Kidney Transplant 101

Kristopher Lepere D.O.

Agenda

Importance of kidney transplantation

Brief history

Patient selection

Pre-transplant evaluation

Transplant surgery

Immunosuppression

Post-transplant care

Complications and challenges

Future developments

Facts

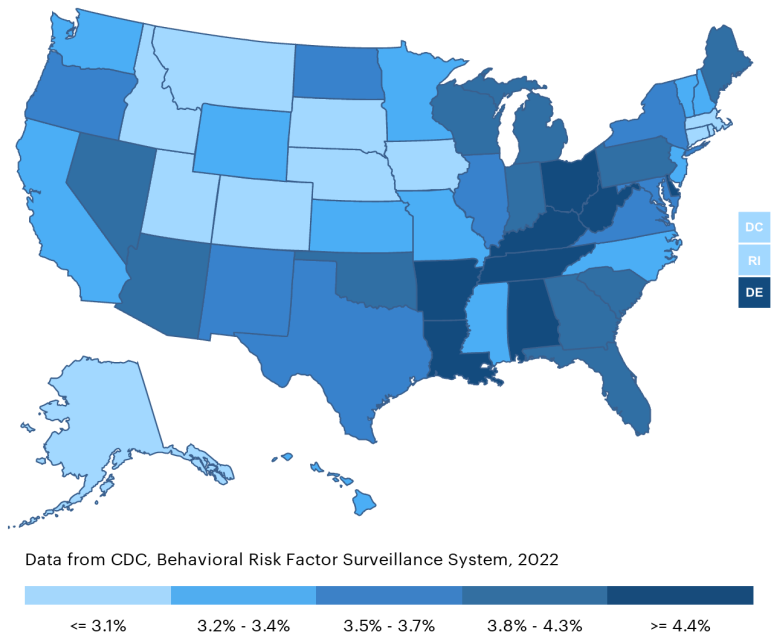
- Kidney disease affects an estimated 37 million people in the US. (15% of the adult population; more than 1 in 7 adults).
- Approximately 90% of those affected do not know they have it. 2/5 with severe CKD don't know they have it.
- 1 in 3 adults in the U.S. (approximately 80 million) is at risk for kidney disease.
- CKD is a leading cause of death in the U.S.
- Approximately 1 in 3 adults with diabetes and 1 in 5 adults with HTN may have CKD.
- CKD causes more deaths than breast cancer or prostate cancer.

National Kidney Foundation. www. Kidney .org/kidney-basics.

Oklahoma- #33 (4%)

Chronic Kidney Disease by State

Percentage of adults who reported ever being told by a health professional that they have kidney disease (excluding kidney stones, bladder infection or incontinence)

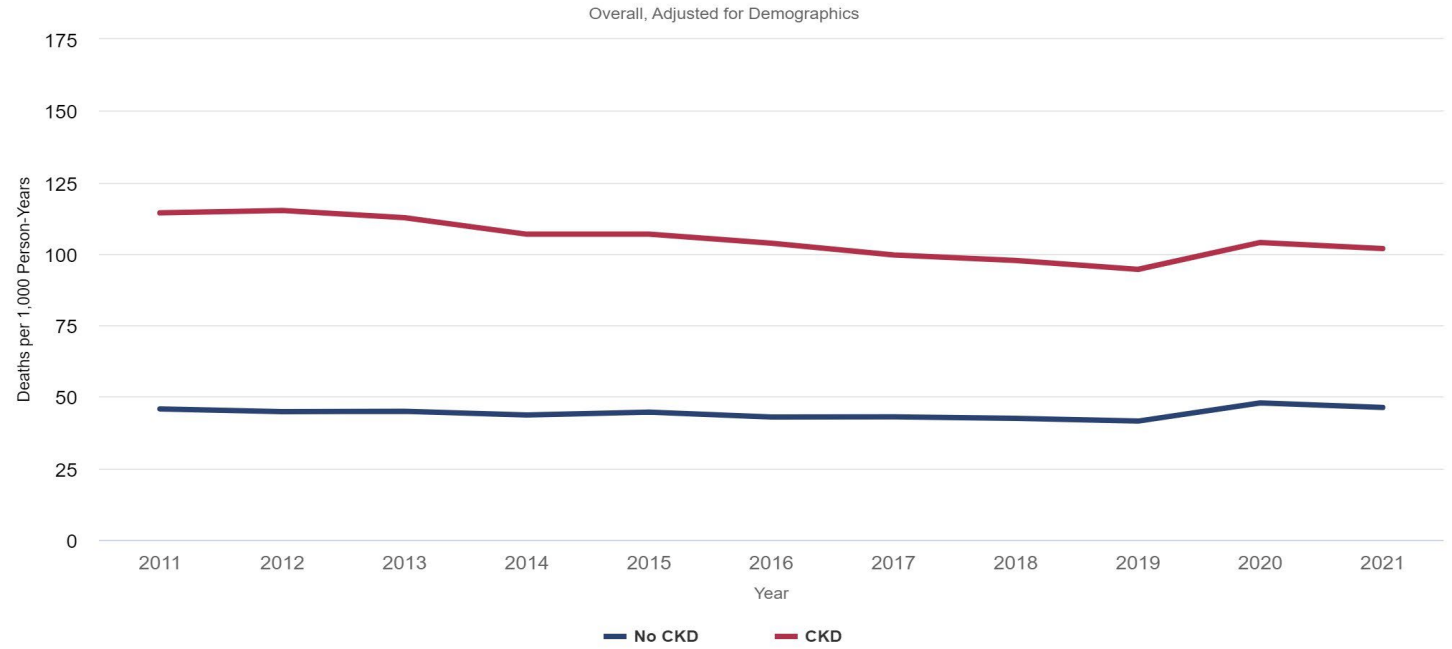


Top States	Rank	Value
Alaska	1	2.4%
South Dakota	2	2.6%
Connecticut	3	2.7%
Iowa	4	2.8%
Montana, Nebraska, Utah	5	3.0%

Bottom States	Rank	Value
Florida, Georgia, Maine, Nevada	39	4.3%
Arkansas, Delaware	43	4.4%
Alabama, Kentucky, Louisiana, Tennessee	45	4.5%
Ohio	49	4.7%
West Virginia	50	4.9%

Americashealthrankings.org/explore/measures/CKD/OK

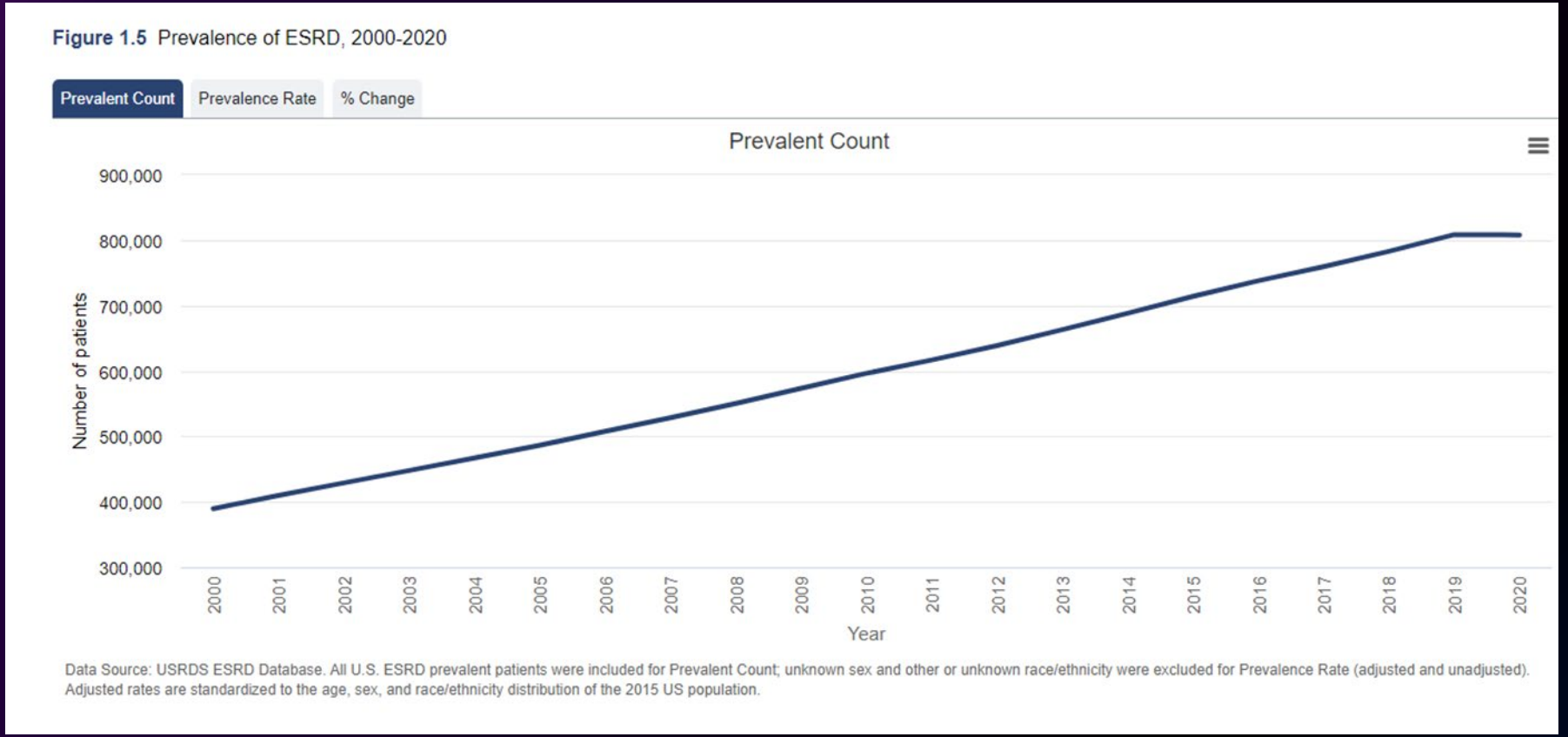
Figure 3.1a All-cause mortality rate in older adults, Medicare FFS, 2011-2021



Data Source: 2023 United States Renal Data System Annual Data Report

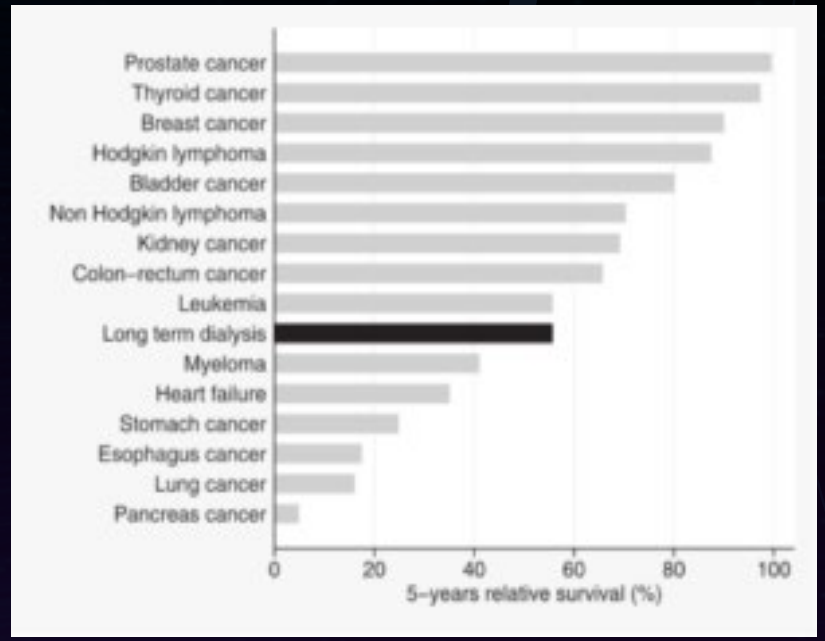
United States Renal Data System. 2023 USRDS Annual Data Report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2023.

Prevalence of ESRD

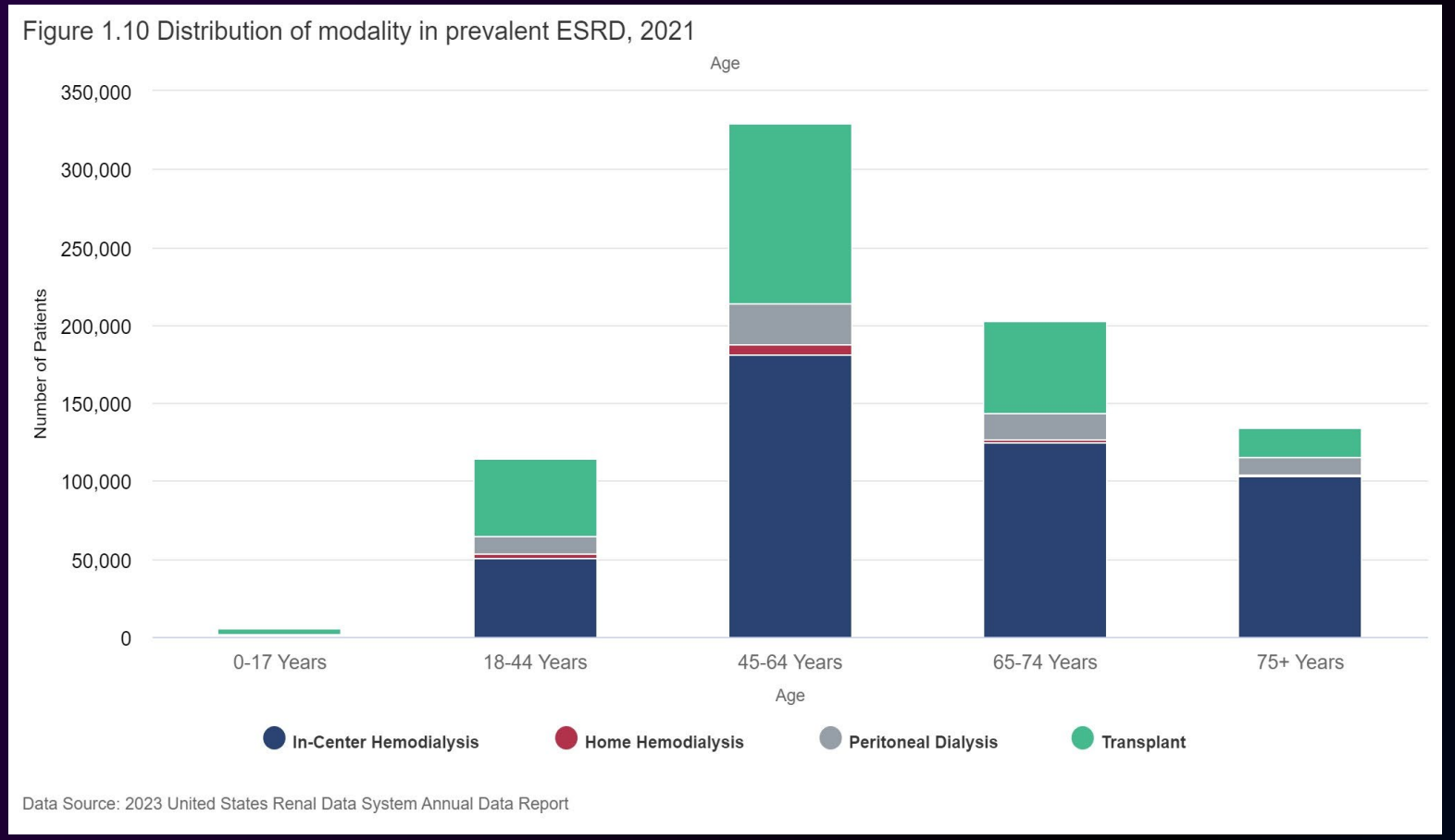


United States Renal Data System. 2023 USRDS Annual Data Report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2023.

- The adjusted survival rate for patients on HD is 57% at 3 years after onset of ESRD as compared to 68% for PD.
- The 5- year survival for patients receiving HD and PD is 42% and 52%, respectively.



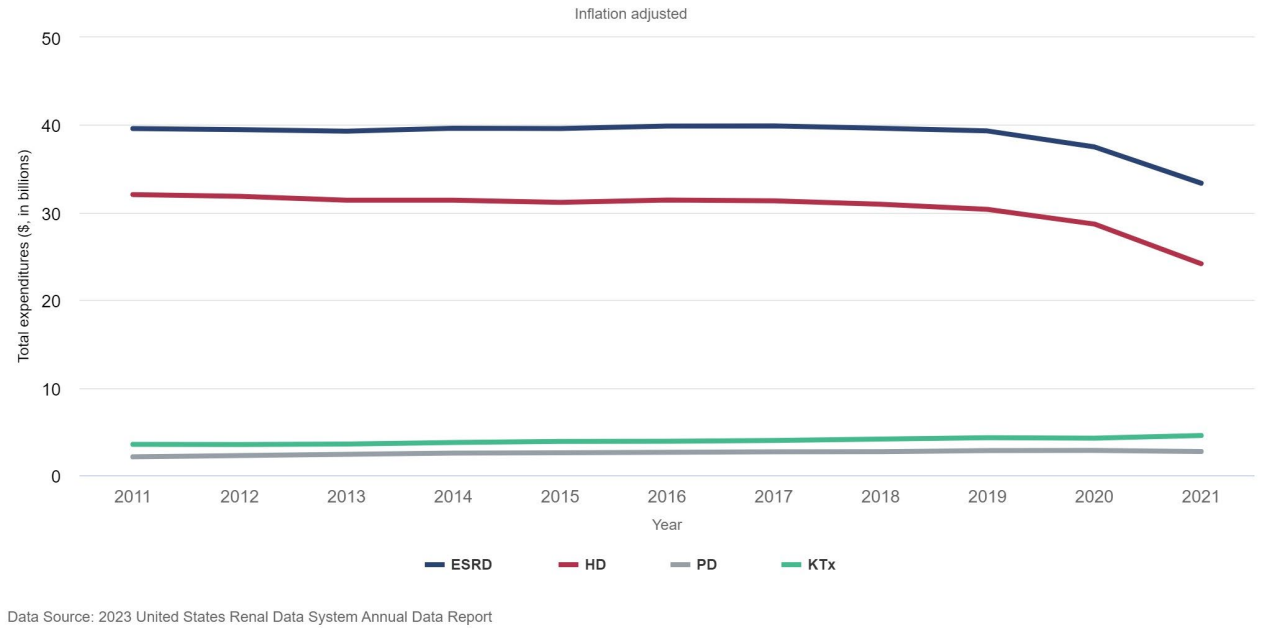
United States Renal Data System. 2023 *USRDS Annual Data Report: Epidemiology of kidney disease in the United States.* National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2023.



United States Renal Data System. 2023 USRDS Annual Data Report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2023.

Expenditure per modality

Figure 9.10 Total Medicare fee-for-service spending for beneficiaries with ESRD, by treatment modality, 2011-2021

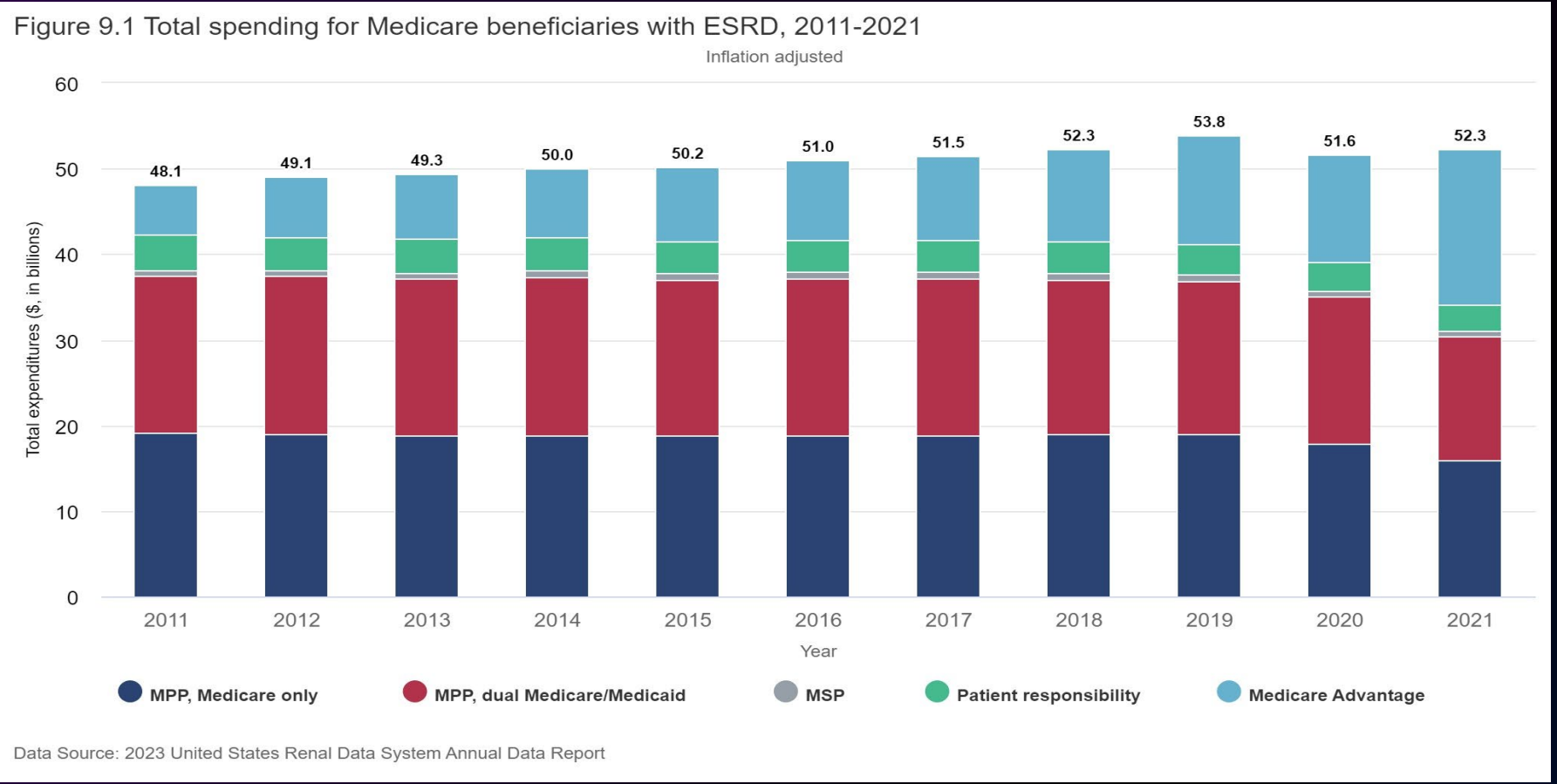


Data Source: 2023 United States Renal Data System Annual Data Report

Medicare spends more than $130 billion, or 24% of total spending, on patients with CKD.

United States Renal Data System. 2023 USRDS Annual Data Report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2023.

Expenditure for ESRD

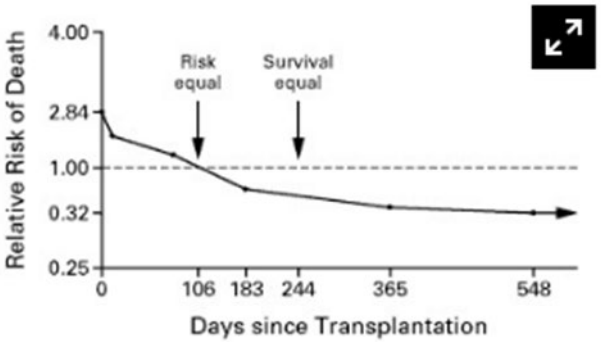


United States Renal Data System. 2023 USRDS Annual Data Report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2023.

ORIGINAL ARTICLE

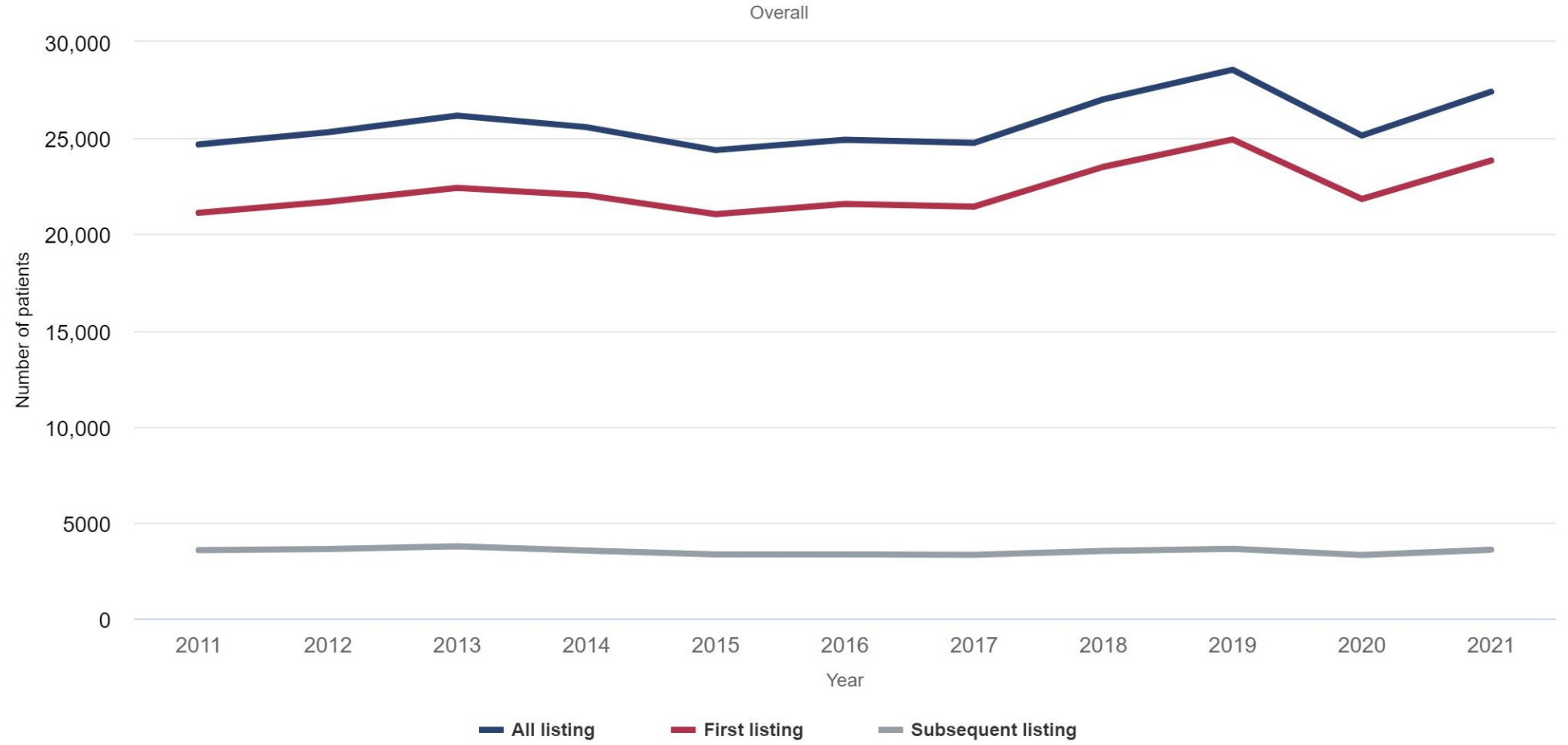
Comparison of Mortality in All Patients on Dialysis, Patients on Dialysis Awaiting Transplantation, and Recipients of a First Cadaveric Transplant

Robert A. Wolfe, Ph.D., Valarie B. Ashby, M.A., Edgar L. Milford, M.D., Akinlolu O. Ojo, M.D., Ph.D., Robert E. Ettenger, M.D., Lawrence Y.C. Agodoa, M.D., Philip J. Held, Ph.D., and Friedrich K. Port, M.D.

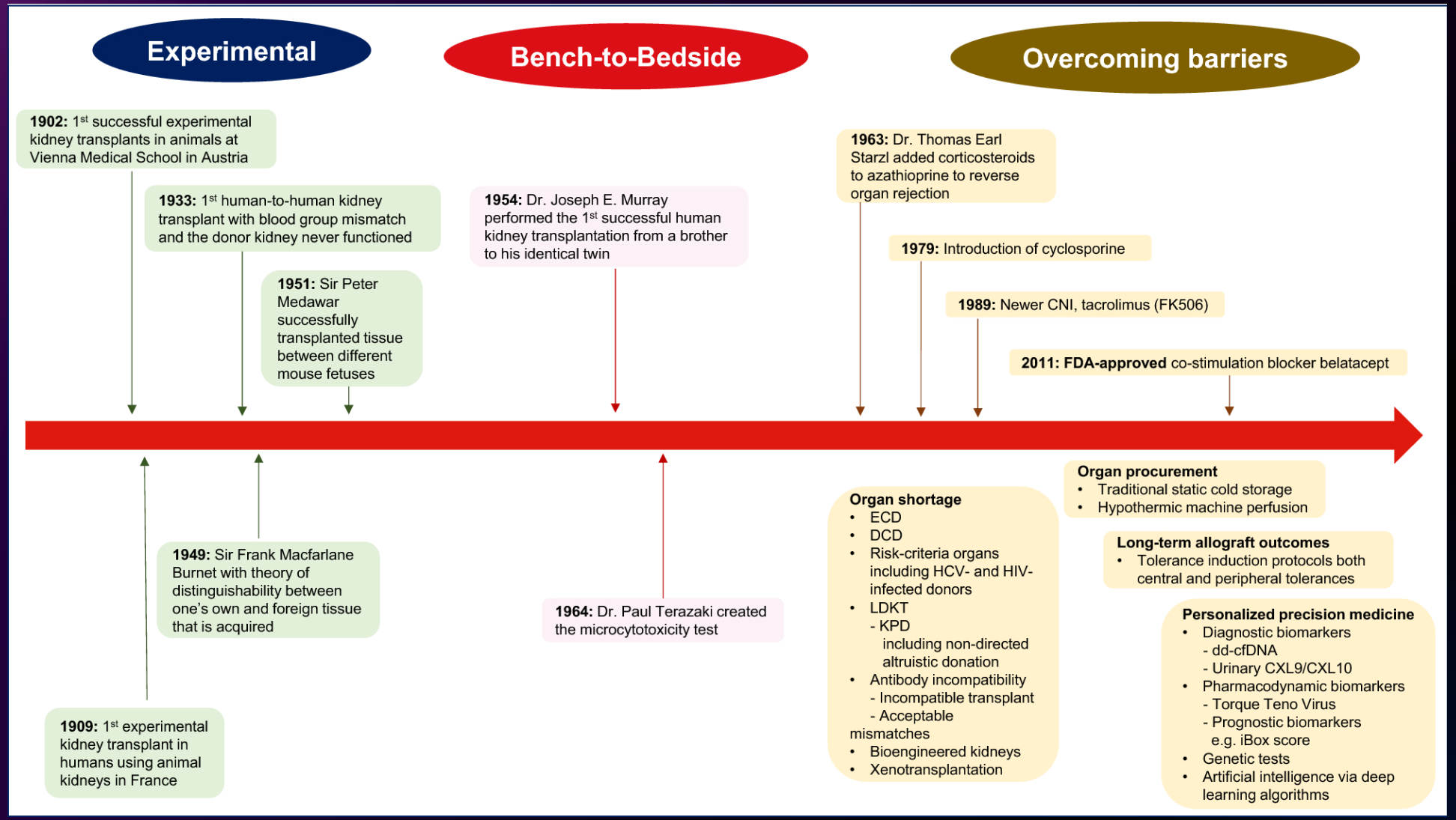


Adjusted Relative Risk of Death among 23,275 Recipients of a First Cadaveric Transplant.

Figure 7.1 Number of ESRD patients added to the waitlist for a kidney transplant, 2011-2021



Data Source: 2023 United States Renal Data System Annual Data Report


Experimental
Bench-to-Bedside
Overcoming barriers
1902: 1st successful experimental kidney transplants in animals at Vienna Medical School in Austria
1933: 1st human-to-human kidney transplant with blood group mismatch and the donor kidney never functioned
1951: Sir Peter Medawar successfully transplanted tissue between different mouse fetuses
1954: Dr. Joseph E. Murray performed the 1st successful human kidney transplantation from a brother to his identical twin
1963: Dr. Thomas Earl Starzl added corticosteroids to azathioprine to reverse organ rejection
1979: Introduction of cyclosporine
1989: Newer CNI, tacrolimus (FK506)
2011: FDA-approved co-stimulation blocker belatacept
1909: 1st experimental kidney transplant in humans using animal kidneys in France
1949: Sir Frank Macfarlane Burnet with theory of distinguishability between one's own and foreign tissue that is acquired
1964: Dr. Paul Terazaki created the microcytotoxicity test
Organ shortage
• ECD
• DCD
• Risk-criteria organs including HCV- and HIV-infected donors
• LDKT
- KPD
including non-directed altruistic donation
• Antibody incompatibility
- Incompatible transplant
- Acceptable mismatches
• Bioengineered kidneys
• Xenotransplantation
Organ procurement
• Traditional static cold storage
• Hypothermic machine perfusion
Long-term allograft outcomes
• Tolerance induction protocols both central and peripheral tolerances
Personalized precision medicine
• Diagnostic biomarkers
- dd-cfDNA
- Urinary CXL9/CXL10
• Pharmacodynamic biomarkers
- Torque Teno Virus
- Prognostic biomarkers e.g. iBox score
• Genetic tests
• Artificial intelligence via deep learning algorithms

Patient Selection

Early referral is essential to optimizing planning and outcomes. The evaluation is aimed at maximizing short- and long-term survival and assessing the impact on quality of life.

- Patients without major contraindications should ideally be referred when they approach stage 4 CKD (GFR < 30 mL/min).
- They cannot accrue time on the waitlist until GFR ≤ 20 mL/min.

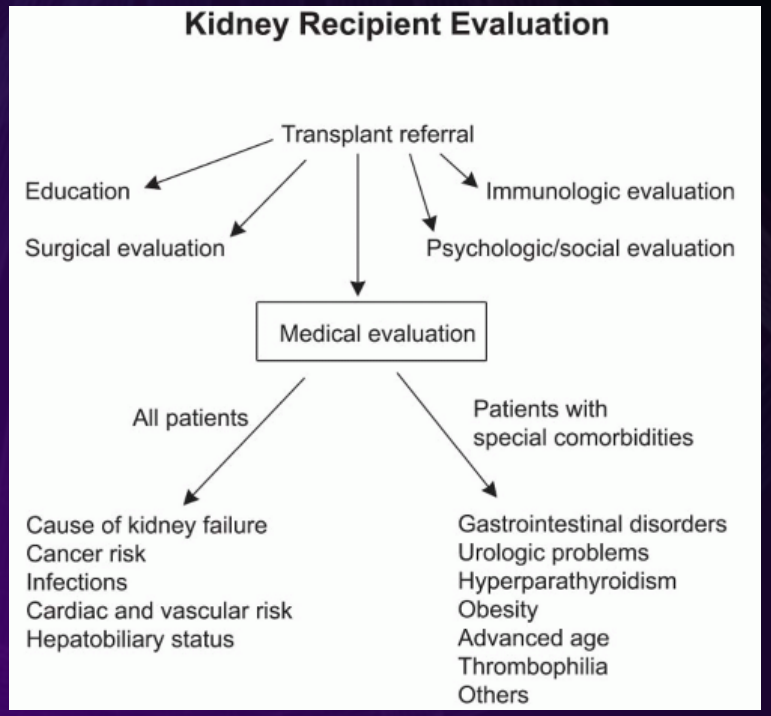
Absolute Contraindications

- Recent or metastatic malignancy
- Untreated current infection
- Severe irreversible extrarenal disease
- Recalcitrant treatment nonadherence
- Psychiatric illness impairing consent and adherence
- Current recreational drug use
- Aggressive recurrent native kidney disease
- Limited, irreversible rehabilitative potential
- Primary oxalosis
- Uncorrectable chronic hypotension

Relative Contraindications

- Morbid Obesity
- Advanced age
- History of multiple myeloma or plasma cell dyscrasia
- Recent balloon angioplasty and/or stent placement

The Evaluation Process



Thorough history and physical as with any patient encounter.

www.abdominalkey.com/recipient-evaluation/

The Evaluation Process

- CBC
- CMP
- PT/INR
- UA with culture
- Hepatitis serology
- HIV
- CMV/EBV serology (TORCH panel)
- RPR
- Type and screen
- PSA (age appropriate)
- Urine toxicology
- Chest Xray
- Coccidioides if from endemic region
- Hypercoagulability panel in selected cases
- PPD or interferon-γ release assay in selected cases
- Age-appropriate pap smear and mammogram

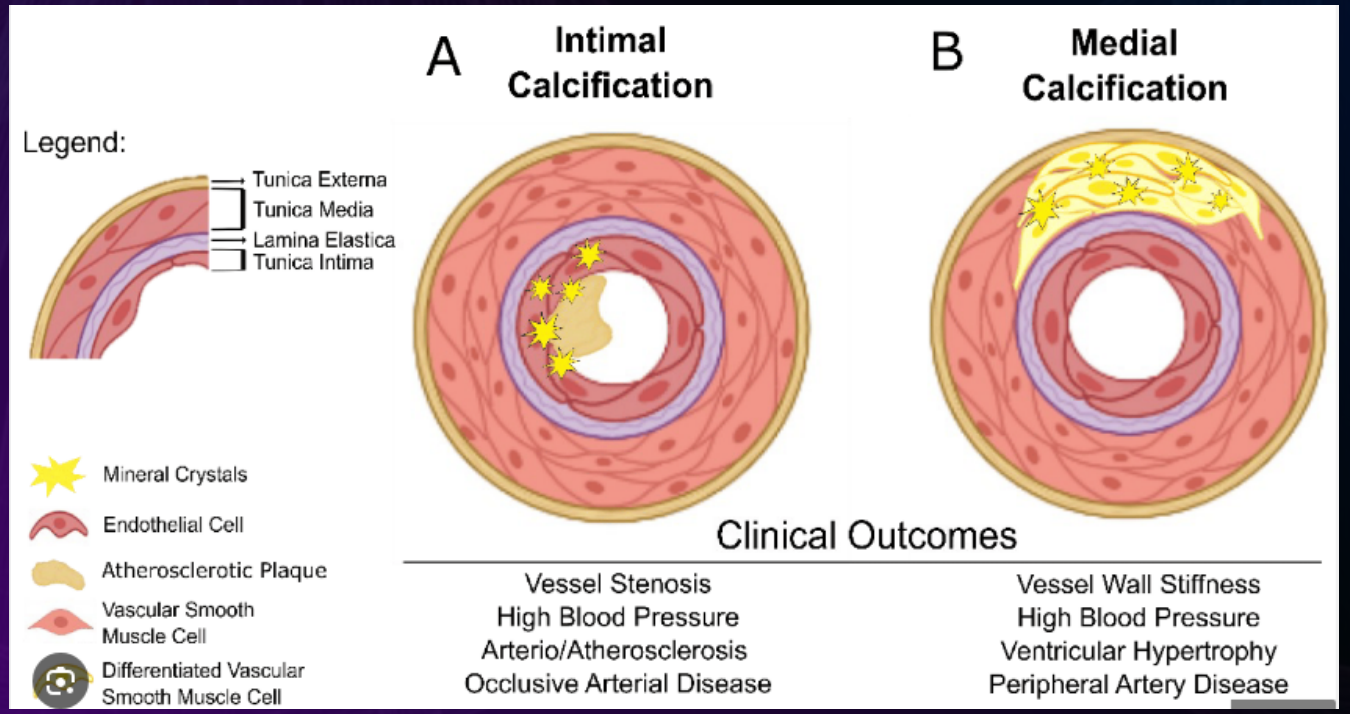
Colon Cancer Screening

For "average-risk" individuals (no family history of colorectal cancer and no risk factors listed in the right column)	For "increased-risk" individuals (defined below)

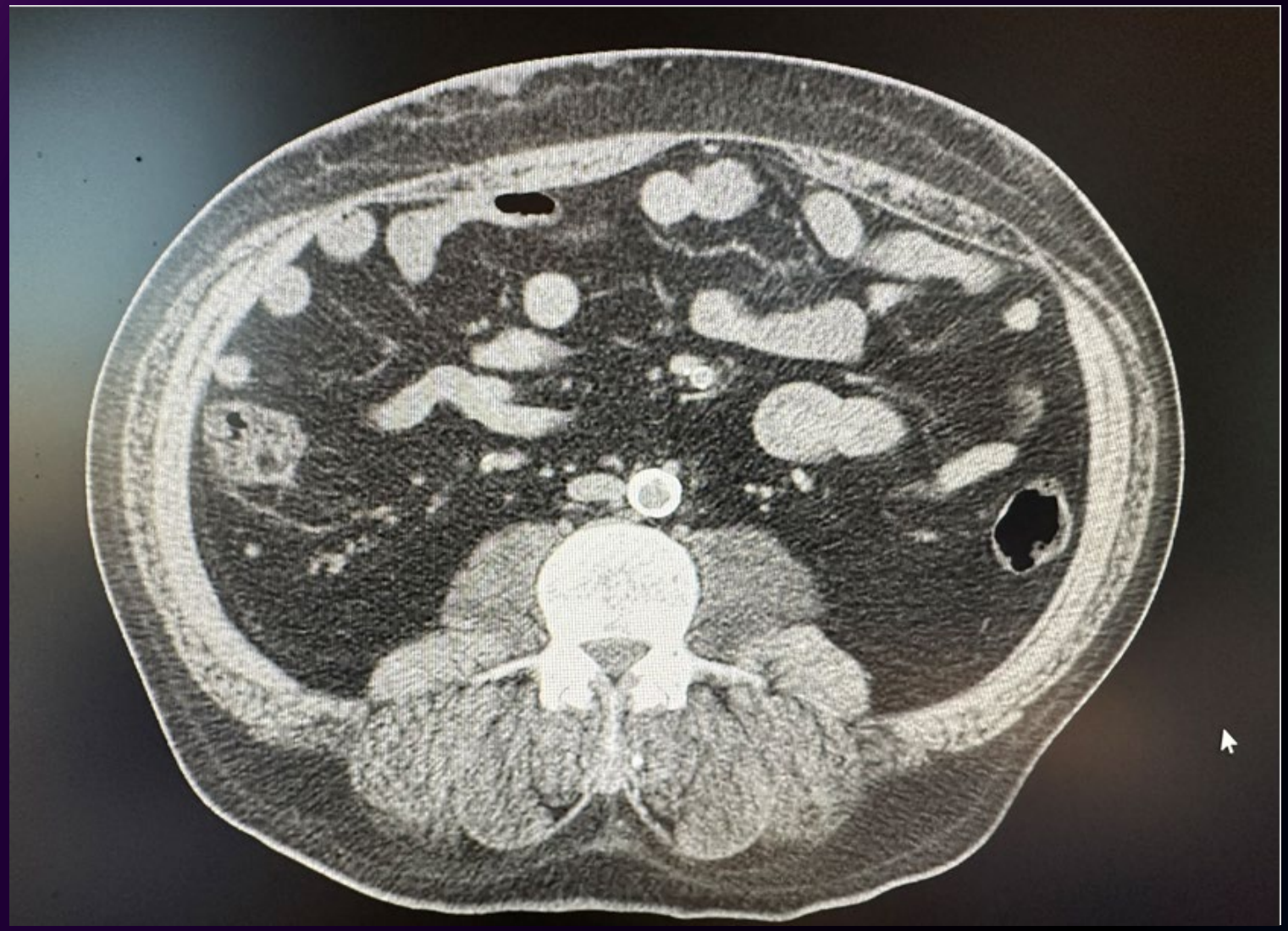
• Most individuals: Screening begins at age 50 y.
• African Americans: Screening begins at age 45 y.
• Repeat colonoscopy every 10 y if no polyps are found.
• Comorbid conditions present (diabetes, obesity, significant smoking, or alcohol use): Consider repeat colonoscopy prior to transplant if >5 y have elapsed.
• Patients with a current colonoscopy in the past 10 y may proceed with transplant if preparation was considered high quality by the endoscopist; otherwise, repeat colonoscopy should be considered.
	Family history of colon cancer in first-degree relative, 60 y at diagnosis
	• Screening begins 10 y prior to the family member's age at diagnosis or age 40 y whichever comes first.
	• If no polyps found: Repeat colonoscopy every 5 y.
	Family history of colon cancer in first-degree relative .60 y at diagnosis
	• Screening begins at age 50 y.
	• If no polyps found: Repeat colonoscopy every 10 y.
	• Comorbid conditions present (DM, obesity, significant smoking, or alcohol use): Consider colonoscopy 10 y prior to the family member's age at diagnosis or 40 y whichever comes first.
	History of abdominal radiation (.30 Gy)
	• Screening begins 10 y after radiation exposure or age 35 y whichever comes first.
	• If no polyps found: Repeat colonoscopy every 10 y.
	Inflammatory bowel disease (IBD) without primary sclerosing cholangitis
	• Screening begins 8 y after IBD diagnosis (ulcerative colitis and Crohn colitis).
	• Random biopsies should be taken.
	• Repeat colonoscopy every 1-2 y.
	Primary sclerosing cholangitis (PSC)
	• Screening begins at PSC diagnosis.
	• Random biopsies to evaluate for subclinical IBD
	  • Biopsies show no IBD: Repeat colonoscopy every 5 y.
	  • IBD confirmed on biopsies: Repeat colonoscopy every 1-2 y.
	Familial colon cancer syndromes
	• Screening begins at various ages dependent on the syndrome.
	Cystic fibrosis
	• Consider screening at age 40 y.
	• If no polyps found: Consider repeat colonoscopy every 5 y.

Pham, Phuong-Chi, T. and Phuong-Thu T Pham. Quick Guide to Kidney Transplantation. Available from: Wolters Kluwer, Wolters Kluwer Health, 2019.

Vascular Calcification in CKD



Marreiros C, Viegas C, Simes D. Targeting a Silent Disease: Vascular Calcification in Chronic Kidney Disease. *International Journal of Molecular Sciences*. 2022; 23(24):16114. https://doi.org/10.3390/ijms232416114



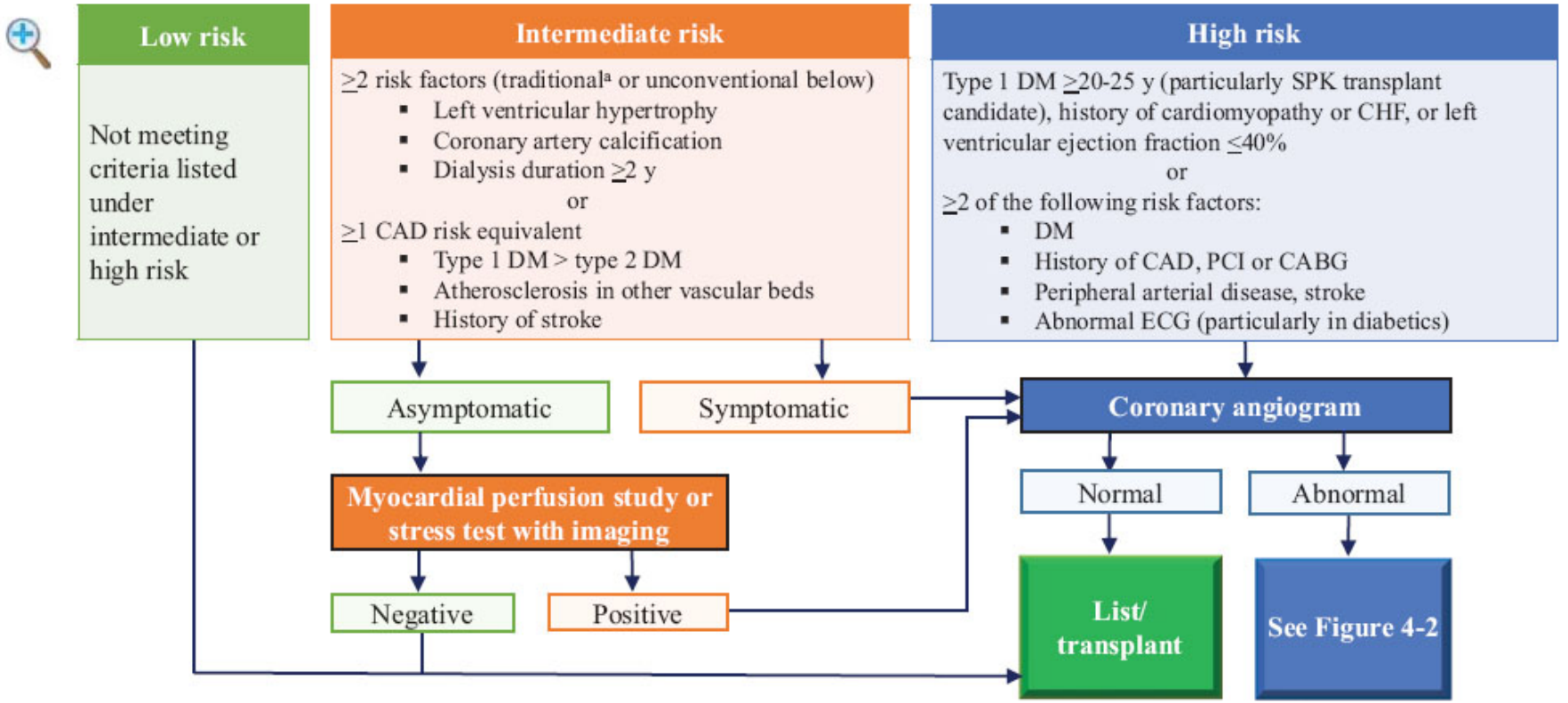
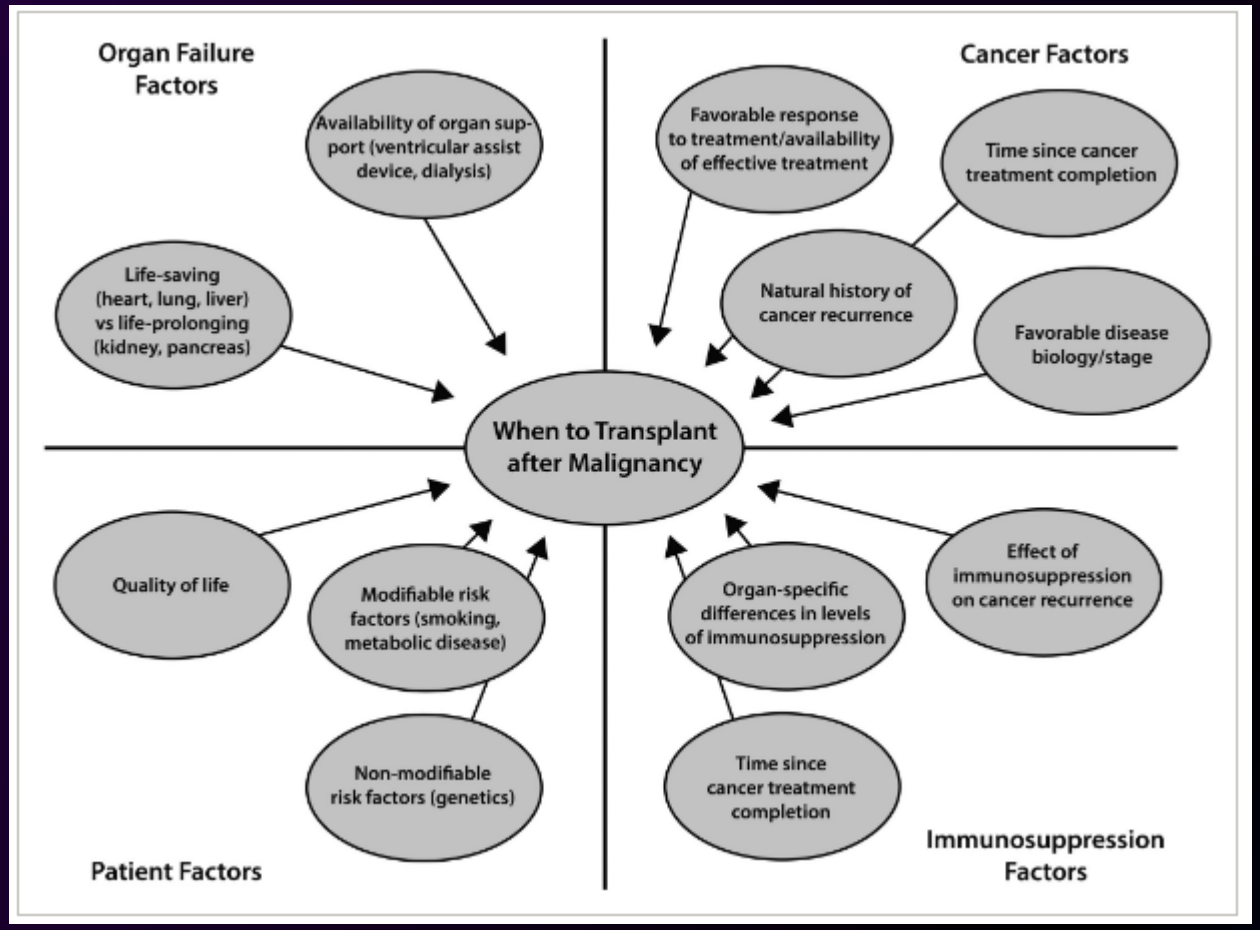


Figure 4-1 Proposed Algorithm for Initial Pretransplant Cardiac Evaluation

CABG, coronary artery bypass grafting; CAD, coronary artery disease; CHF, congestive heart failure; DM, diabetes mellitus; ECG, electrocardiogram; PCI, percutaneous coronary intervention; SPK, simultaneous pancreas kidney. [a]Traditional: hypertension, hyperlipidemia, DM, tobacco use, family history of CAD, age >45 years for male, age >55 years for female.

Pham, Phuong-Chi, T. and Phuong-Thu T Pham. Quick Guide to Kidney Transplantation. Available from: Wolters Kluwer, Wolters Kluwer Health, 2019.

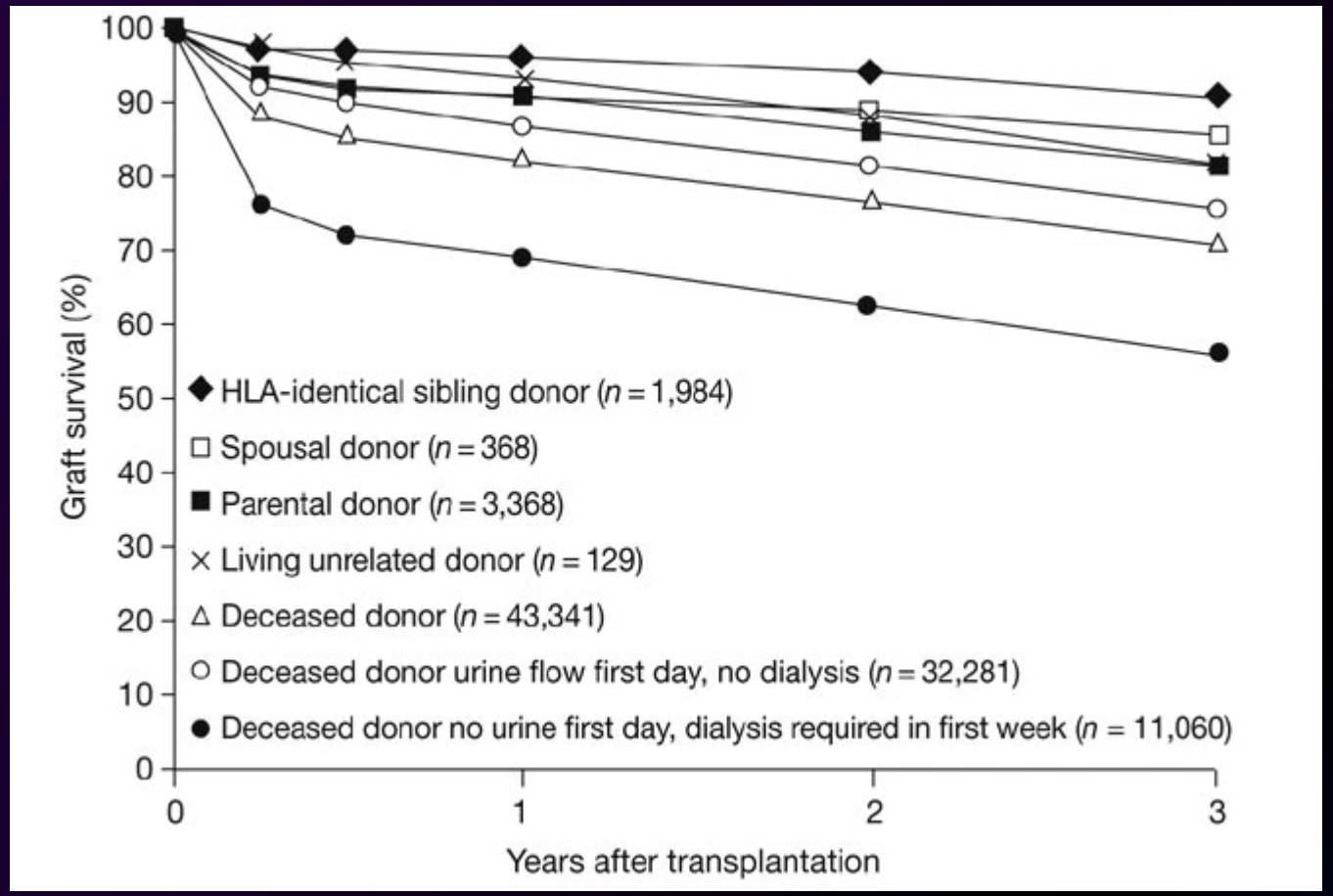

Organ Failure Factors
Availability of organ support (ventricular assist device, dialysis)
Life-saving (heart, lung, liver) vs life-prolonging (kidney, pancreas)
Cancer Factors
Favorable response to treatment/availability of effective treatment
Time since cancer treatment completion
Natural history of cancer recurrence
Favorable disease biology/stage
When to Transplant after Malignancy
Quality of life
Modifiable risk factors (smoking, metabolic disease)
Non-modifiable risk factors (genetics)
Patient Factors
Effect of immunosuppression on cancer recurrence
Organ-specific differences in levels of immunosuppression
Time since cancer treatment completion
Immunosuppression Factors

Society References

Pretransplant solid organ malignancy and organ transplant candidacy: A consensus expert opinion statement
Al-Adra, David P. et al.
American Journal of Transplantation, Volume 21, Issue 2, 460 - 474

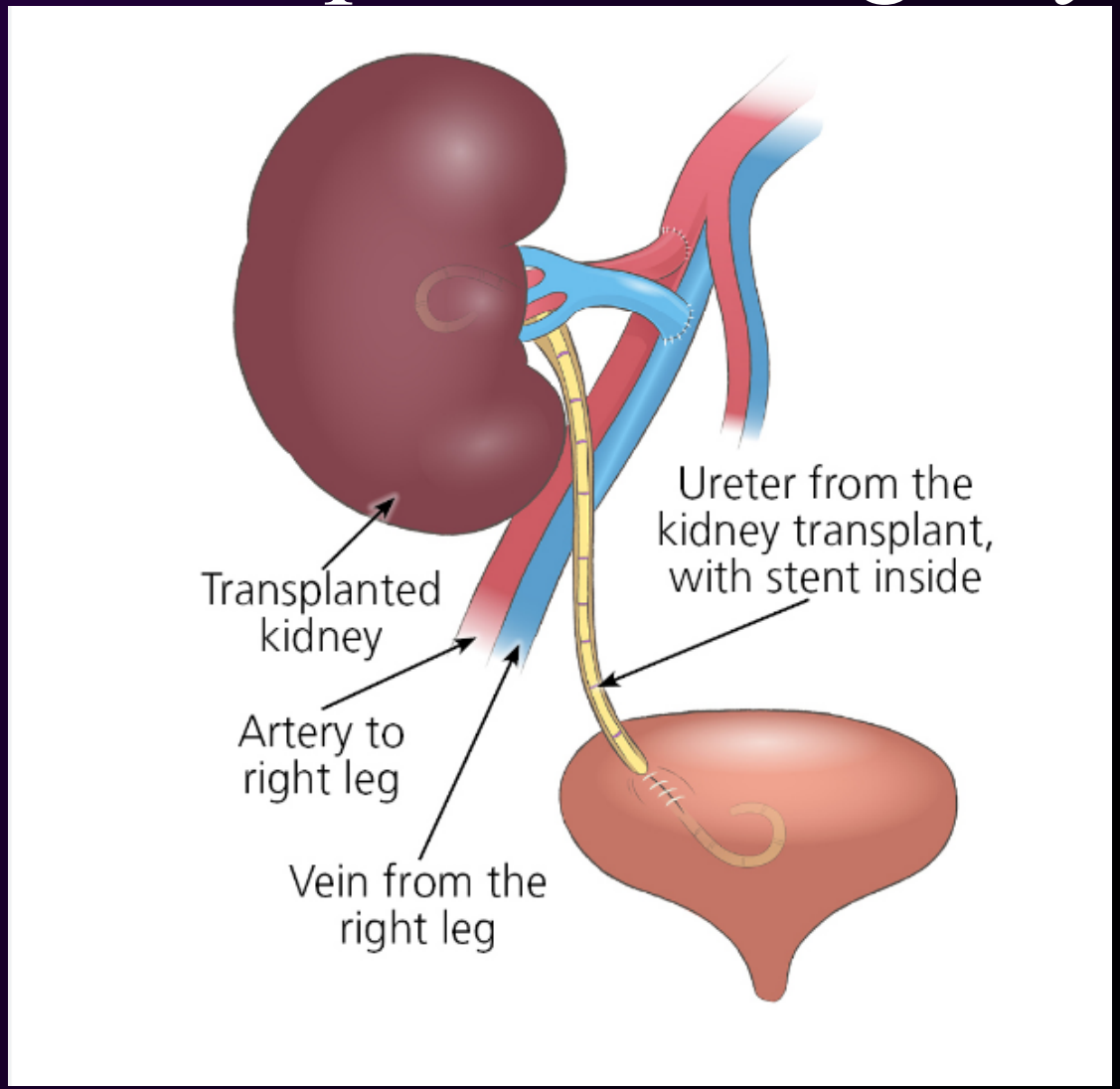
Living Kidney Donation

- Avoid dialysis completely or shorten time on dialysis
- Living kidneys last longer
- Improved patient survival
- Avoid wait associated with deceased donor kidneys
- Timing convenient for donor and recipient
- Minimal delayed organ dysfunction
- Medicines post-transplant may be less aggressive

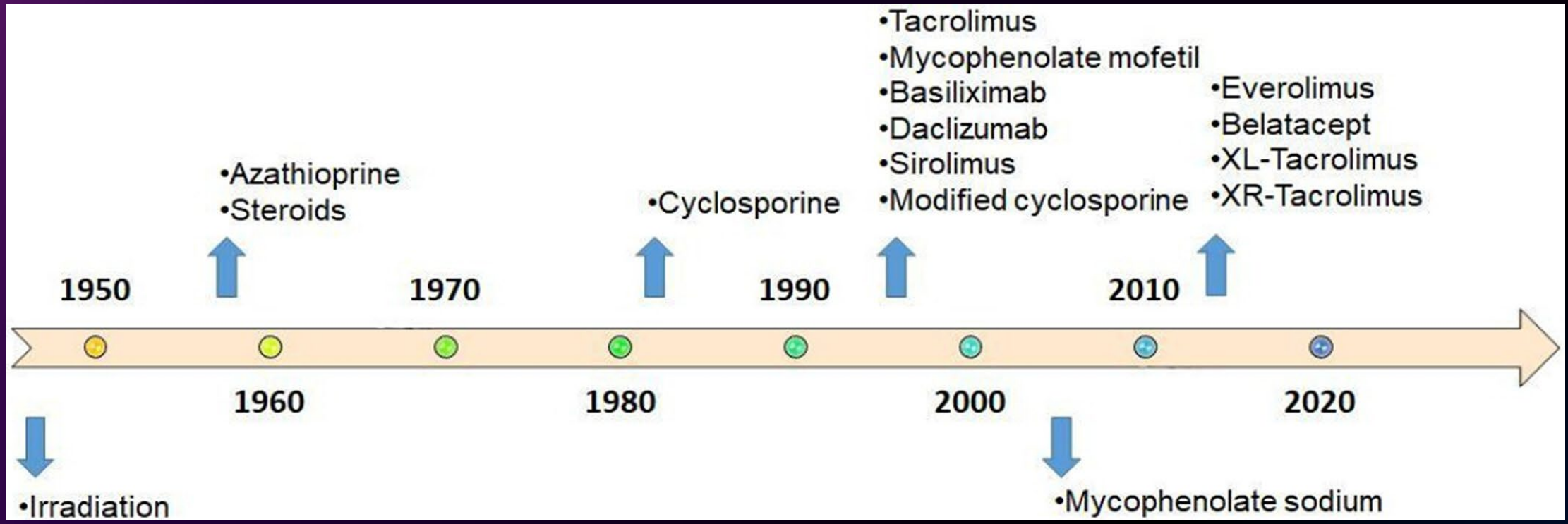


Baid-Agrawal, S., Frei, U. Living donor renal transplantation: recent developments and perspectives. Nat Rev Nephrol 3, 31–41 (2007). https://doi.org/10.1038/ncpneph0383

Transplant Surgery

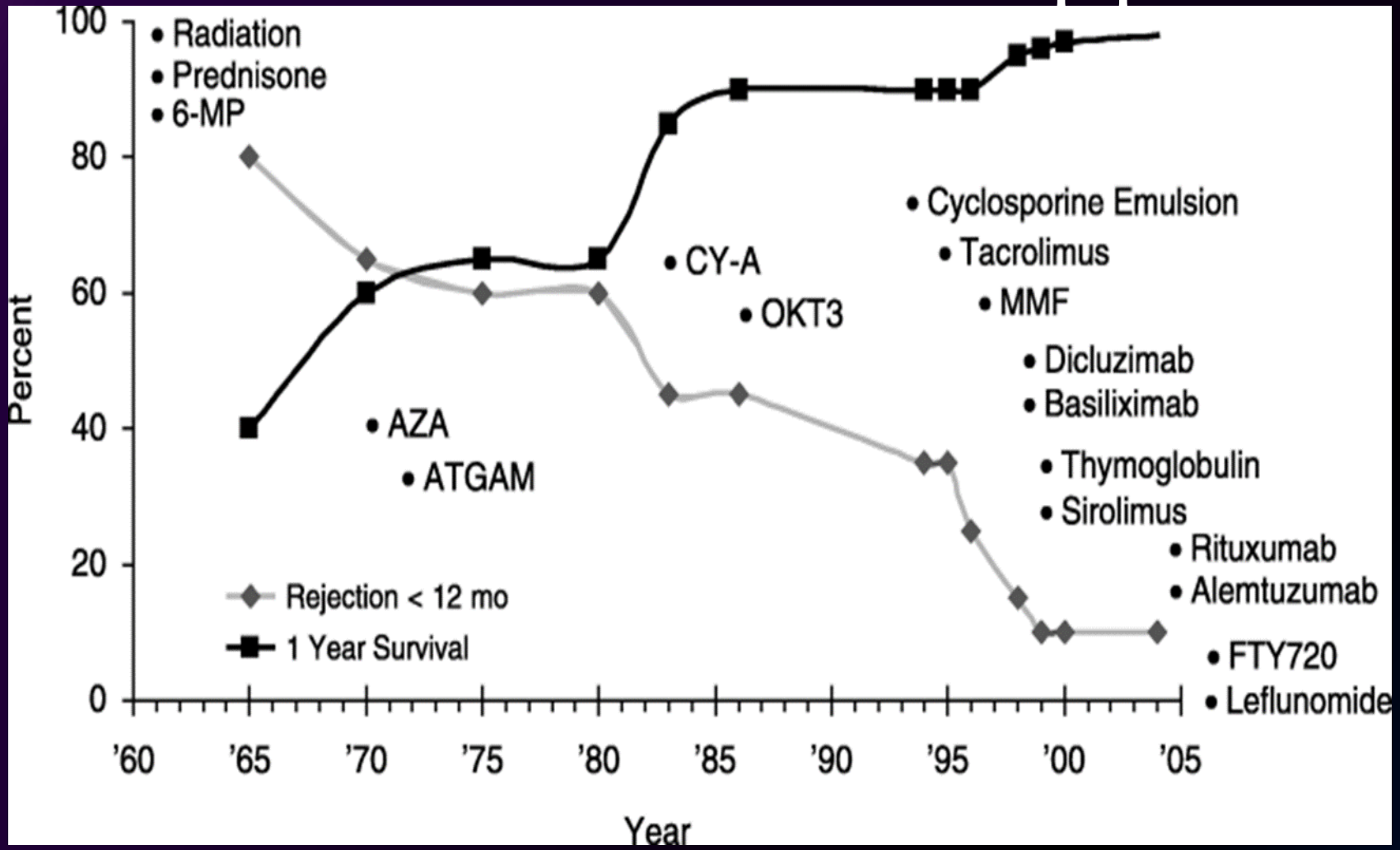


Timeline of Approval of Maintenance and Induction Therapy Agents in Solid-Organ Transplantation



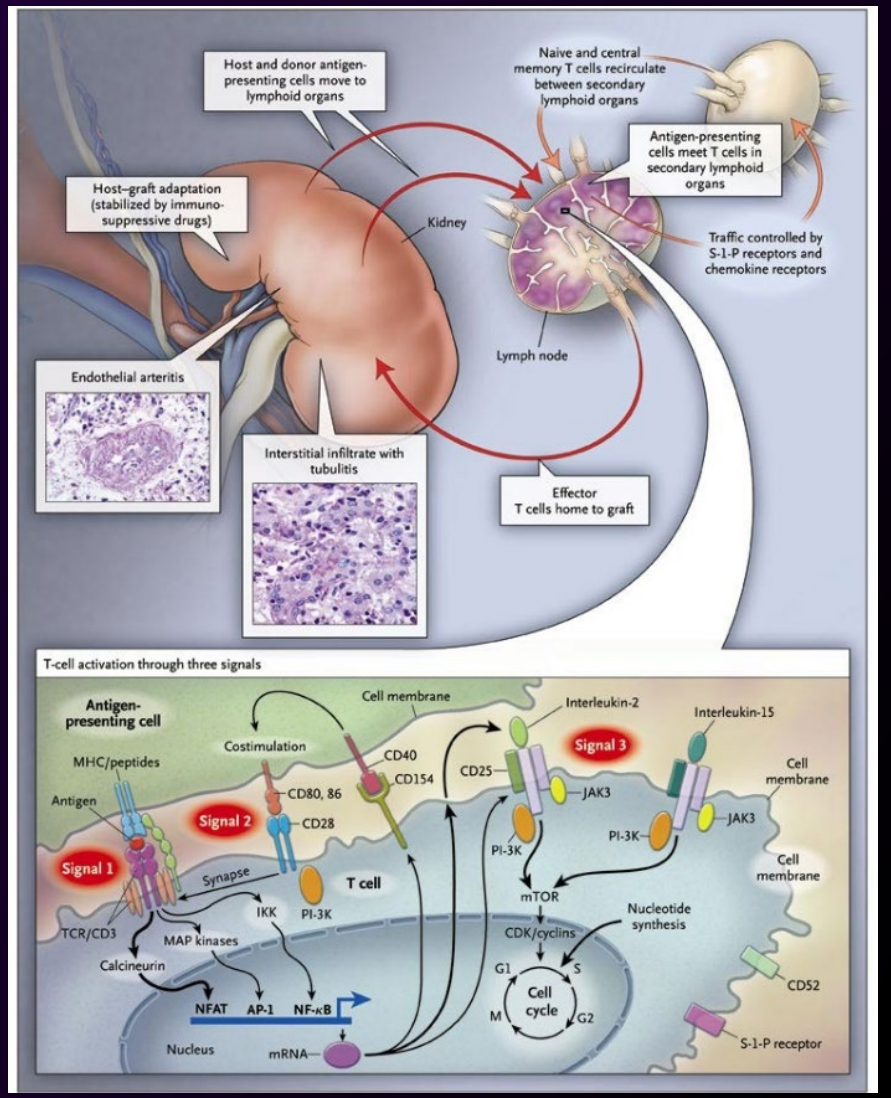
Nelson J, Alvey N, Bowman L, et al. Consensus recommendations for use of maintenance immunosuppression in solid organ transplantation: Endorsed by the American College of Clinical Pharmacy, American Society of Transplantation, and the International Society for Heart and Lung Transplantation. Pharmacotherapy. 2022;42:599-633.

Overview of immunosuppresion



Seminars in Dialysis
Volume 18, Issue 6, pages 511-519, 29 NOV 2005

Overview of Immunosuppression



Immunosuppressive drugs for kidney transplantation. N Engl J Med 2004;351:2715-2729

Approved Immunosuppressive Agents

- Induction agents
  - Lymphocyte depleting agents
    - Anti-thymocyte globulin (Thymoglobulin)
    - Alemtuzumab (Campath)
    - OKT-3
  - Non-Lymphocyte depleting agents
    - IL-2 inhibitor- Basiliximab (Simulect)
  - Glucocorticoids
- Maintenance Immunosuppression
  - Calcineurin Inhibitors
    - Cyclosporin (Neoral)
    - Tacrolimus (Prograf, Envarsus XR, Astrograf)
  - Anti-Metabolites
    - Azathioprine (Imuran)
    - Mycophenolate Mofetil (Cellcept, Myfortic)
  - mTor inhibitors
    - Sirolimus (Rapamune)
    - Everolimus (Zortress)
  - Glucocorticoids
  - Belatacept (Nulojix)
- Treatment of rejection
  - IVIG
  - Rituximab (Rituxin)
  - Bortezomib (Velcade)
  - Eculizumab (Soliris)

Corticosteroids

- Possess both immunosuppressive and anti-inflammatory properties and have been used for over half a century in various inflammatory and immune-mediated conditions.
- Multiple mechanisms of action
  - Inhibition of cytokine production
  - Reduction of adhesion molecule expression
  - Induction of lymphocyte apoptosis
  - Suppression of inflammatory cell activation
- Used for both maintenance immunosuppression as well as for treatment of acute rejection episodes.

Corticosteroids

Adverse effects

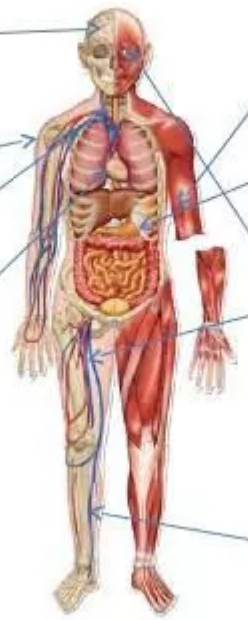
- Occur with prolonged use of high doses
- Cushing's disease

Psychiatric
- Sleep disturbance/activation
- Mood disturbance
- Psychosis

Skin/soft tissue
- Cushingoid appearance
- Abdominal striae
- Acne
- Hirsutism
- Oedema

Neurologic
- Neuropathy
- Pseudomotor cerebri

Cardiovascular
- Hypertension



MSK
- Osteoporosis
- Asceptic necrosis of bone
- Myopathy

Endocrine
- Diabetes mellitus
- Adrenal cortex suppression

Immunologic
- Lymphocytopenia
- Immunosuppression
- False-negative skin test

Opthalmic
- Cataract
- Narrow-angle glaucoma

Developmental
- Growth retardation

https://medizzy.com/feed/34908103

Corticosteroids

- Induction dose- typically Solumedrol 500 mg.
- Maintenance dose- Prednisone 5 mg daily.
- Steroid free protocol
  - Based on immunologic risk however long-term graft function and the risk of chronic rejection have not been thoroughly evaluated.
  - A 2016 Cochrane review suggests that steroid avoidance and withdrawal after transplant significantly increases the risk of acute rejection but there was no difference in patient mortality or graft loss up to 5 years post-transplant.

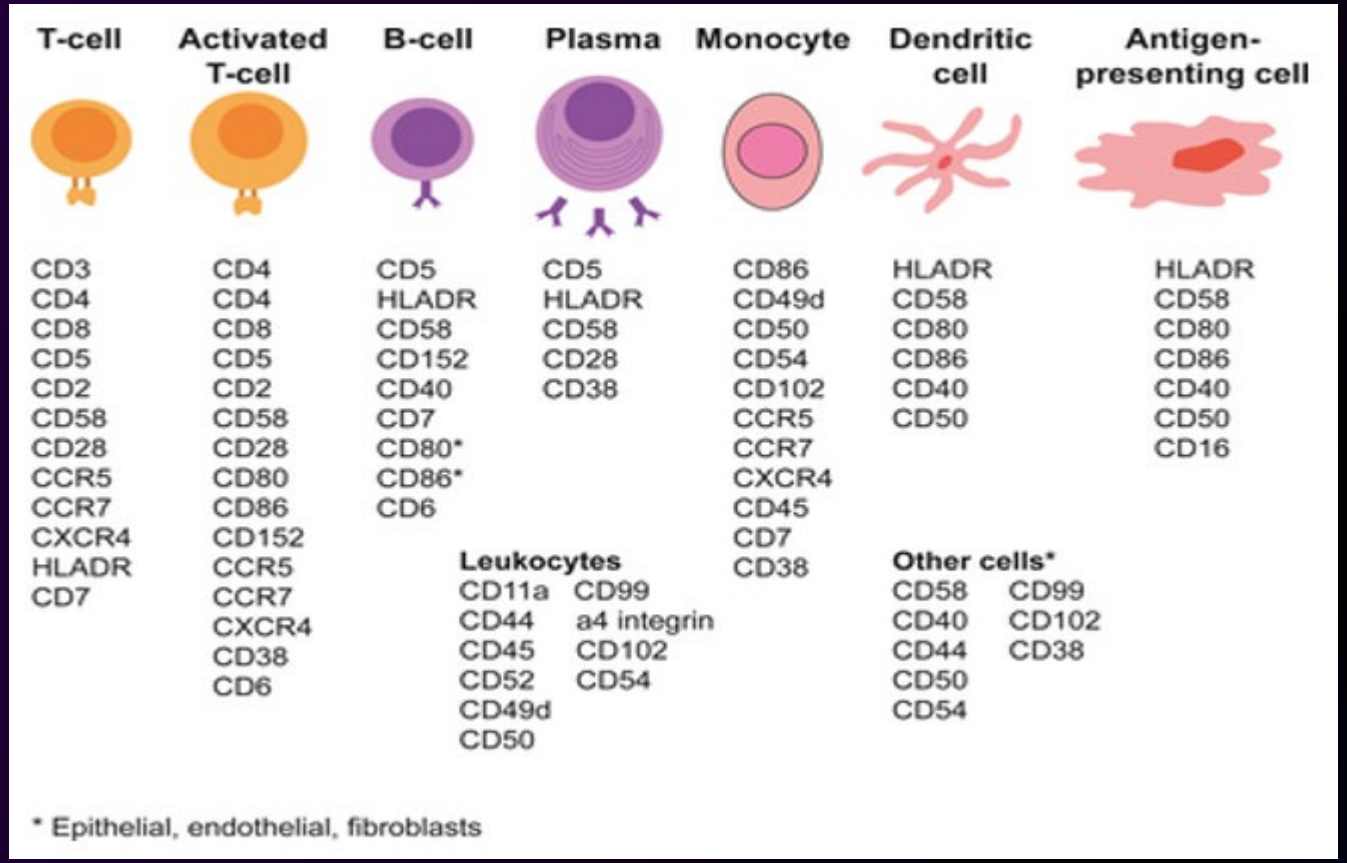
Haller MC, Royuela A, Nagler EV, Pascual J, Webster AC. Steroid avoidance or withdrawal for kidney transplant recipients. Cochrane Database of Systematic Reviews 2016, Issue 8. Art. No.: CD005632. DOI: 10.1002/14651858.CD005632.pub3. Accessed 02 March 2024.

Thymoglobulin

- Purified anti-lymphocyte polyclonal immunoglobulin used for the prevention and treatment of acute rejection
- Thymoglobulin is prepared by immunizing pathogen free rabbits with cell suspension of human thymic tissue.
- Rabbit sera is collected and immunoglobulins against thymocytes are isolated and purified to prepare rATG.
- Samples from more than 26,000 immunized rabbits are pooled to achieve a high-level batch to batch consistency.
- It contains antibodies primarily against T-cells but also against B-cells.

Am J Nephrol 2013: 586-601
World J Transplant 2012 August 24: 51-68

Specificities of anti-bodies detected in Thymoglobulin



Mourad G, Morelon E, Noël C, Glotz D, Lebranchu Y. The role of Thymoglobulin induction in kidney transplantation: an update.

Mechanism of Actioin

- Primary mechanism is T-cell depletion by binding to various cell surface markers and causing lymphocyte depletion of the peripheral blood by complement dependent cell lysis, antibody dependent cellular cytotoxicity and activation induced cell death.
- Other mechanisms still not fully understood but appear to be related to modulation and downregulation of cell surface antigens.

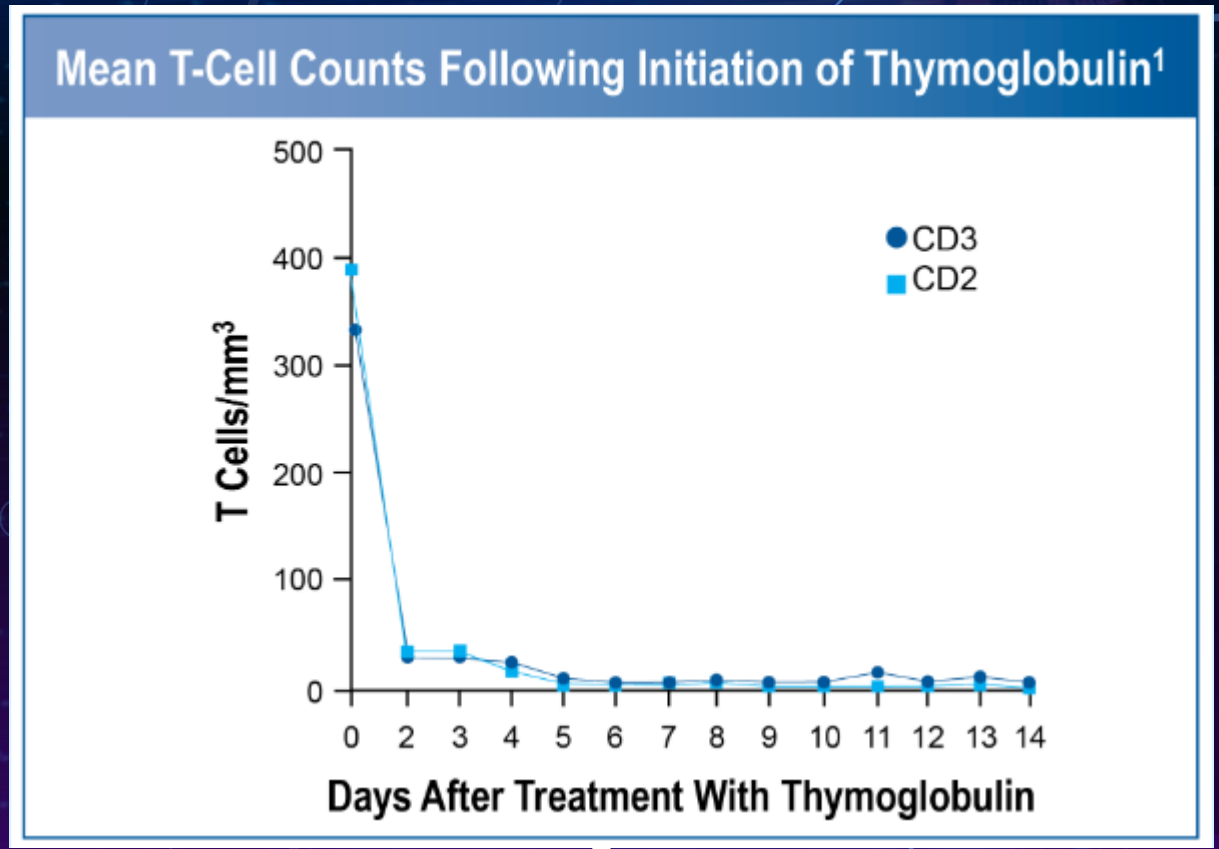
Mourad G, Morelon E, Noël C, Glotz D, Lebranchu Y. The role of Thymoglobulin induction in kidney transplantation: an update.

Thymoglobulin Effects

Rapid lymphocyte depletion.

Recovery occurs gradually with 40% of patients recovering 50% of their initial count at 3 months.

Depletes T-cells at the periphery as well as secondary lymphoid tissue.



https://www.thymoglobulin.com/about

Side Effects

- Cytokine release syndromes
  - Fever, rigors, chills,dyspnea
  - n/v/d, hypo/hypertension,
  - Rash, headache, rarely anaphylaxis
- Hematologic
  - Thrombocytopenia, anemia, leukopenia
- Anaphylaxis
  - Cardiopulmonary arrest, pulmonary edema, MI, death
- Serum Sickness
  - 5-15 days post infusion
  - Delayed immunologic reaction to non-antibody rabbit proteins
  - Presents with fever, rash, arthralgia, myalgia, lymphadenopathy
  - Treatment is with corticosteroids
- Infections
- Malignancy

https://www.thymoglobulin.com/about

Basiliximab

- Chimeric monoclonal murine/human antibody with human Ig G1 constant heavy chain and κ light chain.
- Specifically binds to the IL-2r α chain at the surface of activate T lymphocytes and blocks the CD-25 antigen.
- As the α subunit is expressed only on the activated T-cells, resting T-cells remain unaffected.
- IL-2 signaling is required for T- cell expansion and differentiation.
- Well-tolerated with minimal side effects.
- Actually, only US FDA approved drug for induction.

Kapic E, Becic F, Kusturica J. Basiliximab, mechanism of action and pharmacological properties. Med Arh. 2004;58(6):373-6. PMID: 15648237.

Side Effects

- Hypersensitivity including anaphylaxis
- Cytokine release syndrome

Choice of Induction Agent

Induction agent

No induction < Basiliximab < Alemtuzumab < Anti-thymocyte globulin

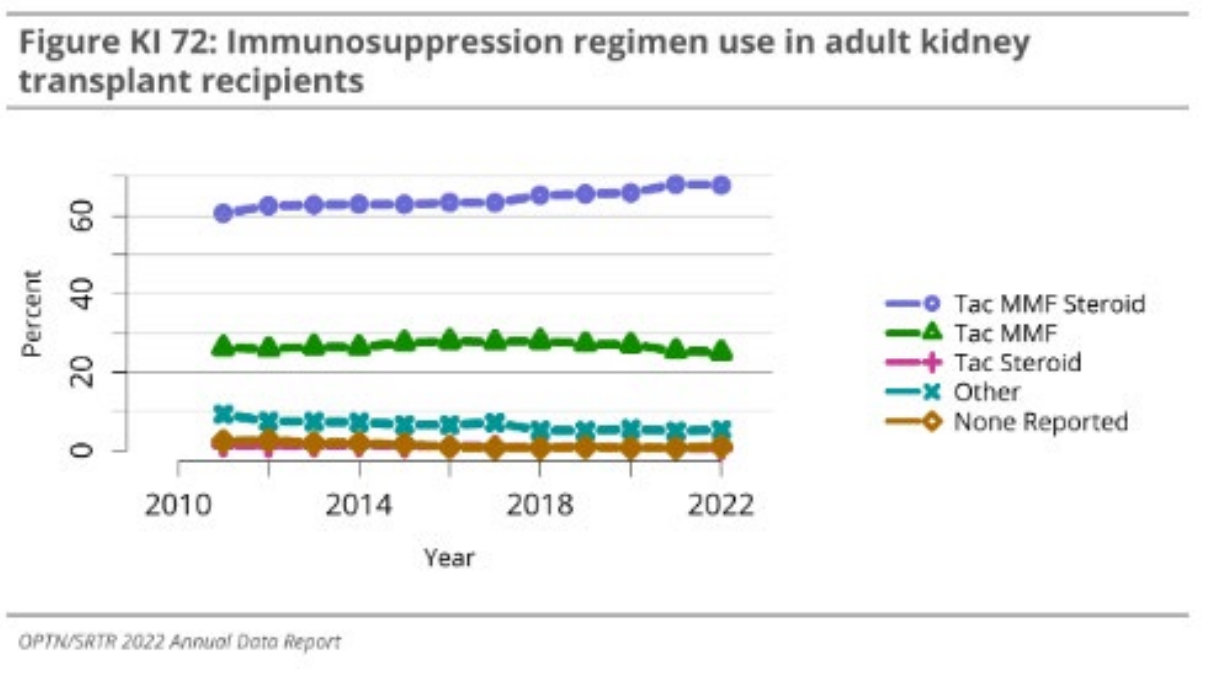
Lower risk	**Higher risk**
Zero HLA mismatch	Increased # of HLA mismatches
Live donor	Younger recipient and older donor age
Caucasian ethnicity	African-American ethnicity
Low panel reactive antibody	High panel reactive antibody
Absence of donor specific antibody	Presence of donor specific antibody
Blood group compatibility	Blood group incompatability
Immediate graft function	Delayed onset of graft function
Short cold ischemia time	Long cold ischemia time
First transplant	Retransplant

Hardinger, K.L., Brennan, D.C. and Klein, C.L. (2013), Selection of induction therapy in kidney transplantation. Transpl Int, 26: 662-672. https://doi.org/10.1111/tri.12043

Maintenance Immunosuppression

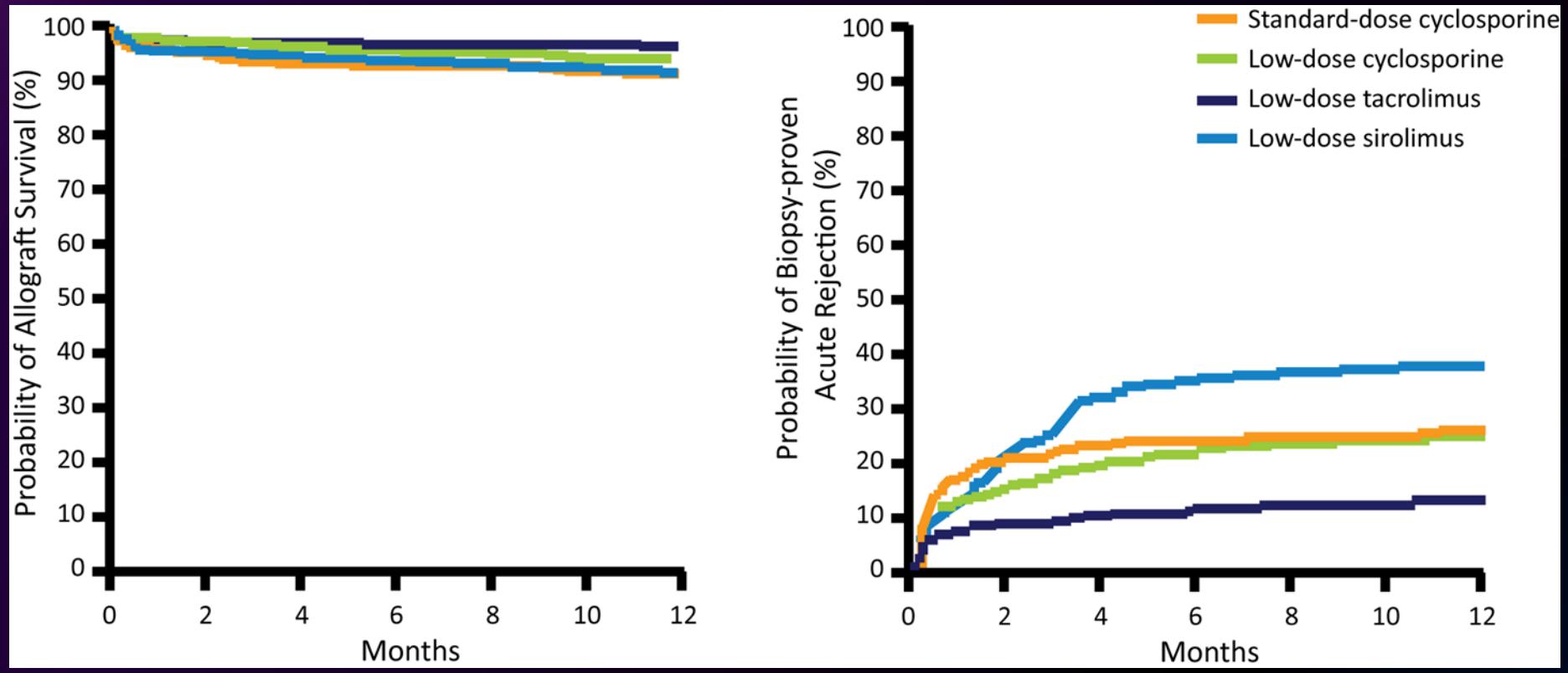
- Calcineurin Inhibitors (CNI)- (Tacrolimus/Cyclosporine)
- Anti-metabolites (Mycophenolate/Azathioprine)
- mTor inhibitors (Sirolimus/Everolimus)
- Corticosteroids
- Belatacept

Trends in Maintenance Immunosuppression



Organ Procurement and Transplantation Network (OPTN) and Scientific Registry of Transplant Recipients (SRTR). OPTN/SRTR 2022 Annual Data Report. U.S. Department of Health and Human Services, Health Resources and Services Administration; 2024. Accessed [3/3/24].

Elite Symphony Trial



SYMPHONY = Efficacy Limiting Toxicity Elimination (ELITE) SYMPHONY
Ekberg H, et al. N Engl J Med. 2007;

CNI's

- Cyclosporine binds to intracellular cyclophilin and forms a complex that inhibits calcineurin phosphatase.
- Tacrolimus binds to FK506 binding protein to form a complex that inhibits calcineurin phosphatase.
- Inhibition of calcineurin phosphatase blocks the migration of nuclear factor of activated T-cells (NFAT) from the cytoplasm to the nucleus and inhibits cytokine formation.

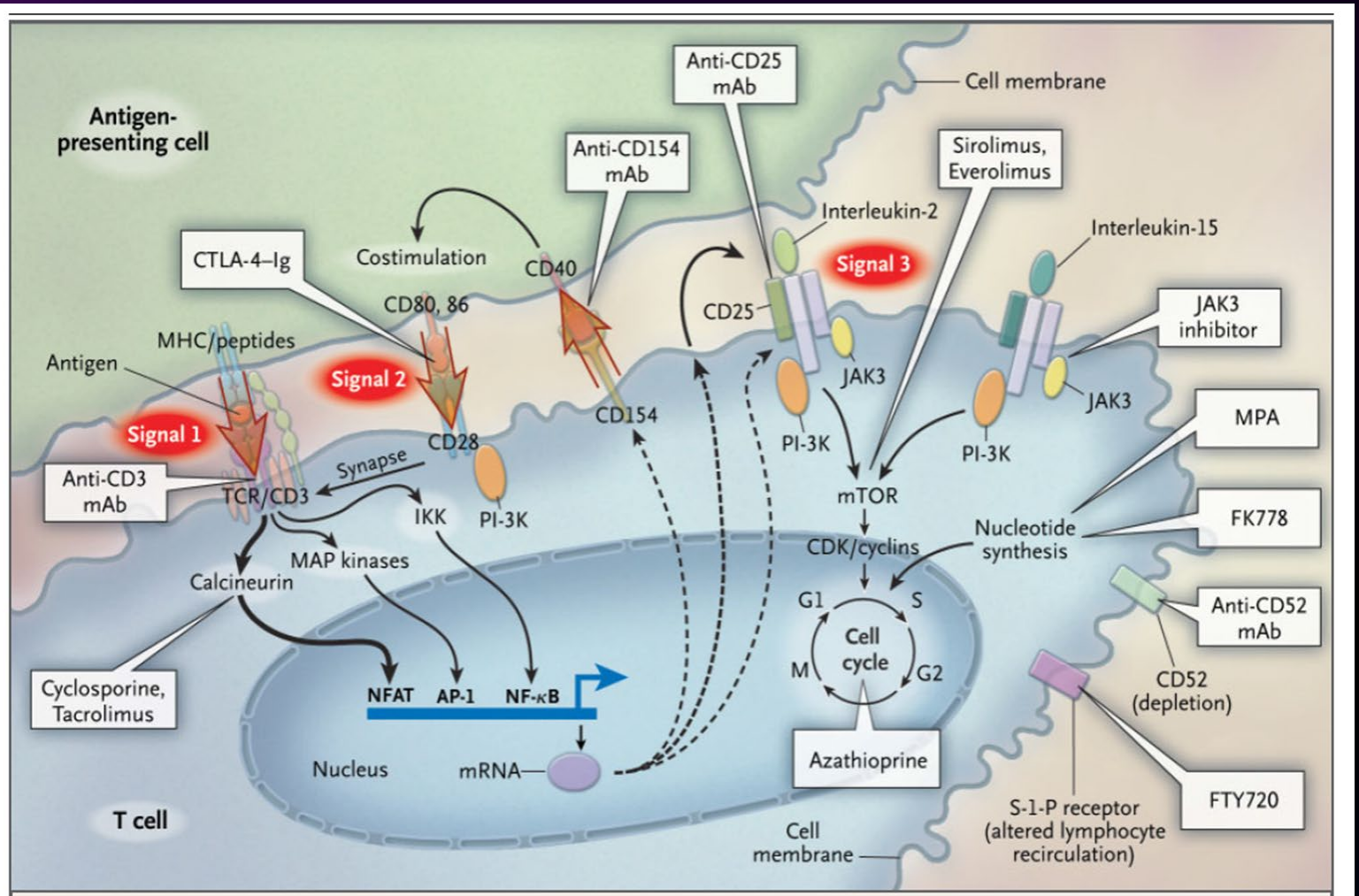


Figure 2. Individual Immunosuppressive Drugs and Sites of Action in the Three-Signal Model.

Anti-CD154 antibody has been withdrawn from clinical trials but remains of interest. FTY720 engagement of sphingosine-1-phosphate (S-1-P) receptors triggers and internalizes the receptors and alters lymphocyte recirculation, causing lymphopenia. Antagonists of chemokine receptors (not shown) are also being developed in preclinical models. MPA denotes mycophenolic acid.

Immunosuppressive drugs for kidney transplantation. N Engl J Med 2004;351:2715-2729

CNI Adverse Reactions

Tacrolimus (vs cyclosporine)
Greater immunosuppressive effects
Association with the glucocorticoid receptor
Lower levels of antibodies production
Inhibition of IL-2, IL-5 and IL-7
Inhibition of primed T-cells
Potentiation of apoptosis
Suppression of IL-10 and IL-10-mediated cytotoxic cell infiltration
Less nephrotoxicity
Not associated with increased TGF-ß production
Decreased TGF-ß type 1 receptor expression

Table 1.2 Major side effects of the calcineurin inhibitors cyclosporine and tacrolimus.

Side effects	Tacrolimus	Cyclosporine
Nephrotoxicity	↑	↑↑
Hypertension	↑	↑↑
Post-transplant diabetes mellitus	↑↑	↑
Hyperlipidemia	-	↑↑
Neurotoxicity	↑↑	↑
Hirsutism	-	↑↑
Gingival hyperplasia	-	↑↑

↑↑ large increase, ↑ small increase, - no increase

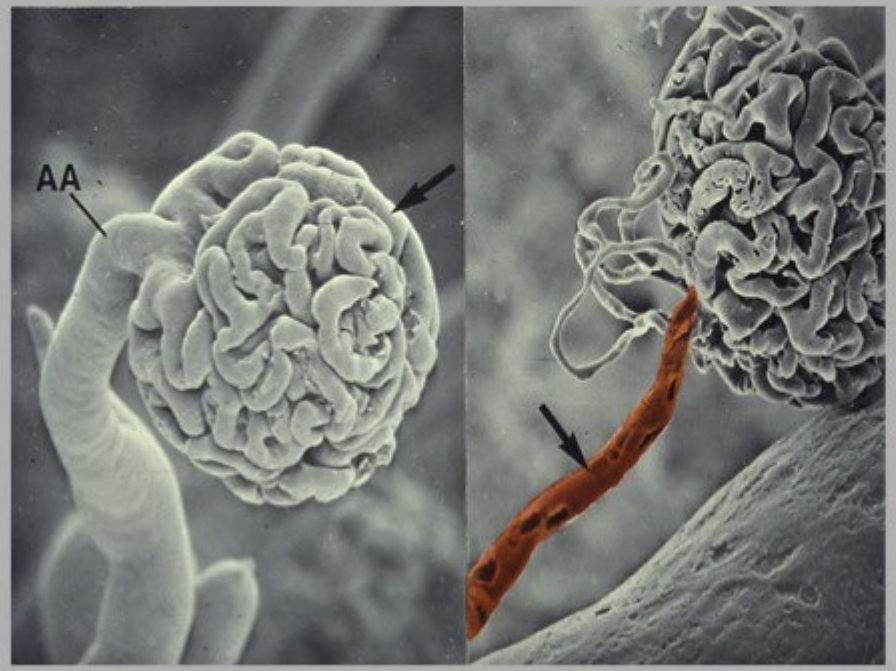
1 Mechanistic differences between tacrolimus and cyclosporine.

TMA-not systemic.

Cheung, Chi Yuen & Wong, Kim & Chan, Hoi & Liu, Allen Yan Lun & Chan, Yiu & Wong, Ho & Chak, Wai-Leung & Choi, Koon & Chau, Ka & Li, Chun. (2006). Paired kidney analysis of tacrolimus and cyclosporine microemulsion-based therapy in Chinese cadaveric renal transplant recipients. Transplant international : official journal of the European Society for Organ Transplantation. 19. 657-66. 10.1111/j.1432-2277.2006.00335.x.

Calcineurin Inhibitors

CIN: Vascular type functional form



Normal afferent arteriole and glomerulus of a rat (left), after CI treatment (right).

Note massive vasoconstriction and glomerular collapse.

English J, Evan A, Houghton DC, Bennett WM. Cyclosporine-induced acute renal dysfunction in the rat. Evidence of arteriolar vasoconstriction with preservation of tubular function. Transplantation. 1987 Jul;44(1):135-41. doi: 10.1097/00007890-198707000-00027. PMID: 3603674.

Drug Interactions

Metabolized extensively by the cytochrome P450 3A4 and 3A5 enzyme pathways.

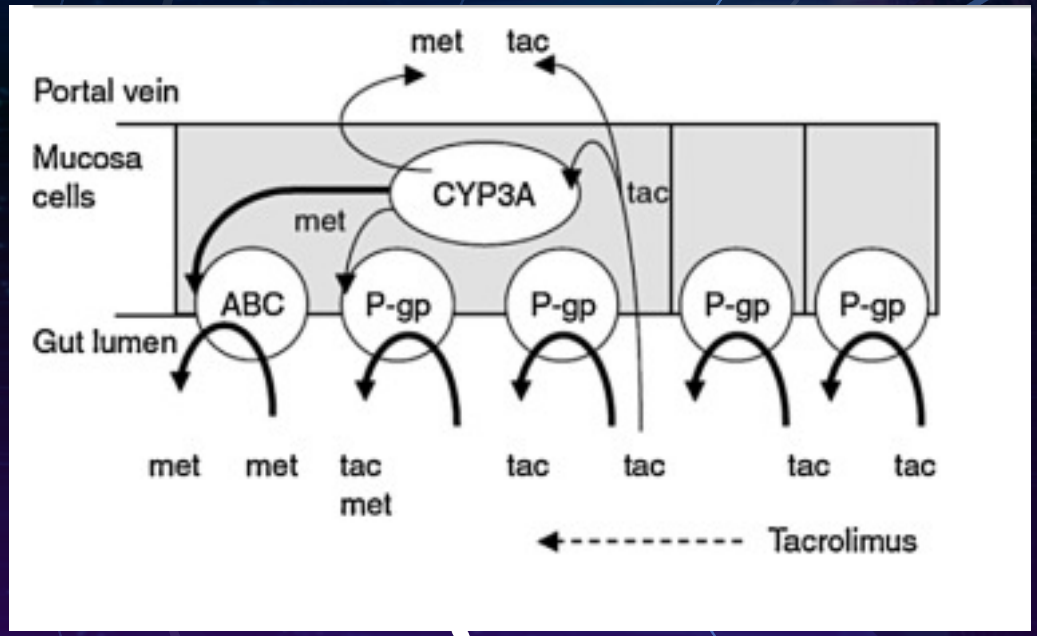
Drugs and Other Substances that Interact with Calcineurin Inhibitors	
Increase Blood Levels (P450-3A4 and/or p-glycoprotein inhibitors)	**Decrease Blood Levels (P450-3A4 and/or p-glycoprotein inducers)**
Ketoconazole Fluconazole Itraconazole Voriconazole Erythromycin Clarithromycin Diltiazem Verapamil Nicardipine Cimetidine Methylprednisolone Metronidazole Ezetimibe Metoclopramide Fluvoxamine HIV protease inhibitors Grapefruit juice Chamomile Wild cherry Lovastatin Atorvastatin Simvastatin Paxlovid	Rifampin Rifabutin Phenytoin Carbamazepine Phenobarbital St John's Wort Caspofungin

Calcineurin inhibitors Drug Interaction (Compreh Clinical Neph 4th Ed)

P-glycoprotein

In the gut CNI's are repeatedly taken up and transported out of intestinal enterocytes by P-gp allowing for reuptake and repeated exposure to CYP3A 4/5 leading to significant pre-systemic metabolism.

Damage to enterocytes (viral GE, etc) can damage P-gp leading to decrease efflux and toxic CNI levels.



Locke, J.E. (2018), Handbook of Kidney Transplantation. Sixth Edition. G. M. Danovitch (Editor) Wolters Kluwar, 2017, 606pp. ISBN: 9781496326157.

Mycophenolate Mofetil

- Anti-metabolite that is a reversible inhibitor of the enzyme inosine monophosphate dehydrogenase (IMPDH).
- IMPDH is a critical, rate limiting enzyme in the *de novo* synthesis of purines and catalyzes the formation of guanosine nucleotides from inosine.
- Depletion of guanosine nucleotides has MMF has a relatively selective antiproliferative effect on lymphocytes as they appear to rely on *de novo* purine synthesis more than other types of cells that have a “salvage” pathway for guanosine nucleotides.

Locke, J.E. (2018). Handbook of Kidney Transplantation. Sixth Edition. G. M. Danovitch (Editor) Wolters Kluwar, 2017, 606pp. ISBN: 9781496326157.

Mycophenolate Mofetil

- Rapidly hydrolyzed to its active metabolite mycophenolic acid (MPA).
- Enteric coated MPA (Myfortic®) results in delayed absorption but slightly better bioavailability (720 mg = 1 g MMF).
- MMF and EC- MPA have comparable GI toxicity, but EC-MPA may be better tolerated in patients with gastroparesis.
- MPA is glucuronidated via transferase in the liver to its inactive form MPAG.
- The primary route of excretion is via the kidneys and the AUC is increased by renal impairment.

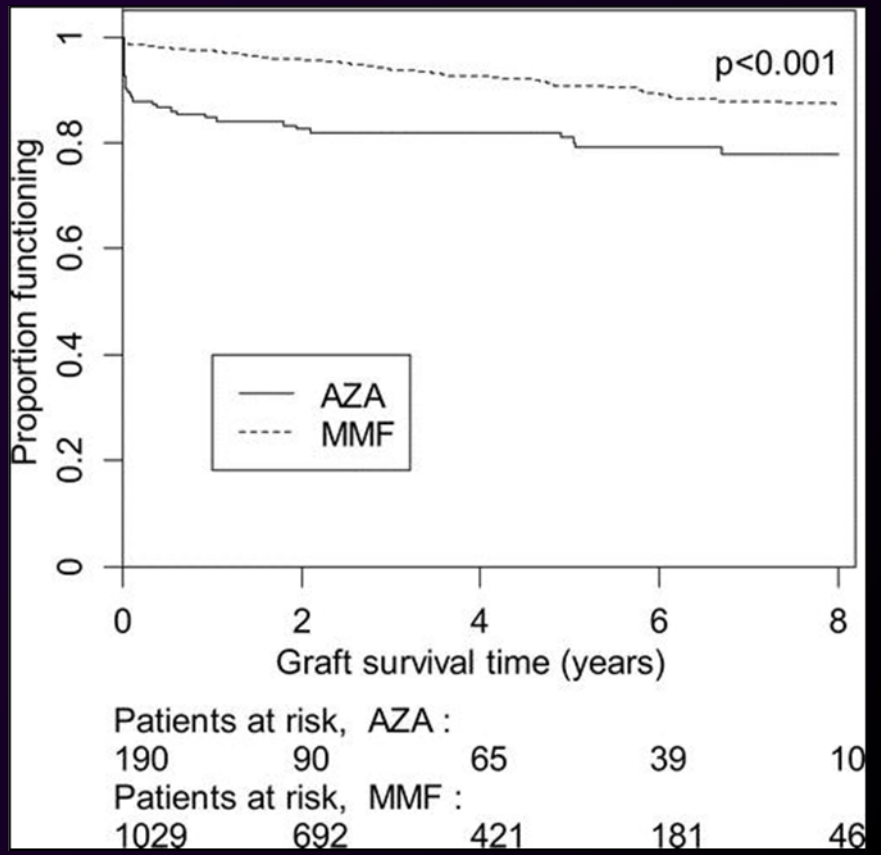
Locke, J.E. (2018), Handbook of Kidney Transplantation. Sixth Edition. G. M. Danovitch (Editor) Wolters Kluwar, 2017, 606pp. ISBN: 9781496326157.

MMF Adverse Reaction and Interactions

- GI- N/V/D, exacerbation of gastroparesis.
- Leukopenia, thrombocytopenia, anemia.
- Teratogenic.
- Absorption decreased by concomitant administration with antacids including PPI's, cholestryramine, sevelamer, oral FeSO4.
- Acyclovir/Ganciclovir/Valganciclovir- increased risk of myelosuppression.

Locke, J.E. (2018), Handbook of Kidney Transplantation. Sixth Edition. G. M. Danovitch (Editor) Wolters Kluwar, 2017, 606pp. ISBN: 9781496326157.

MMF vs. Azathioprine



Kainz A, Heinze G, Korbély R, Schwarz C, Oberbauer R. Mycophenolate mofetil use is associated with prolonged graft survival after kidney transplantation. Transplantation. 2009 Nov 15;88(9):1095-100. doi: 10.1097/TP.0b013e3181bb25f1. PMID: 19898205.

Azathioprine

- An imidazole derivative of 6- mercaptopurine.
- A purine analogue that is incorporated into cellular DNA, where it inhibits purine nucleotide synthesis and interferes with the synthesis and metabolism of RNA. This ultimately leads to inhibition of T- cell activation and proliferation.
- Used as an alternative to MMF during pregnancy (although still labeled pregnancy category D by FDA).

Locke, J.E. (2018), Handbook of Kidney Transplantation. Sixth Edition. G. M. Danovitch (Editor) Wolters Kluwar, 2017, 606pp. ISBN: 9781496326157.

Azathioprine Adverse Reactions

- Mainly hematologic- leukopenia, thrombocytopenia and anemia.
- Pancreatitis-rare.
- Azathioprine is converted to an inactive metabolite, 6- thiouric acid by xanthine oxidase therefor should be avoided with allopurinol.
- If allopurinol needed testing for thiopurine methyltransferase (TPMT) mutations is recommended as TPMT allows for degradation of 6- MP by an alternative pathway. Patients with mutations in this enzyme are at increased risk for severe bone marrow toxicity as there is no alternative pathway for 6- MP metabolism.

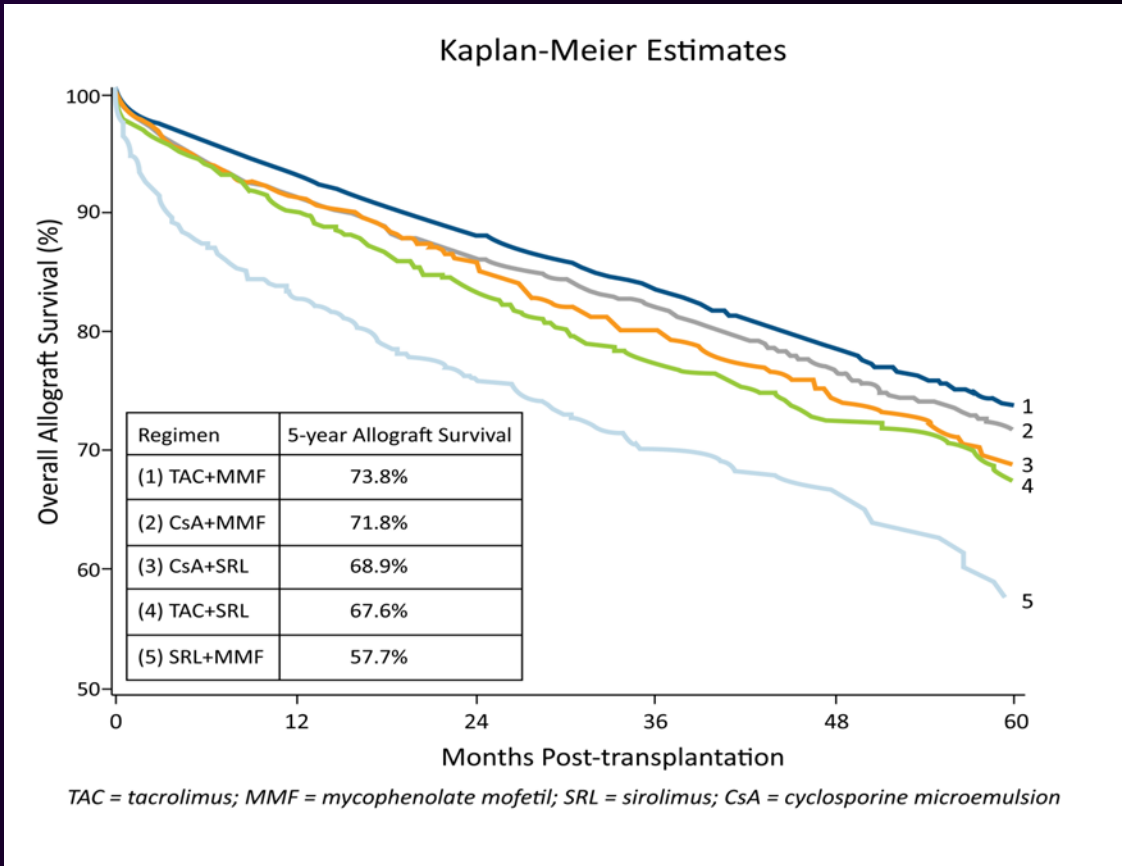
Kainz A, Heinze G, Korbély R, Schwarz C, Oberbauer R. Mycophenolate mofetil use is associated with prolonged graft survival after kidney transplantation. Transplantation. 2009 Nov 15;88(9):1095-100. doi: 10.1097/TP.0b013e3181bb25f1. PMID: 19898205.

mTOR inhibitors

- The mammalian target of rapamycin is a key regulatory kinase in the process of cell division. FDA approved in 1999.
- Sirolimus aka Rapamycin is a macrolide antibiotics which inhibit this kinase.
- Structurally similar to tacrolimus and binds to FKBP however it does not inhibit calcineurin but works on the target of rapamycin pathway (hence its name).

Kainz A, Heinze G, Korbély R, Schwarz C, Oberbauer R. Mycophenolate mofetil use is associated with prolonged graft survival after kidney transplantation. Transplantation. 2009 Nov 15;88(9):1095-100. doi: 10.1097/TP.0b013e3181bb25f1. PMID: 19898205.

Overall Rates of Allograft Survival



Srinivas TR, et al. Am J Transplant. 2007;7:586-594

mTOR inhibitor Adverse Reactions

- Poor Wound Healing/ Lymphocele formation
- Proteinuria/ Podocyte injury/ FSGS
- Lung Toxicity/ BOOP physiology
- Hyperlipidemia/ hypertriglyceridemia
- Thrombocytopenia/leukopenia
- Oral Ulcers
- Ascites and Pleural Effusion
- TMA

Locke, J.E. (2018), Handbook of Kidney Transplantation. Sixth Edition. G. M. Danovitch (Editor) Wolters Kluwar, 2017, 606pp. ISBN: 9781496326157.

mTOR's- Usefullness?

ORIGINAL ARTICLE

Sirolimus and Secondary Skin-Cancer Prevention in Kidney Transplantation

Sylvie Euvrard, M.D., Emmanuel Morelon, M.D., Ph.D., Lionel Rostaing, M.D., Ph.D., Eric Goffin, M.D., Anabelle Brocard, M.D., Isabelle Tromme, M.D., Nilufer Broeders, M.D., Veronique del Marmol, M.D., Ph.D., Valérie Chatelet, M.D., Anne Dompmartin, M.D., Ph.D., Michèle Kessler, M.D., Andreas L. Serra, M.D., et al., for the TUMORAPA Study Group*

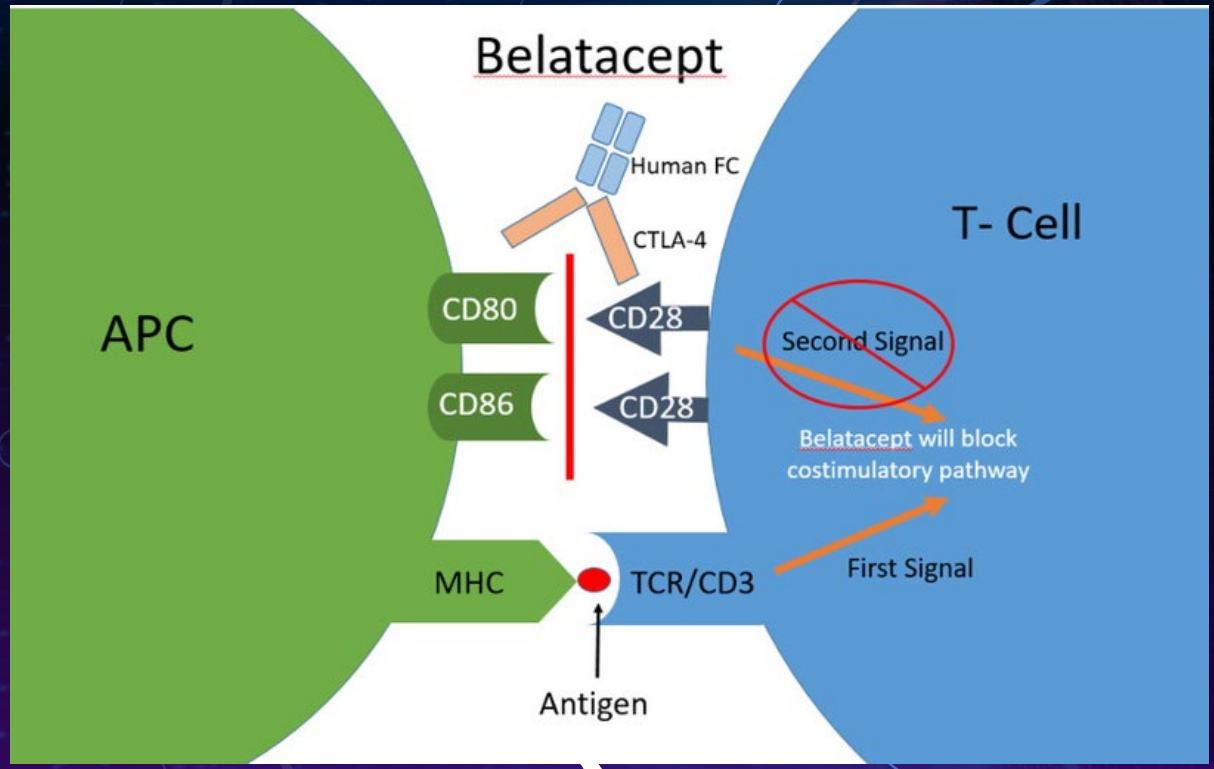
July 26, 2012
N Engl J Med 2012; 367:329-339
DOI: 10.1056/NEJMoa1204166

CONCLUSIONS

Switching from calcineurin inhibitors to sirolimus had an antitumoral effect among kidney-transplant recipients with previous squamous-cell carcinoma. These observations may have implications concerning immunosuppressive treatment of patients with cutaneous squamous-cell carcinomas. (Funded by Hospices Civils de Lyon and others; TUMORAPA ClinicalTrials.gov number, NCT00133887

Belatacept

- Human fusion protein containing cytotoxic T- lymphotoxic associated antigen 4 fused with Fc domain of human IgG1.
- Approved 2011.
- Permits enhanced binding of CD80 (4X) and CD86 (2X) on the antigen presenting cells which lead to a 10-fold increase in T cell inhibition.



Kott, J., Chancay, J., & Tedla, F. M. (2022). Updates on Belatacept in Kidney Transplantation. Kidney News, 14(8), 26-26. Retrieved Mar 5, 2024, from https://www.kidneynews.org/view/journals/kidney-news/14/8/article-p26_15.xml

Export Citation

Locke, J.E. (2018), Handbook of Kidney Transplantation. Sixth Edition. G. M. Danovitch (Editor) Wolters Kluwar, 2017, 606pp. ISBN: 9781496326157

Belatacept

- BENEFIT trial NEJM 2016 showed significantly better GFR and 43% reduced risk of graft loss or death after 7 years of use as compared to cyclosporin. No comparisons to tacrolimus based regimens available.
- Higher initial early rejection rate.
- Higher incidence of post- transplant lymphoproliferative disorder (PTLD) particularly CNS involvement, especially in EBV seronegative patients.
- Higher rates of progressive multifocal leukoencephalopathy (PML).
- Need for monthly infusion.

Locke, J.E. (2018), Handbook of Kidney Transplantation. Sixth Edition. G. M. Danovitch (Editor) Wolters Kluwar, 2017, 606pp. ISBN: 9781496326157

Post-Transplant Care

Hypertension

Hyperlipidemia

Post transplant Diabetes Mellitus

Hypertension

- Kidney Disease Improving Global Outcome (KDIGO) guidelines suggest a BP goal of <130/80 irrespective of the level of albuminuria.
- Calcium channel blockers reduce cyclosporine induced vasocontriction.
  - Non-dihydropyridines increase CNI levels.
  - Dihydropyridines can cause edema.
- Beta blockers good choice in patients with ischemic heart disease, afib, etc.
- Diuretics- good for volume overload and hyperkalemia post transplant.

Hypertension

- Ace Inhibitors- studies are lacking.
- A 2007 systematic review of 21 trials with 1549 patients with median follow up of 27 months published in AJT found:
  - Decrease in GFR by -5.8 mL/min.
  - Lower hematocrit.
  - Reduction in proteinuria.
  - No change in serum potassium.
- Insufficient data to determine the effect on patient or graft survival.

Hiremath S, Fergusson D, Doucette S, Mulay AV, Knoll GA. Renin angiotensin system blockade in kidney transplantation: a systematic review of the evidence. Am J Transplant. 2007 Oct;7(10):2350-60. doi: 10.1111/j.1600-6143.2007.01928.x. PMID: 17845569.

Hypertension

- Ace Inhibitors-
  - Hyperkalemia.
  - GFR impact- confusion with other potential causes of allograft dysfunction.
  - Anemia
  - Renal artery stenosis associated acute renal failure.

Hyperlipidemia

TABLE 14-3 KDIGO and ACA/AHA Guidelines for the Management of Posttransplantation Dyslipidemia

Pharmacologic therapy	
KDIGO guidelines	**ACC/AHA guidelines**

• *Statin* in all kidney transplant recipients (see text for recommendations for patients <30 y of age)
• Ezetimibe for those intolerant to statin
• Follow-up lipid profile not required
Elevated triglyceride
• Therapeutic lifestyle changes
• Low-fat diet (<15% total calories), reduction of monosaccharide and disaccharide intake, reducing the total amount of dietary carbohydrates, and use of fish oils to replace some long-chain triglycerides
• Fibrate use to prevent pancreatitis or reduce CV risk is not recommended (see text)
	• *Statin* therapy should be based on
	  • Clinical judgment (weigh risks and benefits)
	  • Patient preferences
	• Follow-up lipid profile at 4 and 12 wk after treatment to assess medical adherence and then every 3-12 mo as clinically indicated
	Statin: Benefits outweigh risks in patients with
	• Clinical ASCVD
	• Primary elevation of LDL-C >190 mg/dL
	• Diabetes, age 40-75 y, LDL-C 70-189 mg/dL, and without clinical ASCVD
	• Clinical ASCVD or diabetes, LDL-C 70-189 mg/dL, and estimated 10-y ASCVD risk >7.5%
	Elevated triglyceride
	• Not addressed by ACC/AHA

All kidney transplant recipients (kidney transplantation is considered coronary heart disease risk equivalent). Initial assessment of lipid profile (total cholesterol, LDL-C, high-density lipoprotein cholesterol, triglyceride). Therapeutic lifestyle changes (first-line treatment).

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; KDIGO, Kidney Disease: Improving Global Outcomes; LDL-C, low-density lipoprotein cholesterol.

Pham, Phuong-Chi, T. and Phuong-Thu T Pham. Quick Guide to Kidney Transplantation. Available from: Wolters Kluwer, Wolters Kluwer Health, 2019.

Hyperlipidemia

- Preferred agents- Atorvastatin or Rosuvastatin. Avoid Simvastatin.
- Ezetimibe should be considered in patients intolerant to statins or as an addition for treatment of hypertriglyceridemia.
- Use fibrates with caution.
- Bile acid sequestrants can interfere with CNI and MMF absorption.

Pham, Phuong-Chi, T. and Phuong-Thu T Pham. Quick Guide to Kidney Transplantation. Available from: Wolters Kluwer, Wolters Kluwer Health, 2019.

Post Transplant Diabetes Mellitus

Non-modifiable risk factors

- Age≥45 years
- Male recipient
- African-American, Hispanic
- Family history of diabetes mellitus
- HLA mismatch
- HLA A30, B27, B42
- Acute rejection history
- Male donor
- Deceased donor

potentially modifiable risk factors

- Obesity(BMI>30)
- Pretransplant IFG/IGT
- Hypertension
- Hyperlipidemia
- Hepatitis C viral infection
- CMV viral infection
- Corticosteroids, Tacrolimus, Cyclosporine, Sirolimus
- Hypomagnesemia
- Proteinuria

Sharif A, Hecking M, de Vries AP, Porrini E, Hornum M, Rasoul-Rockenschaub S, Berlakovich G, Krebs M, Kautzky-Willer A, Schernthaner G, Marchetti P, Pacini G, Ojo A, Takahara S, Larsen JL, Budde K, Eller K, Pascual J, Jardine A, Bakker SJ, Valderhaug TG, Jenssen TG, Cohney S, Säemann MD. Proceedings from an international consensus meeting on posttransplantation diabetes mellitus: recommendations and future directions. Am J Transplant. 2014 Sep;14(9):1992-2000. doi: 10.1111/ajt.12850. Epub 2014 Aug 6. PMID: 25307034; PMCID: PMC4374739.

Post Transplant Diabetes Mellitus

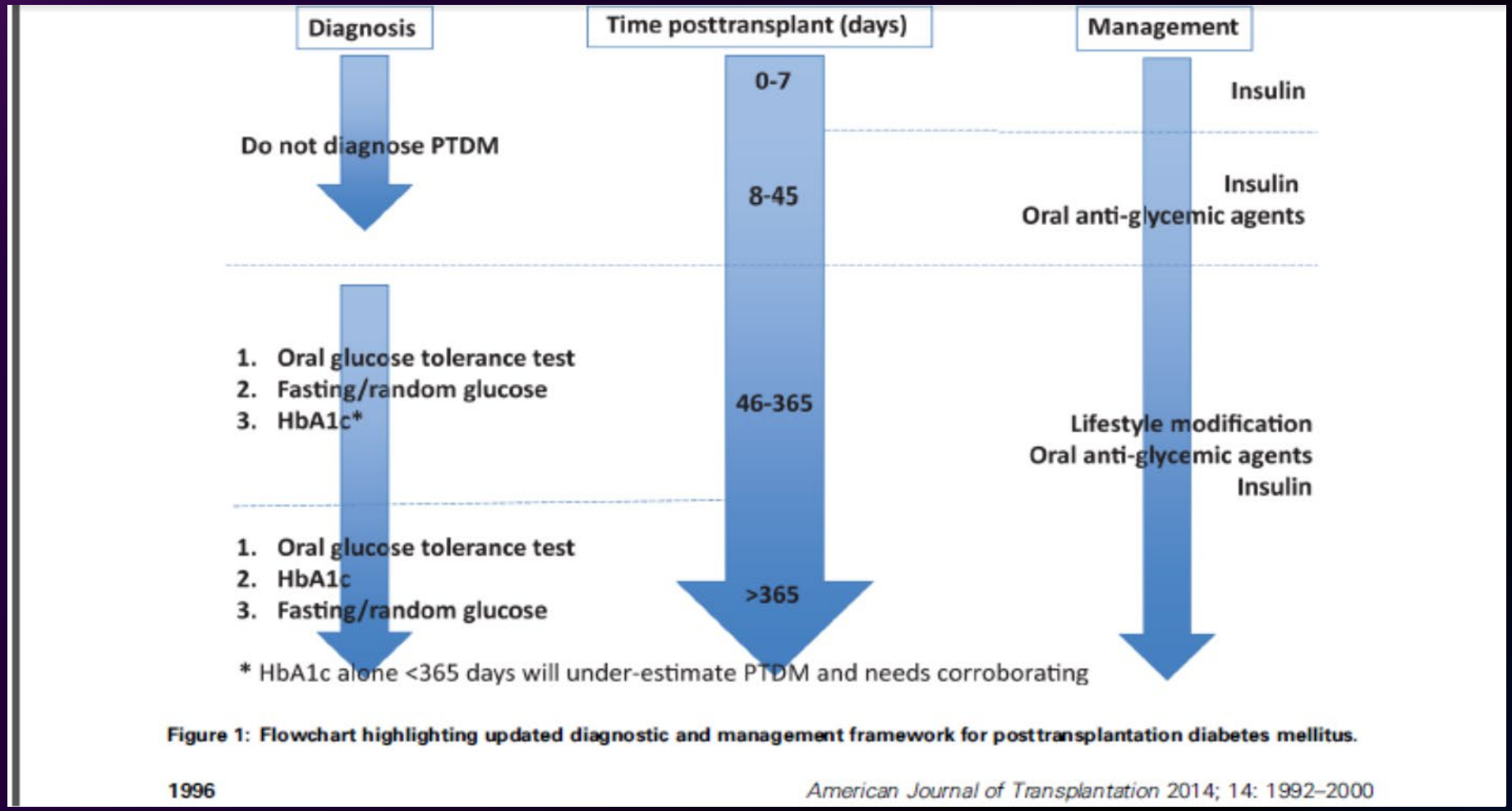


Figure 1: Flowchart highlighting updated diagnostic and management framework for posttransplantation diabetes mellitus.

1996

American Journal of Transplantation 2014; 14: 1992–2000

Sharif A, Hecking M, de Vries AP, Porrini E, Hornum M, Rasoul-Rockenschaub S, Berlakovich G, Krebs M, Kautzky-Willer A, Schernthaner G, Marchetti P, Pacini G, Ojo A, Takahara S, Larsen JL, Budde K, Eller K, Pascual J, Jardine A, Bakker SJ, Valderhaug TG, Jenssen TG, Cohney S, Säemann MD. Proceedings from an international consensus meeting on posttransplantation diabetes mellitus: recommendations and future directions. Am J Transplant. 2014 Sep;14(9):1992-2000. doi: 10.1111/ajt.12850. Epub 2014 Aug 6. PMID: 25307034; PMCID: PMC4374739.

Post Transplant Diabetes Mellitus

- Most but not all studies suggest PTDM is associated with reduced graft survival.
- Only one study suggested PTDM to be a risk factor for death-censored renal graft failure.
- Several small studies suggested PTDM is associated with higher acute rejection episodes, but it is difficult to determine if PTDM causes rejection or if the treatment (high dose steroids) resulted in greater risk of PTDM.
- The greater impact is not likely due to rejection but death with a functioning graft.

Pham, Phuong-Chi, T. and Phuong-Thu T Pham. Quick Guide to Kidney Transplantation. Available from: Wolters Kluwer, Wolters Kluwer Health, 2019.

Post Transplant Diabetes Mellitus

- Management
  - Target A1c 7% - 7.5%, not followed below 6% particularly if hypoglycemic reactions are common (2009 KDIGO guidelines).
  - treatment options: insulin, metformin (renally adjusted), sulfonylureas, DPP-4 inhibitors, GLP-1 agonists.
  - SGLT2 Inhibitors:
    - Empagliflozin in posttransplantation diabetes mellitus: A prospective, interventional pilot study on glucose metabolism, fluid volume, and patient safety- 2018.
    - - 14 (only 8 completed 12 months) patients converted from insulin to empagliflozin.
    - Higher OGTT values, A1c and home glucose measurements and insulin reinstituted in 3 of 8 patients.
    - 5 developed UTI; 1 balanitis; all lost weight.
    - Deemed it could safely be used as add on therapy.

Locke, J.E. (2018), Handbook of Kidney Transplantation. Sixth Edition. G. M. Danovitch (Editor) Wolters Kluwar, 2017, 606pp. ISBN: 9781496326157

Schwaiger E, Burghart L, Signorini L, Ristl R, Kopecky C, Tura A, Pacini G, Wrba T, Antlanger M, Schmaldienst S, Werzowa J, Säemann MD, Hecking M. Empagliflozin in posttransplantation diabetes mellitus: A prospective, interventional pilot study on glucose metabolism, fluid volume, and patient safety. Am J Transplant. 2019 Mar;19(3):907-919. doi: 10.1111/ajt.15223. Epub 2019 Jan 25. PMID: 30585690; PMCID: PMC6590167.

Posttransplant Complications

Infections

Rejections

Malignancy

Infections

Vaccinations for solid organ transplant (SOT) candidates and recipients

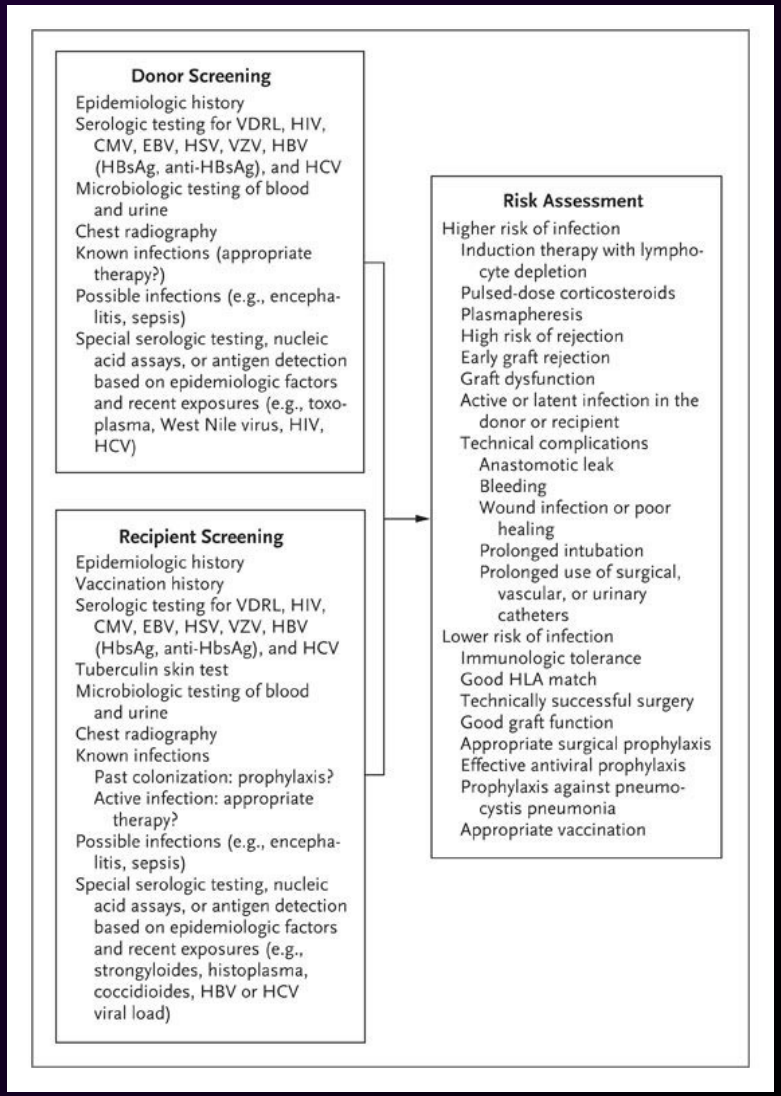
Vaccine type	Vaccine target	Indications
Nonlive (inactivated, killed, subunit, or recombinant)	Pneumococcal vaccines	All SOT candidates and recipients not previously vaccinated or who need booster doses. Vaccine formulation of choice depends on age, national guidelines, and availability.[*]
	RSV[¶]	Offer to all SOT candidates and recipients ≥60 years old and share the decision-making process with the patient.
	Seasonal influenza virus	Annually for all patients ≥6 months old.[Δ]
	HBV	All SOT candidates and recipients who are nonimmune based on serologic testing (eg, HBsAb-negative patients). NOTE: High-dose HBV vaccine or Heplisav-B are preferred to maximize immunogenicity.
	HAV	If not previously vaccinated or immune: ▪ All adult liver transplant candidates and recipients ▪ All pediatric SOT candidates and recipients ▪ At-risk adult nonliver transplant recipients (eg, travel to or residence in an endemic area) NOTE: In the setting of recent outbreaks, reasonable to vaccinate all non-immune SOT candidates and recipients.
	Meningococcus (serotypes A, B, C, W, and Y)	At-risk patients who have not been previously vaccinated, including those treated with eculizumab and those with impaired splenic function. NOTE: Pentavalent MenABCWY vaccine formulation is preferred, when available, to provide the widest coverage against meningococcus.
	Haemophilus influenzae	At-risk patients ≥5 years old who have not been previously vaccinated, including those with impaired splenic function. Children <5 years old should be vaccinated according to the routine schedule.
	HPV	All SOT candidates and recipients not previously vaccinated who meet age-based indications for vaccination.
	DTaP, Tdap, or Td	All SOT candidates and recipients per guidelines for healthy persons (eg, per routine for children).
	RZV	SOT candidates and recipients aged ≥19 years old.
	COVID-19 vaccines[◇]	All SOT candidates and recipients. Choice of vaccine depends on age, national guidelines, and availability.
Live, attenuated[§]	ZVL	SOT candidates aged >50 years old. NOTE: RZV is preferred, when available, over ZVL. **(ZVL contraindicated post-transplantation).**
	Varicella vaccine	Nonimmune SOT candidates prior to transplantation; can be given as early as 6 months of age in children. **Contraindicated post-transplantation and/or for immunosuppressed patients.**[¥]
	MMR	SOT candidates who have not been previously vaccinated and/or lack evidence of measles, mumps, or rubella immunity (ie, IgG seronegative); can be given as early as 6 months of age in children. **Contraindicated post-transplantation and/or for immunosuppressed patients.**[¥]
	Rotavirus	Per usual guidelines for infants prior to transplantation; not indicated for older children and adults. **Contraindicated post-transplantation and/or for immunosuppressed patients.**

As part of the pretransplant evaluation, we review each patient's vaccination history and ensure that the above vaccinations have been received when appropriate. For maximal protection, vaccinations should be given pretransplantation and prior to the start of immunosuppressive therapy. This increases the likelihood of developing a protective immune response and allows for administration of any needed live vaccines, which should be given at least 4 weeks prior to transplantation and are generally contraindicated once immunosuppressive therapy has started.

For complete information on timing of vaccine administration and vaccine schedules, refer to the UpToDate topic on vaccinations in solid organ transplantation. For more detailed description of at-risk populations, refer to the UpToDate topics regarding each vaccine.

Immunizations in solid organ transplant candidates and recipients.

Infections



Fishman J A. Infections in organ-transplant recipients. N Engl J Med 2007;357:2601-2614

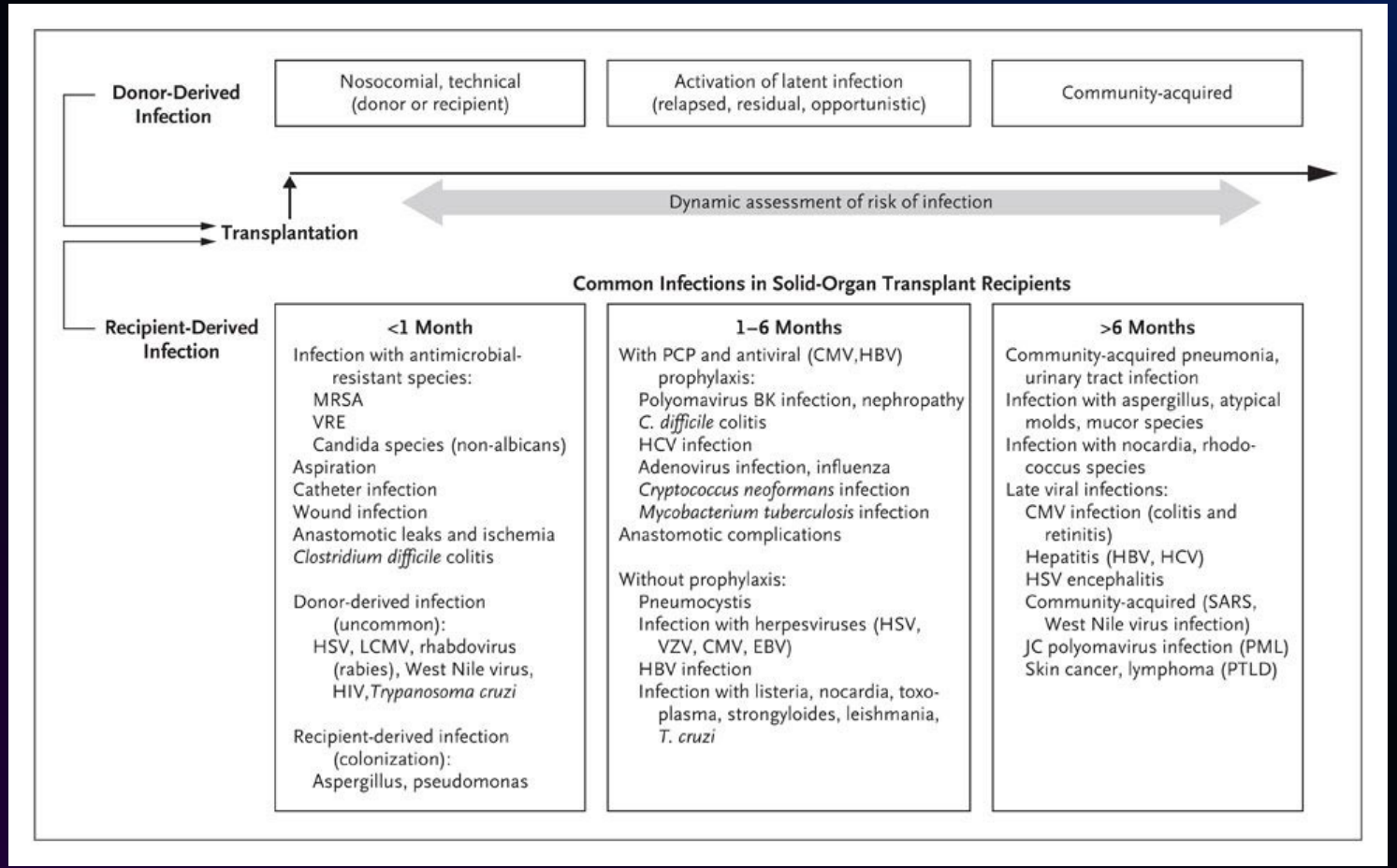
Infections

Prophylaxis:

TMP/SMX

Nystatin/Diflucan

Valganciclovir depending on CMV status.



Fishman JA. Infections in organ-transplant recipients. N Engl J Med 2007;357:2601-2614

CMV

- HHV 5.
- DNA virus.
- Four infectious states:
  - Asymptomatic
  - Congenital disease (TORCHES)- microcephaly, deafness, seizures, mental retardation, and other birth defects.
  - Cytomegalovirus mononucleosis.
  - Reactivation in an immunocompromised patient.

Razonable RR, Humar A. Cytomegalovirus in solid organ transplantation. Am J Transplant 2013;13:93-106.

CMV

- CMV infection- Evidence of CMV replication regardless of symptoms.
- CMV Disease- Evidence of CMV infection with attributable symptoms.
  - CMV syndrome.
  - Tissue invasive disease (allograft commonly involved).
- Latent CMV infection- virus exists as a closed circular DNA and reactivation is induced by many factors in the transplant recipient.
  - Anti-lymphocyte antibodies, cytotoxic drugs.
  - Systemic infection/inflammation.
  - Allogeneic reactions.

CMV Risk Factors

- Donor/Recipient CMV IgG serostatus.
- Degree of immune suppression.
- Use of lymphocyte depleting agents.
- Host factors (age, comorbidities, etc).
- Other (critical illness, cold ischemia time, etc).

Table 2. Risk Stratification Based on Donor and Recipient Serostatus[1,2]		
	Donor status	Recipient status
High risk	+	-
Moderate risk	+/-	+
Low risk	-	-

Fishman JA. Overview: Cytomegalovirus and the herpesviruses in transplantation. Am J Transplant 2013;13:1-8.

Monitoring and Prevention

Monitoring

- Quantitative nucleic acid testing by PCR.

Prevention

Parameters	Pre-emptive therapy	Antiviral prophylaxis
Cost	Increased laboratory cost	Increased drug related cost
Ease of coordination	Difficult to coordinate lab draw, follow up of results and time-appropriate action	Easier to coordinate, however drug toxicity needs to be monitored
Drug toxicities	Lower	Higher
Protection against other Herpes viruses	None	Yes
Protection against "Indirect" effects	Less	Yes
Development of CMV specific immunity	+	–
Incidence of late onset CMV	Low	High in D^+/R^-
Antiviral resistance	+	+
"Escape" infections	Can occur due to rapidly replicating virus	No (breakthrough infections may occur in patients receiving suboptimal dosing)

Ramanan, Poornima & Razonable, Raymund. (2013). Cytomegalovirus Infections in Solid Organ Transplantation: A Review. Infection & chemotherapy. 45. 260-271. 10.3947/ic.2013.45.3.260.

Prevention/Treatment

- Reduce immunosuppression.
- IV ganciclovir.
- Valganciclovir
- Letermovir
- Maribavir

BK virus

- Polyoma virus (DNA)
- Ubiquitous and infections occur worldwide at an early age. Mild or asymptomatic infection.
- 60-80% of adults are seropositive.
- Causes latent infection of the kidney with reactivation with immune suppression.
- Causes sterile pyuria, tubulointerstitial nephritis, ureteral ulceration and obstruction and hemorrhagic cystitis in renal transplant recipients.

Fishman J A. Overview: Cytomegalovirus and the herpesviruses in transplantation. Am J Transplant 2013;13:1-8.
Locke, J.E. (2018), Handbook of Kidney Transplantation. Sixth Edition. G. M. Danovitch (Editor) Wolters Kluwar, 2017, 606pp. ISBN: 9781496326157

BK Virus

- Bimodal distribution- primary infection between 10 days and 6 weeks after transplant and reinfection or reactivation at 5 weeks to 17 months.
- Risk factors- donor seropositivity, degree of immune suppression, treatment of rejection, use of FK and MMF.
- Definitive diagnosis- Biopsy with SV 40 stain.
- Can monitor DNA PCR in plasma and urine. Plasma more specific than urine.
- No specific treatment other than lowering immune suppression.

Fishman J A. Overview: Cytomegalovirus and the herpesviruses in transplantation. Am J Transplant 2013;13:1-8.
Locke, J.E. (2018), Handbook of Kidney Transplantation. Sixth Edition. G. M. Danovitch (Editor) Wolters Kluwar, 2017, 606pp. ISBN: 9781496326157

Rejection

- Acute T-cell mediated rejection- T cell reacting to donor MHC antigens in the tubules, interstitium and vessels.
- Generally occurs after the 1st post-transplant week and most commonly withing the first 3-6 months.
- Treatment includes steroids +/- thymoglobulin depending on severity and optimization of maintenance immune suppression.

Locke, J.E. (2018), Handbook of Kidney Transplantation. Sixth Edition. G. M. Danovitch (Editor) Wolters Kluwar, 2017, 606pp. ISBN: 9781496326157

Rejection

- Antibody mediated rejection- Caused by pre-existing or *de novo* donor-specific antibodies (DSA's).
- Can also involve non-HLA antibodies (MICA, angiotensin II type 1 receptor antibody, etc).
- Generally occurs early after transplantation but may occur at anytime.
- Treatment includes plasma exchange if within the 1st year post-transplant and IVIG. Can consider other therapies such as Rituximab on a case-by-case basis.

Locke, J.E. (2018), Handbook of Kidney Transplantation. Sixth Edition. G. M. Danovitch (Editor) Wolters Kluwar, 2017, 606pp. ISBN: 9781496326157

Malignancy

- The overall incidence of *de novo* malignancies is two to fourfold greater in solid organ transplant recipients compared with that of the general population.
- Approximately twofold higher- colon, lung, prostate, stomach, esophagus, pancreas, ovary and breast.
- Approximately threefold higher- testicular and bladder cancers.
- Approximately fivefold higher- melanoma, leukemia, heptatobiliary tumors, cervical and vulvovaginal tumors.
- Approximately fifteenfold- kidney cancer.
- Approximately twentyfold- Kaposi's sarcoma, non-Hogkin's lymphoma, and nonmelanoma skin cancers.

Kasiske B. Cancer after kidney transplantation in the United States. Am J Tranpslant 2004;4 (6)905-913

Risk Factors

- Duration and intensity of immunosuppression.
- UV radiation exposure.
- Older age.
- Male gender.
- Pre-transplant dialysis duration.
- Smoking history.
- Well described virus associated cancers.

Pham, Phuong-Chi, T. and Phuong-Thu T Pham. Quick Guide to Kidney Transplantation. Available from: Wolters Kluwer, Wolters Kluwer Health, 2019.

Risk Factors

Oncogenic viruses	Specific virus-associated cancers
Epstein-Barr virus	PTLD, non-Hodgkin lymphomas, Hodgkin lymphoma, and plasma cell neoplasms
Human herpes virus 8	Kaposi sarcoma
Hepatitis B and hepatitis C	Hepatocellular carcinoma
Human papillomavirus (HPV)	Vulva, vagina, cervix, penis, anus, oral cavity, and pharynx
Possibly HPV related	Non–melanocytic-related skin cancer

Abbreviation: PTLD, posttransplant lymphoproliferative disorder.

Pham, Phuong-Chi, T. and Phuong-Thu T Pham. Quick Guide to Kidney Transplantation. Available from: Wolters Kluwer, Wolters Kluwer Health, 2019.

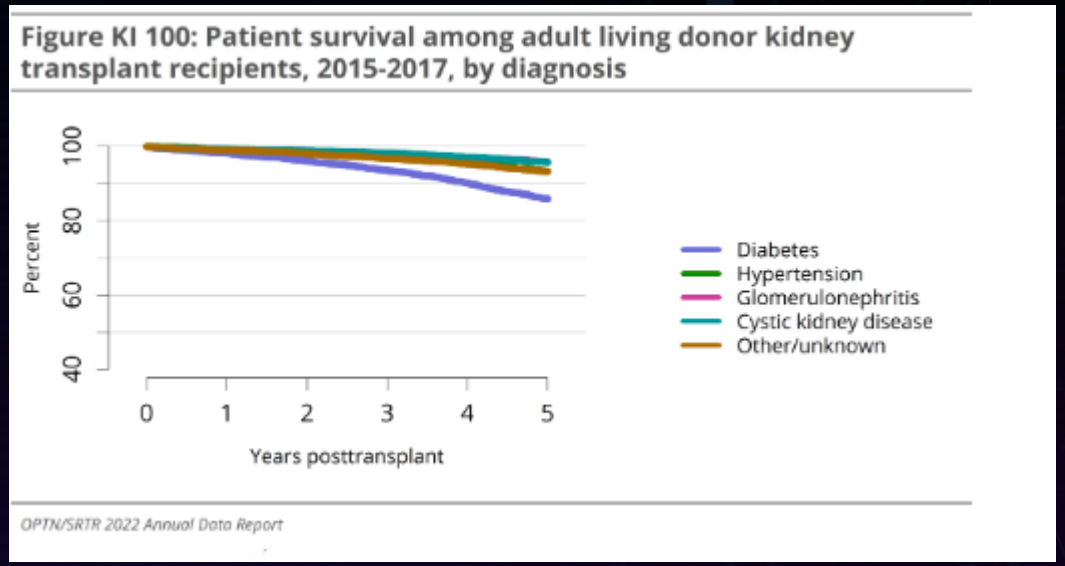
Skin Cancer

- Most common *de novo* posttransplant malignancy.
- SCC>BCC
- 65-100 fold greater incidence compared with the general population.
- Metastatic disease occurs in 3%-8% of patients.
- Azathioprine significantly increased risk of SCC (not BCC).
- Sirolimus Renal Conversion Trial (CONVERT) – patients randomized to sirolimus conversion or continuing CNI based IS regimen.
  - CNI free regimen associated with significant reduction in nonmelanoma skin cancers at 2 years.
  - Sirolimus patients had significant lower incidence of melanoma although the incidence was low to begin with.
  - Non-statistically significant lower rate of other cancers.

Pham, Phuong-Chi, T. and Phuong-Thu T Pham. Quick Guide to Kidney Transplantation. Available from: Wolters Kluwer, Wolters Kluwer Health, 2019.

Alberú, Josefina1,10; Pascoe, Michael D.2; Campistol, Josep M.3; Schena, Francesco P.4; Rial, Maria del Carmen5; Polinsky, Martin6; Neylan, John F.7; Korth-Bradley, Joan8; Goldberg-Alberts, Robert8; Maller, Eric S.8 for the Sirolimus CONVERT Trial Study Group. Lower Malignancy Rates in Renal Allograft Recipients Converted to Sirolimus-Based, Calcineurin Inhibitor-Free Immunotherapy: 24-Month Results From the CONVERT Trial. Transplantation 92(3):p 303-310, August 15, 2011. | DOI: 10.1097/TP.0b013e3182247ae2

So where are we?

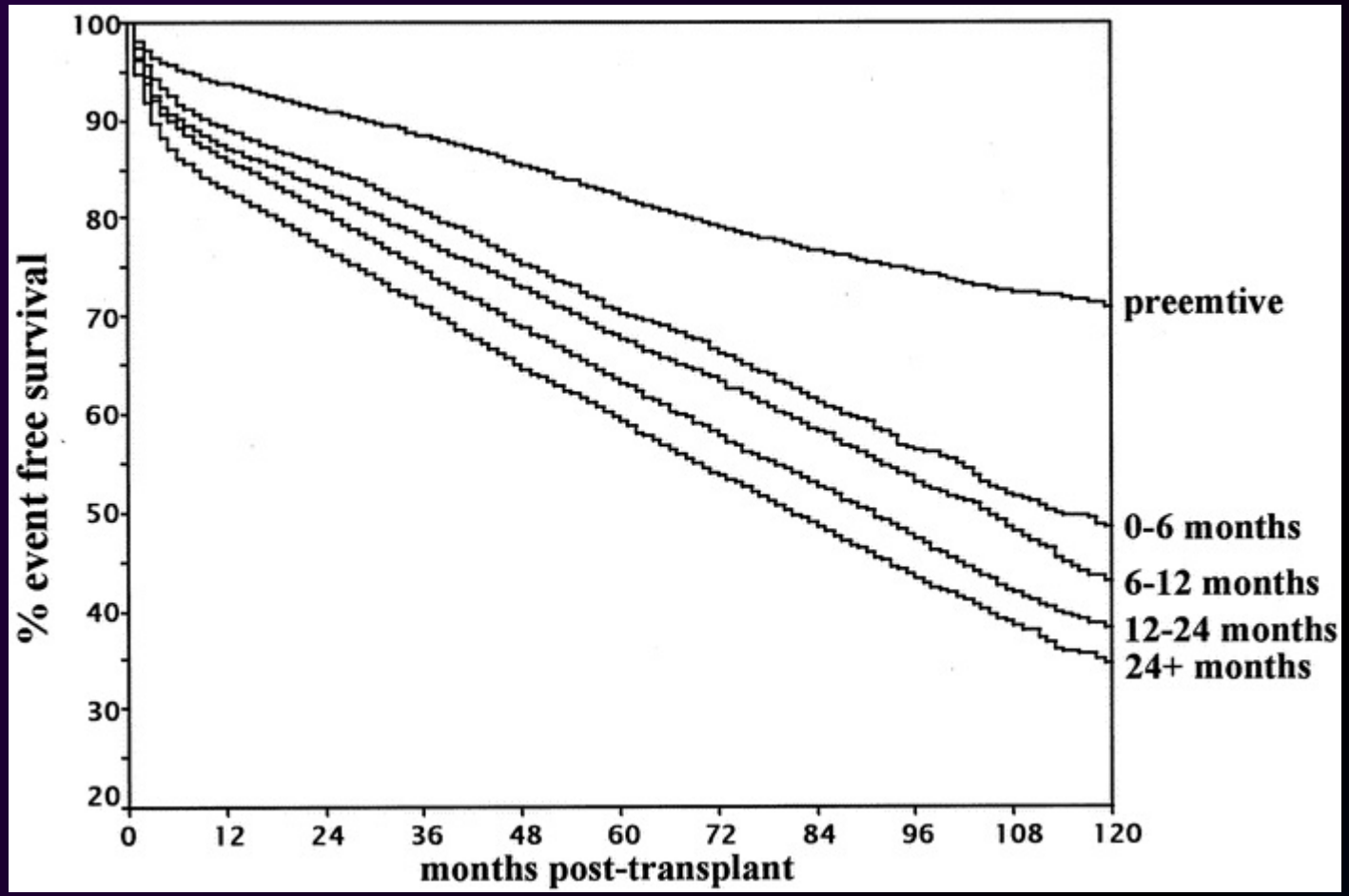


Graft Survival

- Median survival for a deceased donor kidney transplant- 11.7 years.
- Median survival for a living donor transplant- 19.2 years.
- 1 year patient survival >95%.
- 1 year living donor graft survival >95%
- 1 year deceased donor graft survival 90%

Poggio ED, Augustine JJ, Arrigain S, Brennan DC, Schold JD. Long-term kidney transplant graft survival-Making progress when most needed. Am J Transplant. 2021 Aug;21(8):2824-2832. doi: 10.1111/ajt.16463. Epub 2021 Feb 8. PMID: 33346917.

The Vintage Effect



Meier-Kriesche, Herwig-Ulf2,3; Kaplan, Bruce2. Waiting time on dialysis as the strongest modifiable risk factor for renal transplant outcomes: A Paired Donor Kidney Analysis1. Transplantation 74(10):p 1377-1381, November 27, 2002.

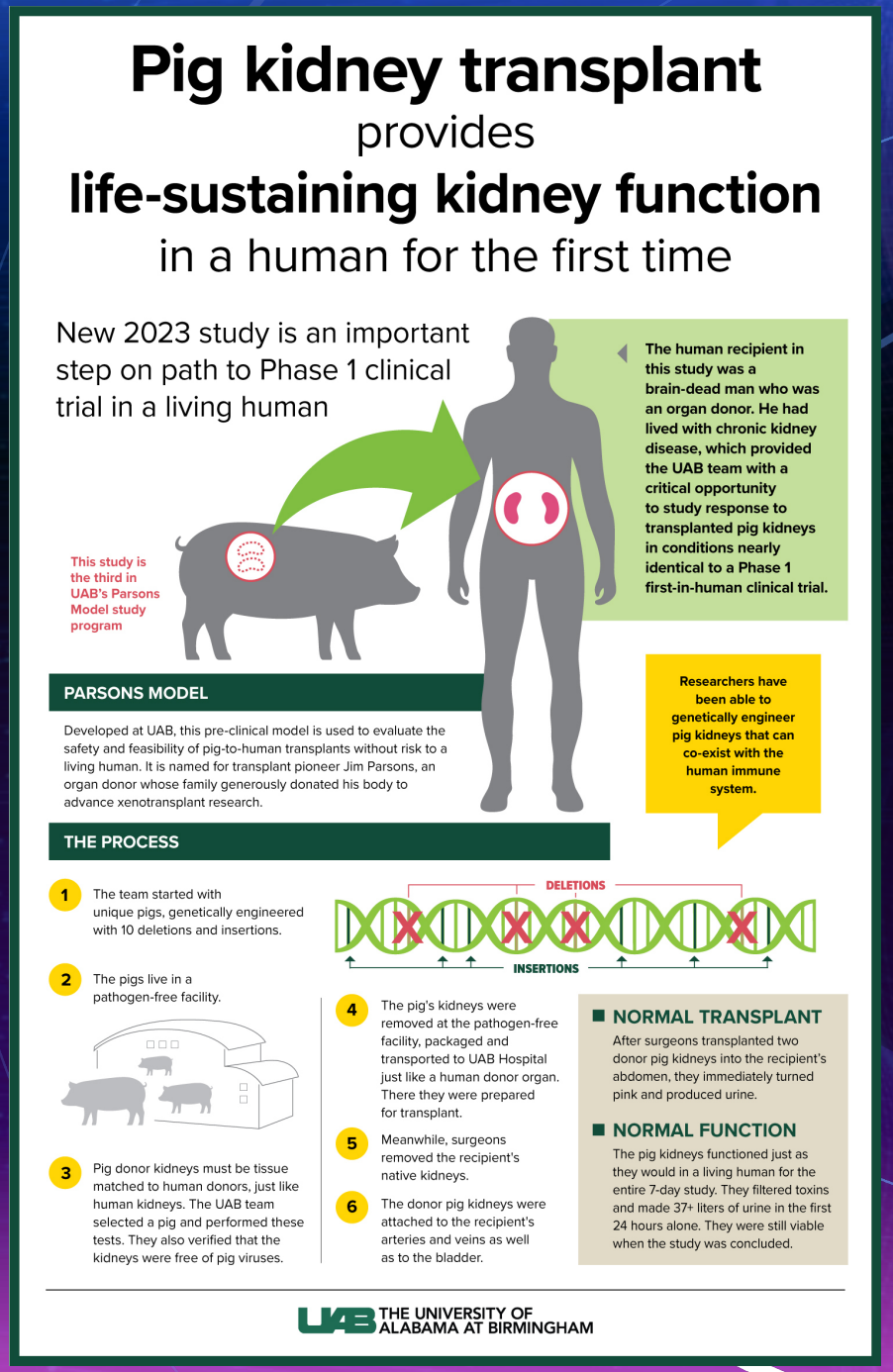
The Future

- Xenotransplantation
  - The GalSafe pig- engineered by Revivicor Inc.
  - By “knocking out” the singe gene that encodes the biomolecule known as alpha-gal- which has been identified as responsible for a rapid anti-body mediated rejection of pig organs- immediate rejection has been avoided in all 5 xenotransplants at NYU Langone. In addition, the pig’s thymus gland was fused with the pig kidney to stave off delayed immune responses.

The Future

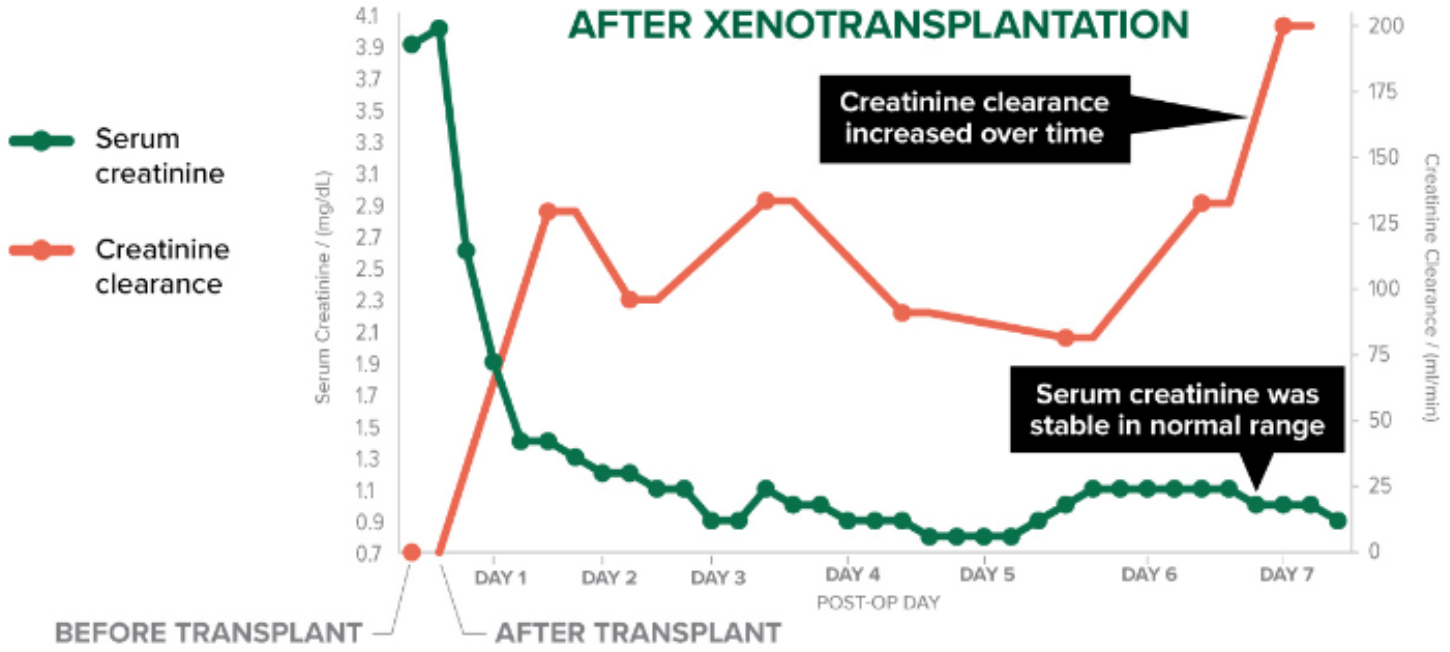
Xenotransplantation

The Parsons model- University of Alabama.



Kidney function over time after a 10-gene-edited pig-to-human xenotransplant

Transplanted pig kidneys showed life-sustaining kidney function after a recent pig-to-human kidney xenotransplant in a pre-clinical human research model.



UAB THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Two-Month Study of Pig Kidney Xenotransplantation Gives New Hope to the Future of the Organ Supply

The NYU Langone Transplant Institute team concluded its two-month study of a transplanted genetically engineered pig kidney into a human. PHOTO: JOE CARROTTA

UCSF Bioartificial kidney

https://youtu.be/K61_IlUFVxc

UCSF The Kidney Project

The bioartificial kidney is a compact, surgically implanted, free-standing device to treat kidney failure. It performs the vast majority of the biological functions of the natural kidney.

Thank you

Kristopher Lepere

405-949-3816

Kristopher.lepere@integrishealth.org