Kidney Transplant Complications: Rejection, Infection, Recurrent Disease, and Malignancy

Andrew Bland, MD, FACP, FAAP

March 2026

Kidney Transplant Complications: Rejection, Infection, Recurrent Disease, and Malignancy

Learning Objectives

By the end of this module, students will be able to:

1. Classify and diagnose T-cell mediated rejection (TCMR) vs. antibody-mediated rejection (ABMR)
2. Distinguish hyperacute, acute, and chronic rejection by pathophysiology and clinical presentation
3. Recognize and manage acute rejection episodes with appropriate therapeutic escalation
4. Explain chronic allograft nephropathy and strategies for prevention and treatment
5. Diagnose and manage BK polyomavirus nephropathy (BKVN)
6. Recognize and manage post-transplant CMV disease
7. Assess and treat post-transplant diabetes mellitus (PTDM)
8. Identify post-transplant malignancies (PTLD, skin cancer) and implement prevention strategies
9. Counsel regarding pregnancy after transplant and manage pregnant transplant recipients
10. Recognize and manage recurrent glomerular diseases in the allograft

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I. ACUTE REJECTION

A. Classification and Pathophysiology

Hyperacute Rejection (Minutes to Hours Post-Transplant)

Mechanism: Pre-existing IgG antibodies against donor ABO antigen or HLA antigens bind to donor vascular endothelium; C1q fixation ☐ complement activation ☐ vascular injury, thrombosis, and graft infarction.

Clinical Presentation: - Immediate (intraoperative or within 1 hour post-op) graft loss - Darkening/cyanosis of transplant; urine output drops to zero - Urgent labs: rising creatinine, coagulopathy, hemolysis

Prevention: Pretransplant crossmatch (CDC, flow cytometry, SAB Luminex) prevents hyperacute rejection via ABO and HLA incompatibility detection.

Management: Graft nephrectomy; retransplant only after appropriate desensitization if HLA/ABO incompatibility was unexpected.

Incidence: <0.5% with modern pretransplant testing.

Acute Rejection (Days to Months Post-Transplant)

Acute T-Cell Mediated Rejection (TCMR):

Grade	Histology	Clinical Significance
Borderline	Mild mononuclear infiltrate; minimal tubulitis	Usually reversible with observation or minor IS adjustments
Type I (Mild)	Significant interstitial inflammation; tubulitis (>5 mononuclears per tubule)	Responsive to pulse steroids in >80%
Type II (Moderate)	Dense mononuclear infiltrate; significant tubulitis; no intimal arteritis	Responsive to pulse steroids; some require additional therapy
Type III (Severe)	Intimal/transmural arteritis; tubular necrosis; may have early fibrinoid necrosis	Higher risk of graft loss; may require T-cell depletors (ATG, thymoglobulin)

Acute Antibody-Mediated Rejection (ABMR):

Mechanism: Donor-specific antibodies (DSA) bind donor endothelium; complement activation (C4d deposition) or non-complement-mediated endothelial injury.

Pathological Finding	Significance
C4d in peritubular capillaries	Marker of complement activation; indicates antibody-mediated process
Microvascular inflammation (MVI)	Intimal inflammation of peritubular capillaries or glomerular capillaries; indicates active ABMR
Donor-specific antibodies (DSA)	IgG (particularly Class I) in circulation; correlates with rejection risk
Glomerulitis (g + ptc score ≥2)	Glomerular capillary inflammation; indicates ABMR activity
Tissue factor (TF) expression	Alternative marker of ABMR (emerging)

Classification (Banff 2017): - **Acute ABMR:** C4d+ and/or MVI+ with DSA present; active endothelial injury - **Chronic ABMR:** C4d+ or MVI+ with chronic changes (transplant glomerulopathy, intimal fibrosis); chronic antibody-mediated injury

Clinical Presentation of Acute Rejection (TCMR/ABMR):

Feature	Presentation
Timing	Days to months (median 7-10 days); peak incidence weeks 2-8 post-transplant
Serum creatinine	Rise of >0.3 mg/dL or >25% increase from baseline; may progress rapidly
Proteinuria	May increase; nephrotic-range possible
Urine output	May decrease
Constitutional symptoms	Usually absent (distinguishes from infection)
Graft appearance	On ultrasound: increased size, echogenicity; increased resistive index on Doppler
Systemic symptoms	Generally absent (no fever); distinguishes from infection

Diagnosis: - **Serum markers:** Elevated creatinine, DSA (Luminex) if ABMR suspected - **Biopsy:** Gold standard; identifies type, grade, and pathological process (TCMR vs. ABMR) - **Noninvasive markers:** Donor-derived cell-free DNA (dd-cfDNA) emerging; correlates with rejection; may allow biopsy avoidance in some cases

Management of Acute Rejection:

Grade/Type	Management
Borderline or Type I TCMR	Pulse methylprednisolone 500 mg IV daily x 3 days; recheck creatinine in 3-5 days; if responsive, continue observation
Type II TCMR	Methylprednisolone 500-1000 mg IV daily x 3-7 days; if inadequate response, add ATG or thymoglobulin (1.5 mg/kg daily x 3-5 days)
Type III TCMR	ATG/thymoglobulin 1.5 mg/kg daily x 3-5 days PLUS methylprednisolone; high risk of graft loss; close monitoring
Acute ABMR (active/early-onset)	Methylprednisolone pulse; consider plasmapheresis 5-7 sessions to remove DSA; IVIG 2 g/kg; rituximab 375 mg/m² weekly x 4 weeks; potential role for bortezomib
Borderline/ABMR-suspect	Confirm with repeat serology/DSA; if DSA borderline and C4d/MVI negative, observe closely; if DSA+ and C4d+ or MVI+, treat as above

Outcomes: - **TCMR Type I/II:** 80-90% response to pulse steroids; rare graft loss if treated promptly - **TCMR Type III:** 60-70% response; 10-20% progress to graft loss despite treatment - **Acute ABMR:** 50-60% response to standard therapy; some may require additional interventions (bortezomib, eculizumab) - **Late acute rejection (>3 months):** Higher risk of chronic changes and graft loss; often reflects inadequate immunosuppression or non-adherence

B. Chronic Allograft Rejection

Chronic Allograft Nephropathy (CAN):

Definition: Progressive renal dysfunction attributable to chronic immunological and non-immunological injury to the transplanted kidney.

Pathophysiology: - Chronic T-cell mediated rejection: gradual accumulation of mononuclear cells in interstitium □ fibrosis - Chronic antibody-mediated rejection: persistent DSA, chronic C4d+ or MVI+, progressive vascular changes - Non-immunological factors: CNI nephrotoxicity, recurrent disease, hypertension, proteinuria, ischemia-reperfusion injury

Pathological Features: - Interstitial fibrosis and tubular atrophy (IF/TA): hallmark of chronic injury - Transplant glomerulopathy (TG): GBM duplication, capillary wall thickening; often associated with chronic ABMR - Intimal fibrosis of arteries and arterioles - Arteriolar hyalinosis (associated with CNI exposure)

Clinical Presentation: - Gradual decline in GFR (fall of 3-5 mL/min/1.73 m^2 per year in later post-transplant period) - Proteinuria (often 0.5-1.5 g/day) - Hypertension (often difficult to control) - Anemia (similar to CKD progression) - No specific symptoms; identified by laboratory trend

Risk Factors: - Prior acute rejection episodes (particularly ABMR) - HLA mismatch burden - Delayed graft function (early sign of injury) - Persistent donor-specific antibodies - CNI exposure (cumulative) - Older donor age - Hypertension - Recurrent disease - Non-adherence to immunosuppression

Prevention Strategies: 1. **Minimize acute rejection:** Appropriate induction, maintenance immunosuppression, adherence 2. **CNI minimization/conversion:** Reduce tacrolimus trough levels over time; consider conversion to sirolimus or belatacept 3. **Treat hypertension aggressively:** Goal BP <120/80; ACEi/ARB preferred (renoprotective via reduced glomerular capillary pressure) 4. **Reduce proteinuria:** RAAS inhibition, weight loss, glucose control 5. **Minimize other nephrotoxins:** NSAIDs avoided; use of aminoglycosides minimized 6. **Donor selection:** Preferentially allocate good-quality kidneys to lower-risk recipients

Management of Established CAN: - Aggressive blood pressure control (goal <120/80 mm Hg) - ACEi/ARB therapy (reduces proteinuria, slows progression) - Reduce immunosuppression judiciously (may slow CNI-related injury) - Consider CNI-to-sirolimus conversion (controversial; mixed evidence) - Statins for dyslipidemia - SGLT2 inhibitors emerging as renoprotective in CKD; limited transplant data - Prepare patient for return to dialysis (late-stage planning)

Prognosis: - Median graft survival with CAN approximately 8-12 years (vs. 15-20 years overall) - Proteinuria >1 g/day predicts accelerated decline - ABMR-related CAN generally has worse prognosis

II. BK POLYOMAVIRUS NEPHROPATHY (BKVN)

A. Epidemiology and Pathophysiology

Background: - BK virus (BKV) is ubiquitous; 50-90% population seropositive - Latent in kidney, ureter, bladder; reactivates in setting of immunosuppression - Occurs in 1-10% of kidney transplant recipients (varies by center, detection method)

Risk Factors for BKVN: - Degree of immunosuppression: intense induction (thymoglobulin, alemtuzumab) carries higher risk - Donor status: BKV+ donor increases risk - HLA mismatch and degree of DSA - CNI trough levels: higher levels associated with increased BKVN risk

Pathophysiology: - BK virus replicates in tubular epithelial cells - Cytopathic effect ☐ tubulitis, tubular necrosis - Inflammatory response contributes to injury - Can mimic acute rejection histologically; differentiation requires immunohistochemistry

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B. Clinical Presentation and Diagnosis

Natural History: - **Asymptomatic viremia (Month 1-3):** BKV DNA in blood; may precede clinical disease - **Viral-Associated Nephropathy (BKVAN):** Progressive renal dysfunction; histopathological evidence of BK involvement - **BKVN:** BKV inclusion bodies in tubular epithelium; associated renal dysfunction

Clinical Features: - Gradual rise in serum creatinine (over weeks to months) - No specific symptoms (distinguish from acute rejection by clinical picture) - Usually no fever, constitutional symptoms - Proteinuria variable (0.5-2 g/day)

Diagnosis:

Test	Interpretation
BK PCR (plasma)	Quantitative viral load; >10,000 copies/mL warrants further evaluation; >100,000 copies/mL highly concerning
Urine BK PCR	Less specific; present in asymptomatic viremia; may precede viremia
Kidney biopsy	Gold standard; identifies BK inclusion bodies (owl's eye appearance) in tubular epithelium; immunohistochemistry (SV40, BK) confirms diagnosis
Histology	Tubulitis (may mimic acute rejection), tubular atrophy, basement membrane disruption

Diagnostic Algorithm: 1. Rising creatinine ☐ obtain BK PCR (plasma) 2. BK PCR <10,000: monitor closely (monthly); reduce IS if possible 3. BK PCR 10,000-100,000: strongly consider biopsy; reduce IS and monitor BK PCR 4. BK PCR >100,000: biopsy recommended; definitive diagnosis informs management

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C. Management

Prevention: - Baseline BK serology (IgG, IgM) - Avoid excessive early immunosuppression (consider less intense induction in low-risk) - Monitor BK PCR at 3, 6, 12 months and annually

Treatment of Asymptomatic Viremia: - Reduce CNI trough levels: goal 5-8 ng/mL (vs. standard 8-12 ng/mL) - Monitor BK PCR monthly; if declining, continue IS reduction - If stable/rising, consider further IS adjustments or CNI conversion

Treatment of BKVN (Confirmed by Biopsy): - **CNI reduction:** Primary intervention; reduce trough from 8-10 to 5-8 ng/mL - **MMF reduction or discontinuation:** Some advocate stopping MMF, though data limited; risky in high-risk recipients - **Conversion to sirolimus:** Some recommend switch from CNI to sirolimus (theoretical antiviral effect); limited evidence - **Antiviral therapy:** Limited options; cidofovir (systemic or intra-lesional) used in some centers but nephrotoxic; outcomes variable - **Leflunomide:** Some case reports of benefit; limited evidence - **Monitoring:** BK PCR every 1-2 weeks; target clearance of viremia

Outcomes: - 20-30% lose graft to BKVN despite intervention - 40-50% have graft dysfunction (reduced GFR) but retain function - Prognosis better if diagnosed early (BK PCR <100,000) and treated promptly - Late diagnosis (advanced histopathology) carries higher graft loss risk

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III. CMV DISEASE POST-TRANSPLANT

A. Epidemiology and Pathophysiology

Background: - CMV seroprevalence: 40-60% developed countries, up to 90% developing countries - Primary infection (R-/D+), reactivation (R+), or superinfection (R+/D+) possible - Highest risk: D+/R- (seronegative recipient of seropositive donor)

Pathophysiology: - Direct viral cytopathic effects: ulceration, tissue necrosis - Indirect immune-mediated effects: activation of alloreactive T cells (molecular mimicry hypothesis)

B. Clinical Presentations

CMV Syndrome (Most Common): - Fever >3 days, malaise, myalgias, arthralgias - Leukopenia (WBC 2-4 K/μL) - Atypical lymphocytosis - Elevated LDH, mild transaminitis - No localized tissue involvement - Occurs months 1-4 post-transplant

Tissue-Invasive CMV Disease:

Site	Manifestation	Diagnosis
GI tract	Esophagitis, colitis; severe diarrhea, abdominal pain, GI bleeding	Endoscopy with biopsy; CMV inclusion bodies or immunohistochemistry
Lungs	Pneumonitis; dyspnea, cough, hypoxia; typical ground-glass opacities on CT	BAL with CMV PCR; biopsy if diagnostic uncertainty

Site	Manifestation	Diagnosis
Eyes	Retinitis (rare post-kidney transplant; more common post-bone marrow); cotton-wool spots, hemorrhages, visual symptoms	Ophthalmology evaluation; fundoscopy
CNS	Encephalitis, ventriculoencephalitis; altered mental status, seizures	CSF CMV PCR (highly specific if positive); MRI may show ventriculitis
Other	Hepatitis, cystitis, myocarditis (rare)	Biopsy if relevant; viral PCR

Diagnosis: - **CMV PCR (blood):** Gold standard; quantitative viral load - <100 copies/mL: negative - 100-1000: low level (monitor) - 1000-100,000: significant (treatment usually indicated) - >100,000: high (treatment urgent) - **CMV PCR (tissue): BAL, CSF, stool** as indicated by site of disease - **Antigenemia:** Less specific; primarily used for monitoring response to treatment - **Biopsy:** Gold standard for tissue-invasive disease; identifies inclusion bodies or immunohistochemistry

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C. Management

Prevention: - **D+/R- recipients:** Valganciclovir 900 mg daily x 3-6 months (standard prophylaxis) - **Other combinations:** Acyclovir 800 mg 5x daily (less effective); oral ganciclovir (rarely used) - **Monitoring:** CMV PCR at regular intervals; earlier in high-risk (D+/R-)

Treatment of CMV Syndrome: - Valganciclovir 900 mg BID x 2-3 weeks (or until viral clearance) - Monitor CMV PCR; target <100 copies/mL - Usually responds well to antiviral therapy

Treatment of Tissue-Invasive CMV: - Intravenous ganciclovir 5 mg/kg BID x 2-3 weeks (superior CNS/lung penetration vs. valganciclovir) - Monitor CMV PCR; continue until viral clearance plus 2-4 weeks - Reduce immunosuppression if possible (particularly IF high-dose steroids for rejection) - Monitor for ganciclovir toxicity: bone marrow suppression, renal dysfunction, neurologic symptoms

CMV Resistance: - Develops in ~1-2% with prolonged exposure to ganciclovir/valganciclovir - Fosfomycin (foscarnet) or cidofovir used for resistant CMV; significant toxicity - Mutation testing (UL97, pol gene) confirms resistance

Outcomes: - CMV syndrome: excellent response to antiviral therapy; 95%+ respond - Tissue-invasive CMV: 60-80% respond to therapy; higher morbidity/mortality - Risk of CMV end-organ disease lower with modern prophylaxis

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IV. POST-TRANSPLANT DIABETES MELLITUS (PTDM)

A. Definition, Epidemiology, and Risk Factors

Definition: New-onset diabetes mellitus diagnosed after transplantation in patient without prior diabetes.

Incidence: 10-20% of kidney transplant recipients (higher in older, obese, or those with impaired fasting glucose).

Pathophysiology: - **Calcineurin inhibitors:** Directly impair β-cell insulin secretion; reduce insulin gene expression; cause insulin resistance - **Corticosteroids:** Increase hepatic gluconeogenesis; increase insulin resistance; impair β-cell function - **mTOR inhibitors:** Associated with hyperglycemia (sirolimus in particular) - **Non-immunological factors:** Obesity, sedentary lifestyle, poor diet, family history, older age, male gender, minority race/ethnicity

Risk Factors for PTDM: - Age >50 years - BMI >25 kg/m² - Family history of diabetes - Hepatitis C serostatus (HCV increases risk) - Impaired fasting glucose pre-transplant - Corticosteroid dose (higher dose increases risk) - CNI choice: tacrolimus >cyclosporine

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B. Diagnosis and Screening

Diagnostic Criteria (ADA Standard): - Fasting plasma glucose ≥126 mg/dL - 2-hour plasma glucose ≥200 mg/dL during OGTT - Random plasma glucose ≥200 mg/dL with symptoms - HbA1c ≥6.5% (48 mmol/mol)

Screening Protocol: - Baseline fasting glucose and HbA1c pre-transplant - Fasting glucose at day 7, week 4, 12 weeks, 6 months, 1 year, then annually - HbA1c at 3 months, 6 months, 1 year, then annually - Earlier screening if fasting glucose 100-125 mg/dL at baseline

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C. Prevention and Management

Prevention Strategies: 1. **Immunosuppression minimization:** - Use tacrolimus at lowest effective trough (6-10 ng/mL vs. 12-15) - Minimize corticosteroid dose; late prednisone withdrawal protocol - Consider conversion to sirolimus (paradoxically associated with hyperglycemia; avoid) or belatacept (favorable metabolic profile)

2. **Lifestyle modification:**
    - Weight loss (goal BMI <25 kg/m²); reduces PTDM risk by 30-40%
    - Regular aerobic exercise (150 min/week moderate intensity)
    - Reduced refined carbohydrate, increased fiber
    - Smoking cessation
3. **Pharmacological prevention (limited evidence):**
    - Acarbose (alpha-glucosidase inhibitor): may delay PTDM onset in high-risk
    - Metformin: limited evidence in transplant population; generally safe if GFR >30

Treatment of Established PTDM:

Agent	Approach	Efficacy	Considerations
Lifestyle	Diet, weight loss, exercise	50-60% achieve normoglycemia if diagnosed early	First-line; should be attempted before pharmacotherapy
Metformin	500 mg daily ☐ titrate to 1000-2000 mg divided	Effective; $; well-tolerated	Avoid if GFR <30; monitor renal function; assess annually
Sulfonylurea (glyburide, glipizide)	Dose titration; rapid action	Effective but risk of hypoglycemia	Avoid in elderly, frail; risk of weight gain
GLP-1 agonist (liraglutide, dulaglutide)	Subcutaneous weekly or daily	Weight loss benefit; cardiovascular benefit in general population	Limited transplant data; cost; injectable
SGLT2 inhibitor (empagliflozin, dapagliflozin)	Daily oral	Weight loss, BP reduction; cardiovascular benefit	Emerging post-transplant; renal-protective effects; monitor DKA risk
Insulin	Basal-bolus or other regimen	Effective in any setting	Risk of hypoglycemia; weight gain; requires patient education

Special Consideration — Immunosuppression Adjustment: - If PTDM develops despite lifestyle modification and first-line agents, consider CNI reduction further - Conversion to belatacept (CNI-free) may improve glycemic control but requires careful patient selection (increased early rejection risk) - Difficult decisions balancing graft rejection risk vs. metabolic complications

Outcomes: - Mortality from cardiovascular disease increased in PTDM recipients - Graft survival modestly reduced - Early detection and aggressive glycemic control reduce complications

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V. POST-TRANSPLANT MALIGNANCY

A. Post-Transplant Lymphoproliferative Disorder (PTLD)

Definition: Aberrant proliferation of lymphocytes (usually B cells, EBV-driven) in setting of immunosuppression.

Epidemiology: - Incidence: 1-5% of kidney transplant recipients (higher in intestinal, heart, lung transplants) - Risk factors: EBV-seronegative recipient receiving EBV-seropositive graft (R-/D+) highest risk - Timing: Can occur within weeks to years; early-onset (<1 year) associated with high EBV serotype mismatch

Pathophysiology: - EBV reactivation/primary infection in setting of profound T-cell immunosuppression (particularly ATG, alemtuzumab induction) - Loss of T-cell surveillance of EBV-infected B cells - Uncontrolled B-cell proliferation; transformation to lymphoma possible

Classification (Pathological):

Type	Histology	Clinical Behavior
Type I (Early)	Polyclonal or monoclonal B-cell proliferation; intact normal lymph node architecture	Often EBV+ in situ hybridization; may be reversible with IS reduction
Type II (Intermediate)	Monoclonal B-cell proliferation; some architectural distortion	Variable clinical course; some respond to IS reduction
Type III (Late)	Monoclonal B-cell lymphoma; destroyed normal architecture; cytologic atypia	Frankly malignant; rarely responds to IS reduction alone; requires chemotherapy

Clinical Presentations: - Fever, night sweats, malaise - Lymphadenopathy - Hepatosplenomegaly - GI involvement: abdominal pain, obstruction, perforation - CNS involvement: focal neurologic deficits, altered mental status - Pulmonary involvement: cough, dyspnea

Diagnosis: - **Clinical suspicion:** Symptomatic lymphadenopathy or systemic symptoms in transplant recipient - **EBV serologies:** EBV IgM (primary infection), EBV PCR (viremia, correlates with PTLD risk) - **Imaging:** CT/MRI to identify sites of involvement; PET-CT useful for staging - **Pathological diagnosis:** Lymph node or tissue biopsy with immunophenotyping, EBV in situ hybridization

Management:

Type	Initial Management	Monitoring/Escalation
Type I	Reduce immunosuppression (50% reduction CNI/MMF; careful graft monitoring); monitor EBV PCR	Repeat biopsy in 4-6 weeks; if resolved, gradually restore IS; if persistent, add rituximab
Type II	Reduce IS; rituximab 375 mg/m² weekly x 4 weeks; monitor EBV PCR	Assess response at 4-6 weeks; if inadequate, consider chemotherapy
Type III	Chemotherapy (CHOP or variant) ± rituximab; consider IS reduction but secondary	Treat as lymphoma; oncology consultation; monitor for secondary infections on chemotherapy

Prevention: - Baseline EBV serology (R- vs. R+, D- vs. D+) - If R-/D+: EBV monitoring (EBV PCR) at months 1, 3, 6, 12, then annually - Avoid intense early induction in R-/D+ (use basiliximab instead of thymoglobulin if possible) - Consider rituximab prophylaxis in selected R-/D+ recipients (controversial; limited data)

Prognosis: - Type I: 80-90% respond to IS reduction; good prognosis - Type II: 60-70% respond to IS reduction + rituximab - Type III: 40-50% respond to chemotherapy; high mortality from disease and treatment toxicity

B. Skin Cancer

Epidemiology: - Most common malignancy post-transplant (40-50% of post-transplant cancers) - Squamous cell carcinoma (SCC) more common than basal cell carcinoma (BCC) in transplant recipients (opposite of general population) - Melanoma: 3-8x increased risk

Risk Factors: - Degree of immunosuppression; intensity of induction - Cumulative sun exposure - Fair skin, male gender, older age - HPV serostatus (associated with SCC) - Azathioprine use (photosensitizing)

Prevention: - UV protection: broad-spectrum sunscreen SPF 30+ daily, protective clothing, sunglasses - Avoid peak sun hours - Regular dermatologic surveillance (baseline skin exam, annual or biannual thereafter; more frequent if high-risk) - Smoking cessation - Minimize immunosuppression (late prednisone withdrawal, CNI minimization)

Management: - Excisional biopsy for suspicious lesions - Mohs micrographic surgery for high-risk SCC (face, ears, lips, genitals) - Standard surgical management for BCC - Systemic chemotherapy for metastatic SCC (rare but aggressive) - Close follow-up after treatment; high recurrence risk

Outcomes: - Excellent prognosis with early detection and surgical excision - Higher recurrence rates vs. non-transplant population - Rarely fatal unless melanoma or advanced SCC at presentation

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VI. PREGNANCY AFTER KIDNEY TRANSPLANTATION

A. General Principles

Feasibility: Pregnancy is possible and generally safe after kidney transplant; outcomes comparable to non-transplant population if careful planning and monitoring.

Timing: Most centers recommend waiting 1-2 years post-transplant: - Allows stabilization of graft function - Allows time for acute rejection episodes to manifest - Permits optimization of medications - Minimizes viral reactivation risk

Prerequisites: - Stable graft function (Cr <1.5 mg/dL or eGFR >50) - No proteinuria (or minimal <1 g/day) - Absence of uncontrolled hypertension - Compliance with immunosuppression - Absence of active infection - Appropriate counseling regarding risks

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B. Impact on Allograft

Graft Outcomes: - Pregnancy does not permanently worsen graft function in stable recipients - Transient increases in proteinuria and creatie during pregnancy (normal pregnancy physiology) - Return to baseline post-delivery - Preeclampsia (5-10% of pregnant transplant recipients) associated with temporary graft function decline but usually reversible

Risk Factors for Graft Loss During Pregnancy: - Preexisting proteinuria >1 g/day - Elevated baseline creatinine (>1.4 mg/dL) - Hypertension - Prior rejection history

C. Immunosuppression Adjustments

Agent	Pregnancy Safety	Considerations
Tacrolimus	Category C; generally safe	Levels may decline during pregnancy; monitor levels frequently (monthly); adjust dose to maintain therapeutic range
Cyclosporine	Category C; generally safe	Similar monitoring to tacrolimus
Mycophenolate (MMF, MPS)	**Category X — teratogenic**	Highly teratogenic; miscarriage risk 25-50%; associated with congenital abnormalities (ear, heart, cleft palate). MUST STOP before conception; switch to alternative IS. MPS may have lower risk but avoid. Switch to alternative (azathioprine)
Azathioprine	Category D but used in pregnancy	Historical experience favorable; use if MMF contraindicated; dose 1-2 mg/kg/day
Corticosteroids	Generally safe	May require dose increase during pregnancy; prednisone preferred; continue at lowest effective dose
Sirolimus	Avoid in pregnancy	Limited data; theoretical concerns; avoid conception on sirolimus
Belatacept	Limited data	IV agent; no accumulated teratogenic data but limited pregnancy experience; use with caution; coordinate with maternal-fetal medicine

Preconception Planning: - Switch from mycophenolate to azathioprine ≥6 weeks before conception (reduce MMF teratogenic exposure) - Optimize tacrolimus levels; target lower-normal range - Control hypertension; avoid ACEi/ARB (teratogenic, particularly 2nd/3rd trimester); substitute labetalol, methyldopa, nifedipine - Optimize glucose control if diabetic - Counsel regarding contraception; discuss planning timeline

D. Obstetric Management and Fetal Monitoring

Prenatal Care: - Coordinate with maternal-fetal medicine specialist - Frequent visits (every 2 weeks after first trimester) - Monthly renal function assessment (Cr, eGFR, proteinuria) - Monthly to biweekly CNI level monitoring (levels change in pregnancy) - Frequent BP monitoring (preeclampsia risk higher) - Fetal monitoring appropriate for gestational age

Complications: - **Preeclampsia (5-10%):** Usually mild; 75% have good outcomes; closely monitor BP, proteinuria, liver/kidney function - **Gestational diabetes:** Increased risk in PTDM recipients; screen carefully - **Preterm delivery:** Slight increased risk; monitor for complications - **IUGR:** Assess with periodic ultrasound - **Fetal anomalies:** No increased teratogenic risk if IS optimized (MMF discontinued)

Delivery Planning: - Vaginal delivery preferred if no obstetric contraindications - Cesarean delivery reserved for standard obstetric indications - Transplant positioned in iliac fossa; rarely obstructs pelvic delivery - Continue immunosuppression peripartum

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E. Neonatal and Postpartum Considerations

Infant Outcomes: - Birth weight slightly reduced (average 200-400 g lower) - Prematurity rate 20-30% (vs. 10% general population); higher in recipients with graft dysfunction - Preeclampsia increases risk of adverse neonatal outcomes - Neonatal exposure to tacrolimus/cyclosporine via breast milk minimal (drug poorly absorbed orally); breastfeeding generally safe

Postpartum Management: - Monitor CNI levels closely in immediate postpartum period (levels often increase as pregnancy effects reverse) - Resume full IS monitoring schedule - Screen for postpartum depression (risk elevated in transplant recipients) - Contraceptive counseling: most methods safe in post-transplant; some interactions with IS agents

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VII. RECURRENT DISEASE IN THE ALLOGRAFT

A. Glomerular Disease Recurrence Rates

Disease	Recurrence Rate	Clinical Impact
IgA Nephropathy (IgAN)	40-50% histologic; 10-15% clinical	Mild; responsive to therapy in most
FSGS	20-40% (higher in aggressive native disease phenotype)	May be severe; plasma exchange beneficial in some
MPGN/C3GN	30-40% (particularly C3 glomerulopathy)	Variable severity; some rapidly progressive
Post-infectious GN	Rare recurrence; usually responds to treatment	Excellent outcomes
Hemolytic Uremic Syndrome (HUS)	10-50% depending on genetic vs. acquired	High risk of graft loss (particularly atypical HUS with genetic mutations)

Disease	Recurrence Rate	Clinical Impact
Membranous Nephropathy	5-10%	Usually mild; can respond to IS or membranous-specific therapy
Lupus Nephritis	Rare in transplant; SLE activity usually quiescent post-transplant	Excellent outcomes if SLE stable
ANCA-associated GN	5-10%; may be higher in pauci-immune	Variable severity; some respond to IS intensification; others progress

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B. Risk Factors for Severe Recurrence

Risk Factor	Disease Association
Aggressive native disease	FSGS, HUS, MPGN
Young age at native disease onset	IgAN, FSGS, HUS
Rapid progression to ESRD	IgAN, HUS, MPGN
Genetic predisposition	HUS (particularly atypical HUS with complement mutations), MPGN/C3GN
Short time to ESRD	Aggressive disease phenotype; higher recurrence risk

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C. Management of Recurrent Disease

General Principles: - Early detection via urinalysis (hematuria, proteinuria trends) and renal function - Confirm diagnosis via kidney biopsy when recurrence suspected - Tailor management to specific disease and severity

IgA Nephropathy Recurrence: - Clinical recurrence (proteinuria, hematuria) in minority; monitor with urinalysis - Proteinuria management: ACEi/ARB, RAAS blockade - Escalated IS if progressive: higher CNI levels, addition of azathioprine, corticosteroid augmentation - Newer agents: complement inhibitors (C5a inhibitor pegcetacoplan, alternative pathway inhibitor danicopan) emerging - Prognosis: 80%+ have stable graft function 5+ years despite recurrence

FSGS Recurrence: - Highest risk of severe recurrence and graft loss (50% loss graft to recurrence in severe cases) - Proteinuria is primary manifestation; often >3 g/day - Plasma exchange beneficial in subset (particularly early, aggressive recurrence); mechanism unclear - IS intensification: higher CNI levels, addition of azathioprine, augmented steroids - RTX (rituximab): case reports of benefit; limited evidence - Prognosis: variable; some respond well to plasma exchange; others progress despite therapy

HUS Recurrence (Particularly Atypical HUS): - Genetic mutations in complement pathway genes (CFH, CFI, C3, THBD, DGKE) confer high recurrence risk - Atypical HUS with CFH

mutation: recurrence risk 80-90%; high risk of graft loss - Management: Eculizumab (C5 complement inhibitor) reduces recurrence risk in complement-mediated HUS - Genetic counseling recommended for affected families - Consider preemptive eculizumab therapy if high-risk mutation and recurrence after prior transplant

MPGN/C3GN Recurrence: - C3 glomerulopathy has high recurrence rates; some progress rapidly - Management: IS optimization; complement inhibitors emerging - Eculizumab or alternative pathway inhibitors (pegcetacoplan, danicopan) reduce recurrence in some

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VIII. CLINICAL PEARLS

1. **Proteinuria is sentinel sign:** New or worsening proteinuria warrants investigation (biopsy if significant change).
2. **CNI toxicity is cumulative:** Late chronic nephropathy may reflect both CNI and other injuries; minimize CNI exposure over time.
3. **Infection and rejection mimic each other:** CMV, BK, and acute rejection all present with rising creatinine; clinical context (fever, viral PCR, biopsy) aids differentiation.
4. **Early rejection is most treatable:** Type I TCMR responds to steroids >80%; Type III requires T-cell depletion; chronic changes may be irreversible.
5. **ABMR is higher-risk rejection:** Acute ABMR has lower treatment response (50-60%) than TCMR; DSA persistence predicts chronic ABMR.
6. **Pregnancy is feasible:** With appropriate timing, planning, and monitoring, transplant recipients have favorable pregnancy outcomes; MMF MUST be stopped preconception.
7. **PTDM is common and serious:** Affects 20%+ of recipients; weight loss and IS minimization primary prevention; early detection improves outcomes.
8. **PTLD is usually EBV-driven:** R-/D+ mismatch highest risk; EBV PCR monitoring guides early detection; Type I/II may respond to IS reduction; Type III requires chemotherapy.
9. **Skin cancer is most common malignancy:** Sun protection essential; annual dermatologic surveillance recommended; early detection improves outcomes.
10. **BK viremia precedes clinical BKVN:** Screening BK PCR allows early detection and IS reduction before severe kidney injury develops.

IX. PRACTICE QUESTIONS

Question 1: A 42-year-old man is 6 weeks post-living donor kidney transplant. Serum creatinine has risen from 1.2 mg/dL (day 7) to 1.8 mg/dL. Urine output is adequate; no fever. Tacrolimus trough is 11 ng/mL. What is the next best step?

A) Increase tacrolimus dose to achieve trough of 14-15 ng/mL
B) Obtain kidney biopsy to assess for rejection
C) Start valganciclovir (CMV prophylaxis not previously started)

D) Reduce tacrolimus dose and check BK PCR

Answer: B. Rising creatinine 6 weeks post-transplant with adequate urine output and normal immunosuppressive levels raises concern for acute rejection. Kidney biopsy is indicated to differentiate TCMR from ABMR, infection (BK, CMV), or early CNI toxicity. Once rejection excluded or confirmed, management can be tailored. CMV prophylaxis should have been started perioperatively if D+ or R- serostatus.

Question 2: A 58-year-old woman is 18 months post-kidney transplant with stable graft function (Cr 1.3). She reports regular menses and desires pregnancy. Current IS: tacrolimus 5 mg daily, mycophenolate 1 g BID, prednisone 5 mg daily. What counseling and changes are appropriate?

A) Pregnancy is contraindicated; advise against conception
B) Switch mycophenolate to azathioprine 6 weeks before conception; counsel on increased preeclampsia risk; monitor CNI levels monthly during pregnancy
C) Continue current IS; pregnancy is safe at this graft function
D) Add eculizumab prophylactically to prevent recurrent disease

Answer: B. Mycophenolate is highly teratogenic (Category X) and must be discontinued ≥6 weeks before conception, replacing with azathioprine or alternative. Pregnancy is feasible at this stable graft function. Counseling should include increased preeclampsia risk (5-10%), potential need for delivery planning, and need for frequent monitoring (monthly CNI levels, renal function, BP monitoring). Eculizumab not indicated without known history of complement-mediated disease.

Question 3: A 35-year-old man is 10 months post-kidney transplant. Serum creatinine is 1.1 mg/dL. CMV PCR (plasma) returns at 25,000 copies/mL. He is asymptomatic. What is the most appropriate management?

A) Start valganciclovir 900 mg BID immediately
B) Monitor CMV PCR monthly; no treatment unless clinical CMV disease develops
C) Reduce CNI trough level to 5-8 ng/mL; monitor CMV PCR monthly
D) Start valganciclovir AND reduce CNI simultaneously

Answer: A (or partial credit for D). CMV PCR >1000 copies/mL warrants treatment regardless of symptoms. Valganciclovir 900 mg BID for 2-3 weeks is standard. Some experts would advocate simultaneous CNI reduction to enhance immune control of virus, but antiviral therapy is the primary intervention. Option B (observation only) is not appropriate for CMV PCR >10,000 copies/mL without symptoms; asymptomatic CMV viremia carries risk of progression to CMV syndrome or tissue disease if untreated.

X. REFERENCES

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