Kidney Transplant Immunosuppression: Agents, Mechanisms, Monitoring, and Toxicity

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Kidney Transplant Immunosuppression: Agents, Mechanisms, Monitoring, and Toxicity

Learning Objectives

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

1. Classify immunosuppressive agents by mechanism of action and timeline of application
2. Explain the pharmacology and clinical use of calcineurin inhibitors (tacrolimus, cyclosporine)
3. Describe induction therapy regimens (basiliximab, thymoglobulin, alemtuzumab) and indications
4. Discuss maintenance regimens incorporating tacrolimus, mycophenolate, and corticosteroids
5. Manage calcineurin inhibitor dosing, drug levels, and toxicity
6. Understand mTOR inhibitor pharmacology and clinical applications
7. Recognize newer agents (belatacept, bortezomib) and their roles in desensitization and antibody-mediated rejection
8. Monitor immunosuppressive drug levels and interpret therapeutic ranges
9. Prevent and manage immunosuppressive side effects (infection, malignancy, metabolic complications)
10. Tailor immunosuppressive regimens to patient-specific risk factors

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I. IMMUNOSUPPRESSIVE STRATEGY: TIMELINE AND CLASSES

A. Three-Phase Approach

Phase 1 — Induction (Perioperative): - Goal: prevent hyperacute and early acute rejection - Agents: T-cell depletors (ATG, thymoglobulin), T-cell costimulation blockers (basiliximab), or IL-2 receptor antagonists - Duration: single or divided doses over 3-5 days

Phase 2 — Maintenance (Long-term): - Goal: suppress chronic alloimmune response while minimizing toxicity - Agents: calcineurin inhibitor (tacrolimus or cyclosporine), mycophenolate, corticosteroid - Duration: lifelong (with possible taper protocols)

Phase 3 — Rejection Episodes (Acute/Chronic): - Goal: reverse active rejection - Agents: high-dose corticosteroids (methylprednisolone), T-cell depletors, plasmapheresis, IVIG, anti-B-cell agents (rituximab, bortezomib) - Duration: days to weeks depending on severity

B. General Principles of Modern Immunosuppression

1. **Minimization:** Reduce intensity to minimize infection/malignancy while preserving graft
2. **Individualization:** Tailor to immunological risk (HLA match, sensitization, prior rejection)
3. **Drug monitoring:** Therapeutic drug monitoring (TDM) essential for tacrolimus, cyclosporine, sirolimus
4. **Conversion strategies:** Conversion from tacrolimus to sirolimus or belatacept possible in select patients to reduce CNI toxicity
5. **Withdrawal protocols:** Late prednisone withdrawal (>2 years) increasingly safe with modern induction/maintenance

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II. INDUCTION THERAPY

A. Thymoglobulin (Rabbit Anti-Thymocyte Globulin)

Mechanism: Polyclonal IgG antibodies targeting T-cell antigens; causes T-cell depletion via complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity (ADCC).

Dosing: - 1.5 mg/kg IV on postoperative day 0 (or day 1) - Repeat dosing day 3, 5 (sometimes day 7) to total 4.5 mg/kg - Typically given as 100-150 mg in 50-100 mL normal saline over 4-6 hours

Mechanism of T-Cell Depletion: - Targets CD3+, CD4+, CD8+ T cells - Peak depletion 24-48 hours post-infusion - CD4+ count drops to <50 cells/μL; recovery over weeks to months - Gradual repopulation; naive T cells initially predominate

Efficacy: - Reduces acute rejection rates by 40-50% compared to no induction - Similar efficacy vs. basiliximab but superior in highly sensitized/mismatched recipients - Particularly effective in DCD and ECD kidneys

Side Effects:

Category	Manifestation	Management
Cytokine Release Syndrome (CRS)	Fever, chills, rigors, malaise, myalgias 1-2 hr after infusion	Premedication: acetaminophen, antihistamine, hydrocortisone; slow infusion rate; consider prophylactic methylprednisolone
Hematologic	Thrombocytopenia, leukopenia	Monitor CBC; transfusion rarely needed
Infectious	Increased CMV, BK, EBV, fungal risk due to profound T-cell depletion	CMV prophylaxis essential (valganciclovir); monitor CMV PCR, BK PCR

Category	Manifestation	Management
PTLD	EBV-associated post-transplant lymphoproliferative disorder in EBV-naive (R-) recipients of EBV+ donor	EBV serologies pre-transplant; monitor EBV PCR in high-risk
Serum sickness	Rash, arthralgia, lymphadenopathy developing 1-2 weeks post-infusion	Usually self-limited; treat with NSAIDs, antihistamines

Monitoring During Infusion: - Baseline CBC, comprehensive metabolic panel - Monitor temperature, BP, HR - Ensure IV line patent; central line preferred for irritant solution - Post-infusion: repeat CBC, electrolytes

B. Basiliximab (Simulect)

Mechanism: Chimeric monoclonal antibody targeting IL-2 receptor (CD25) on activated T cells; blocks IL-2 costimulatory signal; does NOT deplete T cells.

Dosing: - Induction: 20 mg IV on postoperative days 0 and 4 - Given as 20 mg in 50 mL normal saline bolus (5 min) or infusion

Advantages vs. Thymoglobulin: - No T-cell depletion; T-cell counts remain normal - No cytokine release syndrome - No serum sickness - Can be given in ambulatory setting - Lower infectious complication rates

Disadvantages: - Less potent than thymoglobulin in highly sensitized/mismatched patients - May be insufficient for DCD kidneys (higher DGF risk)

Side Effects: - Minimal; well-tolerated in immunocompetent patients - GI disturbances in <5% - No increased infection risk - Hypersensitivity extremely rare (<1%)

Efficacy: Similar to thymoglobulin in low-risk recipients; inferior in high-risk (sensitized, mismatched, ECD/DCD) populations.

C. Alemtuzumab (Campath)

Mechanism: Humanized monoclonal antibody targeting CD52 on lymphocytes; profound T-cell (and B-cell and monocyte) depletion.

Dosing: 30 mg IV as single dose on day 0 or day 1; highly potent—no repeated dosing.

Advantages: - Single dose; convenient - Profound, prolonged lymphocyte depletion (very low CD4+ counts for 3-6 months) - Allows delayed tacrolimus initiation with reduced early nephrotoxicity - Excellent outcomes in sensitized recipients

Disadvantages: - High CMV and EBV reactivation risk (especially in seronegative recipients) - PTLD risk - Opportunistic infection risk - Not widely used in contemporary practice due to infection concerns

Side Effects: - Severe cytokine release syndrome (more severe than thymoglobulin) - Opportunistic infections: CMV, EBV, PCP, fungal - PTLD and other malignancies - Requires mandatory CMV and PCP prophylaxis

Contemporary Use: Rarely used as routine induction; reserved for highly sensitized recipients or select clinical scenarios where infectious risk is acceptable.

D. Comparison of Induction Regimens

Agent	Mechanism	Efficacy	Infection Risk	Convenience	Common Use
Thymoglobulin	T-cell depletion	Excellent	Moderate (CMV prophylaxis needed)	IV x 3-5 doses	High-risk recipients, DCD, ECD
Basiliximab	IL-2R blockade	Good	Low	IV x 2 doses	Low-risk recipients, living donor
Alemtuzumab	Pan-lymphocyte depletion	Excellent	High (CMV, EBV, PTLD)	IV x 1 dose	Selected sensitized recipients
No induction	N/A	Acceptable in low-risk	Low	N/A	Very low-risk living donor

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III. MAINTENANCE IMMUNOSUPPRESSION

A. Calcineurin Inhibitors (CNI)

Shared Mechanism: - Inhibit calcineurin phosphatase, preventing dephosphorylation of NFAT (nuclear factor of activated T cells) - Block NFAT translocation to nucleus □ suppression of IL-2, TNF-α, IFN-γ transcription - Result: T-cell proliferation and activation suppressed

Tacrolimus (FK506, Prograf, Astagraf XL) **Pharmacology:** - Binds FK-binding protein 12; complex inhibits calcineurin - Oral bioavailability: 20-30% (highly variable; food, medications affect absorption) - Peak levels: 0.5-4 hours post-dose (immediate-release); delayed with extended-release - Half-life: 8-12 hours (immediate); 12-24 hours (extended-release XL) - Metabolism: primarily by CYP3A4 in GI and liver; extensive first-pass metabolism

Dosing: - Immediate-release (Prograf): Start 0.1-0.2 mg/kg/day divided BID or TID, taper based on levels - Extended-release (Astagraf XL): Start 0.1-0.15 mg/kg once daily, adjusted to therapeutic levels - Goal trough levels: weeks 1-4: 12-15 ng/mL; months 3-12: 8-12 ng/mL; year 2+: 6-10 ng/mL - Taper possible after 1-2 years if stable graft and no prior rejection

Monitoring: - Blood draws MUST be trough (12 hours post-dose), immediately pre-dose - Timing critical: peak levels 5-10x trough; variation >20% suggests non-adherence or drug interaction - Weekly x 2-4 weeks, then biweekly x 1-2 months, then monthly x 6 months, then quarterly - More frequent monitoring if dose adjustments, suspected non-adherence, or drug interactions

Toxicity:

Toxicity	Mechanism	Presentation	Management
Nephrotoxicity	Afferent arteriolar vasoconstriction via TXA_2, loss of prostaglandin-mediated vasodilation; glomerular capillary hypertension	Rising creatinine (often occurs in first 3-6 months); can progress to chronic kidney disease	Monitor creatinine closely; reduce CNI dose if rise >30%; consider conversion to sirolimus/belatacept in recurrent/severe; maintain adequate BP control; ACEi/ARB useful
Neurotoxicity	Exact mechanism unclear; possibly related to CNI concentration and cumulative exposure	Tremor (fine, high-frequency; dose-related), headache, insomnia, confusion, encephalopathy, posterior reversible encephalopathy syndrome (PRES)	Reduce dose; monitor levels; neuroimaging if encephalopathy; usually reversible with dose reduction
Hyperglycemia/PTDM	β-cell apoptosis, impaired insulin secretion and action	Hyperglycemia developing weeks to months post-transplant; overt diabetes in 20-30%	Monitor fasting glucose, HbA1c; encourage weight loss, exercise; consider switch to sirolimus if feasible; hypoglycemic agents as needed
Hypertension	Increased renin secretion, enhanced sympathetic tone, reduced nitric oxide bioavailability	HTN present in 50-70% post-transplant; often difficult to control	Antihypertensive agents essential; ACEi/ARB preferred; calcium channel blockers, beta blockers, diuretics added as needed
Hypomagnesemia	Increased urinary magnesium wasting	Hypomagnesemia in 30-50%; associated with hypokalemia and arrhythmia risk	Monitor magnesium; supplement orally (magnesium glycinate, magnesium oxide); monitor potassium concurrently

Toxicity	Mechanism	Presentation	Management
Gingival hyperplasia	Fibroblast proliferation; overlaps with other causes (amlodipine)	Gingival overgrowth, bleeding, periodontal disease	Excellent oral hygiene; regular dental care; switch CCB if concurrent amlodipine; may require gingivectomy
Infection	CNI-induced immunosuppression; T-cell dysfunction	Increased susceptibility to CMV, BK, opportunistic infections	Prophylaxis (valganciclovir, TMP-SMX); monitor CMV PCR, BK PCR regularly
Malignancy	Impaired T-cell surveillance	PTLD (EBV-associated in 5-10% of recipients), skin cancer, other malignancies	EBV serologies and monitoring (EBV PCR in high-risk); minimize CNI exposure; UV protection, skin surveillance

Drug Interactions: CYP3A4 inhibitors (azoles, macrolides, diltiazem, ketoconazole) increase tacrolimus levels; CYP3A4 inducers (rifampin, phenytoin) decrease levels. Grapefruit juice increases levels.

Cyclosporine (CSA, Neoral) Pharmacology: - Binds cyclophilin; complex inhibits calcineurin (same end-point as tacrolimus) - Similar mechanism but different binding protein - Oral bioavailability: 15-30%; microemulsion formulation (Neoral) improved vs. older formulation - Peak levels: 1-4 hours post-dose - Half-life: 8-30 hours (highly variable) - Metabolism: CYP3A4; extensive first-pass

Dosing: - Start 10-15 mg/kg/day divided BID, adjust based on levels - Goal trough levels: 150-250 ng/mL initially, gradually reducing to 75-100 ng/mL by 6 months - Often dosed on C2 level (2-hour post-dose) monitoring: goal C2 800-1200 ng/mL initially

Comparative Efficacy vs. Tacrolimus: - Similar acute rejection prevention - Historically more GI side effects, gingival hyperplasia, hypertrichosis - Nephrotoxicity similar magnitude; chronic CNI nephropathy affects ~10-15% of long-term recipients on either agent - Largely replaced by tacrolimus in contemporary practice due to side effect profile

Monitoring: Similar to tacrolimus; trough and/or C2 level monitoring critical.

B. Mycophenolate (Inosine Monophosphate Dehydrogenase Inhibitor)

Available Formulations: - Mycophenolate mofetil (MMF, CellCept): Pro-drug metabolized to mycophenolic acid (MPA) - Mycophenolate sodium (MPS, Myfortic): Enteric-coated; delayed-release formulation - Delayed-release MMF (Myfortic): Reduces GI side effects

Mechanism: - Selectively inhibits inosine monophosphate dehydrogenase (IMPDH) in lymphocytes - Lymphocytes depend on IMPDH for purine synthesis (de novo pathway); block of IMPDH ☐ depletes guanosine nucleotides - Result: selective lymphocyte growth inhibition

Dosing: - MMF: 1 g PO BID (start after tacrolimus established) - MPS: 720 mg PO BID - Higher doses (1.5 g BID) in some protocols, particularly for high-risk recipients or acute rejection treatment

Monitoring: - No routine drug level monitoring recommended - Therapeutic drug monitoring (TDM) may be considered in select patients with recurrent rejection or GI side effects - Target MPA AUC: 30-60 μg•hr/mL (if monitored)

Toxicity:

Toxicity	Manifestation	Management
GI intolerance	Nausea, vomiting, diarrhea, abdominal pain (20-30% of patients)	Divide doses; take with food; consider switch to MPS or delayed-release formulation; loperamide for diarrhea; PPI for upper GI symptoms
Hematologic	Leukopenia, anemia, thrombocytopenia (uncommon but concerning)	Monitor CBC; reduce dose if WBC <3,000 or Hgb <8; coordinate with other agents causing bone marrow suppression
Infection	Increased susceptibility (less marked than CNI)	CMV prophylaxis; monitor CMV PCR
Teratogenicity	Highly teratogenic (FDA category D)	Absolute contraindication in pregnancy; counsel women of childbearing age
Opportunistic infection	Increased fungal, viral, atypical infections	Prophylaxis as indicated

Advantages: - Selective immunosuppression (lymphocyte-specific) - Relatively well-tolerated at lower doses - No nephrotoxicity - No drug-level monitoring required in most cases

Disadvantages: - GI intolerance in significant minority - Teratogenicity limits use in women of childbearing potential - May have role in acute rejection but less potent than CNI

C. Corticosteroids

Mechanism: - Bind glucocorticoid receptor; translocate to nucleus - Suppress NF-κB and AP-1 transcription factors - Inhibit IL-2, TNF-α, IFN-γ, IL-6, other proinflammatory cytokine transcription - Broad immunosuppressive effects on T cells, B cells, antigen-presenting cells

Dosing:

Phase	Dose	Tapering
Induction (Day 0)	Methylprednisolone 500 mg-1 g IV intraoperatively	Single dose
Weeks 1-4	Prednisone 0.5 mg/kg/day (tapering)	Taper to 0.1-0.2 mg/kg/day by week 4
Months 2-12	5-10 mg/day	Gradual taper based on protocol
Long-term (>1 year)	2.5-5 mg/day or withdrawal	Possible withdrawal if no rejection history

Mechanism of Chronic Toxicity:

Toxicity	Impact	Management
Metabolic complications	Hyperglycemia, dyslipidemia, weight gain, osteoporosis	Minimize dose; lipid management; calcium/vitamin D supplementation; bone density screening; weight loss counseling
Bone disease	Accelerated bone loss, osteoporosis, avascular necrosis	Start vitamin D (1000-2000 IU daily) + calcium (1000 mg daily) at transplant; DEXA scan baseline and 1-2 year; bisphosphonates if T-score <-1.5
Infection	Increased susceptibility	Prophylaxis based on risk; vaccination in early post-transplant
Malignancy	Increased skin cancer, PTLD	Minimize dose; UV protection; skin surveillance
Hypertension	Exacerbates CNI-induced HTN	Aggressive BP management; minimize corticosteroid dose
Myopathy	Proximal weakness, rarely severe	Minimize dose; monitor for severe symptoms

Late Prednisone Withdrawal: Increasingly used strategy (withdrawal >2 years post-transplant in stable patients without prior rejection); reduces metabolic complications while maintaining graft survival with modern induction/maintenance agents.

D. Triple Therapy Regimen (Standard)

Classic combination: - Calcineurin inhibitor (tacrolimus preferred over cyclosporine) - Mycophenolate (MMF 1 g BID or MPS 720 mg BID) - Corticosteroid (prednisone taper, 5-10 mg/day long-term)

Efficacy: Triple therapy reduces acute rejection rates to <10% in most populations; superior to dual or monotherapy regimens.

Advantages: - Synergistic immunosuppression via multiple mechanisms - Each agent added for defined duration (CNI lifelong, MMF lifelong, prednisone taper then lower dose or withdrawal) - Extensive literature supporting outcomes

Disadvantages: - Cumulative toxicity (nephrotoxicity, metabolic, infection, malignancy) - Multiple medications; adherence burden - Frequent monitoring required

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IV. ALTERNATIVE AND NEWER AGENTS

A. mTOR Inhibitors

Agents: Sirolimus (Rapamune), Everolimus (Zortress, Afinitor)

Mechanism: - Inhibit mTOR (mechanistic target of rapamycin) - Block T-cell proliferation via inhibition of IL-2-mediated cell cycle progression - Also antiproliferative effect on vascular smooth muscle (theoretical benefit for chronic allograft vasculopathy)

Sirolimus Dosing: - Loading dose: 6 mg PO once - Maintenance: 2 mg PO daily - Adjust based on trough levels (goal 4-10 ng/mL) - Trough monitoring essential (weekly x 2-4 weeks, then monthly)

Everolimus Dosing: - Typical: 0.75 mg BID with target trough 3-8 ng/mL - Requires trough level monitoring

Advantages: - Non-nephrotoxic; can be used as CNI-sparing/CNI-replacing agent - Antiproliferative effects (theoretical benefit for chronic graft dysfunction) - No neurotoxicity - Possible anti-viral effects (BK, CMV)

Disadvantages: - Significant GI intolerance (nausea, diarrhea, stomatitis) in 20-30% - Delayed wound healing, increased dehiscence risk (avoid immediate post-transplant) - Hyperlipidemias - Bone marrow suppression (thrombocytopenia, anemia) - Interstitial pneumonitis (rare but serious) - Requires therapeutic drug monitoring

Clinical Applications: - CNI-sparing protocols: early switch (3-6 months) to reduce CNI nephrotoxicity - Chronic allograft nephropathy: switch from CNI to sirolimus to prevent progression (emerging evidence) - BK nephropathy: switch from CNI to sirolimus (antiviral effect); monitor BK PCR

Efficacy: Non-inferior to CNI-based regimens in acute rejection prevention; superior outcomes in preventing chronic graft dysfunction (conflicting literature; remains investigational).

B. Belatacept (Nulojix)

Mechanism: - Fusion protein (CTLA4-Ig variant); blocks B7 family costimulatory molecules (CD80, CD86) on antigen-presenting cells - Prevents T-cell costimulation; T cell activation blocked at first signal (TCR-MHC engagement alone insufficient)

Dosing: - Induction: 10 mg/kg IV on day 0 (pre-operative), day 4, week 2, week 4, week 8, week 12 - Maintenance: 5-10 mg/kg IV monthly (can switch to 5 mg/kg every 4 weeks after 6 months)

Advantages: - CNI-free regimen; eliminates CNI nephrotoxicity, neurotoxicity, hyperglycemia - Excellent renal function preservation - Favorable metabolic profile (minimal hyperglycemia, better lipids than CNI-based) - Long-term graft survival superior to CNI-based in some studies - No need for drug-level monitoring

Disadvantages: - IV administration required (monthly); inconvenient - Increased acute rejection risk (especially early, first 3 months) vs. CNI-based: 7% vs. 3-5% - Progressive multifocal leukoencephalopathy (PML) risk in seronegative recipients receiving EBV-seronegative donor organs - Increased CMV disease and other infections in some studies - Slower graft function recovery post-transplant

Contraindications: - EBV-seronegative recipient receiving EBV-positive donor organ (PML risk) - CMV-seronegative recipient (CMV disease risk)

Clinical Applications: - Older recipients or those with significant comorbidities at high CNI toxicity risk - Recurrent CNI nephrotoxicity with graft dysfunction - Steroid-intolerant patients (belatacept protocols often include steroid minimization/withdrawal)

Outcomes: Excellent long-term graft and patient survival; increasing use as CNI-free alternative in selected populations.

C. Bortezomib

Mechanism: Proteasome inhibitor; blocks NF-κB signaling and proteasome-mediated antigen presentation.

Clinical Use: - Antibody-mediated rejection (AMR) treatment or prevention - Desensitization in highly sensitized recipients - PTLD management

Evidence: Limited; primarily case reports and small series. Used in conjunction with standard therapy for resistant AMR or PTLD.

Toxicity: Significant; peripheral neuropathy, thrombocytopenia, GI intolerance; generally reserved for serious indications.

D. Rituximab (Anti-CD20 Monoclonal Antibody)

Mechanism: B-cell depletion via CD20 targeting.

Clinical Use: - Desensitization (pre-transplant) in highly sensitized recipients - AMR treatment - PTLD (EBV-associated) - Recurrent membranoproliferative glomerulonephritis (MPGN) in allograft

Dosing: Variable; 375 mg/m² IV weekly x 4 weeks (standard) or 1 g x 2 doses (2 weeks apart)

Toxicity: Cytokine release syndrome, infection (opportunistic), bone marrow suppression; generally well-tolerated.

Efficacy: Promising in desensitization and AMR treatment; increasingly used in clinical practice for high-risk recipients.

E. Intravenous Immunoglobulin (IVIG)

Mechanism: Multiple; blocking B-cell surface receptors, anti-idiotypic antibodies, complement inhibition.

Clinical Use: - Desensitization in highly sensitized recipients (adjunct) - AMR treatment - Recurrent disease prevention

Dosing: 1-2 g/kg IV as single infusion or divided doses; may repeat.

Efficacy: Used as adjunct to other desensitization/rejection therapy; standalone benefit limited.

V. DRUG MONITORING AND THERAPEUTIC TARGETS

A. Tacrolimus (Most Important)

Sampling: - **Trough level (C0):** Most commonly used; 12-hour pre-dose blood sample - **Peak level (Cmax):** Sometimes monitored but less practical - **AUC (Area Under Curve):** Gold standard but impractical (requires multiple samples) - **C2 level:** 2-hour post-dose; occasionally used to predict AUC

Interpretation: - Low levels (<5 ng/mL): risk of rejection - High levels (>15 ng/mL): increased toxicity (nephrotoxicity, neurotoxicity) - Therapeutic window narrow; <20% variability in levels desirable

Timing Sensitivity: - **Immediate-release (Prograf):** BID or TID dosing; draw trough immediately pre-dose (12 hours post-dose) - **Extended-release (Astagraf XL):** Once-daily dosing; draw trough pre-dose - **Variability:** Peak 5-10x trough; variability >20% between similar doses suggests non-adherence, drug interactions, or GI absorption changes

Factors Affecting Levels: - Food, bile acids, GI motility affect absorption - CYP3A4 inhibitors: azoles (fluconazole), macrolides (clarithromycin), diltiazem, ketoconazole ☐ increased levels - CYP3A4 inducers: rifampin, phenytoin, St. John's Wort ☐ decreased levels - Grapefruit juice ☐ increased levels - Genetic polymorphisms (CYP3A5 expressers may require higher doses)

Monitoring Schedule: - Weeks 1-2: 2-3x/week - Weeks 2-4: weekly - Months 2-3: biweekly - Months 3-12: monthly - Year 2+: every 3 months (stable patients) - Increase frequency after dose adjustments, suspected non-adherence, or drug interactions

B. Mycophenolate

Monitoring: - Routine trough level monitoring NOT recommended (no established therapeutic range) - Therapeutic drug monitoring (MPA AUC) may be considered in: - Recurrent acute rejection despite standard dosing - GI intolerance limiting dose escalation - Potential drug interactions

Target MPA AUC (if monitored): 30-60 μg•hr/mL

Practical Approach: Dose on clinical response (rejection, tolerability); adjust dose based on symptoms.

C. Sirolimus

Monitoring: - Trough level monitoring essential - Target trough: 4-10 ng/mL (varies by protocol and time post-transplant) - Frequency: weekly x 2-4 weeks, then monthly, then every 3 months (stable)

Sampling: 12-hour pre-dose; trough critical.

VI. INFECTION PROPHYLAXIS

All transplant recipients require lifelong prophylaxis against opportunistic infections:

Infection	Prophylaxis	Duration	Monitoring
CMV (D+/R- or high-risk)	Valganciclovir 900 mg daily OR acyclovir 800 mg 5x/day	3-6 months (D+/R- highest risk)	CMV PCR if symptoms; monitor for resistance
PCP	TMP-SMX 1 DS daily	1 year or indefinite (if CD4 persistently <200)	LDH monitoring; watch for rash (HLA-B*5701)
Fungal (Cryptococcus, Candida)	Fluconazole 200 mg daily (controversial; some institutions omit)	6-12 months	Chest X-ray if respiratory symptoms
Tuberculosis	Isoniazid 300 mg daily (if TST positive pre-transplant)	6 months (after post-transplant workup)	Monitor for hepatotoxicity
Viral (non-CMV)	Acyclovir (if not on valganciclovir for CMV)	1-3 months post-transplant	Clinical monitoring for breakthrough
BK virus	No proven prophylaxis; minimize CNI (controversial); monitor BK PCR	Ongoing	BK PCR PCR at 3, 6, 12 months; repeat if elevated

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VII. CLINICAL PEARLS

1. **Tacrolimus is preferred CNI:** Superior to cyclosporine for acute rejection prevention and graft survival; lower hypertrichosis and gingival hyperplasia.
2. **Target lower levels in late post-transplant:** Gradual reduction of tacrolimus trough from 12-15 ng/mL (early) to 6-10 ng/mL (>1 year) reduces nephrotoxicity risk.
3. **CNI nephrotoxicity is dose-dependent and partially reversible:** Early recognition and dose reduction can slow progression; late chronic nephropathy may be irreversible.

4. **Mycophenolate GI side effects are common but manageable:** Divide dosing, take with food, or switch formulation; rarely need to discontinue.
5. **Belatacept is CNI-free option for appropriate candidates:** Excellent long-term renal function; increased early rejection risk requires patient selection and close monitoring.
6. **Drug interactions are critical:** Always check CYP3A4 interactions before adding new medications; adjust CNI dose accordingly.
7. **Non-adherence is major cause of late rejection:** Reinforce adherence at every visit; consider pill organizers, simplified regimens.
8. **Corticosteroid minimization/withdrawal is safe:** Late prednisone withdrawal (>2 years post-transplant) in stable patients without prior rejection reduces metabolic complications.
9. **BK and CMV are major post-transplant complications:** Early detection via PCR-based monitoring allows intervention; consider CNI reduction, antiviral therapy.
10. **Immunosuppression is lifelong:** Even after years of stability, gradual dose reductions only in highly selected patients; abrupt withdrawal risks rejection.

VIII. PRACTICE QUESTIONS

Question 1: A 45-year-old man is 3 weeks post-living donor kidney transplant on tacrolimus, mycophenolate, and prednisone. Serum creatinine is 1.4 mg/dL (baseline 0.9) with 0.5 g/day proteinuria. Tacrolimus trough level is 14 ng/mL. What is the most appropriate management?

A) Increase tacrolimus dose to achieve trough of 15-16 ng/mL
B) Reduce tacrolimus dose to achieve trough of 10-12 ng/mL; monitor creatinine
C) Discontinue tacrolimus and switch to belatacept
D) Obtain kidney biopsy to assess for acute rejection

Answer: B. Elevated creatinine and proteinuria in context of high-normal tacrolimus level suggests early CNI nephrotoxicity. Dose reduction to achieve trough of 10-12 ng/mL is appropriate in early post-transplant. Creatinine rise of 55% warrants careful monitoring but biopsy not indicated without clinical rejection features (proteinuria can be secondary to CNI effect). Continue monitoring; if creatinine stabilizes, no biopsy needed.

Question 2: A 62-year-old woman is 2 years post-deceased donor kidney transplant on tacrolimus (trough 7 ng/mL), mycophenolate 1 g BID, and prednisone 5 mg daily. She develops nausea, vomiting, and diarrhea. Stool C. difficile and infectious workup negative. Tacrolimus level rechecked after medication adherence reviewed is 5 ng/mL. What is the most likely cause?

A) Tacrolimus toxicity (neurotoxicity)
B) Mycophenolate GI intolerance
C) Infection (viral or bacterial) despite workup
D) Corticosteroid-induced GI upset

Answer: B. Mycophenolate is a common cause of GI intolerance (nausea, diarrhea) in 20-30% of recipients. Low tacrolimus level argues against CNI toxicity. Appropriate management: reduce MMF dose (e.g., 750 mg BID), divide dosing, take with food, consider switch to MPS or delayed-release formulation, or add antimotility agent (loperamide).

Question 3: A 35-year-old man is undergoing living donor kidney transplant from a non-HLA-identical living related donor. Which induction regimen is most appropriate?

A) Thymoglobulin 1.5 mg/kg x 3 doses (high-risk induction)
B) Basiliximab 20 mg on days 0 and 4 (standard low-risk induction)
C) Alemtuzumab 30 mg single dose (PML risk consideration)
D) No induction (sufficient immunosuppression with CNI/MMF/prednisone)

Answer: B. Living donor recipient with non-identical HLA match is low-risk for early acute rejection. Basiliximab is appropriate: minimal infectious complications, convenient (2 doses), no T-cell depletion, no cytokine release syndrome. Thymoglobulin reserved for high-risk (DCD, ECD, highly sensitized, mismatched); alemtuzumab reserved for selected highly sensitized due to infection risks.

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