

Renal Transplantation

- 1933 First cadaveric renal allograft Voronay in Ukraine – 48 hr survival
- 1951 Azathioprine available for human use
- 1955 First successful Tx - intertwin renal transfer, Murray 1955 (Boston US)
- 1962 Corticosteroids with azathioprine
- 1967 Renal preservation media and pulse preservation
- 1966 Direct crossmatch introduced
- 1970s Brain death laws in US and beating heart cadaveric harvesting
- 1978 Cyclosporin introduced
- 1980s University of Wisconsin media

Outcomes

	Live donor	Cadaveric donor
Patient survival		
1 year	97.8%	95%
3 year	95.2%	89.2%
5 year	90.5%	81.3%
Allograft survival		
1 year	94.7%	89.2%
3 year	87.4%	77.7%
5 year	76.0%	61.3%

Adverse risk factors

- Extremes of recipient age (> 55yrs or < 1 yr)
- Extremes of donor age (> 50 yrs or < 2 yrs)
- Previous failed transplant
- BMI > 30
- Diabetes
- Blacks
- Coronary artery disease
- Hypercoagulability
- Risk factors for recurrent renal disease (#1 diabetes)*

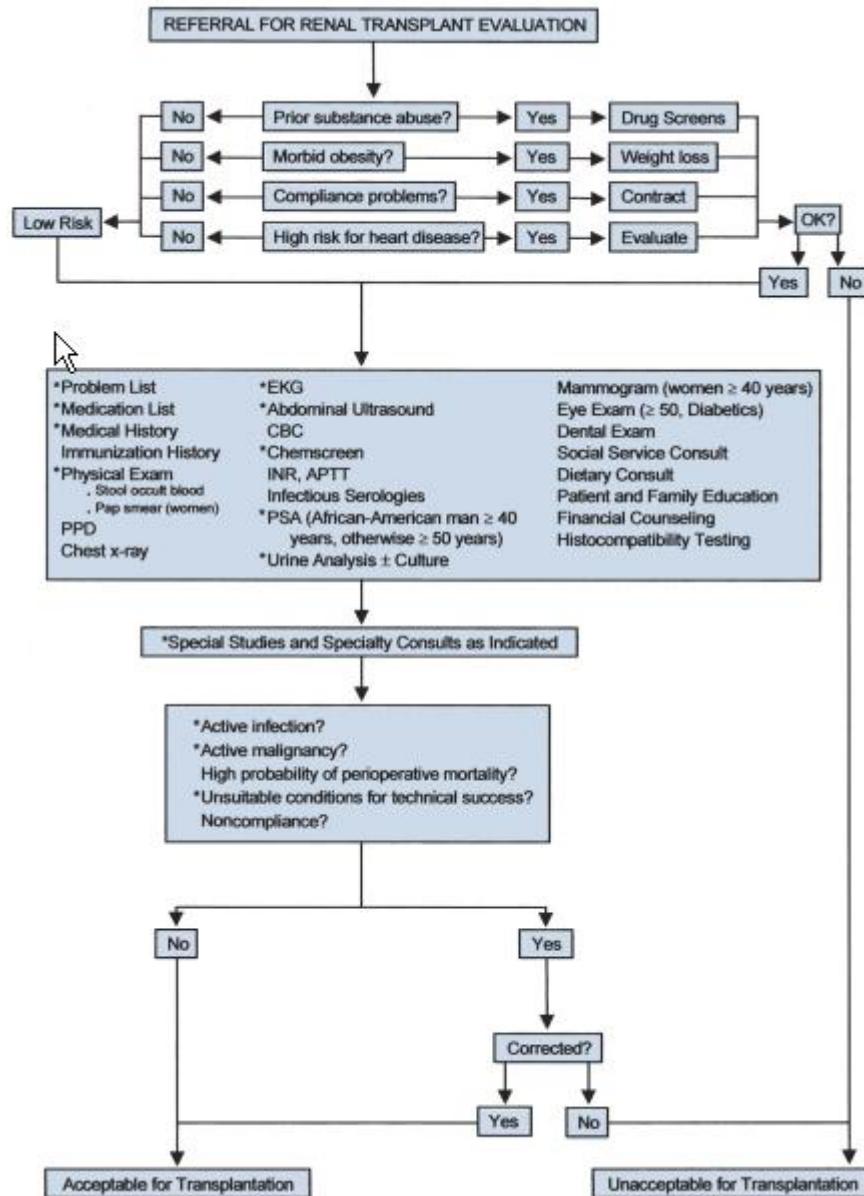
* Systemic or primary renal disease

- | | |
|----------|---|
| Systemic | Diabetes, HUS, HSP, SLE, cryoglobulins, Wegener's, scleroderma, sickle cell, oxalosis |
| Renal | IgA, membranoproliferative, anti-GBM, focal segmental glomerulosclerosis |

NB. HUS, focal segmental glomerulosclerosis and primary oxalosis very high risk of recurrence and graft failure

Recipient evaluation

- Confirm irreversible renal failure
- Exclude significant systemic medical disease (including infection)
- Exclude active malignancy or treated cancer with high risk of relapse
- Exclude substance abuse or ongoing uncontrolled psychiatric disease



Serological testing: HBV, HCV, CMV, syphilis, EBV, HSV, HIV, HTLV-1, Toxoplasma, TB, VZV

Vaccination: Pneumococcus (if < 6yrs)

Influenza

Hepatitis B (0, 1 and 6 months pre-op)

Varicella zoster (if seronegative)

Tetanus diphtheria toxoid

Polio booster

MMR

Cancer: Disease-free intervals of 2-5 years recommended

- Shorter for individual cancers ? low risk RCC
 No wait for skin cancers and CIS cervix or primary brain tumours
 Cholecystectomy for gallbladder polyps > 1cm
Urological:
 History to exclude dysfunctional voiding
 Urinalysis to exclude infection/microhaematuria
 USS and postvoid residual to exclude hydro and poor emptying
 TURP/BNI may be required
 Diversion not necessarily a contraindication: transplant into pouch/conduit reportedly successful
 Biopsy to exclude fibrosis +/- wet augment recommended for patients diverted for reflux – capacity rapidly returns to normal in absence of fibrosis (pre-Tx Nx usually required)
Other:
 ADPKD = cerebral aneurysm screening
 Peripheral arterial or venous disease = dopplers

Indications for pre-transplant nephrectomy (Campbells)

- Renal stones not cleared by minimally invasive techniques or lithotripsy
- Solid renal tumors with or without acquired renal cystic disease
- Polycystic kidneys that are symptomatic, extend below the iliac crest, have been infected, or have solid tumors
- Persistent antglomerular basement membrane antibody levels
- Significant proteinuria not controlled with medical nephrectomy or angioablation
- Recurrent pyelonephritis
- Grade 4 or 5 hydronephrosis

- | | |
|---|------------------|
| S | Stone |
| T | Tumour |
| I | Infection |
| M | Massive |
| P | Proteinuria |
| 4 | Grade 4/5 reflux |

Contraindications to renal transplantation

- Active systemic renal disease (SLE, anti-GBM, HUS, ANCA + GN)
- Oxalosis (combined renal and liver transplant)
- Active infection
- Recently treated or uncontrolled/disseminated malignancy
- Prohibitive extrarenal disease (CVS etc.)
- Active IV or alcohol abuse
- Non-compliance
- Uncontrolled psychiatric disorder

- | | |
|---|-------------------|
| M | Malignancy |
| I | Infection |
| N | Nephropathy |
| C | Compliance issues |

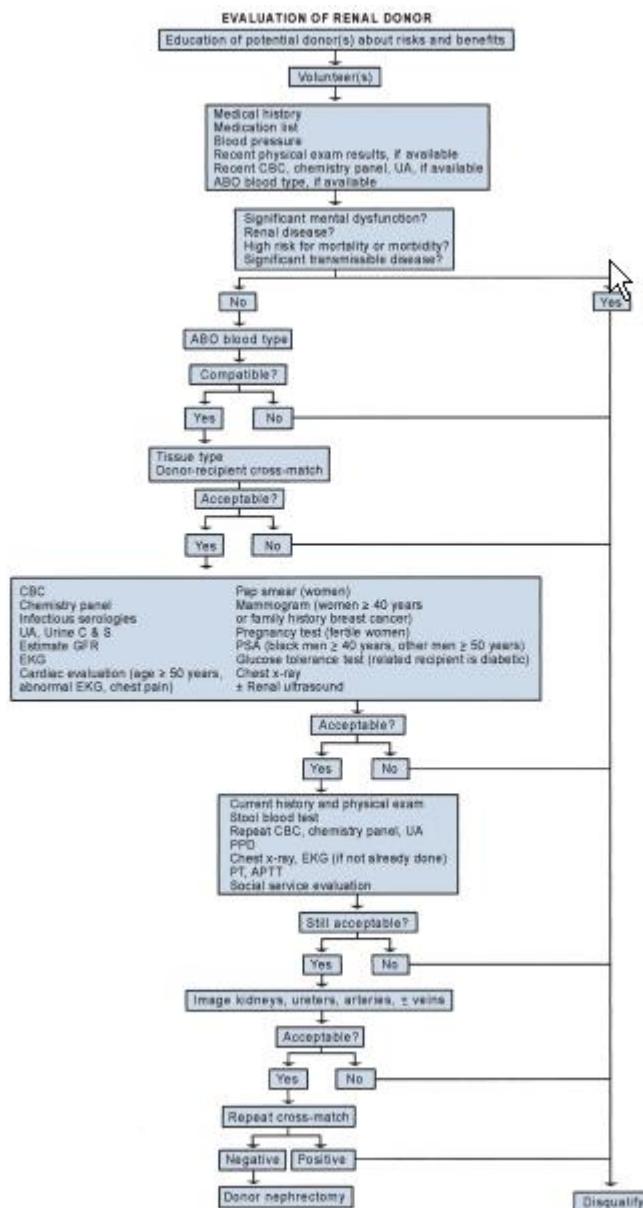
- E Severe extrarenal disease
- S Substance abuse
- O Oxalosis
- P Psychiatric disorder

Living donor evaluation

Exclude renal disease

Exclude active infection

Exclude transmissible malignancy



Best kidney left behind: ~ 80% CrCl achieved post-op – hyperfiltration leads to IL-10 production and TGF-B release.

If both equal choose right side in female of childbearing age

Imaging of choice = 3D CT angiography with delayed images best modality to image arteries, veins and drainage

Most living donor allografts now harvested laparoscopically – cuff of IVC on R

Typically mannitol given prior to renal vessel clamping (diuresis/free-radicals)
 Overall:

Morbidity	1.8-7% general complications (cardiac, thrombotic, lungs) Slightly increased risk of HT and proteinuria vs. general population but clinically insignificant 0.1% risk of ESRF long-term
Mortality	0.02%

Cadaveric donors

Beating heart donors with clinically determined brain stem death

Similar criteria to above re. malignancy, active infection etc.

Age 6 – 50 yrs acceptable

Low numbers resulted in 'extended criteria', but graft survival poorer in those younger than 6 or older than 50. Young donor kidneys can be used as pairs 'en bloc' with attached IVC & aorta. Also Light criteria utilising biopsy findings and clinical criteria used to predict risk of transplant failure

Always go for left-side if possible and single renal vessels.

Organ preservation after procurement

Warm ischaemia – failure of oxidative phosphorylation - ATP depletion – Na/K pump failure – intracellular Na accumulation – cell swelling – no-reflow after revascularisation. Also free-radical production via hypoxanthine

Cold ischaemia reduces energy requirements dramatically

2 methods: Simple cold slush storage (UoW)

Pulsatile perfusion

(i) Cold slush storage

Good kidneys

Storage up to 48 hours at 4°C

Cold ischaemia times > 24 hours a/w higher incidence of delayed graft function. Recommendation <21 hours.

University of Wisconsin solution – better vs. Eurocollins (Ploeg 1992)

UoW constituents

- a. Lactobionate, starch, raffinose – HMW solutes limit swelling
- b. Phosphate – buffer H+ ions
- c. Adenosine – substrate for ATP synthesis
- d. Glutathione – free-radical scavenger
- e. Allopurinol – inhibits xanthine oxidase and free-radicals
- f. Mg and DXM – membrane stabilisers
- g. Penicillin – antibiosis
- h. Insulin

(ii) Pulsatile perfusion

Poor kidneys (elderly donors, marginal criteria)

Allows assessment of flow (> 100ml/min), pressure (<40/25 mmg) and resistance (<0.3) features required for Tx

Transplantation – operative technique

Bench table vascular reconstruction important in cadaveric and LD Nx

lap – removal of staple lines and construction of single venous and arterial channels if necessary

cadaver – use of IVC to lengthen renal vein on right. Construction of single vessel channels

Give antibiotics, steroids and immunoglobulins at induction

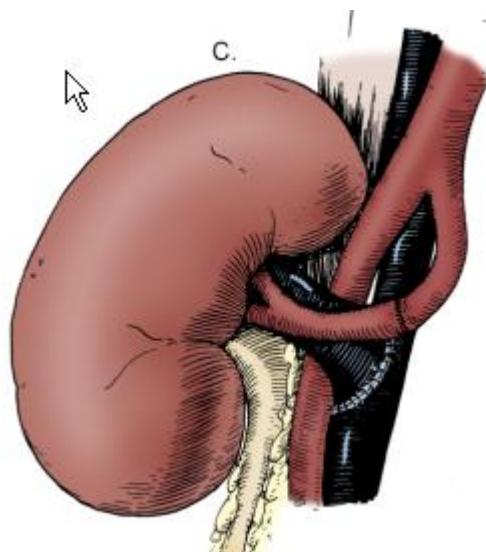
Typically RIF – external iliac vein more superficial cf. left

Extraperitoneal approach favoured in UK (avoids intestinal complications, ease of biopsy, confines surgical mischief)

Rutherford-Morrison type incision pubic symphysis to point 4 fingers above ASIS. Preservation of vas, division of round ligament and inferior epigastric.

Mobilisation of peritoneum medially. Heparin given before vessel clamping. Mannitol at time of anastomosis. End-to-end arterial anastomosis first from renal artery to either hypogastric artery or end-to-side to external iliac artery.

Then venous anastomosis external iliac (arterial anastomosis more critical and reduces external iliac clamping time). Lastly extravesical antirefluxing ureteroneocystostomy (transvesical or extravesical) – Lich Gregoir in UK vs. Leadbetter-Politano in US (higher incidence of reflux in UK but lower incidence of bladder dysfunction).

Post-operative complications

Early and late transplant-related complications and long-term non-surgical complications of renal transplantation.

Surgical complications causing allograft dysfunction divided into renal, vascular or urological complications:

A. Early allograft dysfunction

Renal

Acute tubular necrosis*

Prolonged cold ischaemia time and reperfusion injury*

Acute rejection (see below)

Acute cyclosporin toxicity

Vascular

Venous thrombosis
Arterial occlusion
Haemorrhage
AV fistula
Urological
 Urine leak or fistula
 Urinary obstruction

* Leads to delayed graft function, defined as the need for dialysis in the first week after Tx
The above are investigated by allograft USS with Doppler, cyclosporin levels and if necessary, renal biopsy

B. Late allograft dysfunction

Renal
 Chronic rejection
 Chronic cyclosporin toxicity
Vascular
 Renal artery stenosis
Urological
 Urinary tract obstruction
 UTI
 Urinary stones

C. Medical consequences of renal transplantation

Coronary artery disease
Diabetes
Malignancy
Reproductive

Allograft rejection

Hyperacute, accelerated, acute and chronic:

- (i) Hyperacute
 - Very rare
 - Immediate to 24 hours post-Tx
 - Pre-formed cytotoxic antibodies to allograft MHC – should not occur in absence of negative compatibility screening
 - No Rx – nephrectomy required
- (ii) Accelerated
 - Rare
 - Up to 10 days post-Tx
 - Primary immune response – humoral and cell-mediated
 - Very aggressive and difficult to treat – may result in graft rupture
 - Less common with anti-lymphocyte induction therapy
- (iii) Acute
 - Common – up to 50% of transplants
 - Up to 6 months post-Tx
 - Raised serum creatinine +/- systemic flu-like symptoms, graft tenderness and hypertension
 - Cause unknown – diagnosed on biopsy after exclusion of infection

Typically lymphocytic infiltrate around tubules and vessels - severity graded by Banff criteria
 Usually amenable to corticosteroid anti-rejection Rx (+ antilymphocyte agents if no response at 48 hrs)

(iv) Chronic

Common
 Used to be called chronic allograft rejection – now IFTA (interstitial fibrosis and tubular atrophy)
 Progressive decline in renal function leading to failure
 Thought due to repeated immunological insults/toxicity due to immunosuppressive medications
 Typically intimal proliferation and interstitial fibrosis – relative absence of lymphocytic infiltrate cf. acute rejection (can be difficult to differentiate from chronic cyclosporin toxicity)
 No specific Rx – limitation of other insults (DM etc.)

Vascular complications

Renal artery stenosis

1-15% incidence
 Due to surgeon error (narrowing, kink), arteriosclerosis, fibrosis
 Typically presents with poorly controlled HT +/- bruit
 > 70% stenosis >15mmHg gradient
 Suggested by Doppler, ACEI renography, angiography (best)
 Rx = angioplasty: outcome for surgery poor

Renal artery thrombosis

Rare <5%
 Surgeon error – intimal flap or kink
 Diagnosed on Doppler (no flow) or renogram (photopenia)
 Rarely salvageable – Nx

Renal vein thrombosis

Rare
 Technical error, haematoma, iliofemoral DVT, pro-thrombotic state,
 Diagnosed on renogram (background scintillations) or Doppler
 (reversal of venous flow)
 Rx = Thrombolysis/thrombectomy, Nx common

Urological complications

Infection

Stones

Urinary obstruction (3%)

Early (haematoma, urinoma, lymphocoele, surgeon error) or late (ischaemia or fibrosis, stone, tumour, bladder pathology)
 Non-contrast imaging and standard endourological Mx
 Most ureteric strictures due to ischaemia – exacerbated by BK virus

Fistula (2-3%)

Usually due to devascularisation, ischaemia and necrosis
 Typically distal third ureter (all supply from allograft renal artery)
 Rx small leaks conservative with stent
 Rx large leaks/ necrosis reconstruction options:
 Allograft – native ureteroureterostomy

Allograft – native pyeloureterostomy
 Allograft – native calicoureterostomy
 Calicocystostomy
 Boari flap +/- psoas hitch
 Ileal interposition

Lymphocoele

0.5 – 20% incidence
 Asymptomatic; occasionally graft dysfunction or LUTS
 Often recur following aspiration – open or lap marsupialisation vs.
 aspiration and cavity sclerosis

Medical consequences

Post-transplant diabetes

Incidence 3.4 – 46%
 Generally due to corticosteroids; also reported with cyclosporin and tacrolimus; often settle
 3 wks to 19 yrs post-transplant
 Non-insulin or insulin-dependent
 Worse patient and graft survival

Malignancy

Post-transplant lymphoproliferative disease*	~ 2-3 yrs
Kaposi's sarcoma	~ 2-3 yrs
Squamous carcinomas (skin, cervix, vulva and anus)	~8-10 yrs
All above occur with greater frequency in transplant popn. Due to combination immunosuppression	
No difference for lung, breast, prostate, colon or uterine, but earlier onset and more aggressive	
PSA levels normal in renal failure	
Cytology reliable in transplant patients	
BCG OK but increases risk of sepsis	
Urothelial cancer risk slightly increased due to BK virus (decoy cells on cytology, diagnosed with blood and urine PCR – Rx reduce immunosuppression, Rx urothelial tumour)	
*PTLD	~1% of renal transplants
	Not the same as NHL
	A/w Epstein Barr virus
	Aggressive vs. normal
	Multicentric and extra-nodal
	CNS and allograft involvement relatively common

*EBV infection

Increased risk of post-transplant lymphoproliferative disease
 EBV viraemia on PCR
 Reduce immunosuppression and give Rituximab (if CD25 positive)

CMV infection

Lethargy, respiratory symptoms and hepatitis
 Destauration on mobilisation
 Ground glass appearance on CXR
 Serology and PCR reaction for diagnosis
 Screen donor and recipient
 3 months prophylaxis with septrin

Valganciclovir and for Rx; foscarnet for resistance

Reproductive

Male infertility

Sperm parameters improve following Tx but not to normal levels

– many cases of pregnancy reported

Serum T and FSH/LH usually normalise following Tx suggesting improved Leydig cell function in non-uraemic state

Pregnancy

Possible but increased risks of pre-eclampsia (25%), pre-term labour (~50%) and neonatal morbidity (30%)

Graft function deteriorates in pregnancy, with 5-10% cases developing permanent graft dysfunction

No evidence that graft position impairs foetal delivery

Chromosomal aberrations higher in offspring but no definite increase in haematological malignancy

Attempts at pregnancy generally allowed after ~12 months

Appendix

Histocompatibility

ABO blood groups and major histocompatibility complex (MHC)

(i) ABO blood groups

Blood antigens (eg. A and B) present on endothelial cells in transplant kidney – recipient blood contains antibodies to antigen they lack
 Cross match crucial to assess compatibility
 Occasionally A2 kidneys transplanted into O or B donors with low anti-A2 antibodies

(ii) MHC antigens

Encoded by MHC genes on short arm chromosome 6

Glycoproteins on cell membrane of all cells:

Class 1 MHC antigens	All nucleated cells HLA-A, HLA-B, HLA-C Bind 8-10 amino acids in groove Interacts with CD8 Subtype detected by tissue typing T lymphocytes
Class 2 MHC antigens	B and activated T lymphocytes and antigen presenting cells HLA-DR, HLA-DQ, HLA-DP Bind 12-28 amino acids in groove Interacts with CD4 Subtype detected by tissue typing B lymphocytes

Huge variation in HLA/MHC gene polymorphisms (see below) allows humans as a species to respond to a myriad of potential pathogens

HLA SPECIFICITIES						
A	B	B	C	DR	DQ	DP
A1	B5	B51(5)	Cw1	DR1	DQ1	DPw1
A2	B7	B5102	Cw2	DR103	DQ2	DPw2
A203	B703	B5103	Cw3	DR2	DQ3	DPw3
A210	B8	B52(5)	Cw4	DR3	DQ4	DPw4
A3	B12	B53	Cw5	DR4	DQ5(1)	DPw5
A9	B13	B54(22)	Cw6	DR5	DQ6(1)	DPw6
A10	B14	B55(22)	Cw7	DR6	DQ7(3)	
A11	B15	B56(22)	Cw8	DR7	DQ8(3)	
A19	B16	B57(17)	Cw9(w3)	DR8	DQ9(3)	
A23(9)	B17	B58(17)	Cw10(w3)	DR9		
A24(9)	B18	B59		DR10		
A2403	B21	B60(40)		DR11(5)		
A25(10)	B22	B61(40)		DR12(5)		
A26(10)	B27	B62(15)		DR13(6)		
A28	B2708	B63(15)		DR14(6)		
A29(19)	B35	B64(14)		DR1403		
A30(19)	B37	B65(14)		DR1404		
A31(19)	B38(16)	B67		DR15(2)		
A32(19)	B39(16)	B70		DR16(2)		
A33(19)	B3901	B71(70)		DR17(3)		
A34(10)	B3902	B72(70)		DR18(3)		
A36	B40	B73		DR51		
A43	B4005	B75(15)		DR52		
A66(10)	B41	B76(15)		DR53		
A68(28)	B42	B77(15)				
A69(28)	B44(12)	B7801				
A74(19)	B45(12)	B81				
A80	B46	Bw4				
	B47	Bw6				
	B48					
	B49(21)					
	B50(21)					

However, makes life difficult when trying to find compatible matches

Detecting incompatibility

Originally complement dependent cytotoxicity (CDC) used, utilising donor lymphocytes and recipient sera in direct tests, with rabbit complement to stimulate cell lysis. However dependent on complement pathways and not that sensitive or specific.

Flow cytometry or ELISA based tests (known as panel reactivity antibody testing (PRA)) have now become standard to give an indication of the likelihood of chronic rejection. However ultimate decision to use kidney based on HLA compatibility. In general matching at only 3 loci; HLA-A, HLA-B and HLA-DR:

000 full house match

222 complete mismatch

Low risk 000 or single mismatch at non-DR locus

Medium risk 2B mismatches or 1DR mismatch

High risk 2DR mismatch, 2nd transplant

Life of transplant related to degree of match:

HLA Antigens Mismatched	No.	Half-Life (Yr)
0	4,182	15
1–3	9,391	12
4–6	14,186	10

Before transplantation a manual XM is performed between recipient serum and donor lymphocytes in all cases to exclude hyperacute rejection

Living-related donors (see below)

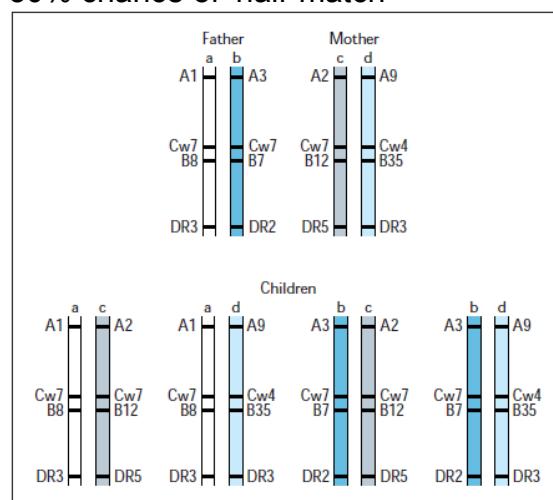
Each individual has 2 x chromosome 6

Parent shares 50% chromosomes with child

Siblings

25% chance of perfect match or mismatch

50% chance of 'half-match'

Immunology of graft rejection

Recognition of allograft as foreign occurs in two ways: direct recognition of donor APCs and recipient processing of donor peptides by host APCs (indirect recognition)

Activation of T-cells requires 3 signals: antigen presentation, glycoprotein binding (CD28 etc.) and IL-2. IL-2 require to provide co-stimulatory signal to drive cytotoxicity. Killing mediated in three ways: cytotoxic T-lymphocytes, antibody mediated (complement activation, opsonisation), delayed type hypersensitivity

Immunosuppressive therapy and side effects

A. Induction therapy designed to prevent rejection in first 3 months

IL-2 receptor antagonist (basiliximab)	anti B-cell
Anti-thymocyte globulin	anti T-cell*
Adeluzumab	anti B and T-cell

* very toxic and requires central line – only for high risk induction

B. Chronic anti-rejection therapy

Typically triple therapy:

- (i) calcineurin inhibitor
cyclosporine, tacrolimus
- (ii) purine inhibitor
azathioprine, mycophenolate mofetil
- (iii) steroids

Combination of above depends on risk of rejection (see above) – each nephrology unit has own protocols. Typically:

- | | |
|-----------|--|
| Low risk | cyclosporine, azathioprine, steroid |
| High risk | tacrolimus, mycophenylate mofetil, steroid |

Recently rapamycin used alone or in combination with cyclosporine in an attempt to reduce steroid intake

Pulsed steroids for acute rejection; anti-lymphocyte agents for non-responders

NB. Cyclosporin and tacrolimus metabolised by cytochrome p450 system – inhibitors increase dose (ABx except anti-TB drugs; Ca-channel blockers); inducers reduced dose (anti-TB ABx; epilepsy drugs)

Immunosuppressant	Mechanism of Action	Interferes with...
Glucocorticoids	Reduce transcription of cytokine genes	Intracellular signaling
Azathioprine	Inhibits purine synthesis	Lymphocyte proliferation
Mycophenolate mofetil	Inhibits purine synthesis	Lymphocyte proliferation
Sirolimus	Inhibits cell cycle progression	Lymphocyte proliferation
Tacrolimus	Inhibits calcineurin and interleukin-2 production	Intracellular signaling
Cyclosporine	Inhibits calcineurin and interleukin-2 production	Intracellular signaling
Monomurab CD3	Depletes T lymphocytes	Antigen recognition
Equine antithymocyte globulin	Depletes T lymphocytes	Antigen recognition
Rabbit antithymocyte globulin	Depletes T lymphocytes	Antigen recognition
Alemtuzumab (off label)	Depletes T and B lymphocytes	Antigen recognition and antibody production
Rituximab (off label)	Depletes B lymphocytes	Antibody production
Basiliximab	Blocks interleukin-2 receptor	Intercellular signaling
Daclizumab	Blocks interleukin-2 receptor	Intercellular signaling

Side Effects of Immunosuppressive Medications

Corticosteroids	Azathioprine
Diabetes	Bone marrow suppression (pancytopenia)
Lipid disorders	Gastrointestinal disturbances
Cushingoid features	Hepatotoxicity
Obesity	Hair loss
Poor wound healing	Antilymphocytic agents
Avascular necrosis (bone)	Polyclonal
Cataracts	Fever, chills
Hypertension, coronary artery disease (CAD)	Leukopenia, thrombocytopenia
Peptic ulceration, gastritis, bowel perforation	Serum sickness
Growth retardation	Local phlebitis
Pancreatitis	Monoclonal
Cyclosporine	Flulike syndrome:
Nephrotoxicity	Fever, chills, tremors, headache, nausea, vomiting, and diarrhea
Hypertension, CAD	Aseptic meningitis
Hyperkalemia	Hypotension
Hyperuricemia	Pulmonary edema
Heptatotoxicity	FK506 (Prograf/Tacrolimus)
Hirsutism	Nephrotoxicity
Gingival hyperplasia	Diabetes
Tremors/seizures	Neurotoxicity
Pancreatitis	Interleukin Inhibitor
Hemolytic-uremic syndrome	Simulect
Mycophenolate Mofetil (CellCept)	Rapamune (Rapamycin)
Leukopenia	Bone marrow suppression
Gastrointestinal disturbances	GI toxicity
GI bleeding, diarrhea, ulceration, esophagitis, gastritis	Skin rash
	Hyperlipidemia

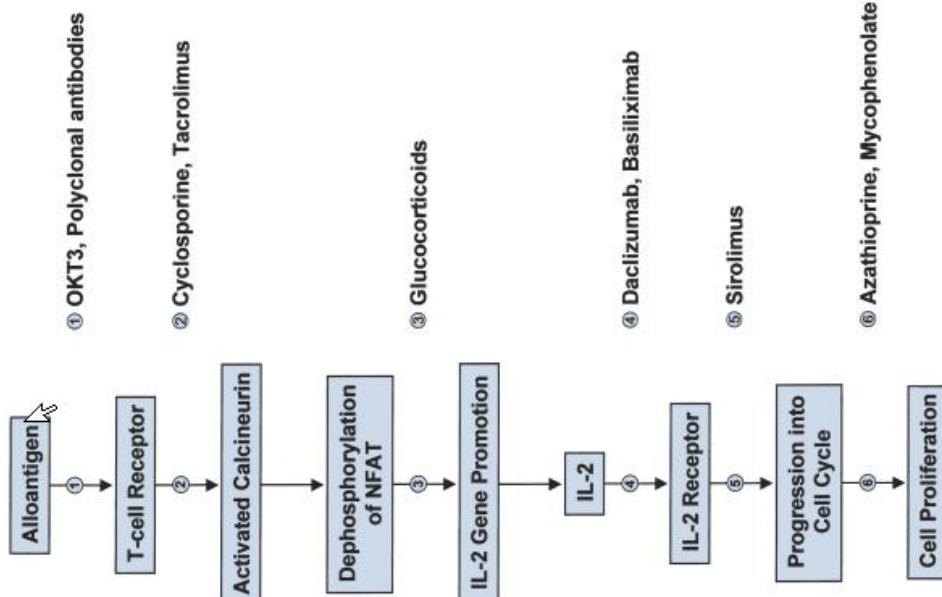


Figure 40-12 Sites of action of commonly used immunosuppressants. IL-2, interleukin-2; ↓, inhibition.

Basic immunologyInnate

NK cells

Complement

Acute phase proteins

Physical and mucosal barriers

Acquired

MHC class I antigens	HLA A, B and C All nucleated cells, including T-cells Interact with CD8 on immune cells
MHC class II antigens	HLA DR, DP, DQ Antigen presenting cells Macrophages Monocytes Some B cells Langerhan's skin cells Dendritic cells Vascular endothelial cells Interact with CD4 receptor on T-cells
Antigen presentation	Occurs in peripheral lymph nodes APCs interact with T-cells

Immune activity vs. infections

Innate and acquired

Extracellular bacteria	Complement killing NK activity Opsonisation and macrophage killing
Intracellular bacteria	T-cell activation required

Immune activity vs. tumours

Tumours are antigenic, but evade immune mediated killing in a number of ways:

Downregulation in MHC class I and II

Decreased expression of transporter antigen proteins (TAPs)

Overexpression of TGF-B