of therapy for hypertension should be ultimately based on patient's risk factors as discussed below.

Heart failure patients can be treated with thiazide diuretics (assuming adequate function of the transplant kidney), beta-blocker, ACE inhibitor or an ARB. Post-MI patients can be treated with beta-blocker and ACE inhibitor. Patients with cardiovascular risk factors can be treated with same anti-hypertensive medications as heart failure patients. Patient with diabetes may benefit from added anti-proteinuric effect of non-dihydropyridine calcium channel blocker such as verapamil. Verapamil can increase the levels of CNIs and levels need to be monitored more closely. Patients with CKD, previous stroke and post transplant erythrocytosis may benefit from ACE inhibitor. ARB can be used as an alternative in cases of CKD and post-transplant erythrocytosis. All of the above indications for specific anti hypertensive regimens for various clinical entities have nicely been summarized by Dunn et al. as well (29).

Renal artery stenosis in allograft is a rare cause of hypertension and should be thought of when blood pressure is persistently elevated despite multiple pharmacologic interventions, patient has flash edema and/or sudden elevations in blood pressure. It usually occurs 3 months to 2 years after transplant, but early occurrences can happen post-transplant (31). Reported incidence is variable between 1 and 23%. Risk factors for renal artery stenosis include deceased donor kidney, delayed graft function, obese patients, severe atherosclerotic disease, CMV infection, difficulties with surgical technique when harvesting the graft or when transplanting the graft in the recipient (31). In this scenario, a Doppler renal ultrasound can be ordered which has 100% specificity and sensitivity when peak systolic velocity is greater than or equal to 2.5m/sec (2). MRI may be needed and should be pursued after discussing risks and benefits of nephrogenic systemic fibrosis with the patient. Stenting or surgery may be necessary if patient does have renal artery stenosis.

5.2. Diabetes

New-onset diabetes after transplant (NODAT) or pre-transplant diabetes is associated with increased CVD risk, especially NODAT. Diabetes is also associated with increased mortality (87% relative risk) and increased graft failure (63% relative risk) (35). Other complications seen in non-transplant patients such as retinopathy, nephropathy and infections especially in immunocompromised state as well as neuropathy resulting in diabetic ulcers can occur. It is estimated that about 30% of patients can have new diagnosis of diabetes post-transplant and another 1/3rd can have impaired glucose tolerance by 1 year post-transplant (32). Risk factors for NODAT are same those for developing diabetes in non-transplant patients including age, obesity, African American race and Hispanic ethnicity, family history and impaired glucose tolerance (2). Tacrolimus more than cyclosporine has been associated with NODAT, perhaps due to its higher toxicity to pancreatic islet cells (34). Furthermore, a strong association has been demonstrated between HCV status and the development of diabetes after kidney transplantation, particularly in patients receiving tacrolimus-based immunosuppression from the time of transplantation (33).

According to 2003 International Consensus Guidelines and subsequent updates, diabetes mellitus after transplantation may be diagnosed at any time after transplantation by any of the following (35, 36):

- Symptoms of diabetes plus random plasma glucose ≥ 200 mg/dL (11.1 mmol/L). Symptoms include polyuria, polydipsia, and unexplained weight loss.
- Fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least eight hours.
- Two-hour plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test with 75g of anhydrous glucose dissolved in water according to WHO guidelines.

Impaired fasting glucose and/or impaired glucose tolerance is diagnosed by:

- Fasting plasma glucose between 100 and 125 mg/dL (5.6 and 6.9 mmol/L) or a two-hour plasma glucose between 140 and 199 mg/dL (7.8 and 11.0 mmol/L) during an oral glucose tolerance test, respectively, according to ADA guidelines.

Management of diabetes includes screening for risk factors, monitoring for biochemical evidence of impaired glucose tolerance/NODAT, modifying immunosuppression as needed and treating diabetes mellitus aggressively.

Stepwise approach to evaluation and management is recommended by International Consensus Guidelines for renal transplant patients (35). Pre-Transplant patients should be screened for diabetes. Post-transplant HbA1c should be checked every 3 months for the 1st year and a HbA1c < 7.0 should be targeted, even if insulin is required. Immunosuppression modulation must be weighed against the risk of rejection and avoided if at all possible. If modulated, glucocorticoids dosage can be reduced first, followed by decreasing dosing of tacrolimus and switching to cyclosporine if still needed. Dietitian, ophthalmologist, endocrinologist and podiatrist should be involved early in management of diabetic patients.

Microalbuminuria should be treated with ACEI or ARB. Non-pharmacologic management should be given a chance including diet, exercise before pharmacologic approach is accepted. Other risk factors including lipids should be managed appropriately as CVD risk factor.

Once decision has been made to initiate oral therapy, oral agent may be alpha-glucosidase inhibitor (e.g., acarbose), biguanide (metformin is the most commonly used biguanide), a meglitinide (e.g., repaglinide), a sulfonylurea, or a thiazolidinedione (e.g., rosiglitazone) (35). Metformin is contraindicated in women with $cr > 1.5 \text{ mg/dl}$ and in men with $cr > 1.4 \text{ mg/dl}$ for concern of lactic acidosis (23). Sulfonylureas are safe in general to use, but glyburide should be avoided in patients with $GFR < 50 \text{ mL/min/1.73 m}^2$ (23). Acarbose should be avoided with $cr < 2 \text{ mg/dl}$ (23). Repaglinide should be started at 0.5 mg with meals if $GFR < 40 \text{ mL/min/1.73 m}^2$ and titrated carefully (23). Thiazolidinediones do not require any dose adjustment. Other medication such as exenatide, an incretin mimetic should be avoided if $gfr < 30 \text{ mL/min/1.73 m}^2$ (23). Dipeptidyl Peptidase-4 inhibitor, sitagliptin needs to be dosed renally (23).

As a complication of pre-existing diabetes if patients do develop diabetic ketoacidosis, they should be managed in intensive care unit. Algorithm is available from American Diabetic Association for management and should be closely followed. Volume resuscitation and insulin drip should be initial treatment. Many liters of normal saline may be required especially in post-op setting. Close eye should be kept on magnesium, potassium and phosphorous and they should be repleted aggressively. Subcutaneous insulin can be switched to once anion gap closes with 3-4 hours overlap with insulin drip.

5.3. Dyslipidemia

Dyslipidemia is common after kidney transplant. Although causative association between kidney transplant and cardiovascular disease (CVD) remains unproven, kidney transplant is considered to be coronary heart disease equivalent risk (37). Accordingly, hyperlipidemia should be managed aggressively.

Elevations in total cholesterol with low-density lipoprotein (LDL) are common, and triglycerides can be elevated often as well (23, 37). High-density lipoprotein (HDL) is usually normal. Cyclosporine, rapamycin and steroids have the greatest effect on serum lipid levels in dose-related fashion (23, 37). Other traditional risk factors as diabetes, obesity, smoking, hypertension, genetic factors and physical inactivity are also of equivalent importance. KDOQI has published guidelines for management of dyslipidemia in CKD patients which should be followed for transplant patients as well. Given the benefits of lowering CVD risk in general population and high risk of CVD in transplant population, the same risk reduction steps in terms of managing dyslipidemia should be taken for the transplant population. Goal LDL should be less than 100 mg/dl (38). Therapeutic lifestyle changes (TLC) should be applied above 100 mg/dl of LDL which include goals for intervention to minimize traditional risk factors. Patients should be counseled in smoking cessation with any necessary pharmacotherapy and psychotherapy, controlling blood

pressure as detailed previously, reducing saturated and trans fats, taking daily 81mg aspirin, at least 30minutes of walking at least 5 days a week or running 15 mins for 3 days a week, weight loss of at least 10% in 1st year and managing diabetes as discussed previously (23, 37). If TLC fails to lower LDL below 100mg/dl, statins should be added to TLC. If the LDL level is 130mg/dl or more, TLC and statins should be initiated simultaneously. Careful attention should be paid to introduction of statins to cyclosporine-based medication regimen. Cyclosporine increases AUC of all statins and especially with fluvastatin can cause rhabdomyolysis (23, 38). A good rule of thumb in this scenario is to use half of the recommended dose of statins with cyclosporine and tacrolimus (23, 37). Bile acid sequestrants such as cholestyramine are not typically recommended because they interfere with absorption of immunosuppressive medications, unless patients have severe coronary disease, have failed maximal medical management and risk of mortality from ischemic heart disease outweighs risk of rejection.

Triglycerides (TGs) should be below 500mg/dl and may need pharmacotherapy above these levels to reduce the risk of pancreatitis in addition to TLC (37). Consideration should also be given, in cases where maximal medical management has failed to lower LDL below recommended levels, to changing the immunosuppressive protocol to one that is less likely to cause high LDL levels, if this can be done without causing undue risk to graft (37).

Non-HDL cholesterol, which is calculated as total cholesterol minus HDL cholesterol may be a better predictor of coronary mortality and may be a surrogate for the major atherogenic protein, apolipoprotein B (38). Lowering non-HDL cholesterol to less than 130mg/dl may ultimately require a combined approach to reduce LDL and TG. If LDL is less than 100mg/dl or more but TGs are 200mg/dl and non-HDL is 130mg/dl or more, treatment of non-HDL to levels below 130mg/dl should be pursued with statin and fibrate or nicotinic acid (37).

The overall prevalence of dyslipidemia during the first year after transplantation is >50% (23). This high prevalence of dyslipidemia justifies screening and monitoring. In all adults, complete lipid profile should be checked (23, 37):

- 2-3 months after transplantation, or
- 2-3 months after change in treatment, or other conditions known to cause dyslipidemias, and
- At least, annually thereafter

5.4. Obesity

Obesity in adults is defined, as it is in major guidelines for the general population, as body mass index (BMI) ≥ 30 kg/m² (23). Because some individuals may have BMI ≥ 30 kg/m² that is not due to excess body fat, it is recommended that the definition of obesity in adults include waist circumference ≥ 102 cm (≥ 40 in.) in men and ≥ 88 cm (≥ 35 in.) in women (23).

Weight gain is common after renal transplant and can be associated with steroid usage (38). Hyperphagia as a side effect of steroid usage also contributes. Obesity contributes to dyslipidemia, hypertension, CVD and diabetes mellitus in transplant patients. Risk factors

for weight gain post-transplant include female gender, African American race and young age (38). Obesity is also a risk factor for DGF (See Delayed Graft Function) and obese renal transplant recipients suffers more surgical complications, including wound infections, delayed wound healing, lymphoceles and perinephric hematomas (1,38, 39). Longer surgical times and hospital stays are also reported in obese transplant recipients (38). Obesity is also a risk factor for decreased pancreas and kidney graft survival in combined pancreas-kidney transplant recipients (1).

Is it beneficial to lose weight before transplantation? DOPPS found that in dialytic population higher BMI (30-34.9 kg/m²) is associated with lower mortality (42); higher mortality is associated with malnutrition (38). Weight loss also remains a difficult goal to achieve in dialytic population. Should the obese patients be excluded from transplant? Evidence has shown that when obese patients are transplanted their mortality rate is lower than the dialytic population (38).

Obesity in transplant patients should be managed with diet, exercise and nutritional counseling. A nutritionist should be involved in management. Small, uncontrolled trials in KTRs suggest that diet and other behavior modifications are safe and help reduce weight over the short term (40, 41). There is no evidence that any one diet is more effective than any other. A reasonable goal is to create a caloric deficit of 500–1000 kcal/day (23). Diets of 1000–1200 kcal/day for women and 1200–1500 kcal/day for men can be effective with increased physical activity in maintaining sustained weight loss (23). Weight loss medications have not been studied in renal transplant patients and as such Orlistat should not be given with cyclosporine as it interferes with its bioavailability and absorption. In cases of morbid obesity, patients may choose to undergo gastric bypass. This procedure may be safe in transplant patients, though, experience is limited (38). Absorption and metabolism of immunosuppressive medications may be altered after gastric bypass. Cyclosporine, tacrolimus, sirolimus and mycophenolic acid levels have been noted to be altered in gastric bypass patients and requires specific levels for those medications to be followed up (43). Gastric bypass also increases risk for hyperoxaluria and oxalate nephropathy, and when undergoing gastric bypass patients should be advised against risks for oxalate nephrolithiasis and secondary CKD (38). When patients develop oxalate nephropathy, reversal of bypass needs to be considered (38).

5.5. Smoking

Given smoking's pleotropic detrimental effects on almost every organ in our body and association with CVD as well as post-transplant cancer, intense efforts should be made to help patients quit smoking. This should include asking at each visit, advising to quit, providing psychiatric and non-psychiatric counseling as needed, initiating pharmacotherapy as needed and helping patients set up target dates to quit smoking. Studies have shown that the patients more likely to quit smoking have been more likely than not been counseled by their physicians. Even counseling for 3 min or less is effective (44). The '5 As' of counseling include: (i) ask about tobacco use, (ii) advise to quit through

clear and personalized messages, (iii) assess willingness to quit, (iv) assist quitting and (v) arrange follow-up and support (44). A number of pharmacological approaches are available to promote smoking abstinence. All nicotine replacement therapies such as lozenges, gum, inhaler, spray and patch are safe to use (23). Varenicline, a partial agonist of nicotinic receptor can also be used in transplant recipients (23). Bupropion increases cyclosporine levels and they should be monitored (23).

5.6. Cardiovascular disease

So far we have discussed the traditional risk factors of CVD. Non-traditional risk factors such as homocysteine, uremia, left ventricular hypertrophy and graft dysfunction also have a significant role to play (21). There is a complex interplay between traditional and non-traditional risk factors causing CVD in kidney transplant patients. The strongest risk factor for cardiac risk is pre-existing CVD prior to transplant. All risk factors as discussed thus far should be managed aggressively whether patient has pre-existing CVD or new-onset CVD. Allograft dysfunction also contributes to CVD risk, whether this is mediated to systemic inflammation or through secondary hypertension, hyperlipidemia and albuminuria is unclear. Homocysteine levels are known to be significantly high in patients who experience cardiovascular events and are associated with higher mortality (45, 46). However, the causal effect of high homocysteine levels on CVD has not been established. High dose folic acid as well as vitamin B6 and B12 can effectively reduce homocysteine levels. When this reduction was achieved using folic acid, vitamin b6 and vitamin b12 in a randomized control trial, it did not reduce the all-cause mortality, ESRD or composite outcome which included cardiovascular death and myocardial infarction among other things (47). Another risk factor that increases CVD risk is anemia and this will be discussed next.

5.7. Anemia

World Health Organization defined anemia in 1968 as $<13\text{g/dl}$ for men and $<12\text{g/dl}$ for women which was based on observations from international nutritional studies (48). Since then there have been multiple attempts at re-defining anemia. Dependent on cut-off level of hemoglobin used for defining anemia, prevalence in post-transplant population varies roughly between 10% and 40% (49-53). Anemia is associated with worse patient and graft survival, higher rates of acute rejection and may further exaggerate left ventricular hypertrophy which is associated with higher cardiovascular mortality.

The belief that enough erythropoietin production with new allograft will resolve any degree of anemia in patients with CKD is not always fully realized (49). There can be many reasons for this phenomenon. In the early-post transplant period, anemia can be related to blood loss from surgery. Later on though the anemia may be related to decline in kidney function and secondary loss of erythropoietin production or from bone marrow suppression from immunosuppressants (50-53). However, other traditional and non-traditional risk factors need such as iron deficiency anemia with or without gastrointestinal bleeding, folate or vitamin b12 deficiency, hemolysis, parvovirus or other viral infections and medications need

to be investigated and treated appropriately (50-53). Iron deficiency anemia is under-recognized and under-treated in post-transplant patients. Up to 60% of patients without initial iron deficiency can become iron-deficiency by 6 months (2). Since iron deficiency is associated with cardiovascular mortality independent of anemia timely recognition and treatment is important. Iron repletion can be estimated by ferritin 200mg/dl and transferrin saturation above 20%. Parvovirus infection which can cause refractory anemia can be treated with intravenous immunoglobulin and by lowering immunosuppression (1). Azathioprine, mycophenolic acid and sirolimus can also cause anemia, and the doses of these medications may need to be reduced (1). Other medications such as ACEIs, ARBs, ganciclovir or trimethoprim-sulfamethoxazole also cause anemia and need to be kept in mind when cause is being investigated (1). When no cause is found, iron stores are adequate, allograft function is impaired and meets indications for treatment as they are stated by KDOQI guidelines for CKD patients, epoetin alfa and aranesp should be administered (1).

5.8. Thrombotic microangiopathy

As a related cause of anemia, thrombotic microangiopathy (TMA) needs to be included in differential diagnosis for causes of hemolysis. TMA is a histology manifestation of several clinical conditions such as TTP-HUS, antibody-mediated rejection (AMR) or toxicity of CNI. TMA may manifest itself limited to allograft or there might be evidence of systemic hemolysis such as increased lactate dehydrogenase, positive direct COOMBs test, increase indirect bilirubin, low haptoglobin and increase reticulocyte index with evidence of fragmented RBCs on peripheral smear. Thrombocytopenia accompanies systemic evidence of TMA. 15% of transplant patients have evidence of TMA and 3% show evidence of TTP (1). Treatment includes substitution of the calcineurin inhibitor with an alternative agent; belatacept and plasmapheresis may be utilized for management. If AMR is suspected, it should be treated accordingly; steroids should be pulsed, rituximab or bortezomib may also be used along with IVIG. Use of bortezomib may be limited by degree of thrombocytopenia. Another potential treatment if all else fails is eculizumab, which remains experimental.

5.9. Erythrocytosis

Post-transplant erythrocytosis (PTE) occurs in 8-15% of recipients (2). It is defined as a hemoglobin concentration greater than 17 g/dL and/or hematocrit greater than 51 percent that occurs following transplantation, persists for more than 6 months and occurs in the absence of another underlying cause (2). Most often PTE occurs within the first 8-24 months after transplantation (2). PTE appears predominantly in patients without native kidney nephrectomy and in those, who had an adequate erythropoiesis prior to transplantation, as evidenced by no or limited use of ESA while on dialysis (54). The pathogenesis of PTE is not well understood and multiple hormonal systems as well as growth factors such as erythropoietin, Insulin-like growth factor-1, serum-soluble stem cell factor (sSCF), rennin-angiotensin system and endogenous androgens have been implicated (2, 55-59). Endogenous erythropoietin appears to play the central role. Persistent erythropoietin

secretion from the diseased and chronically ischemic native kidneys does not conform to the normal feedback. However, erythropoietin levels in most PTE patients still remain within the "normal range," indicating that erythrocytosis finally ensues by the contributory action of additional growth factors on erythroid progenitors, such as angiotensin II, androgens, sSCF and insulin-like growth factor 1 (IGF-1) (55-57, 59). 25% of all patients with PTE may see resolution without any treatment. 60% of patients experience symptoms which can include lethargy, dizziness, plethora, headache among other things (2). 10% to 20% patients experience both venous and arterial thromboembolic events (2). Secondary causes should be excluded: pulmonary disease, erythroleukemia, renal cancer, and hepatitis B or C (2). It is recommended that the hemoglobin be maintained at <17.5 g/dl by ACE inhibitors or ARB even if the patient is normotensive (2, 60). Phlebotomy is used for patients with PTE who do not respond to treatment with an ARB or ACE inhibitor (60, 61). It is also used in conjunction with ACE inhibitors or ARBs for patients who present with hemoglobin greater than 18.5 gm/dL (60, 61). Relapse of PTE is common if therapy is discontinued (2, 60).

5.10. Reproductive Issues

5.10.1. Men

After renal transplantation about 2/3rd of men experience improved libido and sexual function. Males with CKD can experience hypogonadism (63). Balance is restored in hypothalamic-pituitary axis (HPA) after transplantation; however, the degree of pathologic injury to testis determines the reversibility of sexual function (1). Histologically, seminiferous tubular destruction and germinal cell aplasia can be seen (64). Consequently, sperm motility improves but not sperm count or morphology (65). Both sirolimus and cyclosporine can impair biosynthesis of testosterone (1, 66-67). Azathioprine doesn't seem to alter male fertility. It should be kept in mind that beta-blockers and alpha-blockers can induce infertility in transplant patients and calcium channel blockers may cause reversible functional defects in sperm (62). Male patients should be asked about their sexual function and referred to urology as necessary. There are no contraindications to use of agents such as sildenafil for erectile dysfunction in kidney transplant recipients.

5.10.2. Women

Female infertility in CKD results from altered HPA axis with high FSH, LH and prolactin levels. The normal hormonal balance is restored within a year after transplantation (1). Since 1958 over 14000 pregnancies have been reported in renal transplant recipients (69).

5.10.3. Family planning

Pregnancy in transplant patients should be considered high-risk. It used to be that the patients were told to wait 2 yrs after transplant before planning pregnancy (1). Now, guidelines are provided by American Society of Transplantation to help counsel patient (69). Patients can safely plan pregnancy as long as the following conditions are met (68, 69).

- a. Graft function is optimal, defined as a serum creatinine <1.5 mg/dL, (132 micromol/L) with <500 mg/24 h protein excretion
- b. There are no concurrent fetotoxic infections, such as CMV
- c. The patient is not on known teratogenic or fetotoxic medications
- d. The immunosuppressive regimen is stable at maintenance levels

A recent meta-analysis covering 50 studies, 4706 pregnancies and 3570 kidney transplant patients, provides the proof as to why pregnancies in these patient population is deemed high-risk (71). According to that meta-analysis, complications of preeclampsia (27.0%), gestational diabetes (8.0%), Cesarean section (56.9%) and preterm delivery (45.6%) were higher than the general US population (3.8%, 3.9%, 31.9% and 12.5%, respectively). Pregnancy outcomes were more favorable in studies with lower mean maternal ages; obstetrical complications were higher in studies with shorter mean interval between kidney transplant and pregnancy. The overall post-transplant live birth rate was 73.5% compared to 66.7% for general US population; similarly, the overall post-transplant miscarriage rate of 14.0% was lower than 17.1%. Transplant recipients usually deliver late preterm (34-36 weeks), roughly 30-50% pregnancies experience intra-uterine growth restriction to some degree and on average give birth to low birth weight babies (~2.5 grams) (70-72). Pregnancy doesn't increase the risk of rejection (71). In the above mentioned study rejection rate was 4.2% in over 2400 pregnant patients studied for rejection (72). Pregnancy also doesn't increase the risk of graft loss (69, 71).

Patients can be counseled that there are no increase risks of birth defects from taking prednisone, azathioprine, and cyclosporine or tacrolimus during pregnancy (2). For azathioprine, no fetal anomalies have been noted at doses equal to or less than 2 mg/kg while in case of cyclosporine dose elevations may be required due to increase volume of distribution during pregnancy (1). Blood levels should be followed when CNIs are used. MMF and sirolimus should be discontinued 6 months before pregnancy, substituted with alternative agents and patients should be monitored closely for rejection during this time period (2). All pregnancies should be planned.

For the patients who are counseled contraception, barrier contraception is the best modality. The American Society of Transplantation Consensus conference suggested the use of progestin-only oral contraceptives and estrogen/progestin formulations providing blood pressure is adequately controlled (69). Also, for patients taking hormonal contraception, CNI levels should be monitored and patients should be advised on the risk of thromboembolism (2).

5.10.4. Pregnancy

The incidence of hypertension in pregnant kidney transplant patients is four-fold higher than uncomplicated pregnancies. About 30% of pregnancies experience pregnancy-induced hypertension (1). Cyclosporine may add to this burden of hypertension. Methyldopa, hydralazine and labetalol can be safely used to negotiate hypertension during pregnancy (1). ACEIs and ARBs are contraindicated during pregnancy and should be stopped as soon as the patient becomes pregnant (1).

Rejection can occur during pregnancy; given hyperfiltration during pregnancy, it can be difficult to diagnose based on creatinine. Once suspected, kidney allograft can be biopsied using real-time renal ultrasound. Rejection can be treated with steroids. Safety of antilymphocyte globulins or rituximab is unknown in pregnancy. IVIG has been used and has not reported to have adverse effects (2).

To decrease the risk of rejection during perinatal period from stress of labor, stress-dosing of hydrocortisone 100mg every 6-8 hours should be considered (1).

All immunosuppressive medications enter maternal-fetal circulation to varying degrees. There is lack of data on pharmacokinetics and pharmacodynamics for various immunosuppressants making it difficult to predict about *intra utero* medication exposure. The placenta metabolizes prednisone to prednisolone; therefore, only low levels have been detected in the fetal circulation (1). Azathioprine is a prodrug that is rapidly metabolized to 6-mercaptopurine. This moiety does pass into the fetus and a relative fetal lack of the enzyme inosine pyrophosphorylase prevents it from being transformed into its active form thioinosinic acid (72). CNIs readily cross the placenta and enter the fetal circulation (1, 73). In one study, it was found that cyclosporine in fetal blood was able to inhibit T cell function to the same degree as that found in maternal serum (73). Much less is known about the maternal-fetal transport of MMF and sirolimus. Although there appear to be no obvious congenital abnormalities associated with *in utero* exposure to conventional immunosuppressive agents, long-term follow-up of exposed children is needed.

During breast feeding this exposure may continue to the infant. It is not known whether this exposure constitutes a risk to the infant. Currently according to the consensus from American Society of Transplantation, breast feeding is not contraindicated. The American Academy of Pediatrics supports breastfeeding for mothers who are taking prednisone and advises against it for those who are taking cyclosporine (74). There are no specific American Academy of Pediatrics recommendations for mothers who are taking azathioprine or tacrolimus (74).

5.11. Adherence

Nonadherence is associated with high risk of rejection and allograft loss (23). Kidney transplant recipients show most nonadherence with regards to their immunosuppression, as compared to recipients of other organs (23).

Adherence can be defined as 'the extent to which the patient's behavior matches the agreed-upon prescriber's recommendations' (23). Non adherence is defined by KDIGO as deviation from the prescribed medication regimen sufficient to adversely influence the regimen's intended effect' (23). These definitions are derived from a consensus conference on adherence (75). Non adherence can be at the time of transplant or subsequently. It can be complete or partial and encompasses non compliance with timing of medications (23). It is estimated that non adherence to long-term medication is as high as 50% in developed countries and higher in developing countries (76). Risk factors for nonadherence include nonadherence behavior prior to transplantation, psychiatric illness, personality disorders, poor social support, substance

abuse and other high-risk behavior, adolescence, high education level, time since transplantation, lack of adequate follow-up with transplant specialists, inadequate pretransplant education, multiple adverse effects from medications, complex medication regimens, expensive medications and poor access to healthcare (23, 75, 77).

Ongoing patient education and psychosocial support remains two important cornerstones for treating patient nonadherence. The following are some approaches that are more likely to promote adherence and have been divided into two arms: A) education and medical interventions and behavioral and B) psychosocial approaches. Combination of these interventions produces the best results (79-80).

A. Examples of education and medical interventions (23, 77):

1. Ensure that patients know their medications by name, dosage and reason for prescription; reinforce these points during every clinic visit.
2. Inform patients about the adverse effects of drugs.
3. Provide written instructions for each change in medication dose or frequency.
4. Reduce the number and frequency of medications. If possible, medications should be given once daily
5. Ensure the patients understand that they need to continue taking immunosuppressive agents even if the transplanted organ is functioning well.
6. Help establish a system to remind patients to take their medications such as pill boxes or electronic devices that help remind the patient when to take their medications
7. Inquire about problems during every clinic visit, and address specific patient concerns.
8. Monitor compliance with laboratory work, clinic visit and prescription refills.
9. Monitor patients with highest risk of nonadherence (i.e., poorly educated, low family income, patients with history of nonadherence) and provide all possible interventions available

Concomittantly, behavioral strategies and psychosocial approaches also need to be part of the interventions as education and medical interventional strategies are unlikely to suffice on their own.

B. Examples of behavioral and psychosocial approaches (23, 77):

1. Provide positive support feedback for adherence
2. Encourage patient to demonstrate a track record of medication adherence and knowledge.
3. Encourage individual team members to develop rapport with patient.
4. Identify and involve a backup support system (family or friends).
5. Treat depression, anxiety or other psychological issues.

Ultimately there is no single strategy that works for all patients and all of the above approaches need to be individualized to the patient at hand (23). A transplant pharmacist involvement can also improve adherence at 1-year with medication regimens (80, 81)

5.12. Screening

There are as such no randomized control trials to assess risks and benefits of screening for specific health issues.

The following recommendations for cancer screening are based on American Transplantation Society and European Best Practices Guidelines for renal transplantation (82-86):

- A. Breast: Annual or biennial mammography for all women older than 50 yr. Women between 40 and 49 could still undergo screening, but no evidence for or against screening at this age
- B. Cervical: Annual pap smear and pelvic exam once sexually active
- C. Colorectal: Annual FOBT or 5-year flexible sigmoidoscopy for patients older than 50 years
- D. Prostate: Annual Digital Rectal Exam and PSA levels in all male transplant recipients older than 50
- E. Hepatocellular: No firm guidelines, but alpha-fetoprotein and ultrasound can be performed every 6 months in patients at high risk
- F. Skin: Monthly-self exam and annual or biennial exam by dermatologists
- G. Renal: No firm recommendation. Some physicians choose to do ultrasound of native kidneys on a regular basis.
- H. PTLD: Patients should be screened for EBV antibodies prior to or at the time of transplantation

For oral health, again, there are no specific recommendations, but certain general management strategies have been agreed upon by dentists.

- Routine dental exam should be avoided until 6 months after transplant. For emergency dental exams, it may be preferred to manage these patients in a hospital setting. Annual or biennial dental exam with a dentist should be pursued for long-term dental care.
- All routine dental procedures will need antibiotic prophylaxis and the choice of antibiotics should be made after consulting with patient's transplant physician.
- The most common *oral manifestations* in transplant patients are: viral, bacterial and fungal infections, gingival hyperplasia due to cyclosporine and higher risk in developing oral malignancy, and patients should be screened for them on routine dental exams (87).

Transplant patients should not be given a live vaccine. The following vaccines are recommended for transplant patients (1):

- i. Haemophilus Influenza b: Recommended before and after transplant
- ii. Hepatitis B: Recommended before and after transplant
- iii. Human Papillomavirus: Recommended before and after transplant
- iv. Influenza, injected: Recommended before and after transplant
- v. Measles, mumps and rubella (MMR): Recommended only before, but not after transplant

- vi. Meningococcal (conjugated or polysaccharide): Recommended before and after transplant for adults with asplenia, terminal complement deficiencies, first-year college students living in dormitories and other patients identified to be at-risk
- vii. Pneumococcal (conjugated or polysaccharide); Recommended before and after transplant
- viii. Tetanus, Diphtheria, Acellular Pertussis (Td/Tdap): Recommended before and after transplant
- ix. Varicella: Recommended only before, but not after transplant
- x. Zoster: Recommended only before, but not after transplant

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