

Kidney Transplantation

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Disclosures

- Consultant/member of advisory board for Veloxis Pharmaceuticals



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Learning Objectives

- Evaluate effects of nonadherence on long-term allograft survival.
- Assess non-pharmacologic and pharmacologic risks of patients undergoing kidney transplant evaluation.
- Distinguish between absolute and relative contraindications to kidney transplant.
- Differentiate pathophysiology of and design management strategies for allograft specific complications.
- Design modifications to therapy that account for patient-specific factors, immunologic risk, and complications after kidney transplant.
- Assess barriers after kidney transplant and implement strategies to improve adherence.

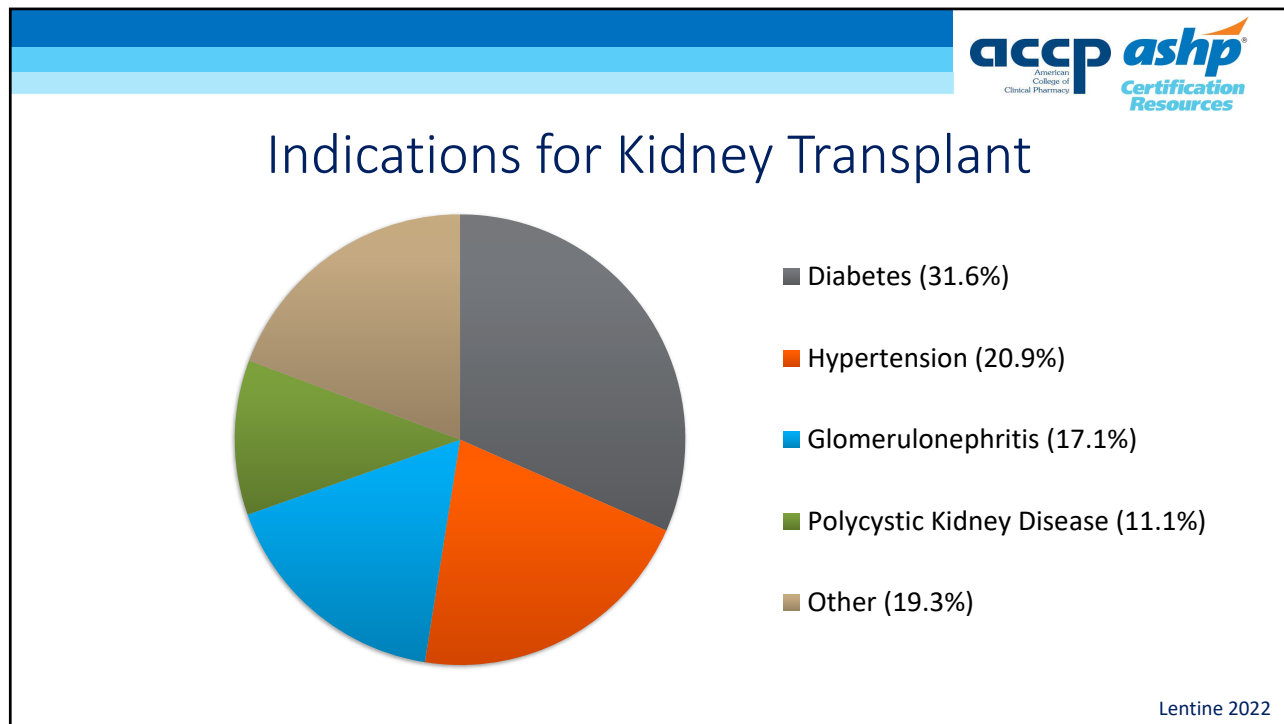
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Benefits of Kidney Transplantation

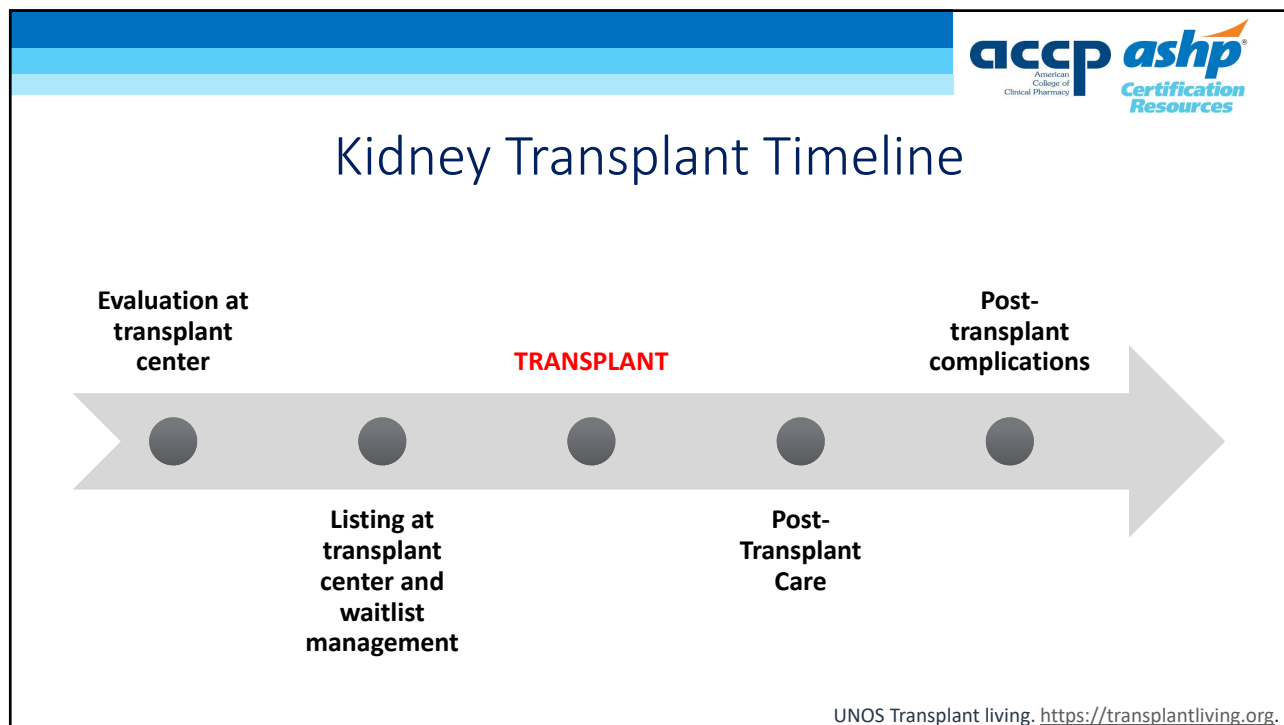
- Improved quality of life
- Increased survival
- Economic benefit
 - Return to work after transplant
 - Avoidance of dialysis in pre-emptive living donor recipients
 - Kidney transplant has lower cost per quality-adjusted life-year than maintenance dialysis

Wolfe 1999;Axelrod 2018;Chadban 2020

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Kidney Transplant Evaluation Process

- Early referral from nephrologist
 - All patients with chronic kidney disease (CKD) with glomerular filtration rate (GFR) < 30 mL/min/1.73 m² who are expected to reach end-stage renal disease (ESRD) should be informed of, educated about, and considered for kidney transplantation regardless of socioeconomic status, sex, gender identity, or race/ethnicity
- Multidisciplinary team approach to assess candidacy for transplant and address modifiable factors that may affect outcomes
 - Surgeon
 - Nephrologist
 - Social worker
 - Pharmacist
 - Dietician
 - Financial coordinator
 - Transplant coordinator

Kasiske 2001;Bunnapradist 2007;Pham 2010; Chadban 2020

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Kidney Transplant Evaluation Process

- Baseline labs, routine imaging, and screening per institution protocol
 - Basic labs to evaluate organ function
 - Viral serologies, blood type, and immunological assessment
 - Cardiac clearance (Chest x-ray, electrocardiogram (ECG), echocardiogram (ECHO), cardiac stress test)
 - Cancer screening where applicable (colonoscopy, mammography, pap smear, prostate exam)
 - Other screening per insurance request for listing
- Patient and family education
 - Establishment of caregivers

Kasiske 2001;Bunnapradist 2007;Pham 2010; Chadban 2020

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Assessment of Non-Pharmacologic Risk



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Surgical and Medical Risk Factors

- Cardiovascular risk
 - Leading cause of death after transplant
 - High risk patients undergo cardiac catheterization
 - Percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) and cardiac rehabilitation are completed before transplant
- Imaging based on risk factors and symptoms with appropriate intervention prior to transplant if applicable
 - Cerebrovascular disease
 - Peripheral arterial disease
 - Pulmonary disease
 - Neurologic disease
 - Gastrointestinal and liver disease
 - Congenital urinary disease

Kasiske 2001;Pilmore 2006;Bunnapradist 2007;Pham 2010; Chadban 2020

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Surgical and Medical Risk Factors

- Hematologic disorders
 - More extensive studies in patients with unprovoked venous thromboembolism (VTE), multiple fistula or graft thromboses, or females with high miscarriage rate
 - Identify patients that require peri-and post-operative anticoagulation plan
- Understanding cause of ESRD
 - Review of family history and native kidney biopsy if available
 - Risks and management after transplant
 - Disease specific risk of recurrence and graft loss

Kasike 2001;Pilmore 2006;Bunnapradist 2007;Pham 2010; Chadban 2020

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Infection History

- Immunization history and optimization of immunizations before transplant
- Appropriate treatment and clearance of active infection
- Evaluation and initiation of treatment for latent infection
- Human immunodeficiency virus (HIV)
 - Stable HIV infection at time of transplant
 - CD4 > 200 cells/microliter
 - Undetectable viral load
 - No evidence of opportunistic infection
- Hepatitis B (HBV) or Hepatitis C (HCV) infection
 - Treatment history and resistance

Kasike 2001;Blumberg 2019;Danziger-Isakov 2019;Chadban 2020

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Malignancy History

- Transplant recipients are at an increased risk of developing de novo and recurrent malignancy
 - Age-appropriate cancer surveillance prior to transplant
- Patients with history of malignancy
 - Document history of malignancy and prior treatment
 - Evaluation of risk of recurrence under immunosuppression
 - Clearance for transplant from hematology/oncology specialist
 - Tumor free waiting period generally ranges 2 to 5 years before kidney transplant
 - Depends on type of cancer, risk of recurrence, and institution protocol

Kasiske 2001;Bunnapradist 2007;Pham 2010; Chadban 2020

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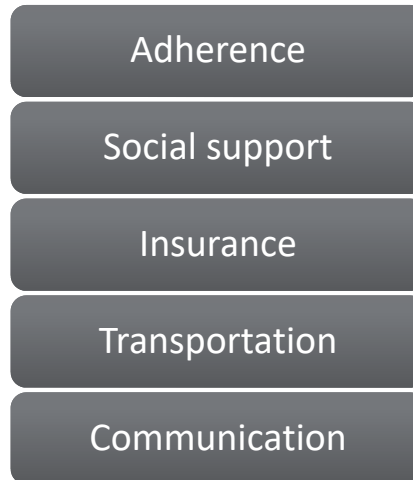
Nutrition Evaluation

- Identification of malnutrition
 - Dialysis and chronic inflammation contribute to malnutrition
 - Optimize current intake and supplement as needed
- Identification of obesity and metabolic syndrome
 - Weight loss if body mass index (BMI) cut off at institution
- Modifications in diet and lifestyle to minimize post-transplant morbidity

Weil 2009

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Social and Financial Evaluation



Kasiske 2001;Maldonado 2015

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Substance Abuse

- Risk of acute kidney injury, drug interactions, infection, adverse behavioral effects, and non-adherence after transplant
 - Chronic narcotic and/or anxiolytic use
 - Assessment of fill history and prescriber history to identify drug-seeking behavior
 - Establishment of pain management contract with non-transplant provider
 - Modifications to peri-operative pain management planned prior to transplant
 - Alcohol and substance abuse
 - Alcohol abuse is rare after kidney transplant but can lead to non-adherence
 - Screen for nicotine use and offer treatment for smoking cessation
 - Active illicit drug use is a contraindication to transplant
 - Tetrahydrocannabinol (THC) and cannabidiol (CBD) use
 - Increased use reported with increasing legalization
 - Identify indication for use, frequency of use, and route of administration

Parker 2013;Maldonado 2015;Rai 2017;Alhamad 2019

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Assessment of Pharmacologic Risk



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Allergy and Medication History

- Proper documentation of allergies
 - Identification of alternative plan for true allergy or intolerance if medication required after transplant
 - Peri-operative antibiotics
 - *Pneumocystis jiroveci* (PCP) and urinary tract infection (UTI) prophylaxis
 - Immunosuppression
 - Aspirin or heparin
 - Pain medications
- Complete and accurate list of home medication that includes discussion of over-the-counter supplements and herbal products

Maldonado 2015

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Clinically Significant Drug Interactions

- Identification of clinically significant drug interactions that should be addressed prior to transplant
 - Inducers and inhibitors of cytochrome P-450 3A4 and P-glycoprotein
 - Involvement of other healthcare providers before transplant to determine if drug interactions can be minimized
 - Optimize regimens to decrease drug interactions and pill burden without compromising long-term outcomes
 - Epilepsy medications
 - HIV medications
 - Mental health medications

Kasiske 2001;Maldonado 2015;Blumberg 2019

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Anticoagulation

- Identify agent used, indication for anticoagulation, risk for thromboembolism, and need for bridging in peri-operative period
- Risk of holding anticoagulation must be weighed against risk of bleeding
- Unable to discontinue anticoagulation in a timely manner in setting of deceased donor transplant
 - May require use of reversal agents depending on timing and urgency of transplant

Douketis 2012;Maldonado 2015

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Antiplatelet Agents and Warfarin

- Low dose aspirin
 - Continue peri-operatively without interruption
- Adenosine diphosphate (ADP) receptor inhibitors
 - For planned surgeries, consider holding irreversible ADP receptor inhibitors 5 days prior to surgery
 - May not be held based on surgeon's level of comfort or patient's cardiovascular (CV) risk
- Warfarin
 - For planned surgeries, hold warfarin 5 days prior to surgery
 - Reversal agents include vitamin K, fresh frozen plasma (FFP), and prothrombin complex concentrates (PCC)
 - Resume anticoagulation 12 to 24 hours after surgery if no concern for bleeding
 - Need for bridging per guidelines; weigh risk of bleeding with thrombosis risk

Douketis 2012;Maldonado 2015

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Direct-Acting Oral Anticoagulants (DOAC)

- Dabigatran, rivaroxaban, apixaban, and endoxaban
 - Use varies based on surgeon level of comfort, prior experience with DOAC, and establishment of protocols for use
 - If listed for deceased donor, center may consider converting DOAC to warfarin as patient approaches organ offer
 - Reversal agents (idarucizumab, andexanet alfa) may not be available at institution based on formulary
 - Four-factor PCC and activated PCC (APCC) may be used if reversal agents unavailable
 - Unreliable assays to measure hemostasis
 - Hold 2 to 4 days prior to surgery based on medication, half life, and renal function
 - Resume 24 hours after transplant if low risk of bleeding and 48 to 72 hours if high risk of bleeding

Burnett 2016;Doherty 2017;Salerno 2017;Steffel 2018,Cuker 2019;Lichvar 2020

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Immunosuppression History

- Documentation of transplant history
 - Induction, treatment for rejection, cause of graft failure, adherence, complication history
- Assessment of severity of prior intolerance and risk of similar response
- Identify if deviations needed from protocol immunosuppression regimens
 - If less effective regimen needed, risk should be conveyed to patient and discussed at multidisciplinary listing meeting
- Current immunosuppression use (rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), multiple sclerosis, Crohn's disease)
 - Risk of infection and malignancy should be weighed with controlling symptoms of underlying disease
 - Modifications to immunosuppression or autoimmune therapy coordinated with transplant team and rheumatologist or other healthcare provider
 - Assess risk for complications as a result of over immunosuppression

Maldonado 2015

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Fertility and Pregnancy after Transplant

- Return of fertility can occur within weeks after transplant
- Pregnancy should be avoided for the first year after transplant, in patients with unstable graft function, and those at high risk for rejection or infection
 - Continued education on contraception and pregnancy planning vital to preventing unwanted pregnancy, early miscarriage, or harm to fetus
 - Benefits and risk of each contraceptive method should be weighed
- Mycophenolate risk evaluation and mitigation strategy (REMS) discussion
 - Females of child-bearing age placed on mycophenolate products after transplant

Maldonado 2015

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Nonadherence After Kidney Transplant

- Adherence is the extent to which a patient's behavior matches the agreed upon prescriber's recommendations
 - Medications, clinic appointments, and lifestyle choices
- Dynamic process that affects 15% to 40% of kidney transplant recipients
- Nonadherence increases annual healthcare costs by \$100 to \$300 billion
 - Annual increase of \$11,000 per patient after kidney transplant

Vlaminck 2004;Sellares 2012;Maldonado 2015;Nevins 2017;Russell 2020

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Nonadherence After Kidney Transplant

- Nonadherence is the main reason long-term graft survival has not improved despite advances in immunosuppression
- Three-fold increase in late acute rejection in nonadherent patients
- Majority of long-term graft failure or loss is due to antibody mediated rejection (AMR) or mixed cellular rejection and AMR
 - Poor prognosis and response to treatment

Vlaminck 2004;Sellares 2012;Maldonado 2015;Nevins 2017;Russell 2020

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Understanding Risk Factors for Nonadherence

- Health care provider factors
 - Public versus private insurance
 - Loss of insurance or unaffordable copays
 - Decreased access to care or communication with provider
 - Transition from pediatric to adult nephrology care
- Condition related factors
 - Time after transplant and better perceived health
 - Living donor transplant
 - Physical limitations
- Treatment related factors
 - Complexity of regimen
 - Side effects with immunosuppression
 - Inability to swallow large pills or poor taste

KDIGO 2009;Nevins 2017

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Understanding Risk Factors for Nonadherence

- Social and demographic factors
 - Age
 - Low socioeconomic status
 - Family distress
- Patient and psychosocial factors
 - Prior nonadherence
 - Low health literacy
 - Psychological distress
 - Psychiatric illness or substance abuse
 - Poor social support or lack of caregiver engagement
 - Easily forgetful or cognitive issues
 - Changes to daily routine

KDIGO 2009;Nevins 2017;Belaiche 2017

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Assessment of Pre-Transplant Adherence

- Nonadherence pre-transplant is a predictor of nonadherence post-transplant
- Documentation of a patient's adherence is a vital part of evaluation and should be discussed as part of multidisciplinary listing
 - Discussion of patient's self perceived adherence with medications, home monitoring of vitals, diet, exercise, alcohol and tobacco recommendations
 - If available, review other provider's assessment with adherence to recommendations and clinic appointments
 - Missed appointments after transplant are also correlated with nonadherence

Maldonado 2015;Doyle 2016;Taber 2017

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Active Learning Case 1

Which of the following is most concerning when assessing pre-transplant adherence?

- A. A 30-year-old woman with type 1 diabetes who misses 3 to 4 sessions of dialysis per month due to conflicts with work
- B. A 59-year-old man with type 2 diabetes who is prescribed 25 units of long-acting insulin at bedtime but has not taken in 2 weeks because his blood sugars have been low
- C. A 29-year-old woman with elevated phosphorus levels and does not take her sevelamer because it makes her nauseous
- D. A 65-year-old man seen in clinic who did not bring caregivers to clinic due to language barrier

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Active Learning Case 2

A 47-year-old Asian woman with past medical history significant for SLE on dialysis for 5 years, hypertension, and atrial fibrillation on warfarin ($\text{CHA}_2\text{DS}_2\text{-VASc} = 3$) is evaluated in clinic by a PharmD as part of multidisciplinary evaluation for a living donor renal transplantation. Current medications include aspirin 81 mg daily, atorvastatin 40 mg daily, metoprolol 50 mg 2 times daily, hydroxychloroquine 200 mg daily, and warfarin 3 mg daily. Which of the following recommendations is most appropriate regarding this patient's anticoagulation plan in the peri-operative period?

- A. Warfarin does not need to be held prior to transplant
- B. Warfarin should be held 3 days prior to transplant and this patient will require bridging with heparin due to moderate risk for thromboembolism
- C. Warfarin should be held 5 days prior to transplant and this patient will not require bridging with heparin due to moderate risk for thromboembolism
- D. Warfarin should be held 7 days prior to transplant and this patient will require bridging with heparin due to high risk for thromboembolism

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Kidney Transplant Listing

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Absolute Contraindications to Kidney Transplant

- Reversible renal failure
- Severe irreversible extrarenal disease
- Active infection
- Active or untreatable malignancy
- Primary oxalosis
- Life expectancy less than 2 years
- Limited irreversible rehabilitative potential
- Poorly controlled psychiatric illness
- Active illicit drug use
- Ongoing nonadherence

Bunnapradist 2007;Pham 2010; Chadban 2020

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Relative Contraindications to Kidney Transplant

- Age
 - No strict cutoff but not routinely done in patients over 80 years old
 - Centers may have different protocols for living versus deceased donor restrictions
 - Patients should not be excluded because of age alone
 - Increasing number of kidney transplants done in elderly patients
 - Twenty-two percent of all patients transplanted in 2020 were over the age of 65
 - In appropriately selected candidate, a survival benefit remains in transplanting elderly patients
 - This benefit also extends to patients greater than 70 years of age

Rao 2007;Wall 2019;Hart 2020;Chadban 2020;Lentine 2022

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Relative Contraindications to Kidney Transplant

- Frailty
 - Up to 20% of candidates are considered to have decreased reserve after kidney transplant
 - Pre-transplant frailty is associated with decreased listing of candidates and increased waitlist mortality
 - Post-transplant frailty is associated with delirium, increased length of stay, increased readmission rates, intolerance to immunosuppression, decreased quality of life, cognitive decline, and decreased survival
 - No validated tool for assessment in kidney transplant candidates
 - Validated tools in liver transplant (liver frailty index) and geriatric population (Fried frailty phenotype) extrapolated to kidney transplant population

Haugen 2019;Wall 2019

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Relative Contraindications to Kidney Transplant

- BMI, obesity, and abdominal circumference
 - Accepted BMI levels at transplant centers are rising to accommodate the increasing prevalence of obesity
 - BMI > 40 kg/m² often considered a relative contraindication
 - Some centers refer patients for bariatric procedures before or at time of transplant
 - Improved changes in surgical technique and control of comorbidities post-transplant have improved survival after transplant
 - Post-transplant increased risk of surgical site infections, delayed graft function (DGF), and complications from cardiovascular disease
 - Strongest survival benefit in recipients with high BMI undergoing living donor transplantation

Lentine 2012;Gill 2013;Wall 2019

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Benefits of Living Donation

- Decreased time on waiting list
- Improved patient and graft survival
 - Improved donor organ quality, decreased ischemia time, improved donor and recipient health
- Compatible living donor transplantation is more cost effective than deceased donor transplantation
 - Avoidance of dialysis in pre-emptive transplant candidate
 - Decreased costs associated with improved graft survival
- Expanding donor pool with kidney paired donation (KPD)
- Pre-transplant desensitization protocols for positive crossmatch and ABO incompatible transplants

Orandi 2016;Lee 2019

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Kidney Paired Donation (KPD)

- Incompatible donor-recipient pair enter a registry to be paired with other incompatible donor recipient pairs to make a compatible exchange
- Often allows for better immunologic, size, and age match
- Single center or multicenter KPD
 - Multicenter registries include national kidney registry (NKR), alliance for paired donation, and United Network for Organ Sharing (UNOS)
 - Exchange can be initiated by deceased donor or altruistic living donor
 - Logistics and timing must be carefully planned prior to surgery

Lee 2019

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Deceased Donation: Expanding the Donor Pool

- Donors previously described as standard criteria donor (SCD) or extended criteria donor (ECD)
 - Recipients of ECD donors had increased risk of DGF and rejection, and decreased graft survival compared to SCD
 - ECD definition
 - Donor ≥ 60
 - Donor ≥ 50 with 2 of the following risk factors
 - Cerebrovascular accident, hypertension, or serum creatinine > 1.5 mg/dL
 - Donation after cardiac death (DCD)
 - Anticipated cold ischemic time ≥ 24 hours

Metzger 2003;Durrbach 2010

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Deceased Donation: Expanding the Donor Pool

- Kidney donor profile index (KDPI)
 - Assessment of donor factors that summarizes likelihood of graft failure after deceased donor kidney transplant
 - Donor age, height, weight, ethnicity, history of hypertension, history of diabetes, cause of death, serum creatinine, HCV status, and DCD status
 - Lower KDPI associated with longer graft function
 - Consent required for acceptance of KDPI $> 85\%$
- Estimated post-transplant survival (EPTS)
 - Assigned to all waiting list candidates and includes time on dialysis, diabetes diagnosis, prior transplant, and age
 - Candidates with scores $< 20\%$ receive priority for kidneys from donors with KDPI $< 20\%$

Rao 2009;Massie 2014;OPTN <https://optn.transplant.hrsa.gov>

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Deceased Donation: Expanding the Donor Pool

- Risk criteria present for acute transmission of HIV, HBV, or HCV infections
 - Previously labeled as public health service (PHS) high risk donors
 - Similar patient and graft survival compared to standard risk donors
 - Survival benefit compared to waiting for standard risk donors
- Hepatitis B core antibody positive donors
 - Prophylaxis in patients recommended in patients without immunity
- HCV positive donors in HCV negative or previously treated recipient
 - Transmit and treat versus prophylaxis approach
- HIV positive donors
 - HIV donor positive/recipient positive donation with approved research protocols through 2013 HIV Organ Policy Equity (HOPE) Act

Seem 2013;Hupikar 2015;Levitski 2017;Bowring 2018;Blumberg 2019; Jones 2020

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Active Learning Case 3

Which of the following is an absolute contraindication to kidney transplantation?

- A. A 43-year-old man with history of nonadherence that has completed a compliance contract and shown adherence with medications and dialysis for the past 6 months
- B. A 32-year-old woman with bipolar disorder who is currently stable on her medication regimen and presents with her parents and husband as caregivers
- C. A 67-year-old man with decompensated heart failure and left ventricular ejection fraction of 20%
- D. A 55-year-old man found to have latent tuberculosis during transplant evaluation is is currently being treated with isoniazid

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Post-Transplant Complications and Considerations



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Surgical Complications

- Bleeding
 - Close monitoring of complete blood count (CBC) after transplant
 - Return to operating room (OR) for hematoma evacuation if requiring significant blood products without improvement
- Wound infection
 - Decreased incidence due to improved surgical technique and use of peri-operative antibiotics
- Deep vein thrombosis (DVT) or pulmonary embolism (PE)

Veale 2009

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Surgical Complications

- Lymphocele
 - Collections of lymph caused by leakage from severed lymphatics
 - Can cause pain, ureteral obstruction, venous compression, bladder compression, scrotal masses, and vena cava obstruction leading to VTE
 - Drain placement during surgery can reduce risk of development
 - Diagnosis with ultrasound and needle aspiration of fluid
 - Aspiration of lymphocele required only if concern for leak, obstruction, or infection
- Renal artery stenosis
 - Diagnosis with angiography
 - Peak systolic velocity > 250 cm per second
 - Tardus-parvus arterial waveform
 - Requires surgical revision of anastomosis or angioplasty

Veale 2009

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Surgical Complications

- Renal artery thrombosis
 - Occurs within first week after transplant and causes sudden decrease in urine output
 - Increased risk in recipients prone to thrombosis, use of multiple arteries during operation, or atherosclerosis of vessels
 - Diagnosis with ultrasound to look for blood flow to allograft
 - Requires emergent opening of artery and removal of clot
- Renal vein thrombosis
 - Occurs in early post-operative period
 - Results from kinking of renal vein, stenosis of venous anastomosis, hypotension, hypercoagulable states, or acute rejection
 - Requires a return to OR for emergent removal of clot

Veale 2009

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Surgical Complications

- Urine leak
 - Occurs at ureteric anastomosis early after transplant and results in increased wound drainage, decreased urine output, and graft tenderness and pain
 - Diagnosis includes assessment of fluid creatinine and cystogram or nephrostogram
 - If ureteral stent, drain, and catheter already in place can monitor for resolution
 - Other interventions include placement of nephrostomy with drainage and stent placement or surgical exploration to reimplant ureter
- Ureteral obstruction
 - Caused by catheter blockage, blood clots, extrinsic ureteric compression, ureteral stricture, stones, and prostatic hyperplasia
 - Diagnosis includes graft dysfunction and presence of hydronephrosis on ultrasound
 - Interventions include placement of nephrostomy tube

Veale 2009;Wilkinson 2009

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Infectious Complications

- Asymptomatic bacteriuria
 - No urinary or systemic signs of infection but greater than 10^5 colony forming unit (CFU)/mL pathogen in urine
 - Consider treatment within first 1 to 2 months of transplant if 2 consecutive urine samples with greater than 10^5 CFU/mL pathogen
 - Early treatment may promote antimicrobial resistance
- Recurrent urinary tract infection (UTI)
 - Greater than 3 UTIS within 12 months
 - Work-up for anatomical and functional abnormalities
 - Treatment of each episode with appropriate course of antibiotics and may consider prophylaxis after treatment

Goldman 2019;Nicolle 2019

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Infectious Complications

- Cytomegalovirus (CMV)
 - Increased risk of chronic allograft nephropathy and kidney transplant graft loss
 - Increased risk of other bacterial, viral, and fungal infections, post-transplant lymphoproliferative disorder (PTLD), and acute rejection
- BK virus (BKV)
 - Main cause of polyomavirus-associated nephropathy after kidney transplantation
- Pneumocystis jiroveci pneumonia (PJP)

Hirsch 2019;Razonable 2019;Fishman 2019

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Delayed Graft Function (DGF)

- Delayed Graft Function
 - Requirement for dialysis within the first 7 days after transplant caused by acute tubular necrosis
 - Donor risk factors (female gender, age, BMI, deceased donor, DCD, donor serum creatinine)
 - Recipient risk factors (gender, ethnicity, BMI, prior transplant, diabetes)
 - Procurement techniques and ischemia reperfusion injury
 - Cold ischemic time (CIT)
 - Associated with increased risk of rejection and decreased long-term graft survival

Siedlecki 2011;Mannon 2018

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Electrolyte Abnormalities

- Hyperkalemia
 - Prompt and effective management to avoid dialysis after transplant
- Mineral bone disease
 - Increased risk of bone fractures, morbidity, and mortality after transplant
 - Parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23) remain elevated for weeks to months after kidney transplant
 - Hypophosphatemia more aggressive in patients with early allograft function
 - Continued monitoring of calcium, phosphorus, vitamin D, and PTH after transplant

Kalantar-Zadeh 2012;Bahn 2017

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Recurrent Disease

- Recurrent glomerular disease after transplant
 - Primary disease can recur in up to 20% of transplants
 - Risk of recurrence and graft failure depends on type of glomerulonephritis
 - Third most common cause of graft failure
 - Graft loss in 8.4% of grafts 10 years after transplant
 - Limitations to accurate diagnosis
 - Close monitoring of proteinuria and hematuria
 - Indication for kidney biopsy with graft dysfunction
 - Treatment options post-transplant limited and not well defined
 - Limited to case reports and case series

KDIGO 2009;Wilkinson 2009;Blosser 2017;Chadban 2020

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Other Complications

- Rejection
 - Acute cellular rejection (ACR)
 - Antibody mediated rejection (AMR)
- Complications of immunosuppression
 - Medication side effects
 - Calcineurin inhibitors (CNI)
 - Antimetabolites
 - Prednisone
 - Chronic allograft injury
 - Replacing or minimizing CNI if indicated
 - Malignancy and post-transplant lymphoproliferative disorder (PTLD)

KDIGO 2009;Wilkinson 2009

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Common Medication Regimen

- Immunosuppression
 - Induction and maintenance (CNI + antimetabolite +/- prednisone)
- Prophylaxis
 - Herpes simplex virus (HSV) (1 month) or CMV prophylaxis (3 to 6 months)
 - PJP prophylaxis (6 months to 1 year)
 - Thrush prophylaxis (depending on steroid taper)
 - DVT prophylaxis
- Pain and bowel regimen
- Calcium and Vitamin D
- Magnesium and phosphorus supplements
- Chronic maintenance medications prior to transplant

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Active Learning Case 4

A 47-year-old man with end-stage renal disease due to focal segmental glomerulosclerosis (FSGS) and diabetes received a deceased donor kidney transplant 4 months ago. He is currently on tacrolimus with troughs ranging 6-8 ng/mL and mycophenolic acid 720 mg 2 times daily. His post-transplant SCr nadir is 1.2 mg/dL. He is seen in clinic and reports increased bilateral swelling in lower extremities and hematuria. For the past 2 weeks, his SCr has been increasing and is 2 mg/dL in clinic today. His protein creatinine ratio has doubled. A kidney ultrasound indicates patent vasculature and perfusion to transplanted kidney. What is the most appropriate intervention at this time?

- A. Decrease mycophenolic acid to 360 mg BID
- B. Obtain a kidney biopsy
- C. Check lower extremity dopplers
- D. Admit for treatment of pulse steroids

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Monitoring Allograft Function

- Optimization of immunosuppression regimen
 - Minimizing risk of rejection and donor specific antibody (DSA) formation
 - Reducing immunosuppression in setting of infection
 - Adjusting regimens for adverse effects or intolerance
- Appropriate renal adjustment of medications with changing allograft function
- Optimization of underlying medical conditions including diabetes and hypertension to improve patient and graft outcomes

KDIGO 2009

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Monitoring Allograft Function

- Work-up of renal allograft dysfunction
 - Initial assessment should include kidney ultrasound
 - Rule out dehydration, infection, obstruction, and suprathreshold CNI levels
 - Kidney biopsy for persistent unexplained increase in creatinine
- Role of protocol biopsies
 - Acute rejection, CNI toxicity, or injury can occur in absence of a measurable decline in kidney function
 - Early detection and treatment may improve outcomes

KDIGO 2009

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Monitoring Allograft Function

- DSA monitoring
 - Development of DSA is associated with increased rejection and decreased graft survival
 - Monitor DSA at least once within first 3 to 12 months in recipients at low risk for AMR
 - Routinely monitor DSA in recipients at high or intermediate risk for AMR
 - Check DSA with changes in immunosuppression regimen, concern for nonadherence, graft dysfunction, or transfer of care to another center

Tait 2013

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Monitoring Allograft Function

- Donor-derived cell free DNA (ddcfDNA)
 - AlloSure®, Prospera®, TRAC®
 - Detection of disparate single nucleotide polymorphisms across an entire genome that allows separation of DNA of any 2 individuals
 - Elevated levels may indicate allograft injury and rejection
 - May also be elevated in patients with ATN or infection
 - Noninvasive monitoring for acute rejection
 - Patients unable to receive biopsy
 - Detection of subclinical rejection in patients with stable allograft function

Bloom 2017;Jordan 2018;Sigdel 2018;Filippone 2020

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Monitoring Allograft Function

- Gene Expression Profiling (TruGraf®)
 - Detection of subclinical rejection in patients with stable renal function
 - Age > 18 and more than 90 days post-transplant
 - Stable renal function defined as serum creatinine < 2.3 mg/dl or < 20% increased compared to average of 3 prior levels
- Combination of ddcfDNA and gene expression profiling
 - OmniGraf® (TRAC® and TruGraf®)
 - KidneyCare® (Allosure® and Allomap®)

TransplantGenomics.com; CareDx.com

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Special Populations

- Increasing prevalence of obesity and bariatric procedures
 - Most common procedures include laparoscopic sleeve gastrectomy or roux-en Y gastric bypass
 - Allows for improvements in weight loss and comorbidities after transplant without affecting patient or graft survival
 - Minimal studies evaluating pharmacokinetics of immunosuppression in this population
 - Continued monitoring and understanding of how different procedures can alter drug absorption
 - Reduced stomach size affects bioavailability
 - Reduced intestinal length affects bioavailability and gastric transit times
 - Change in gastrointestinal surface area affects drug exposure
 - Change in gastric and intestinal pH affects solubility

Maldonado 2015;Yemini 2018

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Special Populations

- Gastroparesis after transplant
 - Patients with long-standing history of diabetes
 - Symptoms of nausea, vomiting, anorexia, and abdominal pain which can be exacerbated by immunosuppression
- Hyperoxaluria
 - Overproduction of oxalate results in increased urinary excretion and formation of calcium oxalate crystals
 - Secondary hyperoxaluria caused by dietary intake and fat malabsorption
 - Medical management with increased fluid intake and alkalization of urine

Cashion 2004;Camilleri 2013;Bhasin 2015

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Active Learning Case 5

A 25-year-old man with IgA nephropathy is seen in clinic 10 months after his transplant. His current immunosuppression regimen includes tacrolimus 1 mg 2 times daily with levels ranging 5-8 ng/mL and mycophenolic acid 360 mg 2 times daily. Patient reports compliance with immunosuppression regimen and significant tremor in clinic. Post-transplant course has been complicated by cytomegalovirus (CMV infection) for which he has completed treatment and remains on maintenance therapy with valganciclovir. He presents to clinic today with an increased SCr and found to have de novo DSA on routine monitoring. A kidney biopsy is negative for rejection. What changes should be made to current immunosuppression regimen?

- A. Increase tacrolimus goal to 10-12 ng/mL
- B. Increase mycophenolic acid 720 mg 2 times daily
- C. Start prednisone 5 mg daily
- D. Start leflunomide 20 mg daily

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Detection of Nonadherence Post Transplant

- Difficult to determine if medications are being taken as prescribed (adherence) and duration and consistency of behavior (persistence)
 - Wide spectrum of complete nonadherence, partial nonadherence, and complete adherence
- Can occur at any time after transplant
 - More susceptible during transition from pediatric to adult nephrology care
 - Electronic monitoring has shown it can happen very early after transplant
- May not be detected until recipient presents with rejection
 - Decreased frequency of labs and clinic visits further out from transplant
 - Transition of care to outside nephrologist if patient is not followed lifelong at transplant center
- Understanding risk factors and patient perspectives are vital for detection and prevention of nonadherence after transplant

KDIGO 2009;Nevis 2017

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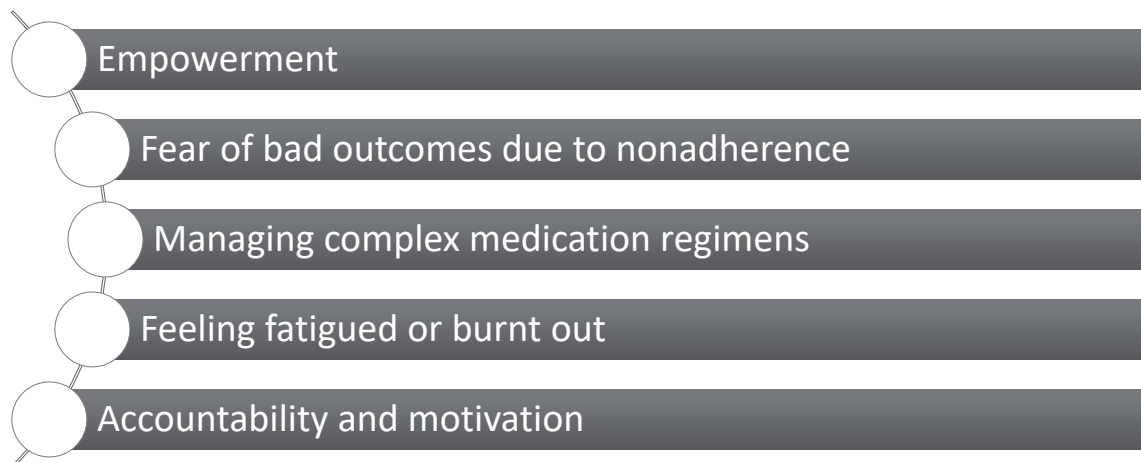
Assessment of Adherence Post-Transplant

- Several advantages and disadvantages of options to assess for nonadherence
 - Pill counts
 - Prescription refills
 - Electronic bottle monitoring
 - Patient questionnaires or diaries
- Patient perception of how often doses are missed within past month can identify patients that may need intervention
 - Will not capture patients unwilling to admit nonadherence or too forgetful
- Coefficient of variation of immunosuppression drug levels
 - Exclude nonroutine drug levels as it should reflect levels at steady state
 - High tacrolimus trough concentration variability associated with increased risk of graft loss

Nevins 2017;Taber 2017;Kuypers 2019

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Patient Perspective on Nonadherence



Nevins 2017

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Interventions to Improve Adherence

- Education and counseling with patient and caregivers throughout transplant care
- Medical interventions
 - Minimize frequency of medications if possible
 - Treatment or minimization of adverse effects of immunosuppression
- Behavioral interventions
 - Positive support
 - Discussion of barriers and motivations
 - Setting goals and problem solving
 - Feedback on adherence if electronic monitoring utilized
 - Involve support system
- Psychosocial interventions
 - Treat underlying depression and anxiety
 - Address high cost of medications or insurance changes

Doyle 2016;Nevins 2017

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Effective Interventions

- Current interventions are not improving overall transplant outcomes
 - Small sample sizes and short follow-up in current studies
 - Unrealistic expectations with current staffing models
- What have we learned?
 - Support system and caregivers need to be engaged and actively present
 - Non-intrusive and direct monitoring strategies preferred
 - Coefficient of variation of immunosuppression drug levels
 - Multicomponent interventions better than single changes
 - One size does not fit all
 - Interventions should be tailored to patient's unique needs, motivations, and barriers
 - Assessment and interventions cannot stop once adherence improves

Nevins 2017;Duncan 2018;Russell 2020

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Active Learning Case 6

A 63-year-old man that received a living donor kidney transplant 5 months ago is seen by a PharmD in clinic where he reports forgetting to take his evening medications 2 or 3 times per month due to falling asleep. His current medications include tacrolimus 2 mg 2 times daily, azathioprine 100 mg daily, prednisone 5 mg daily, sulfamethoxazole-trimethoprim 400-800 mg daily, valganciclovir 900 mg daily, nifedipine 90 mg daily, carvedilol 25 mg 2 times daily, magnesium oxide 800 mg 2 times daily, and neutra-phos 2 tabs 2 times daily. His labs in clinic include Na 138, K 4.8, Cl 101, CO₂ 24, SCr 1.1, mag 1.6, phosphorus 1.8. Which of the following would be the most effective intervention to help with nonadherence in this patient?

- A. Stop phosphorus supplement
- B. Change tacrolimus to tacrolimus XR
- C. Encourage patient to set evening alarms
- D. Change carvedilol to controlled release formulation

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Key Takeaways

- Evaluation of non-pharmacologic and pharmacologic risk factors in kidney transplant candidates requires a multidisciplinary team approach
- Immunosuppression regimens and post-transplant monitoring should be tailored to immunologic risk of patient and allograft specific complications
- Nonadherence decreases long-term graft survival and risk factors, and patient perspectives should be considered when assessing and making interventions post-transplant

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