Transplant Nephrology Reference Guide

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A comprehensive pocket guide for transplant nephrology fellows, covering epidemiology, surgical considerations, immunology, pharmacology, rejection management, and infectious disease protocols.

1. Epidemiology & Basics

Statistics

- **Waitlist Candidates:** ~90,000 active (≈94,000 total)
- **Transplants/Year**: ~28,000 (2023 SRTR data)
- **Dialysis Mortality**: 15-20% (Annual Risk)
- **Tx Survival – Living Donor:**
  - 1-yr graft: ~97–98%
  - 5-yr graft: ~88–92%
  - Half-life: ~15–20 yrs
- **Tx Survival – Deceased Donor:**
  - 1-yr graft: ~93–95%
  - 5-yr graft: ~78–83%
  - Half-life: ~8–12 yrs
- Kidney - Scientific Registry of Transplant Recipients
- National data - OPTN

Donor Types & Risk

- **DBDKT (Donor after Brain Death)**: Heart beating until procurement. Standard risk profile.
- **DCDKT (Donor after Circulatory Death)**: Cardiac arrest prior to organ recovery. **Key Risk**: Higher Delayed Graft Function (DGF) rates due to warm ischemia.

- **LRKT (Living Related)**: Best outcomes due to genetic similarity and elective timing (minimal ischemia).

2. Surgical & Ischemia

Cold Ischemia Time (CIT)

Source: CCF Notes; OPTN

Definition: Time from aortic cross-clamp (donor) to removal from ice (recipient).

- **The Clock**: Every hour counts.
- **Impact**: Prolonged CIT (>18-24 hours) is a major independent risk factor for Delayed Graft Function (DGF).
- **Logistics**: Includes transport time (flying/driving) and time on pump/ice.

Warm Ischemia Time (WIT)

Source: CCF Notes

Definition: Time where the organ is metabolically active but not perfused.

1. **Donor Warm Ischemia (First Warm)**
    a. **Specific to DCD**. Time from withdrawal of life support/cardiac arrest until cold perfusion starts.
    b. High risk for ATN/DGF.
2. **Recipient Warm Ischemia (Second Warm)**
    a. Time from removing the kidney from ice to reperfusion.
    b. **Target**: < 45 mins (Anastomosis time).

Surgical Complications Differential

Differential for oliguria/anuria immediately post-op (Rule of U's)

- **Urine**: **Urine Leak**. High drain output. Drain creatinine >> Serum creatinine.
- **Ureter**: **Obstruction/Stenosis**. Hydronephrosis on Ultrasound.
- **Vascular**: **Thrombosis**. Renal Artery or Vein thrombosis. **Surgical Emergency**. No flow on Doppler.

3. Immunology & Allocation

The Crossmatch (XM)

Source: STAR 2017 Working Group Report; CCF Care Path

1. **Virtual XM (Pre-Op)**
    a. **Method**: Computer comparison of Recipient Anti-HLA Antibody profile (Luminex) vs. Donor HLA typing.
    b. Predicts compatibility before blood is even mixed.
2. **Flow Cytometry XM (Sensitive)**
    a. **Method**: Recipient Serum + Donor Lymphocytes + Fluorescent Anti-IgG tag. Run through a flow cytometer.
    b. Detects low-level binding (Channel Shift). Positive Flow + Negative CDC = Low risk (monitor closely).
3. **Cytotoxic (CDC) XM (Specific)**
    a. **Method**: Recipient Serum + Live Donor Lymphocytes + Rabbit Complement. If antibodies bind, complement lyses the cells.
    b. Positive CDC = Cell Death = Hyperacute Rejection Risk (Contraindication).

Risk Scores

Source: OPTN/UNOS Policy 8; Kidney Allocation System (KAS)

- **KDPI (Kidney Donor Profile Index)**: Donor Quality. 0-100%. **Lower is better**. KDPI >85% is "Marginal" (Formerly ECD).
- **cPRA (Calculated Panel Reactive Antibody)**: Sensitization. % of US donors are incompatible with the recipient. **High Score = Priority Points**.
- **EPTS (Est. Post-Tx Survival)**: Recipient score. Top 20% EPTS candidates receive Top 20% KDPI kidneys to maximize graft life years.

4. Pharmacology

Clinical Protocols

Low Immunological Risk

Source: CCF Care Path: Low Risk Protocol Criteria: Primary Tx, Living Donor, cPRA < 20%, Neg Crossmatch.

- **Induction**: Basiliximab (20mg IV POD 0, 4) OR Thymoglobulin (3 mg/kg total).
- **Tacrolimus**: Start POD 1. Target 8-12 (0-90d), 7-10 (3-6m), 5-8 (>6m).
- **MMF**: 750 mg PO BID if Received Basiliximab, 500 mg PO BID if received Thymoglobulin.
- **Steroids**: Rapid taper to 5mg daily by ~2 months.

Moderate-to-High Risk

Source: CCF Care Path: High Risk Protocol Criteria: cPRA > 40%, Re-transplant, DSA+, DGF anticipated, African American.

- **Induction**: Thymoglobulin (3.0 - 4.5 mg/kg total).
- **Tacrolimus**: Start POD 1 or when renal function allows.
- **MMF**: 500-750 mg PO BID (Higher in AA recipients).
- **Steroids**: Standard slow taper.

Steroid Avoidance

Source: CCF Care Path: Steroid Avoidance

- **Induction**: Thymoglobulin (3.0 - 4.5 mg/kg total).
- **MMF**: Higher dose (1,000 mg PO BID).
- **Steroids**: Rapid withdrawal. Solumedrol POD 0-3, then OFF by Day 4.

Induction Agents

Source: KDIGO & CCF Guidelines

- **Thymoglobulin (ATG)**: Lymphocyte Depleting. Polyclonal antibody (Rabbit). Profound T-cell depletion.
    - **Side Effects**: Cytokine Release Syndrome (Fever/Chills/Rigors), Serum Sickness, Leukopenia, Thrombocytopenia.
- **Alemtuzumab (Campath)**: Humanized Monoclonal Antibody (anti-CD52). Profound and prolonged depletion of T-cells, B-cells, and monocytes.
    - **Side Effects**: Infusion reactions (fever, chills, hypotension, rash), prolonged neutropenia, anemia, and thrombocytopenia, increased risk of secondary autoimmune conditions (e.g., ITP, thyroid disease, anti-GBM disease), and a high risk for opportunistic infections such as CMV and BK virus.
    - Not used routinely in CCF.
- **Basiliximab (Simulect)**: Non-Depleting. IL-2 Receptor Antagonist (CD25). Blocks activation.
    - **Side Effects**: Very well tolerated. Rare hypersensitivity. No Cytokine release.

Maintenance

Calcineurin Inhibitors (CNI)

- **Tacrolimus (Prograf®) – IR (immediate release)**:
    - Twice a day.
    - **Side Effects**: Tremor, Nephrotoxicity (afferent constriction), Hyperkalemia, Hypomagnesemia, HTN, Post transplant diabetes (PTD), Hair loss.
    - **Monitor**: Trough 12hr post-dose.
- **Envarsus XR**: Extended release. MeltDose technology.
    - Once a day.
    - Lower Cmax (peak) = **Less Tremor**. Otherwise, similar SE as Prograf.
    - Requires 80% of IR dose (increased bioavailability).

MeltDose technology is a proprietary drug delivery platform designed to enhance the bioavailability of poorly soluble drugs by incorporating them into a solid solution or dispersion. The process involves melting the drug with a vehicle and spraying it onto an inert particulate carrier, which reduces the drug to a nanocrystalline state with a significantly increased surface area. This formulation allows for more efficient absorption and improved dissolution, resulting in reduced peak-to-trough variability and the ability to achieve therapeutic blood levels with a lower total daily dose compared to conventional immediate-release versions.

Antimetabolites & Steroids

- **Mycophenolate (CellCept® / Myfortic®)**: Inhibits purine synthesis by inhibiting inosine monophosphate dehydrogenase (IMPDH).
    - Twice a day.
    - **Side Effects**: GI Toxicity (Diarrhea/Nausea), Leukopenia, Anemia, teratogenicity.
    - CellCept® 1,000 mg BID ≈ Myfortic® 720 mg BID
    - Myfortic® preferred in patients with significant GI toxicity

- **Prednisone**:
    - **Side Effects**: Hyperglycemia, Weight Gain, Mood changes, Osteoporosis, HTN, Cataracts, Skin fragility.

mTOR in hibitors

- **Everolimus (Zortress®)**: Inhibits the mammalian target of rapamycin (mTOR) → blocks IL-2–mediated T-cell proliferation and cell-cycle progression.
    - Twice a day.
    - **Side Effects**: Hyperlipidemia, proteinuria, cytopenias, impaired wound healing, edema
    - Often combined with reduced-dose tacrolimus
    - May lower risk of post-transplant malignancy especially SCC compared with CNI-based regimens
    - Considered during BK virus management as part of CNI minimization or antiproliferative adjustment.
    - **Monitoring:** Trough level (target range protocol-dependent; typically, lower when combined with CNI)

Calculators (Conversion Factors)

- **PO to Sublingual (SL)**: For NPO patients. Ratio **2:1** (PO Dose / 2 = SL Dose).
- **Tacrolimus IR to Envarsus XR**: Conversion factor **0.8** (80% of TDD). Once Daily (AM).
- CellCept® 1,000 mg BID ≈ Myfortic® 720 mg BID, 750 ≈ 540, 500 ≈ 360, 250 ≈ 180

5. Graft Dysfunction

Delayed Graft Function (DGF)

Source: Rao PS et al.; CCF Care Path

- **Definition**: Requirement for dialysis within the first 7 days of post-transplant.
- **Risk Factors**: DCD Donor (Warm Ischemia), Cold Ischemia Time > 24h, High KDPI, High BMI.
- **Management**: Avoid Hypotension, adjust meds (Hold ACEi), **Biopsy** if no recovery by Day 7-14 to rule out rejection. Consider Belatacept conversion.

TCMR (T-Cell Mediated Rejection)

- T-Cell Mediated Rejection is characterized by the infiltration of the allograft by host T-lymphocytes and other mononuclear cells, leading to tubulointerstitial and/or vascular injury. It is categorized by the location and severity of the inflammation:
    - Tubulointerstitial: Involves inflammation of the interstitial space (i-score) and the invasion of the tubular epithelium (t-score, known as tubulitis).
    - Vascular (Endothelialitis): Characterized by subendothelial mononuclear cell infiltration within the arterial wall (v-score), which is a sign of more severe rejection.
    - Chronic Active: A newer focus in Banff 2022 is Chronic Active TCMR (CA TCMR), which involves inflammation in areas of interstitial fibrosis and tubular atrophy (i-IFTA).

- **Categories of TCMR:**
    - **Borderline:** Interstitial inflammation involving 10%–25% of the unscarred parenchyma (**i1**) with at least mild tubulitis (**t1, t2, or t3**).
    - **Grade IA:** Interstitial inflammation >25% (**i2 or i3**) and moderate tubulitis (**t2**: 5–10 cells per tubular cross-section).
    - **Grade IB:** Interstitial inflammation >25% (**i2 or i3**) and severe tubulitis (**t3**: >10 cells per tubular cross-section).
    - **Grade IIA/B (Vascular):** Mild-to-moderate (**v1**) or severe (**v2**) intimal arteritis in one or more arterial cross-sections.

    - **Grade III:** Transmural arteritis and/or fibrinoid change and medial smooth muscle necrosis (**v3**).

- Treatment per CCF:
    - **Borderline/IA**: Pulse Solumedrol 500mg x 3.
    - **IB/II/III**: Thymoglobulin 1.5 mg/kg/day (Target 4-7 mg/kg total).
    - Followed by Oral Steroid Taper.

ABMR (Antibody Mediated Rejection)

- ABMR is an immune response where host antibodies (typically anti-HLA donor-specific antibodies) target the graft's vascular endothelium. This triggers a cascade of complement activation and recruitment of innate immune cells (NK cells, neutrophils, and macrophages) into the microvasculature.
- Unlike TCMR, which focuses on the tubules and interstitium, ABMR is primarily a **vascular and endothelial disease**.

For a definitive diagnosis of **Active ABMR**, the Banff classification generally requires evidence from three "pillars":

1. Morphologic Evidence of Acute Tissue Injury

- **Microvascular Inflammation (MVI):** Defined as **g > 0** (glomerulitis) and/or **ptc > 0** (peritubular capillaritis).
- **Intimal or Transmural Arteritis (v > 0):** While also a feature of TCMR, it can be the primary manifestation of ABMR.
- **Acute Thrombotic Microangiopathy (TMA):** In the absence of other causes (like CNI toxicity or HUS).
- **Acute Tubular Injury (ATI):** In the absence of other apparent causes.

2. Evidence of Antibody Interaction with Endothelium

- **C4d Deposition:** Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF; C4d > 0 by IHC).
- **Moderate MVI:** A score of **g + ptc ≥ 2**.
- **Molecular Transcripts:** Increased expression of thoroughly validated gene transcripts indicative of ABMR (e.g., endothelial-associated transcripts).

3. Serologic Evidence

- **DSA Positive:** Presence of circulating donor-specific antibodies (HLA or non-HLA).

New Phenotypes Introduced in Banff 2022

The 2022 update acknowledged that histology and clinical reality don't always align with the "three-pillar" model:

- **MVI, DSA-negative, and C4d-negative:** This category is for biopsies with significant microvascular inflammation (**g + ptc ≥ 2**) but where no antibodies or complement (C4d) are found. This may be due to non-HLA antibodies or "missing self" NK cell activation.
- **Probable ABMR:** Used when DSA is positive and some histologic features of ABMR are present, but they do not meet the full diagnostic thresholds (e.g., g1 + ptc0 and C4d negative).
- **Chronic Active ABMR (caABMR):** Requires the same criteria as active ABMR **plus** evidence of chronic tissue injury, most notably **transplant glomerulopathy (cg > 0)-**the doubling of the glomerular basement membrane.

- Treatment per CCF:
    - **Plasmapheresis**: x 6 sessions (3/week x 2 weeks).
    - **IVIG**: 0.5 g/kg after each Plex (Total 2 g/kg).
    - **+/- Rituximab**: Anti-CD20.

Banff 22 website

6. Infectious Disease

CMV Prophylaxis & Treatment

Source: CCF Care Path: Viral Infections

- **High Risk (D+/R-)**: Valganciclovir or Letermovir/Acyclovi (Not renally dosed) x 6 months.
- **Intermediate (D-/R+ or D+/R+)**: Valganciclovir x 3 months.
- **Treatment of CMV Disease**:
    - **Valganciclovir**: Renally dosed.
    - **IV Ganciclovir**: Renally dosed. Use for severe disease/malabsorption.
    - Reduce Immunosuppression (Stop MMF).
    - Keep treating until negative PCR x 2 weeks.

CrCl	Induction/treatment dose	Maintenance/prophylaxis dose
≥60 (mL/minute)	900 mg twice daily	900 mg once daily
40 to <60 (mL/minute)	450 mg twice daily	450 mg once daily
25 to <40 (mL/minute)	450 mg once daily	450 mg every 2 days
10 to <25 (mL/minute)	450 mg every 2 days	450 mg twice **weekly**
<10 (mL/minute)	Not recommended by manufacturer; may consider using oral solution 200 mg 3 times weekly **or** if oral solution is not available, 450 mg (tablet) 3 times weekly.	Not recommended by manufacturer; may consider using oral solution 100 mg 3 times weekly **or** if oral solution is not available, 450 mg (tablet) twice weekly.

Source: Senior Editorial Team: Bruce Mueller, PharmD, FCCP, FASN, FNKF; Jason A. Roberts, PhD, BPharm (Hons), B App Sc, FSHP, FISAC; Michael Heung, MD, MS.

PTLD (Post-Transplant Lymphoproliferative Disorder)

Source: CCF Notes; AST Guidelines

- **Definition**: Malignancy driven by EBV proliferation of B-cells.
- **Risk Factors**: EBV D+/R- (Highest), Heavy T-cell depletion (Thymo).
- **Presentation**: Fever, Weight Loss, Lymphadenopathy, Rise in Creatinine.
- **Management**:
    - **Reduce Immunosuppression**: 1st line (Regression possible).
    - **Rituximab**: Anti-CD20 monoclonal antibody.
    - **Chemotherapy**: Cyclophosphamide, Doxorubicin, Vincristine (Oncovin), and Prednisone (CHOP) for non-responders.

PJP Prophylaxis

Source: CCF Care Path: PJP

- **Drug**: Bactrim (TMP-SMX). 1 SS Daily OR 1 DS 3x/week.
- **Duration**: Life of Allograft (or min 18 months).
- **Sulfa Allergy**: Dapsone 100mg daily or Atovaquone 1,500 mg once daily orally or Pentamidine for one year.

  How to order pentamidine:
  1. Message Scott Marlow RRT to coordinate appointments. Let him know how many months of therapy are anticipated.
  2. To order search pentamidine -> Facility List -> Clinic administered medications -> Order pentamidine + albuterol. This enters as needed albuterol and pentamidine for a year.

Fungal / HSV

Source: CCF Care Path

- **HSV / VZV**: Acyclovir 400mg BID x 3 months (if not on Valcyte).

BK Virus (Polyomavirus)

Source: CCF Care Path: BKV

- **Screening**: Monthly PCR for up to 6 months, then q3 months.
- **Management (Stepwise)**:
    - Reduce Immunosuppression (30-50%).
    - Reduce Tacrolimus targets to **4-7 ng/mL**.

- Decrease MMF dose by 50%.
- Consider IVIG (Second line).

7. Landmark Studies

Key Trials in Transplant Nephrology

Immunosuppression Maintenance

ELITE-Symphony (Ekberg et al., NEJM 2007)

- **Population**: 1,645 de novo kidney transplant recipients
- **Intervention**: Low-dose Tacrolimus + MMF + Steroids + Daclizumab
- **Comparison**: Standard-dose Cyclosporine, Low-dose Cyclosporine, or Low-dose Sirolimus regimens
- **Outcome**: Low-dose Tacrolimus had the best eGFR, lowest acute rejection rate, and highest graft survival.
- PubMed Link

CNI-Sparing

BENEFIT Trial (Vincenti et al., Am J Transplant 2010)

- **Population**: 666 kidney transplant recipients (standard criteria/living donors)
- **Intervention**: Belatacept (More Intensive or Less Intensive)
- **Comparison**: Cyclosporine (Standard Care)
- **Outcome**: Belatacept showed superior renal function and metabolic profiles, but higher rates/grades of early acute rejection.
- PubMed Link

Induction

Brennan Induction (Brennan et al., NEJM 2006)

- **Population**: 278 high-risk kidney transplant recipients
- **Intervention**: Rabbit Anti-Thymocyte Globulin (rATG) induction
- **Comparison**: Basiliximab (IL-2 RA) induction

- **Outcome**: rATG significantly reduced acute rejection (15.6% vs 25.5%) but increased infection risk; survival was similar.
- PubMed Link

Steroid Withdrawal

Woodle Steroid Withdrawal (Woodle et al., Ann Surg 2008)

- **Population**: 386 low-to-moderate risk recipients
- **Intervention**: Early Steroid Withdrawal (stopped by day 7)
- **Comparison**: Chronic Corticosteroid Maintenance
- **Outcome**: No difference in patient/graft survival at 5 years. Withdrawal group had slightly higher rejection but better metabolic outcomes.
- PubMed Link

Special Populations

HOPE Study (Durand et al., NEJM 2019)

- **Population**: 75 HIV-positive kidney transplant candidates
- **Intervention**: Kidneys from HIV-positive deceased donors
- **Comparison**: Kidneys from HIV-negative deceased donors
- **Outcome**: No significant difference in graft survival or rejection, validating the safety of HIV-to-HIV transplantation.
- PubMed Link

THINKER Trial (Goldberg et al., NEJM 2017)

- **Population:** 10 HCV-negative kidney transplant candidates
- **Intervention:** Kidneys from HCV-viremic (genotype 1) deceased donors followed by elbasvir–grazoprevir treatment
- **Comparison:** Standard of care (avoiding HCV-positive donors for HCV-negative recipients)
- **Outcome:** 100% cure rate (SVR12) of donor-derived HCV infection with excellent early graft function, proving the feasibility of using HCV-viremic organs in uninfected recipients.
- PubMed Link

mTOR Inhibitors

TRANSFORM Study (Pascual et al., J Am Soc Nephrol 2018)

- **Population**: 2,037 de novo recipients
- **Intervention**: Everolimus + Reduced-exposure CNI
- **Comparison**: Mycophenolic Acid (MPA) + Standard-exposure CNI
- **Outcome**: The Everolimus regimen was non-inferior for composite endpoint (rejection/graft dysfunction) with different side-effect profiles (wound issues vs viral).
- PubMed Link

Historical/Antimetabolites

Tricontinental MMF (The Tricontinental Study Group, Lancet 1996)

- **Population**: 503 cadaveric kidney recipients
- **Intervention**: Mycophenolate Mofetil (MMF)
- **Comparison**: Azathioprine + Cyclosporine + Steroids
- **Outcome**: MMF significantly reduced biopsy-proven acute rejection compared to Azathioprine.
- PubMed Link

Desensitization

Montgomery Desensitization (Montgomery et al., NEJM 2011)

- **Population**: 211 HLA-sensitized patients with incompatible living donor
- **Intervention**: Desensitization + Live Donor Transplant
- **Comparison**: Waitlist (Dialysis or eventual compatible transplant)
- **Outcome**: Significant survival benefit for desensitized patients compared to those remaining on dialysis/waitlist.
- PubMed Link

Infectious Disease

IMPACT Study (Humar et al., Am J Transplant 2010)

- **Population**: 318 high-risk (CMV D+/R-) recipients

- **Intervention**: Valganciclovir prophylaxis for 200 days
- **Comparison**: Valganciclovir prophylaxis for 100 days
- **Outcome**: 200-day prophylaxis significantly reduced CMV disease at 12 months without increased toxicity.
- PubMed Link

CNI Minimization

CAESAR Study (Ekberg et al., Am J Transplant 2007)

- **Population**: 536 de novo recipients
- **Intervention**: Cyclosporine Withdrawal (stopped by month 6)
- **Comparison**: Low-dose or Standard-dose Cyclosporine maintenance
- **Outcome**: Complete Cyclosporine withdrawal led to significantly higher acute rejection rates.
- PubMed Link

Pediatrics

TWIST Study (Grenda et al., Am J Transplant 2010)

- **Population**: Pediatric recipients (low risk)
- **Intervention**: Steroid-free regimen (Tac + MMF + Daclizumab)
- **Comparison**: Standard Steroid Maintenance
- **Outcome**: The Steroid-free group had better linear growth with no increased risk of rejection or graft loss.
- PubMed Link

Conversion Strategies

ZEUS Study (Budde et al., Lancet 2011)

- **Population**: 300 de novo recipients
- **Intervention**: Early conversion to Everolimus (4.5 months) + CNI elimination
- **Comparison**: Continue Cyclosporine
- **Outcome**: Conversion improved renal function (GFR) but was associated with a higher rate of mild acute rejection.
- PubMed Link