Transplant Evaluation and Selection

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Overview

Kidney transplantation offers superior outcomes to dialysis for appropriate candidates: improved quality of life, longer survival, and lower cost per patient-year compared to dialysis [1]. Comprehensive pretransplant evaluation identifies absolute contraindications, assesses medical/surgical risk, and screens for malignancy, infection, and cardiovascular disease. Immunologic workup (HLA typing, PRA assessment, crossmatching) guides donor selection and immunosuppression strategy. This guide synthesizes transplant evaluation, donor-recipient matching, immunosuppression regimens, and post-transplant complication management.

Key Clinical Pearl

"The best renal transplant is a preemptive living-donor transplant from a biologically related donor with minimal immunologic mismatch. However, even an older, EBV+ donor kidney in a well-screened recipient with excellent adherence is superior to a lifetime on dialysis."

Part 1: Transplant Evaluation Framework

Timing of Referral

KDIGO Recommendation: - **G3b CKD (eGFR 30–44):** Offer education on all RRT options (dialysis, transplant, conservative care) - **G4 CKD (eGFR 15–29):** Refer for transplant evaluation if appropriate - **G5 CKD (eGFR <15):** Complete evaluation and list if transplant-eligible - **Preemptive transplant:** Ideal; can occur before dialysis initiation (especially living-donor)

Goals of Transplant Evaluation

1. **Determine transplant eligibility:** Identify absolute/relative contraindications
2. **Optimize health status:** Treat cardiovascular disease, diabetes, infections
3. **Assess immunologic risk:** HLA sensitization, crossmatch compatibility
4. **Educate on RRT options:** Living vs deceased donor, risks/benefits
5. **Assess psychosocial readiness:** Adherence capacity, social support, mental health

Part 2: Contraindications to Transplantation

Absolute Contraindications (Transplant Not Offered)

Contraindication	Rationale	Duration
Active malignancy	Immunosuppression accelerates tumor growth	Until treatment complete
Active infection (systemic)	Uncontrolled sepsis; immunosuppression worsens outcome	Until resolved
Active tuberculosis (untreated)	Immunosuppression causes dissemination	Until fully treated (6 months)
Uncontrolled psychiatric disease	Risk of non-adherence; transplant failure	Until stabilized
Inability to comply with immunosuppression	Ensures graft survival; non-adherence = rejection	Lifelong
Life expectancy <5 years (from non-renal disease)	Risk/benefit unfavorable	N/A
Uncorrected cardiac disease with high operative risk	Cannot tolerate transplant surgery	Until correctable
Severe hepatic cirrhosis (Child-Pugh C)	Poor synthetic function; cannot metabolize drugs	Permanent

Relative Contraindications (Assessed Case-by-Case)

Contraindication	Assessment	Decision Pathway
History of malignancy	Type, stage, time since treatment	>2–5 years cancer-free may be acceptable
Age >70 years	Functional status, comorbidities, life expectancy	Chronologic age alone not contraindication
Severe obesity (BMI >40)	Surgical risk, graft function, compliance	May accept if motivated; weight loss recommended
Significant proteinuria (>2 g/day)	Etiology; assess for GN	May transplant if stable; treat underlying disease
History of nonadherence	Assess reasons; psychosocial support	Intensive counseling may improve outcomes
Active substance abuse	Addiction active vs in remission	Usually requires 6 months sobriety
Severe coronary artery disease	Assess with stress testing; revascularize if possible	May accept high-risk CAD if revascularized

Contraindication	Assessment	Decision Pathway
Hepatitis C antibody positive	HCV RNA+ state; assess liver fibrosis; transplant HCV- donor if possible	Direct-acting antivirals cure HCV; may improve candidacy
Hepatitis B surface antigen+	Assess HBeAg, HBV DNA; vaccination status	Lamivudine/TDF prophylaxis minimizes progression

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Part 3: Immunologic Workup

HLA Typing

HLA (Human Leukocyte Antigen): Polymorphic proteins on cell surface that trigger immune recognition.

HLA Classes: - **Class I (HLA-A, -B, -C):** On all nucleated cells; target of acute/chronic rejection - **Class II (HLA-DR, -DQ, -DP):** On antigen-presenting cells; elicit T-helper response

Clinical importance: - **Identical twins:** 0 HLA mismatch; no rejection risk (theoretically) - **Haplo-identical (one parent/sibling):** 3 HLA mismatch (one haplotype shared); acceptable - **Unrelated:** Often 6 HLA mismatch (highest rejection risk without sensitization history)

Effect on graft survival: Each additional HLA mismatch ~5% reduction in 5-year graft survival.

Panel Reactive Antibody (PRA) and Sensitization Assessment

PRA (% panel reactive antibody): - **Definition:** Percentage of donors in a panel to whom recipient has preformed anti-HLA antibodies - **Measured by:** Flow cytometry, Luminex (most sensitive) - **Interpretation:** - **PRA 0%:** Non-sensitized; low rejection risk; easiest to match - **PRA 1–49%:** Moderately sensitized; acceptable transplant candidates with good matching - **PRA >50%:** Highly sensitized; need compatible donor or desensitization; longer wait times

Causes of sensitization: - **Prior transplant rejection** (most common) - **Multiple blood transfusions** - **Pregnancy (female recipients)** - **Prior exposure to alloantigen** (repeat transfusions, failed prior grafts)

Donor-Specific Antibodies (DSA)

Definition: Antibodies against specific donor HLA antigens (determined after donor identified).

Test: Single-antigen Luminex bead assay (identifies exact HLA antibodies).

Clinical significance: - **Donor-specific IgG antibodies:** HIGH risk of antibody-mediated rejection (AMR); may necessitate desensitization or declining donor - **Donor-specific IgM antibodies:** Variable risk; typically lower than IgG - **Complement-fixing antibodies:** Higher rejection risk than non-complement-fixing

Crossmatch Test

Definition: In vitro test of recipient serum against donor lymphocytes to detect anti-donor antibodies.

Test methods (from least to most sensitive): 1. **Complement-dependent cytotoxicity (CDC):** Gold standard historically; detects IgG/IgM 2. **Flow cytometry crossmatch:** More sensitive; detects low-level IgG; better predictor of rejection 3. **Luminex:** Single-antigen beads; identifies exact HLA antibodies vs donor antigens

Interpretation: - **Negative crossmatch:** Safe to proceed (IgG antibody unlikely to cause hyperacute rejection) - **Positive IgG crossmatch: CONTRAINDICATION to transplant** (hyperacute rejection risk; graft loss within hours) - **Positive IgM only:** Acceptable; IgM typically clears quickly

ABO Incompatibility

Traditional rule: ABO-incompatible transplants were contraindicated (hyperacute rejection from IgM ABO antibodies).

Modern approach (ABO-incompatible transplant): - **Desensitization:** Plasmapheresis, low-dose IVIG, rituximab (anti-CD20) - **Result:** Successful ABO-incompatible transplants now possible (5-year graft survival ~80% vs 85% for ABO-compatible) - **Advantage:** Expands living-donor pool; reduces wait times for O recipients

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Part 4: Living vs Deceased Donor Selection

Characteristic	Living Donor	Deceased Donor	Impact on Graft
Donor evaluation	Comprehensive; healthy baseline	Variable; often limited pre-mortem history	Living = better outcomes
HLA matching	Often related (0–3 mismatch)	Usually unrelated (3–6 mismatch)	Each mismatch ~5% 5-yr graft loss
Cold ischemia time	0 (immediate transplant possible)	12–24+ hours	Longer ischemia time = more dysfunction
Delayed graft function (DGF)	5–10%	20–40%	DGF increases acute rejection risk
Acute rejection rate	20–30%	40–45%	Living > deceased in intermediate-term
Graft survival at 5 years	80–85% (living-related); 75–80% (living-unrelated)	70–75%	Living-related superior
Recipient survival	Better (better health; pre-emptive options)	Variable	Living donor recipients have better outcomes

Characteristic	Living Donor	Deceased Donor	Impact on Graft
Cost analysis	Higher upfront surgical cost (evaluating donor + surgery)	Lower upfront but more dialysis time before Tx	Long-term cost similar; transplant always cheaper

Kidney Paired Donation (KPD)

Definition: Cross-matching incompatible recipient-donor pairs to find compatible matches.

Example: - Patient A incompatible with Donor A - Patient B incompatible with Donor B - BUT: Patient A compatible with Donor B; Patient B compatible with Donor A - **Solution:** Swap donors → two successful transplants

Impact: Increases transplant options for highly sensitized recipients and ABO-incompatible pairs.

Part 5: UNOS Allocation System for Deceased Donors

Kidney Allocation System (KAS) Principles

Goals: 1. Maximize graft longevity (longer-surviving grafts to younger recipients) 2. Eliminate transplant list waiting time based solely on time accumulated 3. Achieve better HLA matching when possible 4. Improve equity across geographic regions

Key Metrics

Kidney Donor Profile Index (KDPI): - Composite score (0–100) predicting donor kidney function - **Low KDPI (<35%):** Better quality; longer expected survival - **High KDPI (>85%):** Lower quality; shorter expected survival

Estimated post-transplant survival (EPTS): - Score predicting recipient's expected lifespan post-transplant - **Low EPTS (<20%):** Longer life expectancy; allocated best kidneys - **High EPTS (>80%):** Shorter life expectancy; lower-quality kidneys may be appropriate

Allocation priority: - High-KDPI kidneys → low-EPTS recipients (best match) - Low-KDPI kidneys → can be allocated based on compatibility/geography

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Part 6: Induction and Maintenance Immunosuppression

Induction Therapy (At Time of Transplant)

Goal: Prevent acute cellular rejection in immediate post-transplant period.

Options:

Agent	Type	Dosing	Use	Mechanism
Basiliximab	Anti-IL-2R mAb	20 mg IV day 0, 4	Standard induction	IL-2 receptor blockade
Daclizumab	Anti-IL-2R mAb	1 mg/kg day 0, 4	Alternative (rarely used)	IL-2 receptor blockade
Alemtuzumab	Anti-CD52 mAb	0.3 mg/kg IV day 0	Highly sensitized; ANCA+	T-cell and B-cell depletion
Rituximab	Anti-CD20 mAb	375 mg/m² day 0	B-cell targeting; ABO-incompatible Tx	B-cell depletion
Antithymocyte globulin (ATG)	Polyclonal antibody	1.5 mg/kg daily × 3–5 days	Induction; steroid-sparing	T-cell depletion

Preferred approach: Basiliximab induction + calcineurin inhibitor + MMF + corticosteroids (standard triple therapy).

Maintenance Therapy (Long-Term)

Standard triple therapy:

Agent	Class	Dosing	Mechanism	Monitoring
Tacrolimus	Calcineurin inhibitor	1–2 mg 2×/day (level 5–12 ng/mL initially)	Inhibits IL-2 T-cell signal	Trough level; renal function; K; Mg
Mycophenolate mofetil (MMF)	Antimetabolite	500–1000 mg 2×/day	Inhibits IMPDH; depletes GTP in T/B cells	CBC (monitor for leukopenia)
Prednisone	Corticosteroid	5–10 mg daily (taper from 20 mg day 0)	Anti-inflammatory; blocks cytokine production	Weight; glucose; BP; osteoporosis risk

Alternative combinations:

Scenario	Preferred Regimen	Rationale
EBV-negative recipient	Basiliximab + tac + MMF + pred	Standard

Scenario	Preferred Regimen	Rationale
CNI-intolerant (diabetes, nephrotoxicity)	Basiliximab + sirolimus + MMF + pred	Avoid CNI nephrotoxicity
High immunologic risk (sensitized)	Alemtuzumab + tac + MMF + pred	More intensive T/B-cell depletion
Older recipient, excellent match	Lower-intensity (belatacept + pred alone)	Belatacept (T-cell co-stimulation blocker)

Calcineurin Inhibitor (CNI) Toxicity

Tacrolimus and cyclosporine both cause: - **Nephrotoxicity:** Chronic CNI nephropathy → GFR decline 5–10 mL/min/yr over 5 years - **Hypertension:** 50–80% of recipients (vasoconstriction) - **Hyperkalemia:** Impairs K secretion; requires careful monitoring - **Hypomagnesemia:** Increases cardiac arrhythmia risk - **Diabetes (new-onset):** 15–20% of recipients; glucose intolerance

Management: - Monitor trough CNI levels (narrow therapeutic window) - Monitor renal function; decline >20% warrants assessment - Antihypertensive therapy (aim SBP <130 mmHg) - Potassium monitoring; restrict K if elevated - Screen for NODAT (new-onset diabetes after transplant)

Part 7: Post-Transplant Complications

Acute Cellular Rejection (ACR)

Timing: Usually 1–12 months post-transplant (can occur anytime).

Pathophysiology: T-cell mediated infiltration of graft; interstitial inflammation, tubulitis.

Clinical presentation: - Rising serum creatinine (30–50% above baseline) - Decreased urine output - Possible fever, graft tenderness, proteinuria

Diagnosis: Renal biopsy (gold standard); shows mononuclear infiltrate, tubulitis.

Treatment: - **Mild-moderate ACR:** Increase corticosteroid dose (pulse methylprednisolone 500 mg IV daily × 3 days) - **Severe/steroid-resistant:** Antithymocyte globulin (ATG 1.5 mg/kg daily × 3–5 days) OR rituximab

Outcomes: 80–90% respond to treatment; steroid resistance associated with worse long-term outcomes.

Antibody-Mediated Rejection (AMR)

Pathophysiology: Donor-specific antibodies (anti-HLA, anti-MICA, anti-endothelial) activate complement; endothelial inflammation.

Presentation: - Rising Cr - Proteinuria - May be accompanied by acute cellular rejection (“mixed rejection”)

Diagnosis: Renal biopsy with IF shows C4d deposition (along peritubular capillaries); DSA+ serum.

Treatment: - **Acute AMR:** Plasmapheresis (remove DSA) + IVIG (inhibit complement) + rituximab (deplete B cells producing antibodies) - **Chronic AMR:** Long-term plasmapheresis, IVIG, rituximab; prognosis poor (median graft survival ~5 years)

Chronic Antibody-Mediated Rejection (cAMR)

Definition: Slower decline in graft function associated with persistent DSA + C4d+ and/or chronic pathologic lesions (transplant glomerulosclerosis, transplant vasculopathy).

Pathologic features: - Transplant glomerulosclerosis (TGS): Duplication of GBM, capillary collapse - Transplant vasculopathy: Intimal hyperplasia in arteries - Interstitial fibrosis/tubular atrophy (IF/TA): Secondary to chronic rejection

Outcomes: Progressive graft loss; median 5–10 year graft survival with cAMR.

Infections Post-Transplant

Timeline and pathogens:

Timing	Common Pathogens	Pathophysiology
0–1 month	Bacterial UTI, wound infection, HSV (reactivation)	Post-surgical; high-dose initial immunosuppression
1–6 months	CMV (primary/reactivation), PCP, Toxoplasma, Cryptococcus, Aspergillus	Peak immunosuppression period; opportunistic
>6 months	Community organisms (S. pneumoniae), mycobacteria, late CMV	Immunosuppression lower; community exposure

CMV Prophylaxis: - **High-risk (seropositive donor, seronegative recipient):** Valganciclovir 900 mg daily × 3–6 months - **Lower-risk:** IVIG or valganciclovir based on risk stratification

PCP Prophylaxis: - **CD4 <200 or heavy immunosuppression:** TMP-SMX double-strength daily or 3×/week

Fungal prophylaxis: - **Nystatin oral rinse** for first 3 months (Candida) - **Fluconazole** if high-risk or previous fungal infection

Malignancy Post-Transplant

Increased risk: 4–5× higher than general population due to chronic immunosuppression.

Most common: 1. **Skin cancer (basal cell, squamous cell, melanoma):** 40% of cancers 2. **Post-transplant lymphoproliferative disorder (PTLD):** EBV-driven B-cell lymphoma; 1–2% of recipients 3. **Renal cell carcinoma:** Native kidney cancer (not graft); slightly elevated risk 4. **Cervical cancer** (women); anal cancer; lung cancer

Risk factors: - Duration of immunosuppression - Type of immunosuppression (higher risk with mTOR inhibitors, azathioprine) - EBV serostatus (EBV-negative recipients: higher PTLD risk) - Sun exposure, HPV infection, age

Screening: - Annual skin exam (dermatology) - Cervical cancer screening (pap smear annually) - Cancer awareness; report symptoms promptly

PTLD management: - **Early lesion:** Reduce immunosuppression + observation - **Advanced/symptomatic:** Rituximab ± chemotherapy (CHOP)

BK Virus Nephropathy

Etiology: BK polyomavirus reactivation in immunosuppressed recipients; direct viral cytopathic effect on tubular epithelium.

Presentation: - Rising Cr months 3–12 post-transplant - Often asymptomatic; discovered on lab monitoring - Decoy cells on urine cytology (pathognomonic)

Diagnosis: Biopsy shows viral inclusions in tubular epithelium; PCR in urine/serum >10,000 copies indicates active viremia.

Treatment: - Reduce immunosuppression (lower CNI target level; reduce MMF dose) - Antivirals: Cidofovir (nephrotoxic; use with caution) or fluoroquinolones (limited evidence) - Monitor viral load with serum/urine PCR

Prognosis: ~50% progress to graft loss despite treatment; early detection improves outcomes.

CMV Infection/Disease

CMV viremia vs disease: - **Viremia:** Positive blood culture/PCR without symptoms; may progress to disease - **Disease:** Viremia + end-organ involvement (colitis, esophagitis, retinitis, pneumonitis)

Diagnosis: PCR quantitative (viral load in blood); tissue biopsy with viral culture/histology.

Treatment: - **CMV viremia:** Valganciclovir 900 mg 2×/day until PCR negative - **CMV disease:** IV ganciclovir (organ involvement requires higher doses) or valganciclovir

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Part 8: Long-Term Graft Function and Outcomes

Determinants of Graft Longevity

Factor	Impact	Modifiable
HLA matching	Each mismatch ~5% 5-yr loss	No (donor selection)
Donor age	Older donors → shorter graft lifespan	No
Cold ischemia time	>24 hrs associated with slower function recovery	No (deceased donor timing)

Factor	Impact	Modifiable
Recipient age	Younger = longer lifespan available for graft	No
Acute rejection	Any ACR episode associated with worse long-term outcomes	Yes (optimize induction/maintenance)
Serum creatinine trajectory	Early GFR decline (>10% first year) = poor prognosis	Yes (monitor CNI levels, BP, proteinuria)
Proteinuria	Proteinuria >1 g/day associated with worse outcomes	Yes (RAAS blockade)
Blood pressure control	SBP >130 associated with graft loss	Yes (antihypertensives)
CNI minimization	Long-term CNI toxicity; belatacept-based regimens may extend graft life	Yes (alternative induction/maintenance)
Adherence to immunosuppression	Non-adherence = #1 cause of late graft failure	Yes (education, monitoring, psychosocial support)

Recurrent and De Novo Glomerulonephritis

Recurrent GN: Original disease recurring in transplanted kidney.

Frequency: 10–15% depending on primary disease.

High-risk diseases: - **IgA nephropathy:** 30–50% recurrence; 10% graft loss at 10 years - **Lupus nephritis:** 5–10% recurrence; often milder - **FSGS:** 20–40% recurrence (very high if primary form); can cause immediate graft dysfunction - **Membranoproliferative GN:** 20–30% recurrence

De novo GN: New glomerular disease in transplanted kidney (unrelated to original disease).

Management: - Monitor for proteinuria; repeat biopsy if rising Cr + proteinuria - Treat with RAAS blockade - Immunosuppression adjustment based on diagnosis

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Part 9: Key Warnings

Warning 1: Non-Adherence is the Leading Cause of Late Graft Failure

50% of late graft failures due to non-adherence to immunosuppression. Risk factors: - Young age (forget medications) - Complex regimens (>3 medications) - Side effects (tremor, hirsutism, gum hyperplasia) - Psychiatric comorbidity, substance abuse

Prevention: Intensive patient education; psychosocial screening; simplified regimens when possible; consider directly-observed therapy if high-risk.

Warning 2: Acute Rejection in First 3 Years Predicts Poor Long-Term Outcomes

Any acute rejection episode (ACR or AMR) associated with 2–3× higher risk of chronic rejection and graft loss. Modern approach emphasizes preventing rejection through adequate induction + maintenance immunosuppression.

Warning 3: Calcineurin Inhibitor Nephrotoxicity Accelerates Chronic Graft Dysfunction

CNI-induced chronic nephropathy causes 30–50% GFR decline over 10 years. However, discontinuing CNI increases acute rejection risk. **Balance:** Monitor CNI levels; keep at lowest effective trough; consider switching to belatacept if CNI toxicity severe and HLA match good.

Warning 4: Sensitized Recipients Require Special Strategies

PRA >50%: Higher waiting time; longer time to compatible donor. Options: - **Desensitization:** For living-donor transplants (plasmapheresis + IVIG + rituximab) - **Paired kidney exchange:** Match with compatible donor pair - **Accepting higher-risk donor:** Older/lower-KDPI donor if waiting time prohibitive

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Related Resources

- ← Back to Transplant Hub
- ← Back to Nephrology Hub
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