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# CPD Program for Primary Care
## Renal for the Busy Clinician
## Renal Transplant Update

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# Faculty/Presenter Disclosure

- **Faculty:** Julie Ho, MD FRCPC

- **Relationships with commercial interests:**
  - **Speaker Fees:** Canadian Transplant Forum March 2017 – Astellas Pharma

- **Mitigating potential bias:**
  - Not applicable

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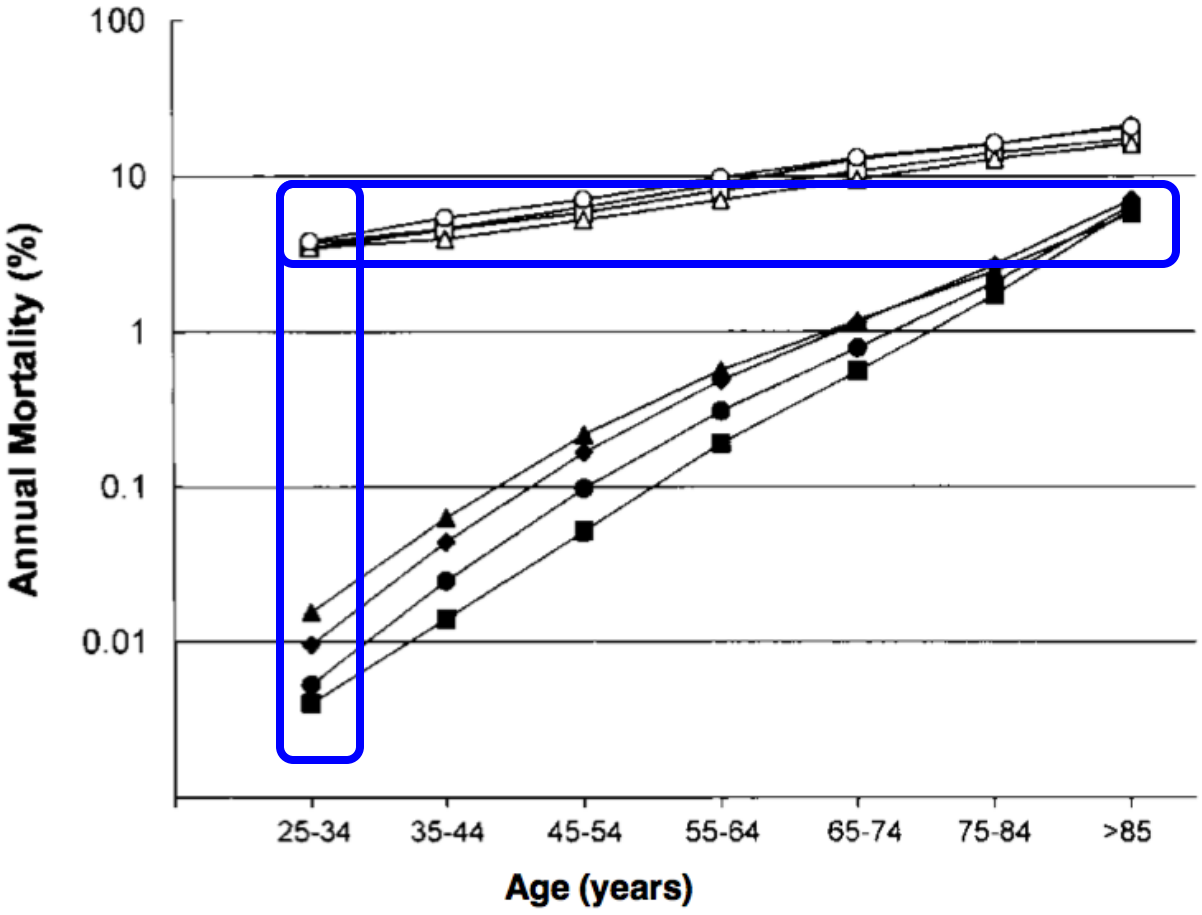
# Learning Objectives

**At the conclusion of this educational activity, the participants will be able to:**

- Describe the importance of kidney transplantation for ESRD patients
- Develop an understanding of different types of kidney transplant donors
- Discuss pre- and post-kidney transplant management considerations that are relevant to primary care

# Kidney Disease is a Silent Killer

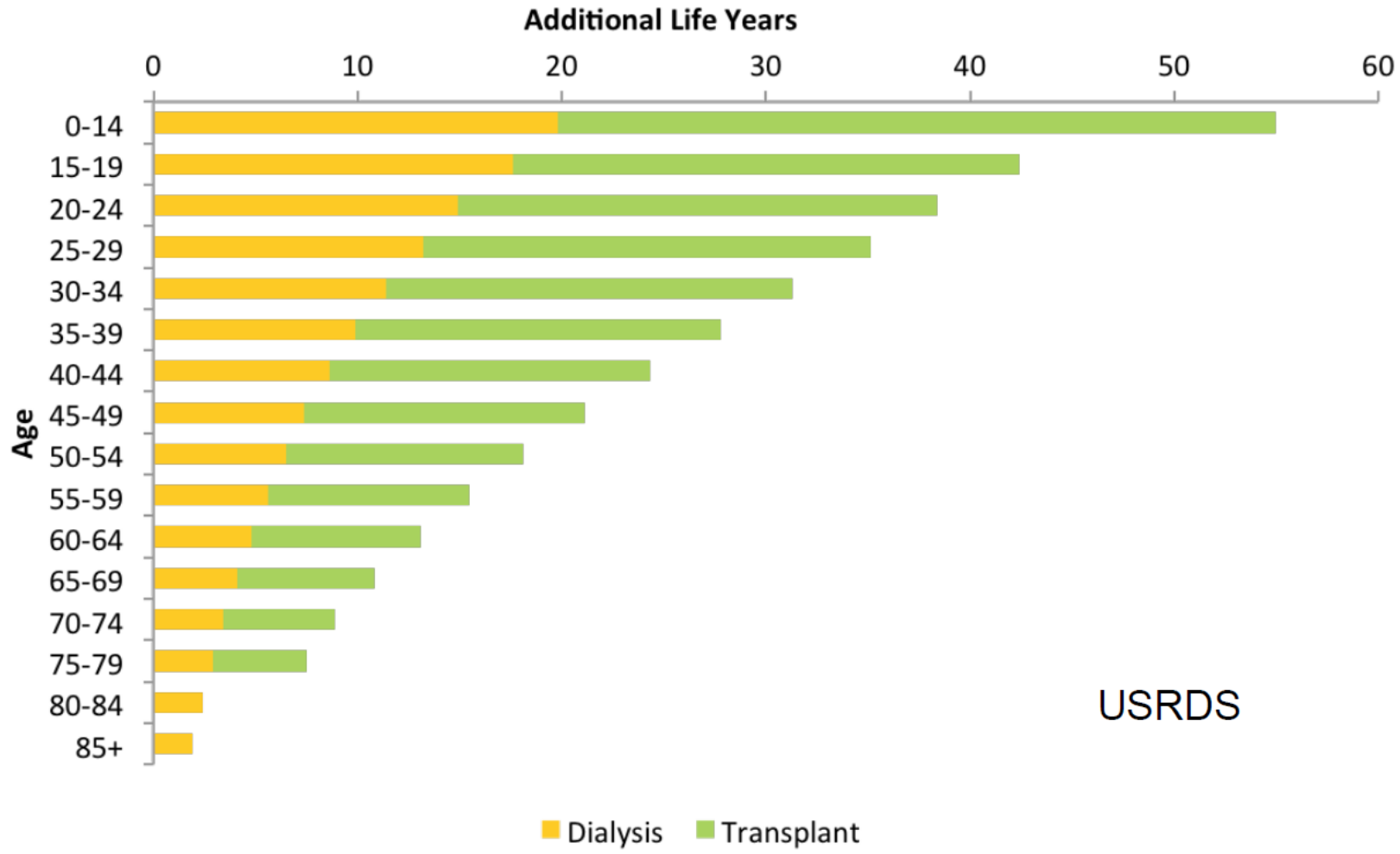
—◆—, GP male; —■—, GP female; —▲—, GP black; —●—, GP white; —◇—, dialysis male; —□—, dialysis female; —△—, dialysis black; —○—, dialysis white.




Foley R et al. Am J Kid Dis 1998; 32(5 Suppl 3): S112-119

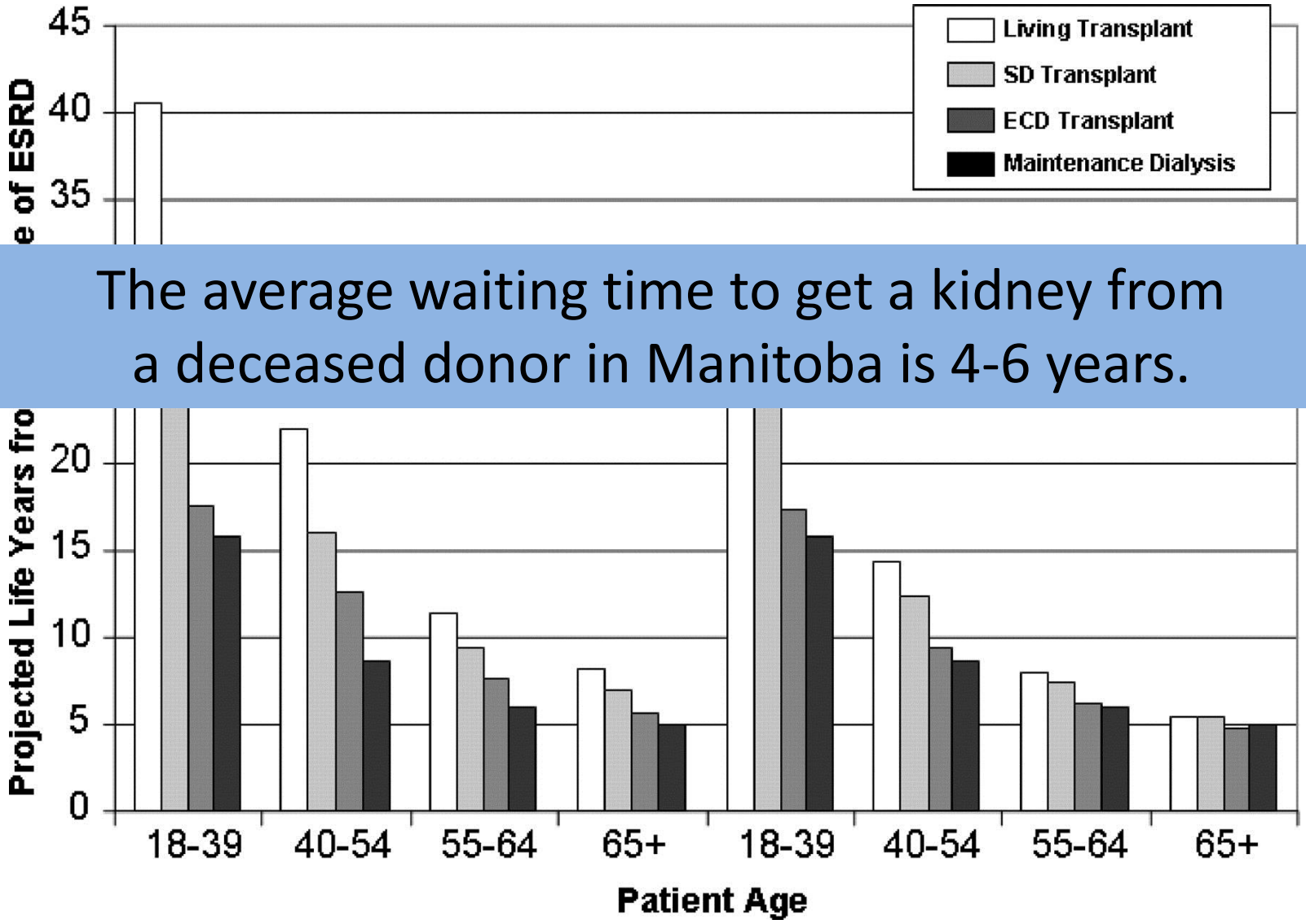
# *Life Years: Remaining on Dialysis vs. Receiving a Transplant*

***(Estimated based on age of onset of end-stage kidney disease)***




Slide courtesy of Dr. Peter Nickerson

# Kidney Transplantation Saves Lives




The average waiting time to get a kidney from a deceased donor in Manitoba is 4-6 years.

Schold and Meier-Kriesche CJASN 2006;1:532-538

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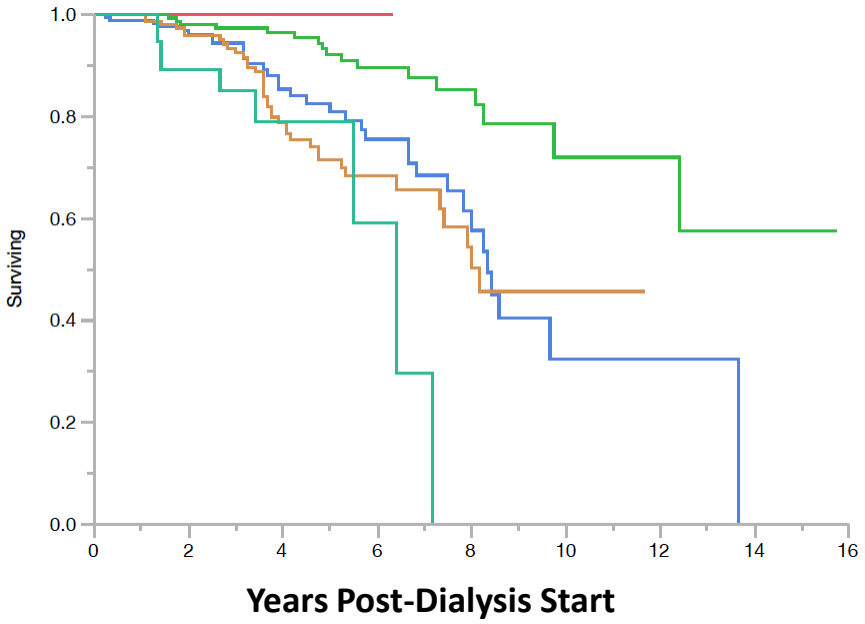
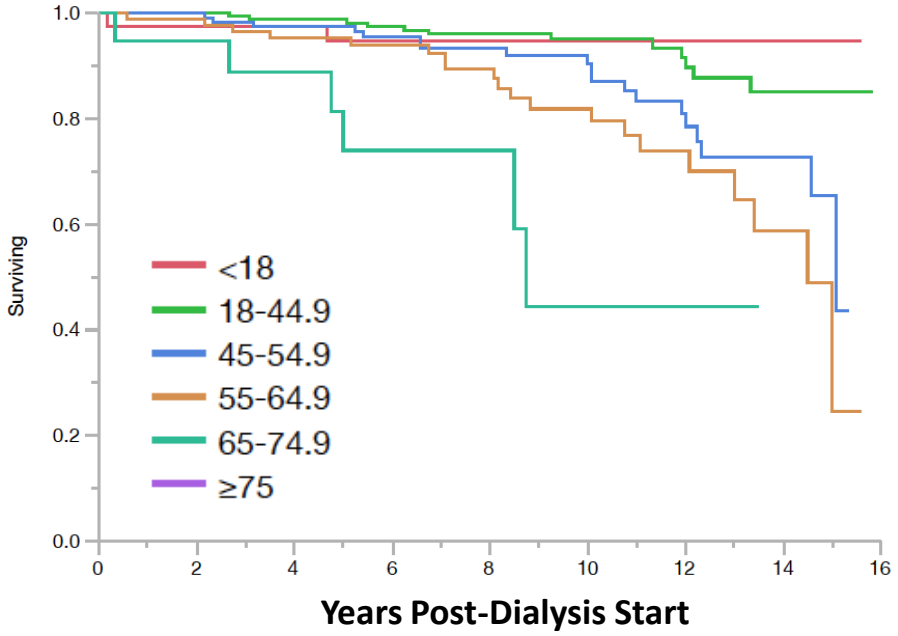
# Manitoba Waitlist Dialysis vs. Transplant Patient Survival$_{2000+}$

## Waitlist Patient remaining on Dialysis




## Waitlist Patient Transplanted

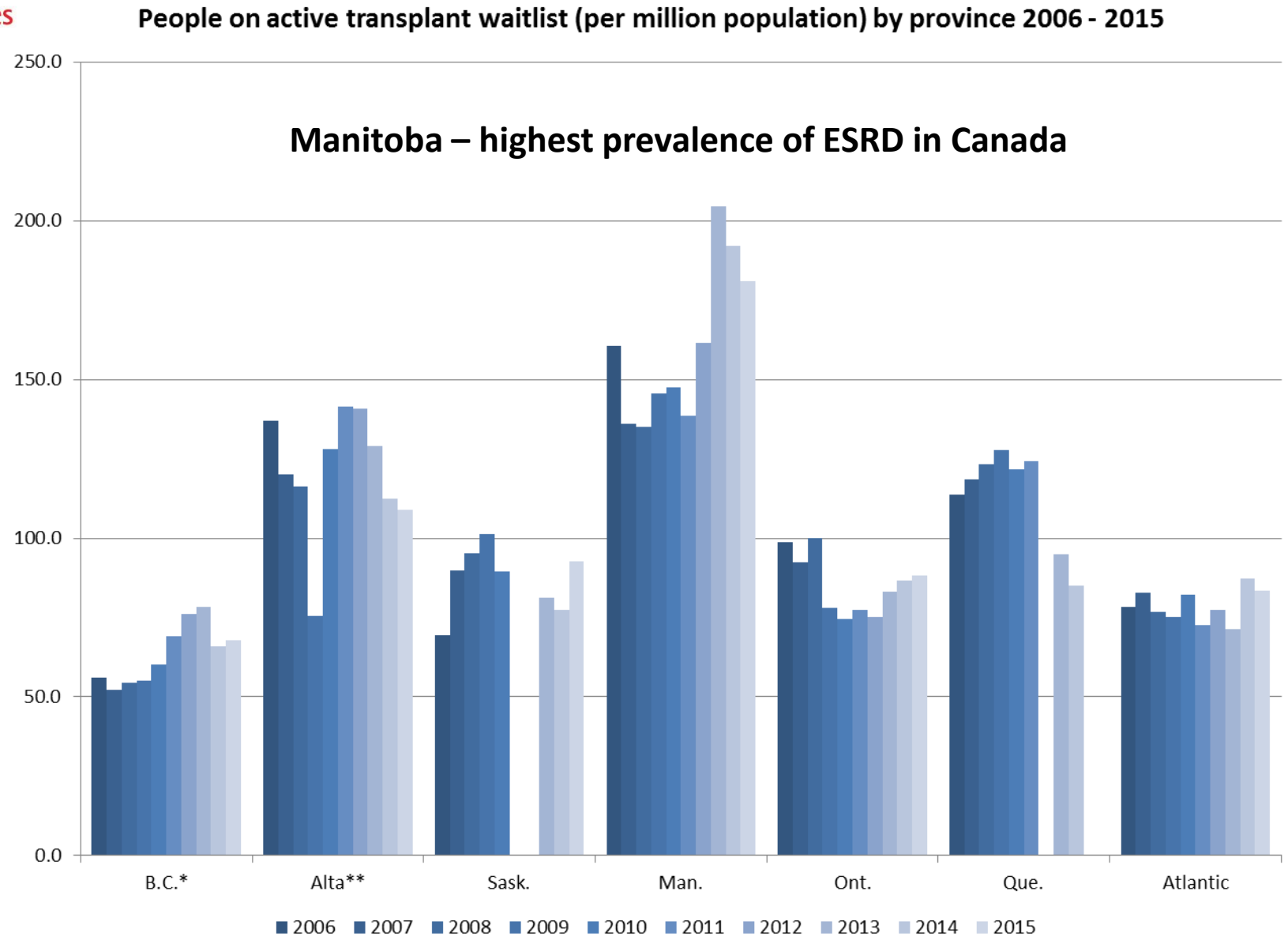



**For all age groups, patients eligible for transplant live longer with a transplant**

Slide courtesy of Dr. Peter Nickerson

Canadian Blood Services

# Canadian Kidney Transplant Waitlists




*Rates for B.C. - population of Yukon is included
**Rates for Alta. - populations of NWT & Nunavut are included

**Source – CORR estats 2006 – 2014, CBS survey 2015**
**NOTE – no data available for Sask. 2011 & 2012, Que. 2012 & 2015**

Slide courtesy of Dr. Peter Nickerson

# Kidney Transplantation Improves Quality of Life


I don't care what day it is.
Four hours is four hours.

I do sympathize with you, sir, but I'm afraid it cannot be viewed as 'carry on' luggage.

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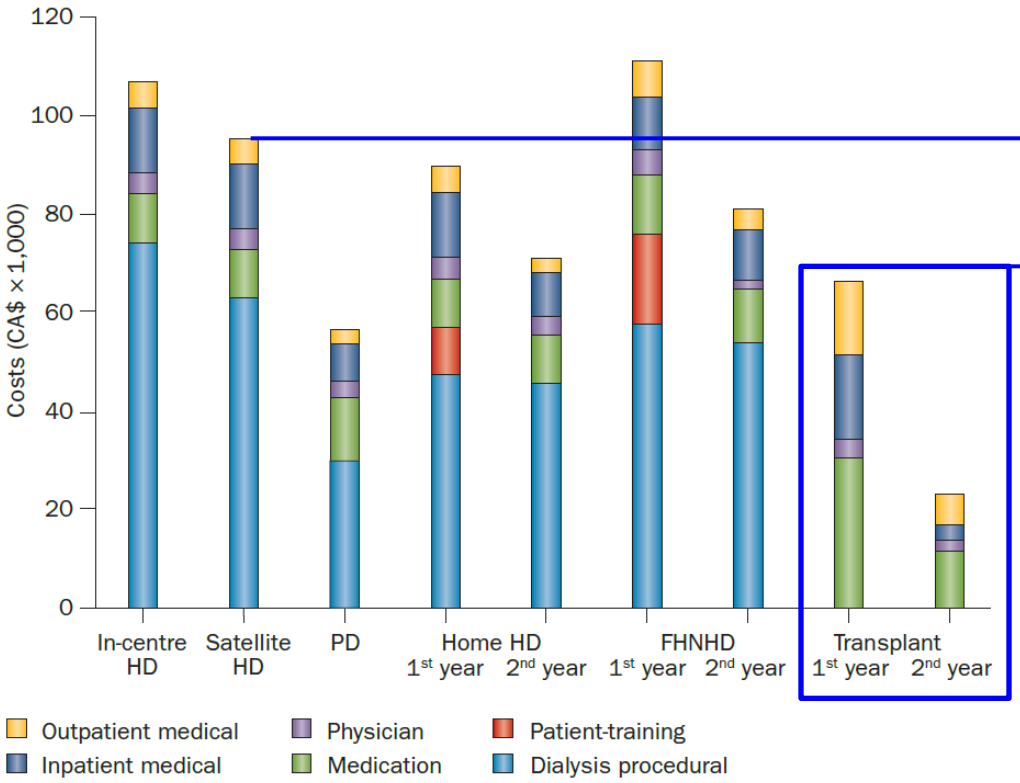
# Cost Effectiveness of Kidney Transplantation

**Annual health care costs of dialysis & transplant in Canada**




**Satellite HD in Manitoba is more costly than the Canadian average:**

Annual per patient / year cost:

1. $80,372-$215,918 (range)
2. $99,888 ($89,057-$122,640, median IQR)

Ferguson TW et al. PLoS One 10(8): e0135587, 2015

**After the 1st year of kidney transplantation:**

Annual per patient / year cost $22K/year

Conservative estimating $85,000/patient/year for dialysis, the cost-savings of kidney transplant is:

1. $20,000/patient in the 1st year
2. $63,000/patient/year from the 2nd year post-transplant onwards.

**In 2016, we did 57 kidney transplants which is a cost-savings of 3.59M in the 2nd year post-transplant alone.**

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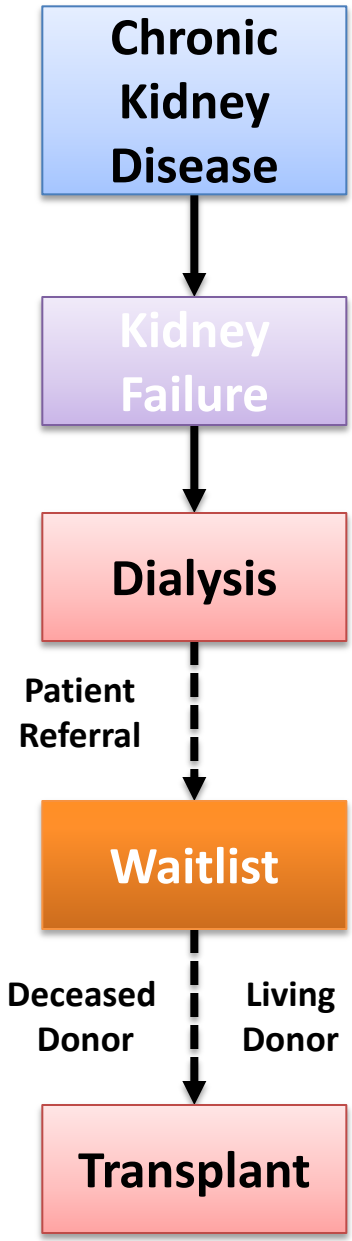
# Kidney Transplantation Patient Care Map




71,758 chronic kidney disease patients, MCHP 2015 report

1565 prevalent dialysis patients

255 new dialysis patient referrals/year for transplant work-up

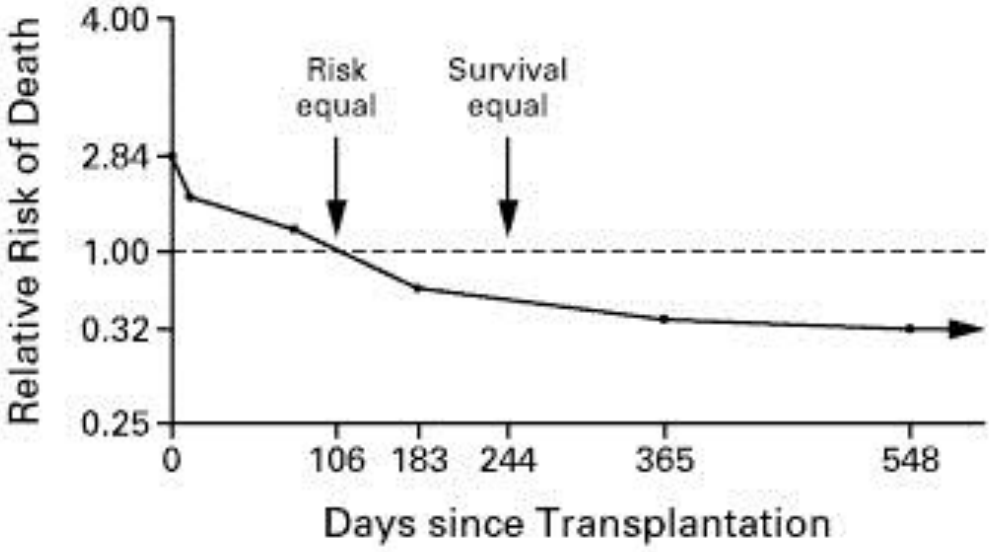
250 active in work-up
250 ready for transplant
150 on hold due to inter-current illness

208 living donors in work up

700 prevalent transplant patients followed in clinic (by end 2017)

# Canadian Society of Transplantation consensus guidelines on eligibility for kidney transplantation

Knoll G et al. Can Med Ass J 2005;173(10):S1




Wolfe RA et al. N Engl J Med 1999;341:1725-1730

**Who will do well post-transplant?**

1. Short-term – peri-operative risk
2. Long-term – immunosuppression

**Domains of evaluation:**

1. Medical
    1. Chronic infections
    2. Malignancy
    3. Systemic disease
2. Surgical/peri-operative
3. Immunological risk
4. Psychosocial/adherence

**Pre-transplant testing – average 6-12 months to complete**

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# Kidney Transplant Donors

## Living donors
1. Graft survival ~20-25 years
2. Pre-emptive - possibility

>

## Deceased donors
1. Graft survival ~ 13-15 years
2. Wait time

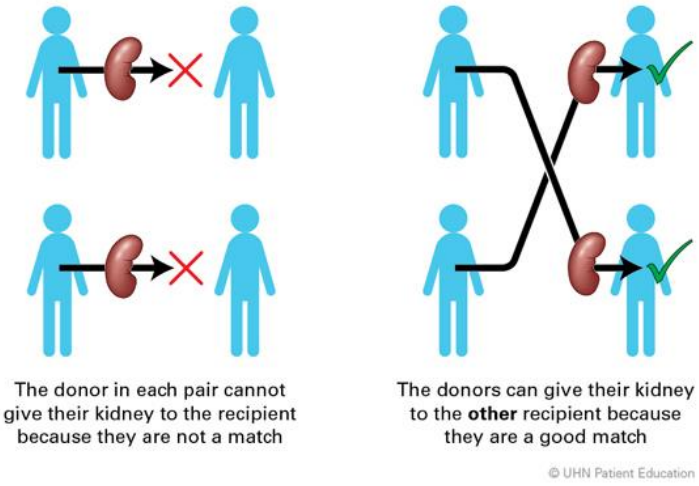
**Types of living kidney donors**
1. Direct donation
2. Kidney paired exchange (KPD)
3. Altruistic, non-directed

**Types of deceased kidney donors**
1. Neurological determination death (NDD)
2. Donation after cardiac death (DCD)
3. Medical Assistance in Dying (MAID)

**Describing Donor Quality - KDPI**
1. Standard criteria donor (SCD)
2. Extended criteria donor (ECD)
3. High infectious risk donor (IRD)
4. Exceptional distribution donor (ED)

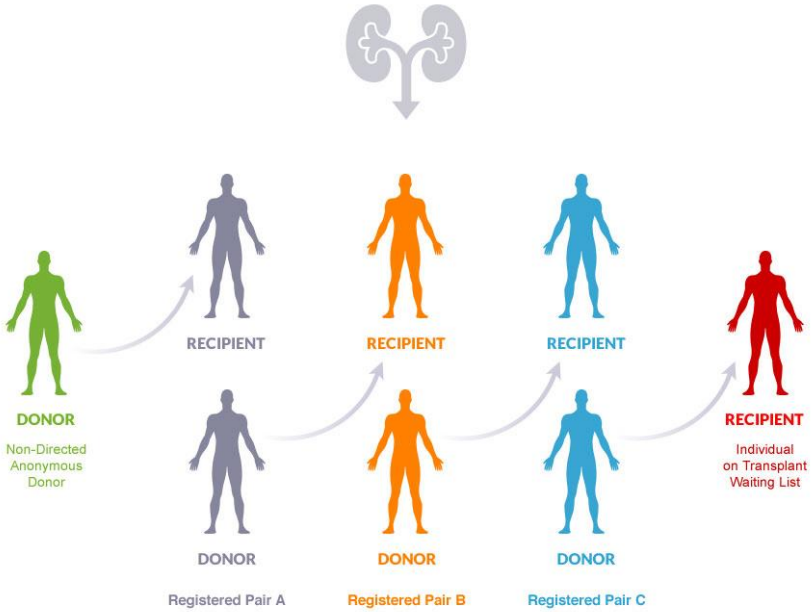
# Kidney Paired Exchange Program

## Closed chains




University Health Network

## Domino chains



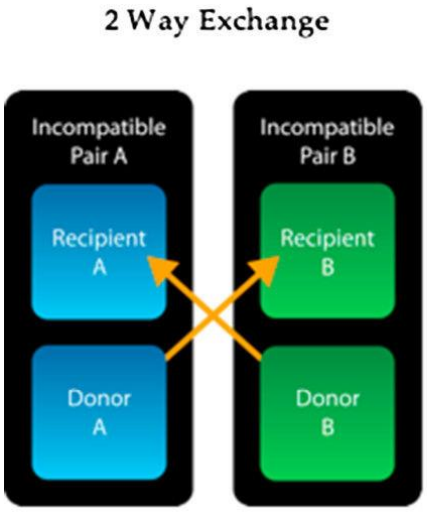

Canadian Blood Services

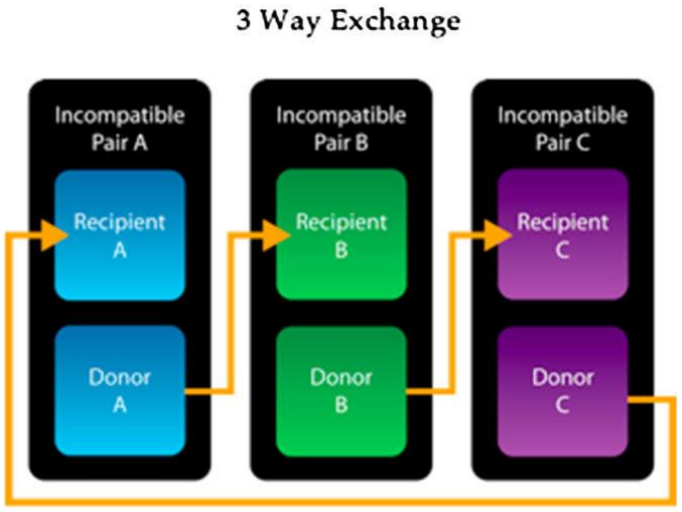
Canadian Blood Services

# Power of the Domino Exchange

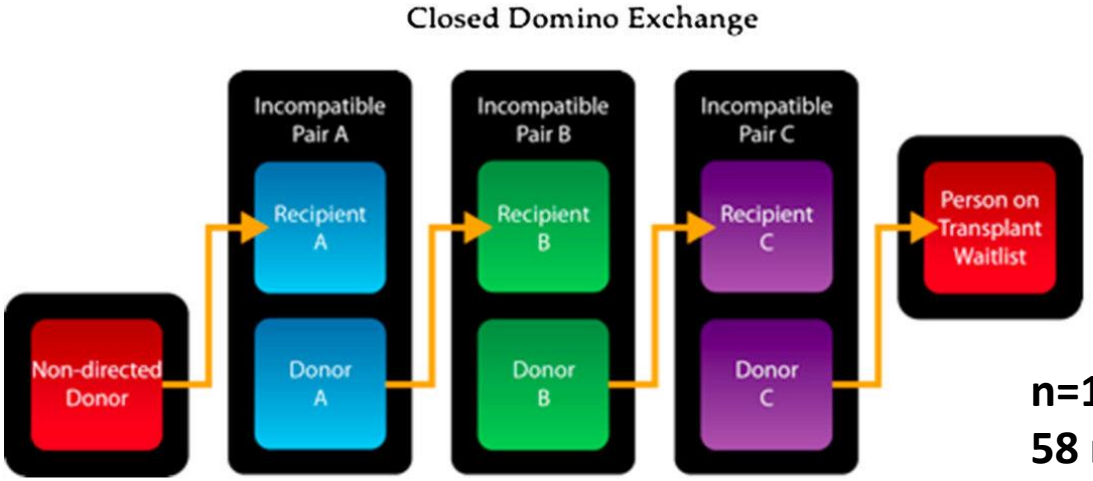
## 235 kidney transplants (2009-2013)

n=20




n=55
3,4 or 5 length chains




n=160
58 non-directed altruistic donors

Malik S and Cole E. Can J Kid Health Dis 1:6, 2014

# Kidney Transplant Recipients

**Standard kidney transplant recipients**

- Low or high immunological risk based on HLA match, antibody memory

**Highly sensitized kidney transplant recipients (~20% waitlist, previously 1% transplants)**

- PRA >95%
- Highly sensitized patient registry, since 2013
- Minneapolis

# Deceased Donor Organ Allocation Policy (February 2017)

**NDD and DCD* Deceased Donors**
*Only adult, not pediatric recipients to be considered for DCD's

**ABO Compatibility**
All compatible blood groups to be considered for Overriding and some High Priority recipients; for all other categories, priority given to staying within the same blood group

**Overriding Priority**
Medical Urgency
Highly sensitized (cPRA ≥95%) with a negative virtual crossmatch

**High Priority**
Pediatric Recipient (all compatible blood groups)
Zero HLA Mismatch (all compatible blood groups)
Previous Living Donor (identical blood groups only)

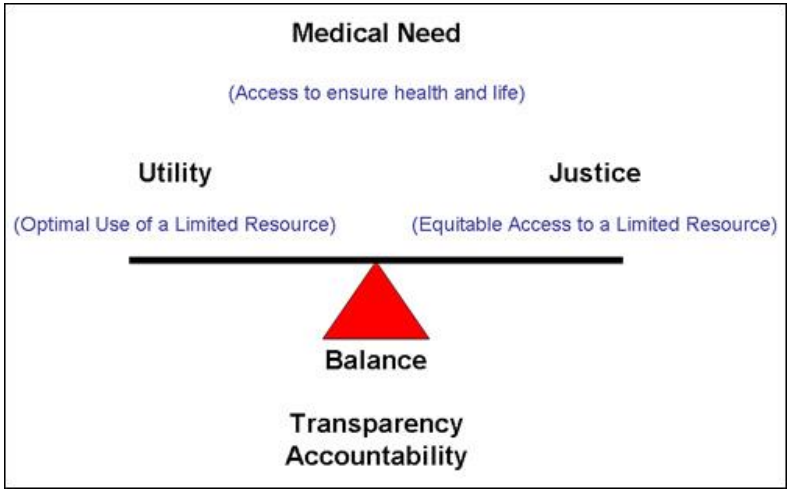
**Normal Priority**

| KDPI <20 | KDPI 20 – 59 | KDPI 60 – 85* |
|---|---|---|
| ↓ | ↓ | ↓ |
| Recipients <60 | All Recipients | Recipients ≥60 |

*NDD's with KDPI >85 – 95 may be considered and used as single or dual
*DCD's with KDPI >85 should not be used unless specific circumstances exist

**Priority Score = Wait-time + HLA Match + Sensitization**
Wait-time from start of dialysis: each year = 1 point
HLA Matching: Maximum of 3 points
3 pt = 0 MM (DRB1/3/4/5 + DQB1)
2 pt = 1 MM (DRB1/3/4/5 + DQB1)
1 pt = 2 MM (DRB1/3/4/5 + DQB1)
Sensitization: Maximum of 1.88 points
0.02 * cPRA (0-94%)

**No Priority**
Pre-emptive transplantation



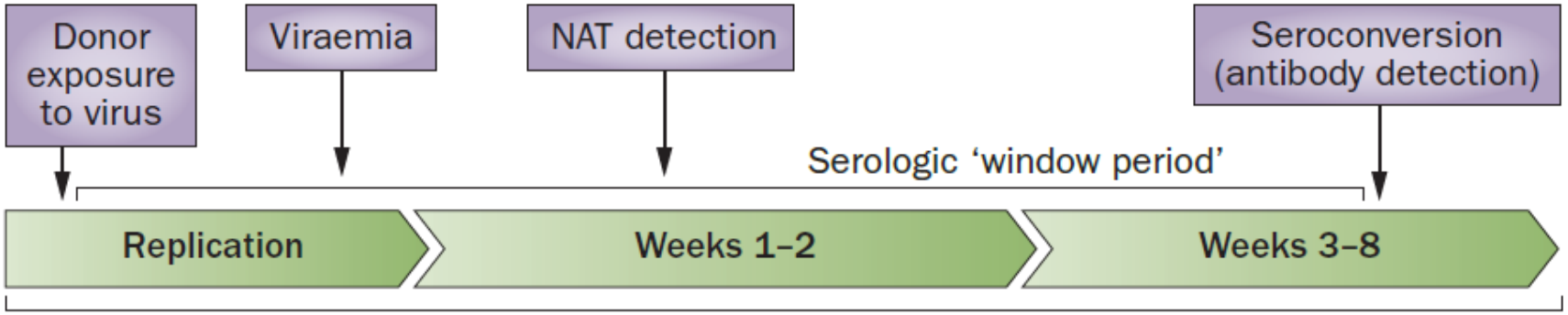

## Kidney Allocation Policy

1. Objective criteria
2. Publically available
3. External oversight

# Donor-Derived Infections

**Key points**

- Unusual clinical syndromes or clusters of infections in recipients of organs from the same donor suggest donor-derived infection as a possible source of transmission
- The incidence of transmission of unexpected infection by organ allografts is low, but precise data are lacking
- Screening of donors for common pathogens involves both epidemiologic history and microbiological assays, and is highly effective for preventing the transmission of HIV and hepatitis B and C viruses
- Donor screening for uncommon pathogens must be guided by knowledge of changes in the local epidemiology of infection
- The key element in the detection of donor-derived infection is suspicion on the part of the clinicians caring for organ recipients
- Application of newer microbiological techniques will increase the speed of donor screening and enhance transplant safety




Fishman JA et al. Nat Rev Nephrol 10: 663-672, 2014

# High Infectious Risk Donors

**TABLE 3.** Risk per 10,000 donors of an HIV infection occurring during the window period, by ELISA and NAT. Assumes a WP of 21 days for ELISA and 7 days for NAT

| Risk category | ELISA per 10,000 | NAT+ELISA per 10,000 | Risk of window period infection for NAT and ELISA expressed as ratio |
|---|---|---|---|
| Men who have sex with men | 5.8 (5.2–6.6) | 2.4 (2.1–2.7) | 1:4167 |
| Intravenous drug use | 6.6 (6.1–7.2) | 2.7 (2.5–3.0) | 1:3704 |
| Commercial sex worker | 3.7 (3.0–4.8) | 1.5 (1.2–2.0) | 1:6667 |
| Sex with a partner in above categories | 0.7 (0.5–0.9) | 0.3 (0.2–0.4) | 1:33,333 |
| Percutaneous injury resulting in HIV exposure through blood | 1.5 (0.8–2.4) | 0.6 (0.4–1.0) | 1:16,667 |
| Incarcerated | 1.0 (0.8–1.2) | 0.4 (0.3–0.5) | 1:25,000 |

**High infectious risk donors tend to have healthier kidneys**

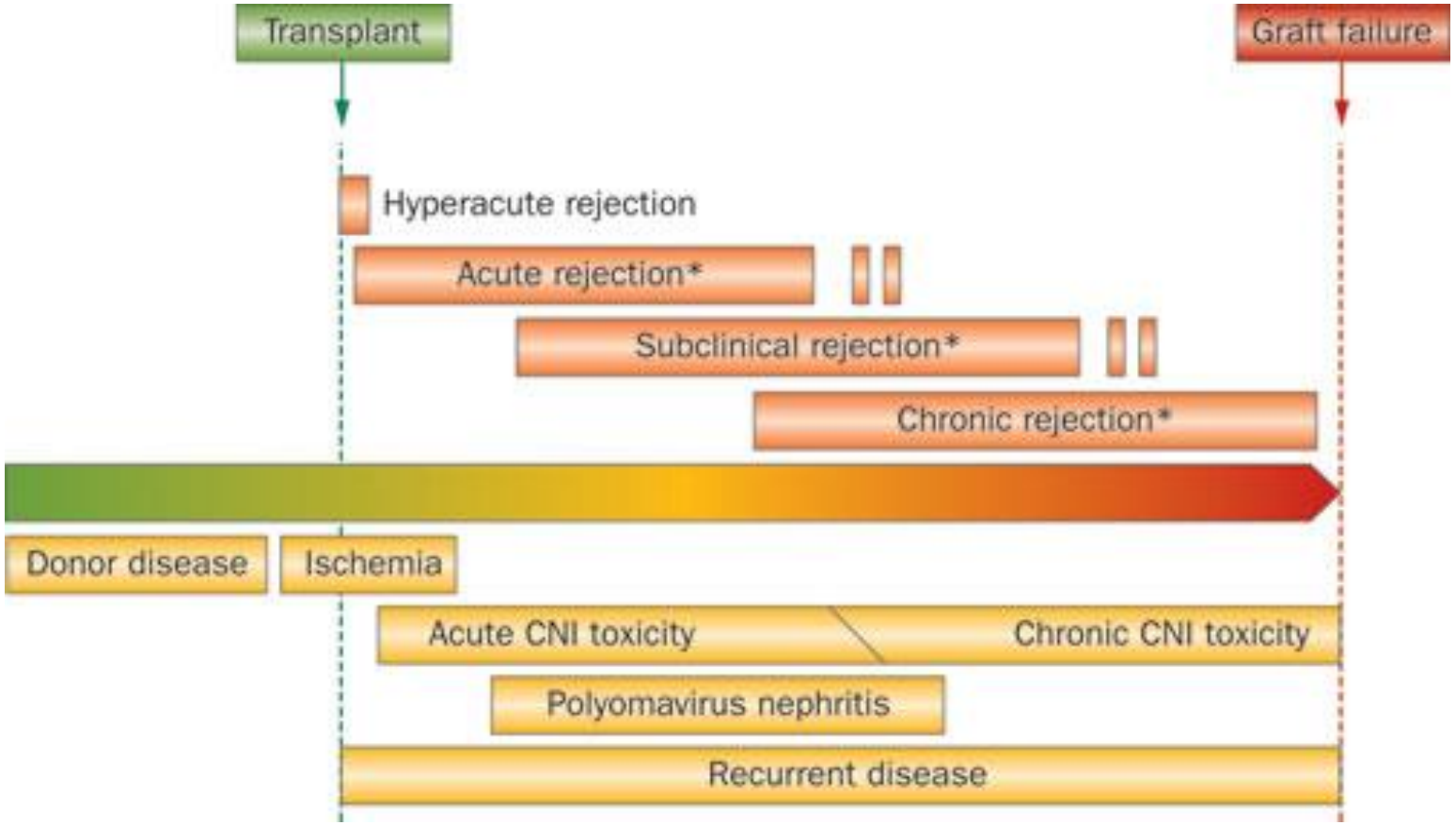
**New HCV therapies – ++ high sustained virologic response rates = ↓ risk chronic HCV infection**

**TABLE 4.** Risk per 10,000 donors of an HCV infection occurring during the window period, by ELISA and NAT

| Risk Category | ELISA per 10,000 | NAT and ELISA per 10,000 | Risk of window period infection for NAT and ELISA expressed as ratio |
|---|---|---|---|
| Men who have sex with men | 14.3 (10.7–17.3) | 1.5 (1.1–1.8) | 1:6667 |
| Intravenous drug use | 377.4 (346.0–412.1) | 40.8 (37.4–44.6) | 1:245 |
| Commercial sex worker | 270.8 (242.6–298.9) | 29.1 (26.1–32.2) | 1:344 |
| Sex with a partner in above categories | 168.3 (157.7–191.4) | 18.0 (16.9–20.5) | 1:556 |
| Percutaneous injury resulting in HCV exposure through blood | 13.9 (2.9–44.6) | 1.4 (0.3–4.3) | 1:7143 |
| Incarcerated | 107.8 (102.4–116.7) | 11.5 (10.9–12.5) | 1:870 |

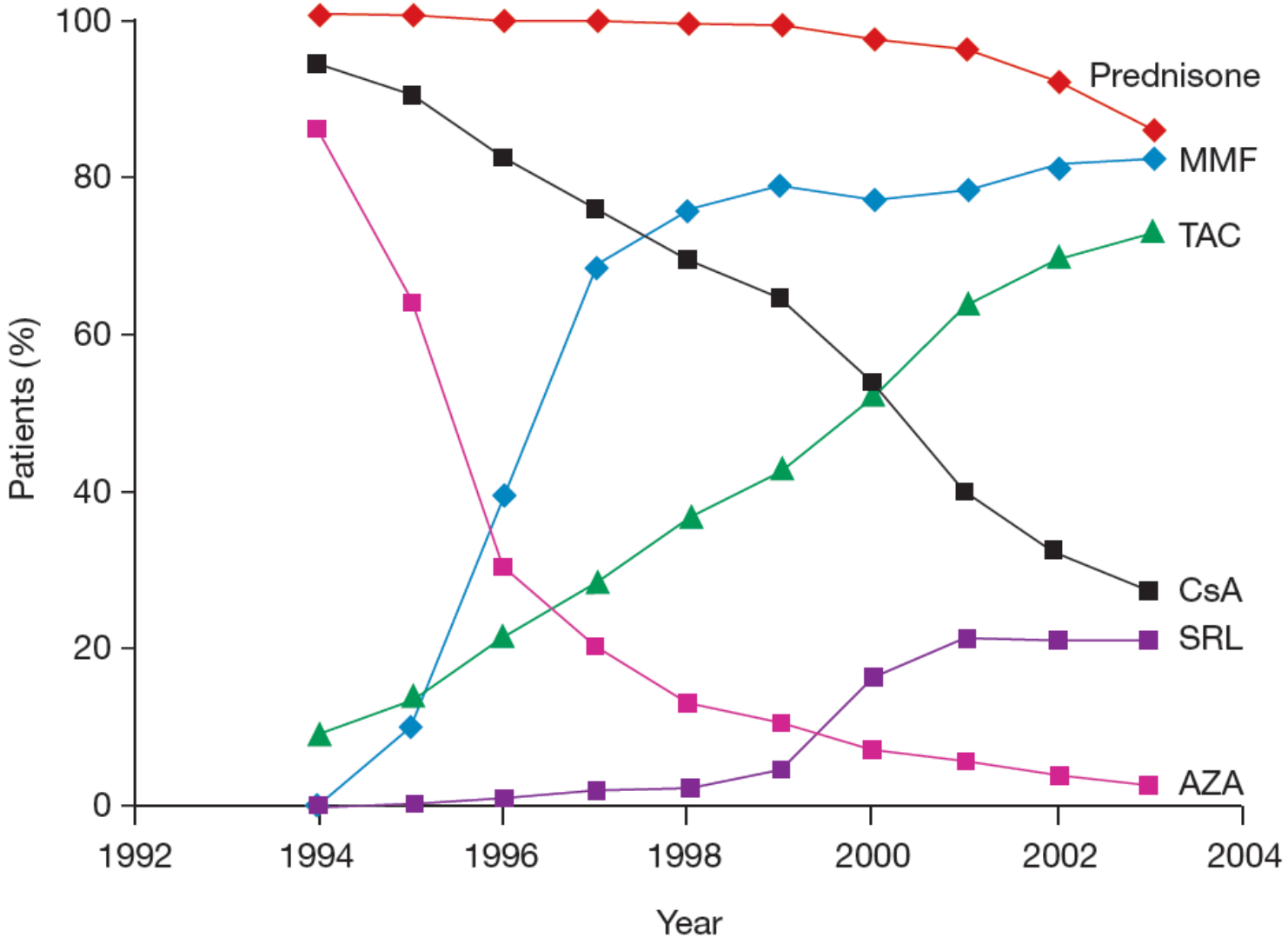
CST/CNTRP increased risk donor working group et al. Transplantation 98: 365, 2014

# Timing of Post-Kidney Transplant Complications



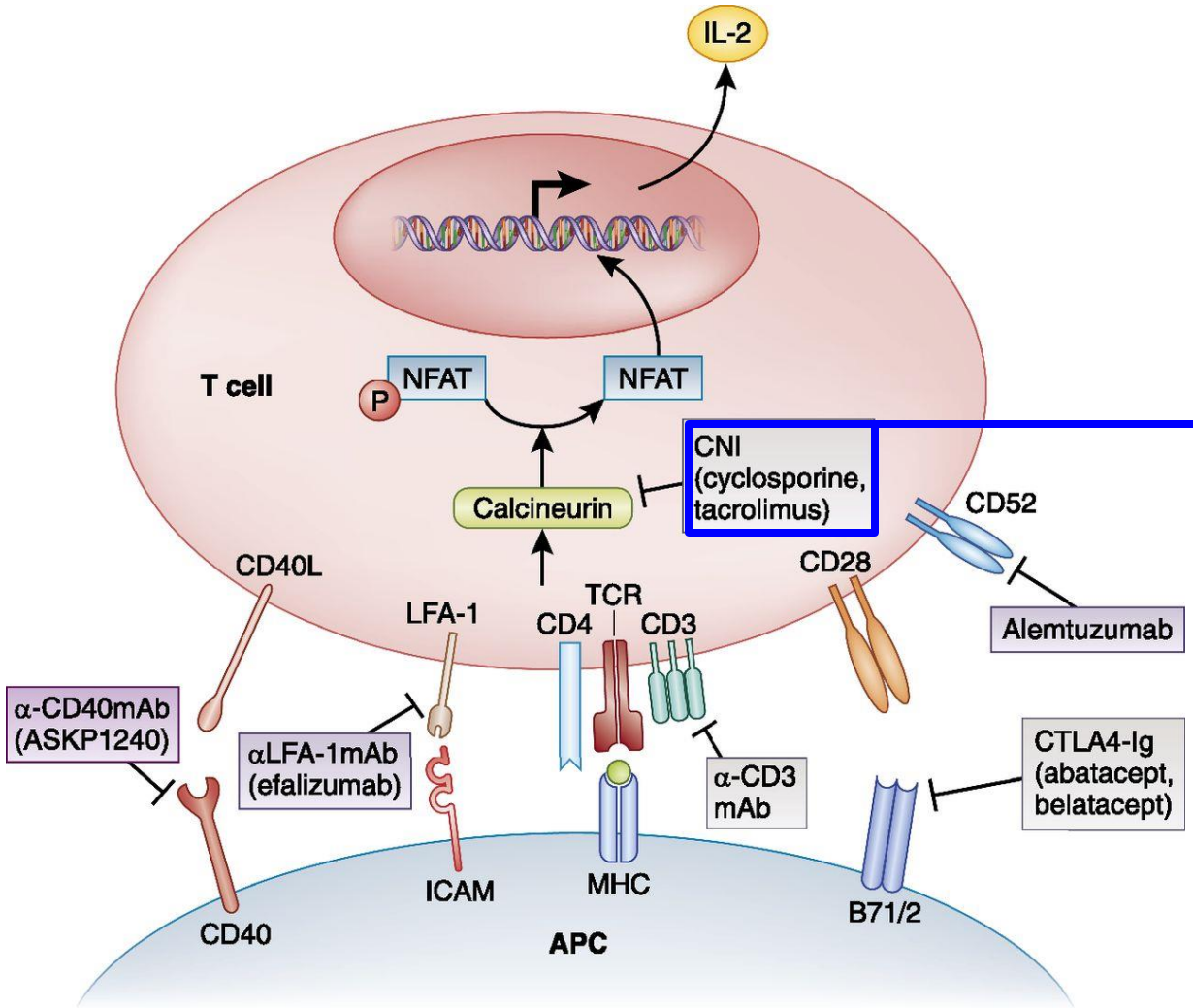

Williams WW et al. Nat. Rev. Nephrol 8: 110-121, 2012

# Trends in Maintenance Immunosuppression




Samaniego M et al. Nat Rev Nephrol 2(12): 688-699, 2006

# Mechanisms of Immunosuppression
# Inhibition T-cell signal 1 – interaction of TCR & APC




Inhibition calcineurin-dependent gene transcription

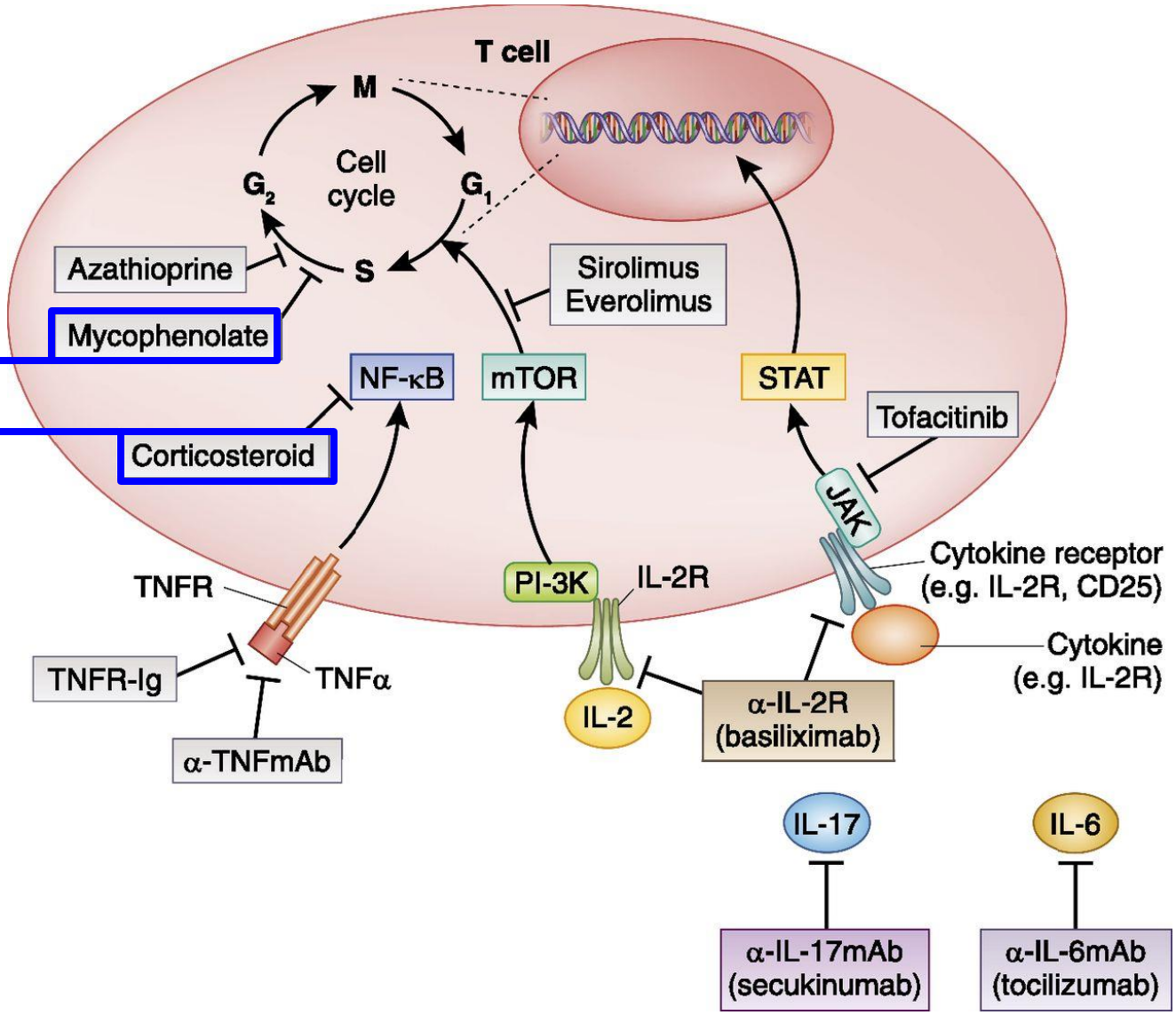
Wiseman AC. Clin J Am Soc Nephrol 11: 332-343, 2016

# Mechanisms of Immunosuppression
# Anti-metabolites

MMF inhibits IMPDH, the rate-limiting enzyme of guanine nucleotide synthesis, which is critical for de novo purine synthesis (and therefore DNA synthesis).

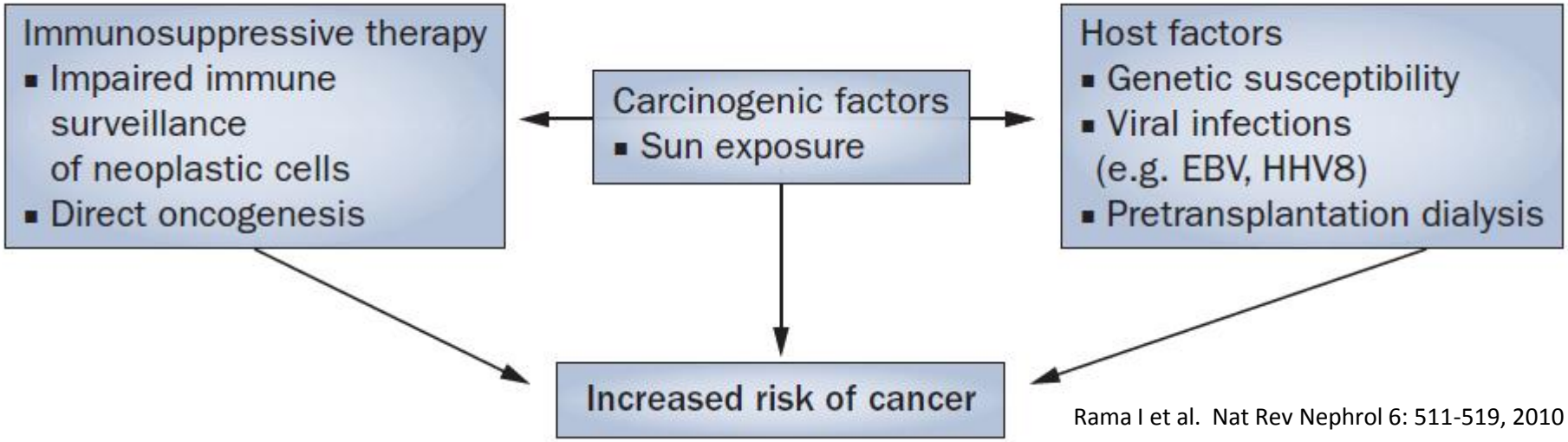
Inhibit cytokine transcription with downstream effects:

1. T-cell depletion
2. Eosinophil apoptosis
3. Macrophage dysfunction
4. Impaired PMN migration

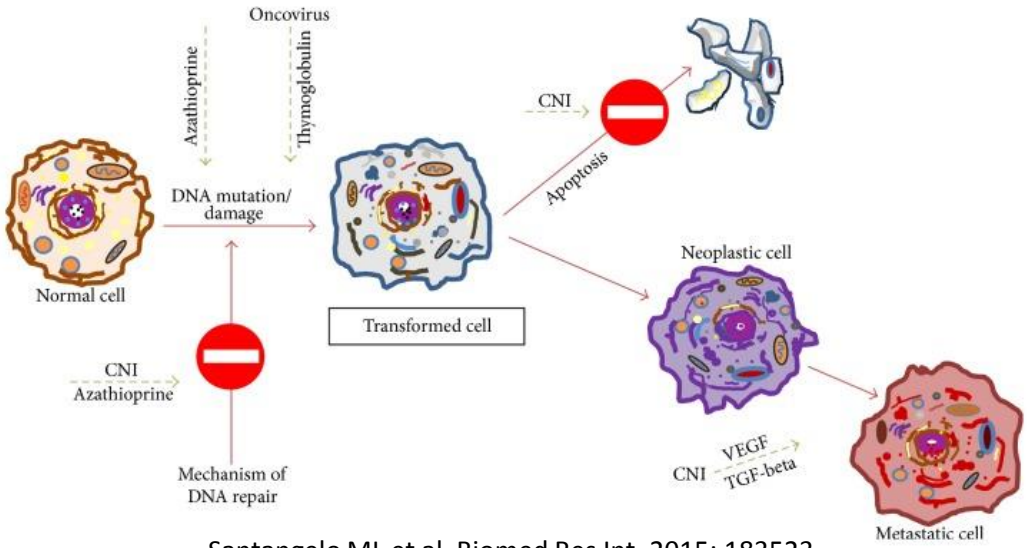



Wiseman AC. Clin J Am Soc Nephrol 11: 332-343, 2016

# Increased Risk of Malignancy




Rama I et al. Nat Rev Nephrol 6: 511-519, 2010




Santangelo ML et al. Biomed Res Int. 2015: 183523

# CMV Viremia

**Viral syndrome**

- Fever, malaise, myalgias
- Leukopenia, thrombocytopenia & other lab abnormalities

**Tissue invasive disease**

- Hepatitis
- Pneumonitis
- Colitis
- Carditis
- Nephritis
- Pancreatitis
- Retinitis

| CMV | Risk | Valganciclovir prophylaxis |
|---|---|---|
| D+ R - | High | Yes |
| D+/- R + and thymo induction | High | Yes |
| D+/- R + and no thymo induction | Intermediate | Monitor |
| D - R - | Low | Monitor |

# EBV Viremia & Post-Transplant Lymphoproliferative Disease

Table 1

**World Health Organization Classification of Post-transplant Lymphoproliferative Disorder (PTLD)**

| Category | Subtype |
|---|---|
| Early lesions | Plasmacytic hyperplasia<br>Infectious mononucleosis–like lesion |
| Polymorphic PTLD<br>Monomorphic PTLD<br>(classify according to lymphoma they resemble) | B-cell neoplasms<br>– Diffuse large B-cell lymphoma<br>– Burkitt lymphoma<br>– Plasma cell myeloma<br>– Plasmacytoma-like lesion<br>– Other[a]<br><br>T-cell neoplasms<br>– Peripheral T-cell lymphoma NOS<br>– Hepatosplenic T-cell lymphoma<br>– Other |
| Classical Hodgkin lymphoma-type PTLD | cT1-2 gr 3<br>cT3-4 |

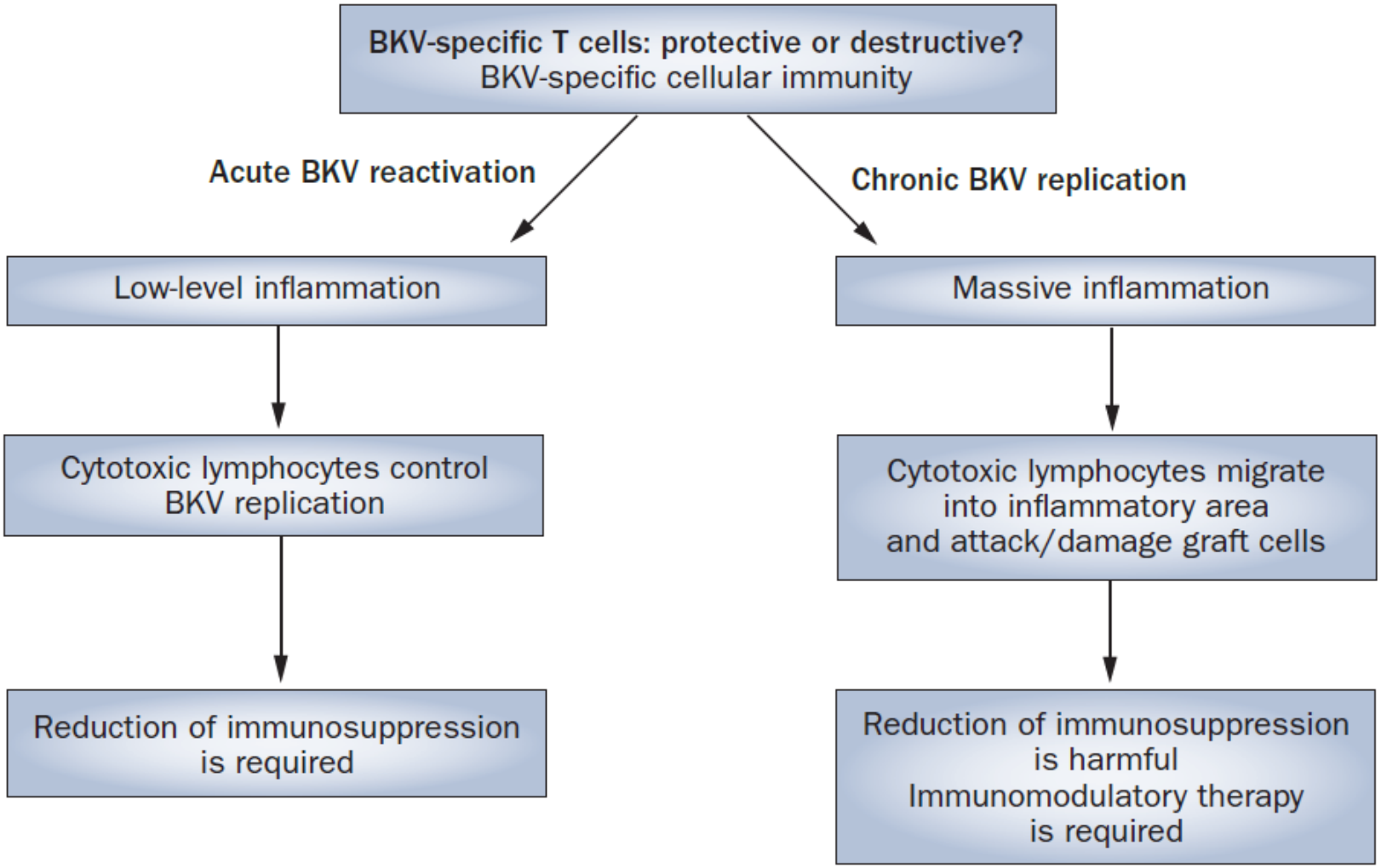
Table 2

**Risk Factors for the Development of PTLD**

| Risk Factor | Degree of Risk | Study Reference(s) |
|---|---|---|
| **EBV seronegativity pretransplant** | 24 × average risk | 11–13 |
| **Younger age at transplantation** | 4–8 × adult risk | 1,11 |
| **Type of immune suppression** | | |
| – Tacrolimus | 2–5 × risk with cyclosporine | 1,16,17 |
| – OKT3 and/or ATG | 3–4 × risk without these drugs | 1 |
| **Type of organ transplant** | | 9 |
| Kidney | 1%–3% of all transplant patients | |
| Liver | 1%–3% of all transplant patients | |
| Hear | 1%–6% of all transplant patients | |
| Heart-lung | 2%–6% of all transplant patients | |
| Lung | 4%–10% of all transplant patients | |
| Small bowel | 20% of all transplant patients | |
| **Time from transplant < 1 year** | 5–10 × risk at > 1 year | 1 |
| **De novo CMV infection:**<br>CMV-positive recipient of a CMV-positive organ | 4–6 × risk of CMV-negative recipient | 21 |

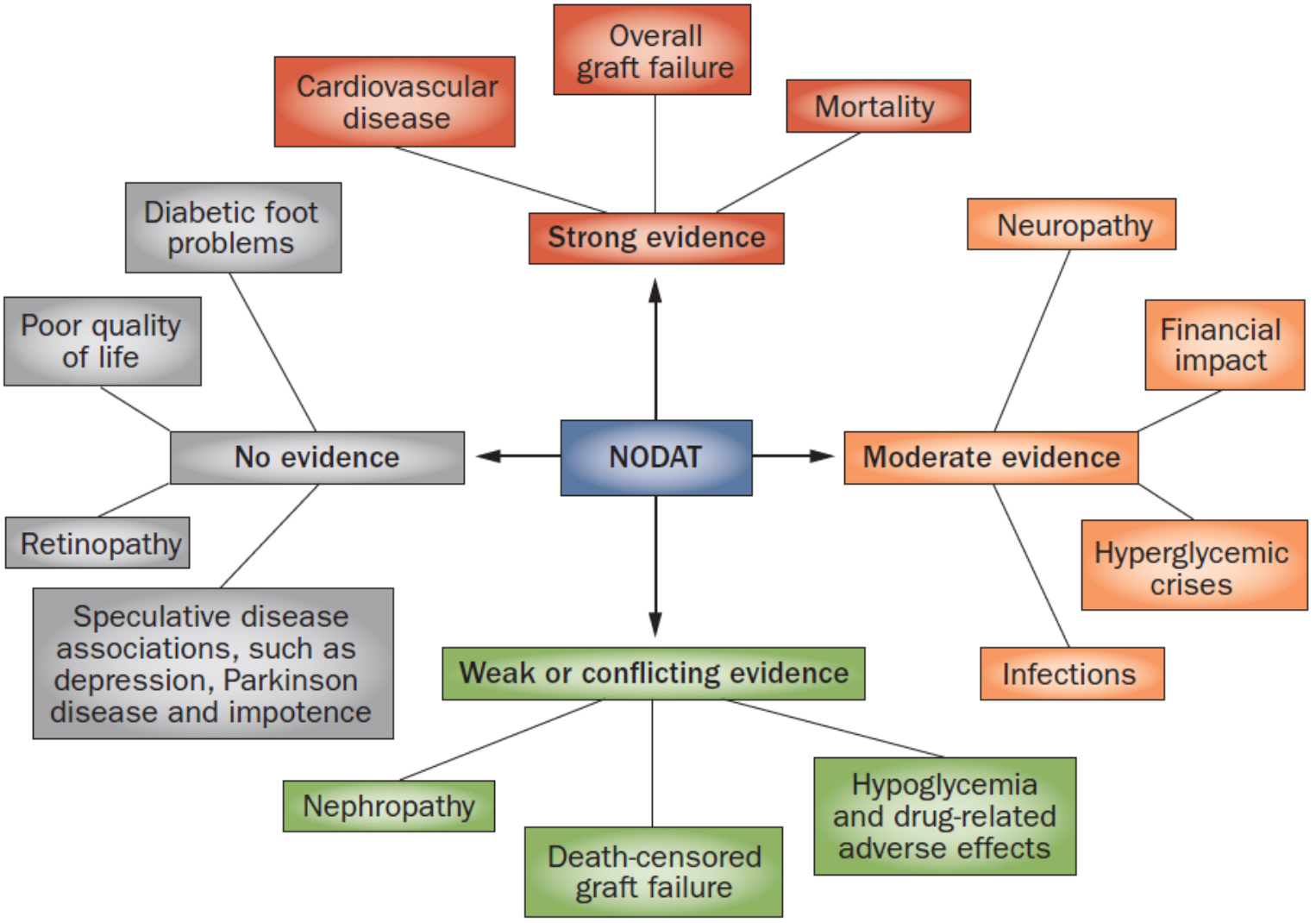
Jacobson CA et al. Oncology J, Sept 15 2010, 1-13. www.cancernetwork.com

# BKV Viral Infection




Babel N et al. Nat Rev Nephrol 7: 399-406, 2011

# NODAT – New-Onset Diabetes 2 After Transplant




Sharif A et al. Nat Rev Nephrol 8: 34-42, 2012

# Immunosuppression – Adverse Effects

**Drug interactions**:

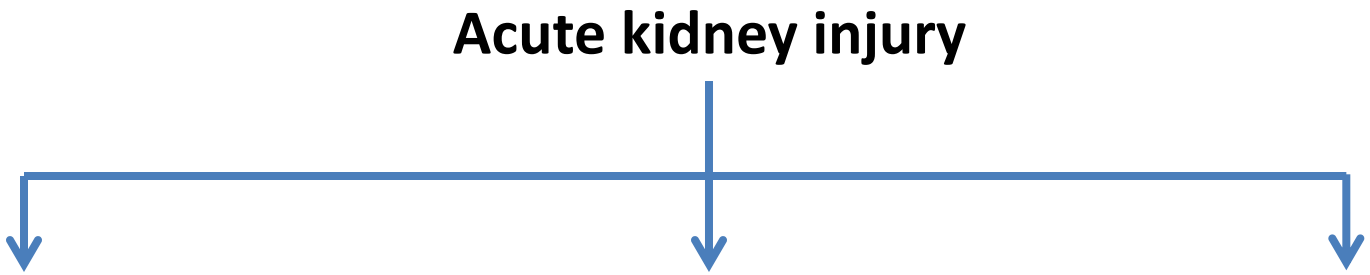
1. Azathioprine / allopurinol
2. Tacrolimus – multiple CYP3A4 interactions, examples include:
    1. Statins
    2. Antibiotics - macrolides
3. Non-dihydropyridine CCB – e.g. diltiazem
4. Antibiotics
5. Grapefruit juice

**Transplant pharmacists – 204-787-3138**

**Please avoid NSAIDS…**

Samaniego M et al. Nat Rev Nephrol 2(12): 688-699, 2006

# Acute Kidney Injury in the Kidney Transplant Patient




## Pre-renal

1. Renal artery anastomosis stenosis
2. Pyleonephritis
3. ACEi / ARB
4. NSAIDs

## Renal

1. Rejection
2. Polyoma nephropathy
3. Recurrent or de novo GN
4. Calcineurin inhibitor toxicity

## Post-renal

1. Ureteric stricture / leak
2. Lymphocele
3. PTLD

***In addition to the usual suspects…***

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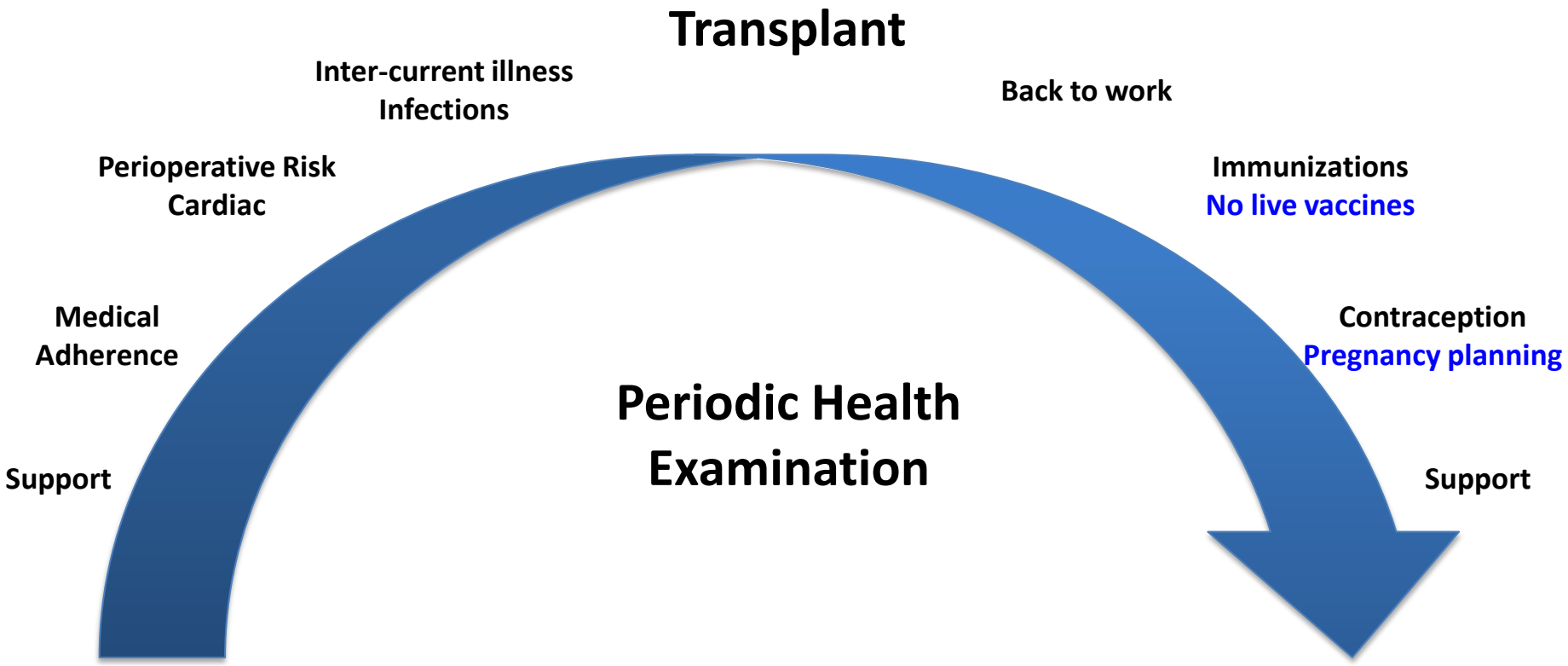
# Primary Care of the Kidney Transplant Patient




## Living kidney donors:

1. ↑ risk HTN
2. eGFR 60-80% pre-donation
3. Annual BP & renal function check

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# Summary

- Kidney transplant is the therapy of choice for most patients with ESRD
  - Mortality benefit
  - Quality of life, cost-effective

- Transplant suitability is assessed through multiple domains – to determine if the benefits of transplant outweigh the potential risks for that recipient.

- Modern maintenance immunosuppression consists of triple therapy with an anti-metabolite (MMF), CNI (tacrolimus) and prednisone.

- Common post-transplant complications – infections, malignancy, DM etc.

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# Resources & Recommended Reading

- Canadian Society of Transplantation consensus guidelines on eligibility for kidney transplantation. CMAJ 173(10): S1
- KDIGO clinical practice guideline for the care of kidney transplant recipients: a summary. Kidney Int. 77: 299-311
- Immunosuppressive medications. CJASN 11(2): 332-43, 2016
- www.transplantmanitoba.ca
- https://www.signupforlife.ca/

DONATE LIFE