Current challenges in immunosuppression

Dr Peter Dupont

Consultant Nephrologist & UCL Honorary Senior Lecturer

What are the issues?

- Efficacy
  - Short term outcomes
  - Long term outcomes
- Tolerability
  - Nephrotoxicity
  - Infection
  - Cancer
  - Diabetes mellitus
  - Cardiovascular risk
- Non-adherence

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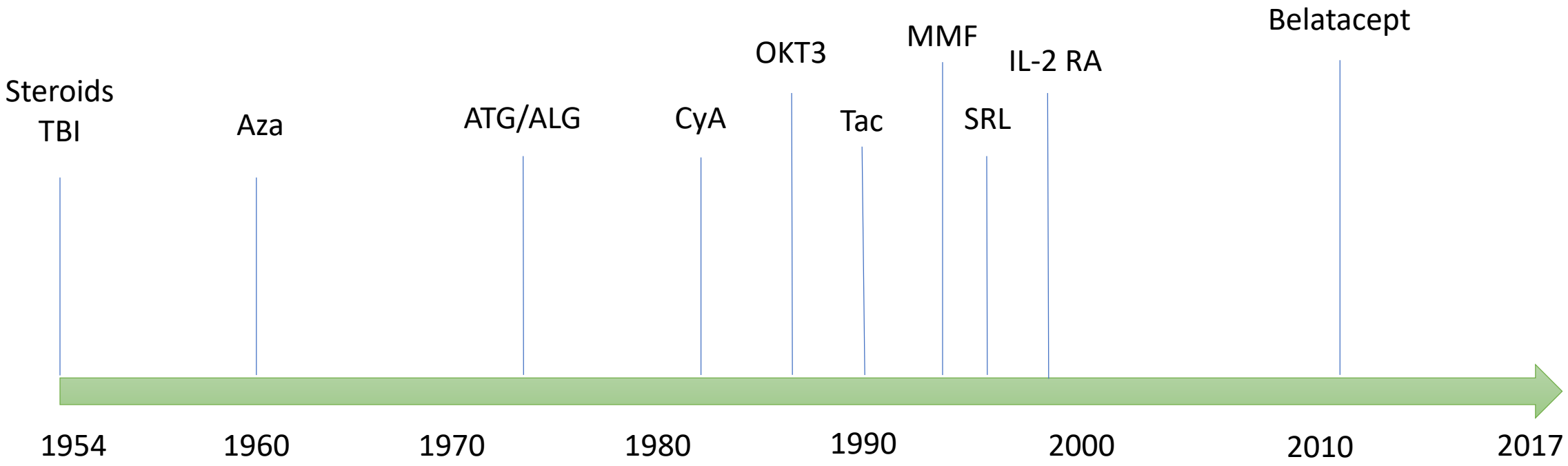
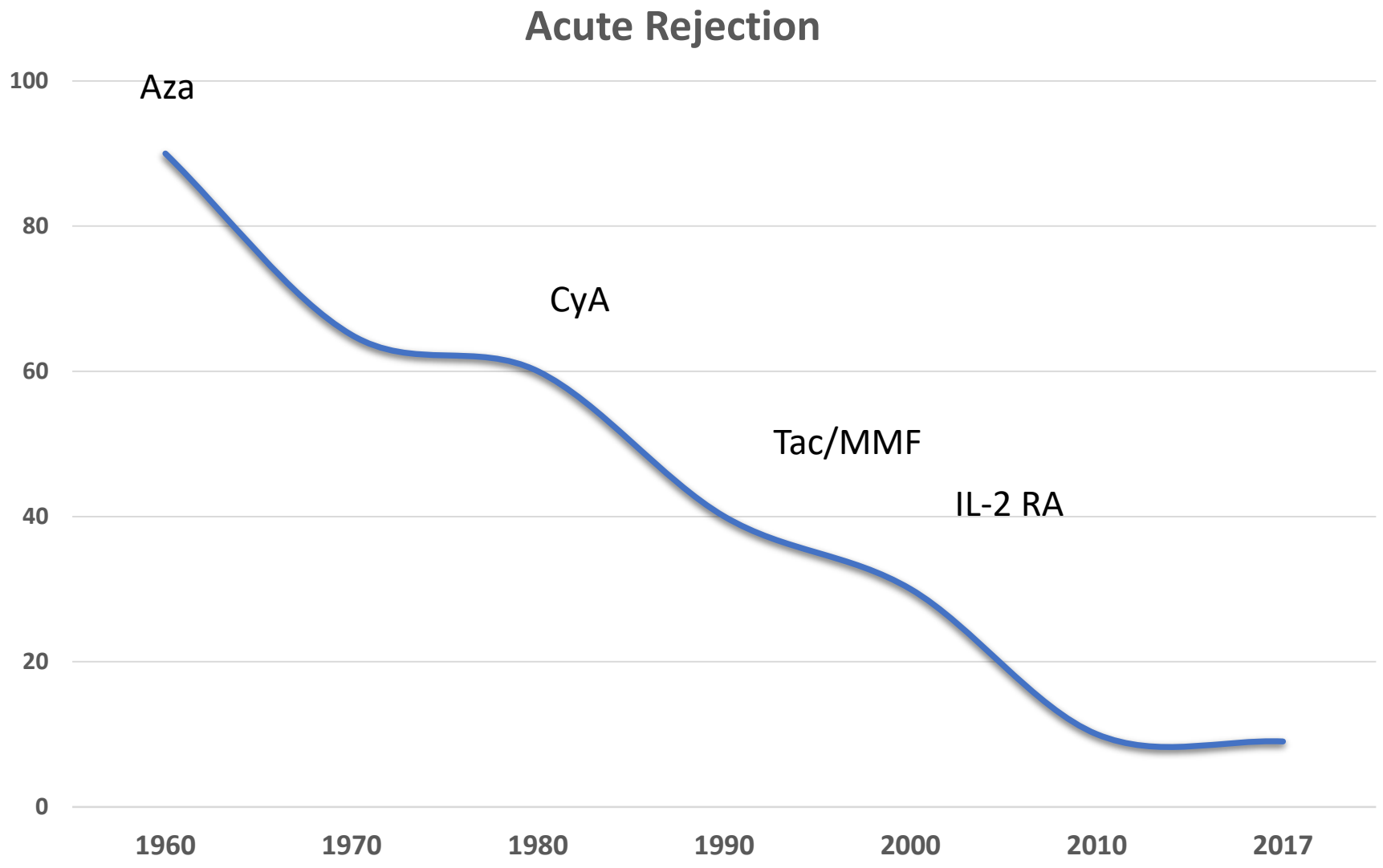
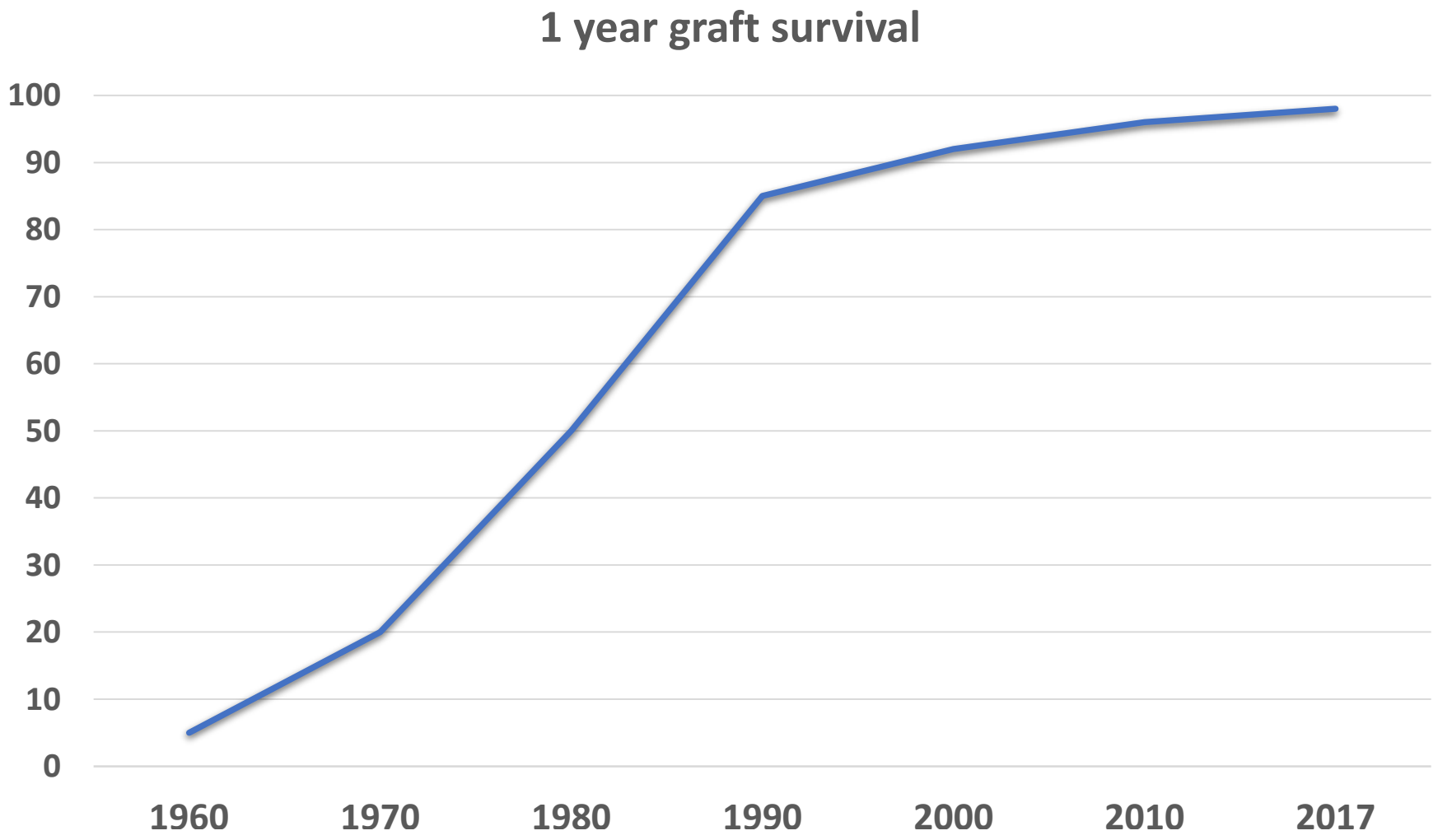
Historical perspective




Acute Rejection
100
80
60
40
20
0
Aza
CyA
Tac/MMF
IL-2 RA
1960
1970
1980
1990
2000
2010
2017


1 year graft survival
100
90
80
70
60
50
40
30
20
10
0
1960
1970
1980
1990
2000
2010
2017

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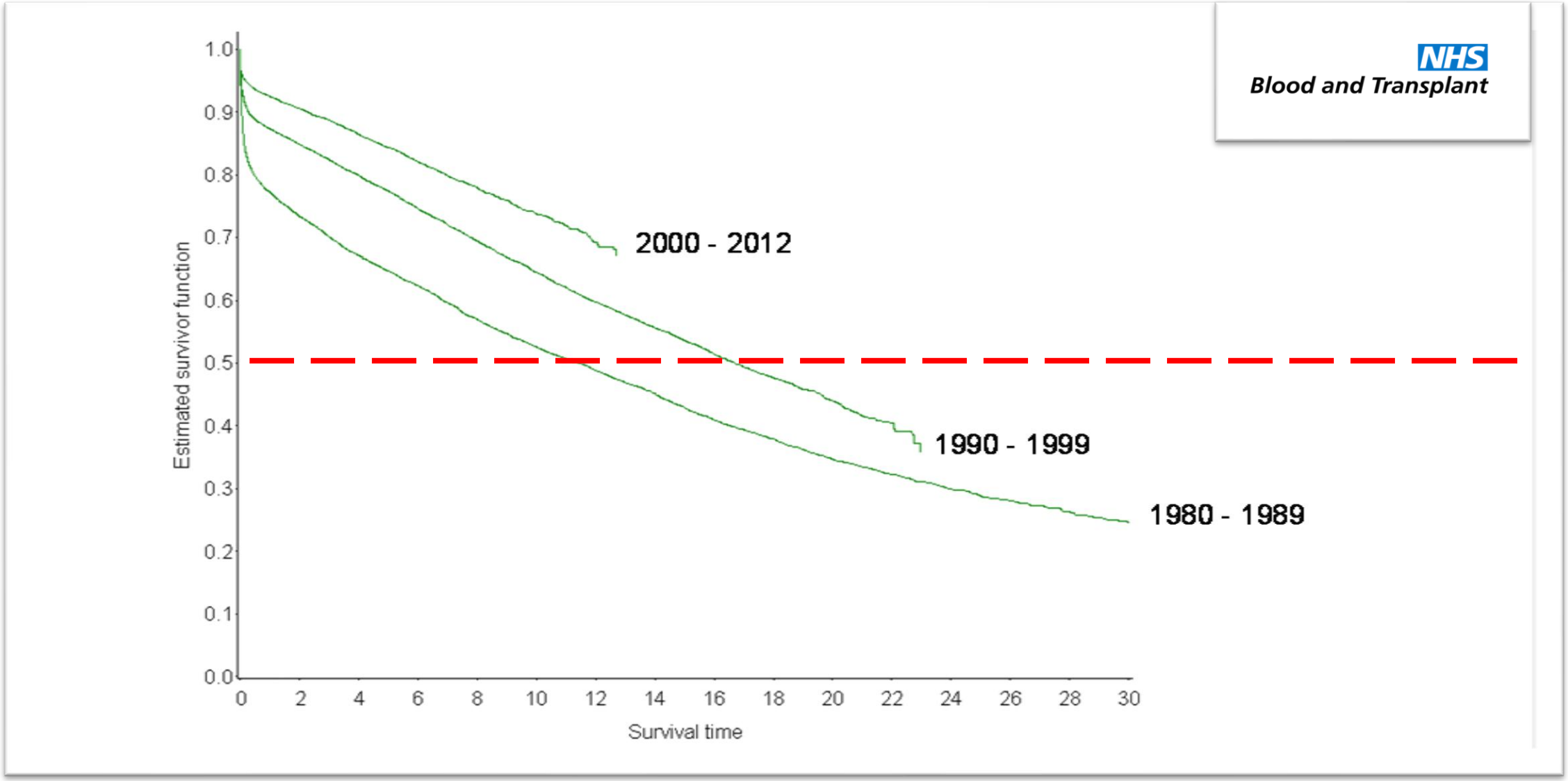
Graft survival by era



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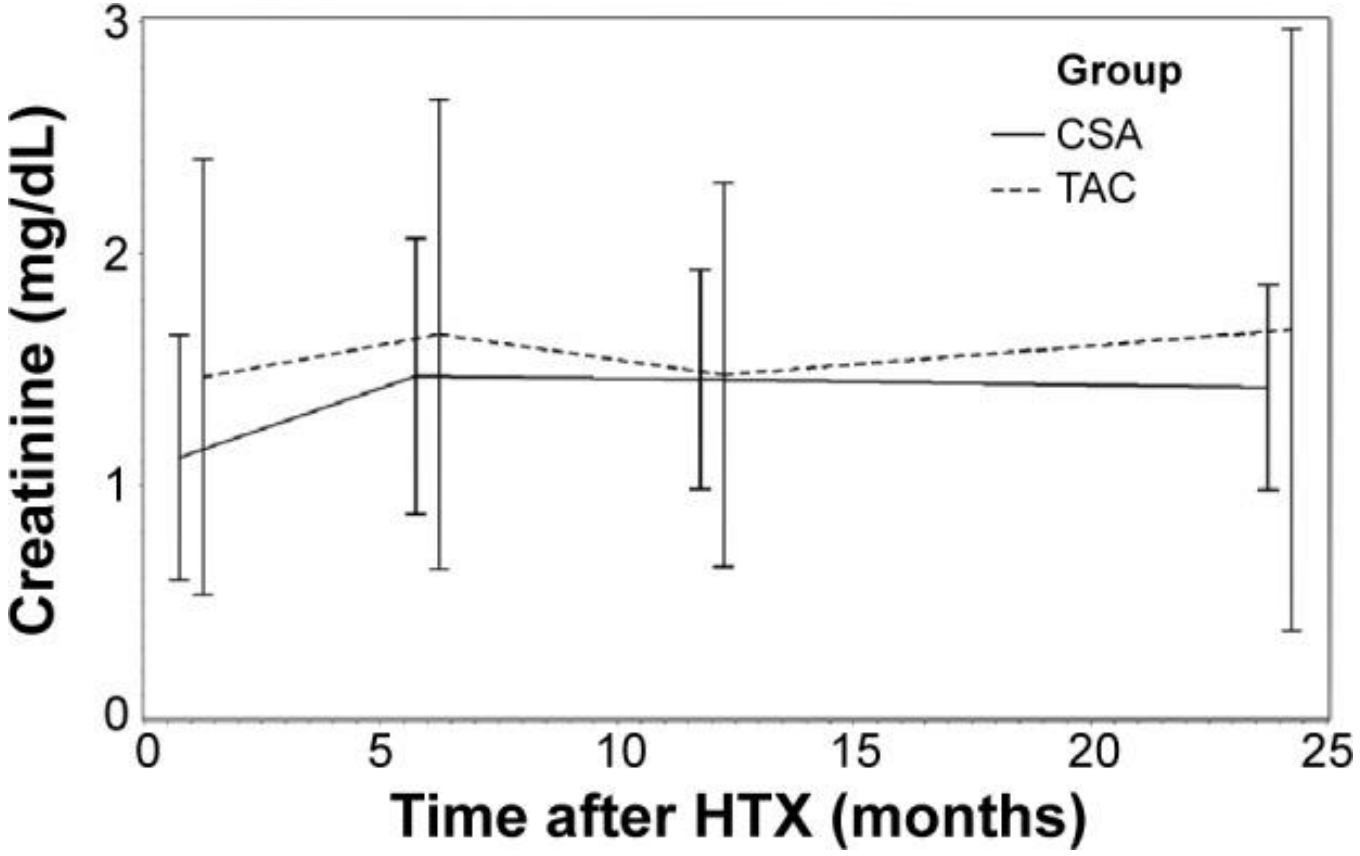
CNI toxicity – the Achilles heel

	CyA	Aza	p value
GFR (mL/min)	51±4	93±3	<0.005
Renal plasma flow (mL/min)	320±21	480±30	<0.001
Transglomerular transport (neutral dextrans)	↓	↔	0.10

Myers et al. NEJM 1984

Tac vs CyA



Helmschrott et al. Drug Des Ther 2015

Alternatives

- CNI withdrawal
  - Associated with inferior outcomes

- mTORi
  - Adverse effects limiting
  - Efficacy?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Belatacept and Long-Term Outcomes in Kidney Transplantation

Flavio Vincenti, M.D., Lionel Rostaing, M.D., Ph.D., Joseph Grinyo, M.D., Ph.D., Kim Rice, M.D., Steven Steinberg, M.D., Luis Gaite, M.D., Marie-Christine Moal, M.D., Guillermo A. Mondragon-Ramirez, M.D., Jatin Kothari, M.D., Martin S. Polinsky, M.D., Herwig-Ulf Meier-Kriesche, M.D., Stephane Munier, M.Sc., and Christian P. Larsen, M.D., Ph.D.

ABSTRACT

BACKGROUND

In previous analyses of BENEFIT, a phase 3 study, belatacept-based immunosuppression, as compared with cyclosporine-based immunosuppression, was associ-

From the University of California, San Francisco, San Francisco (F.V.), and Sharp Memorial Hospital, San Diego (S.S.) —

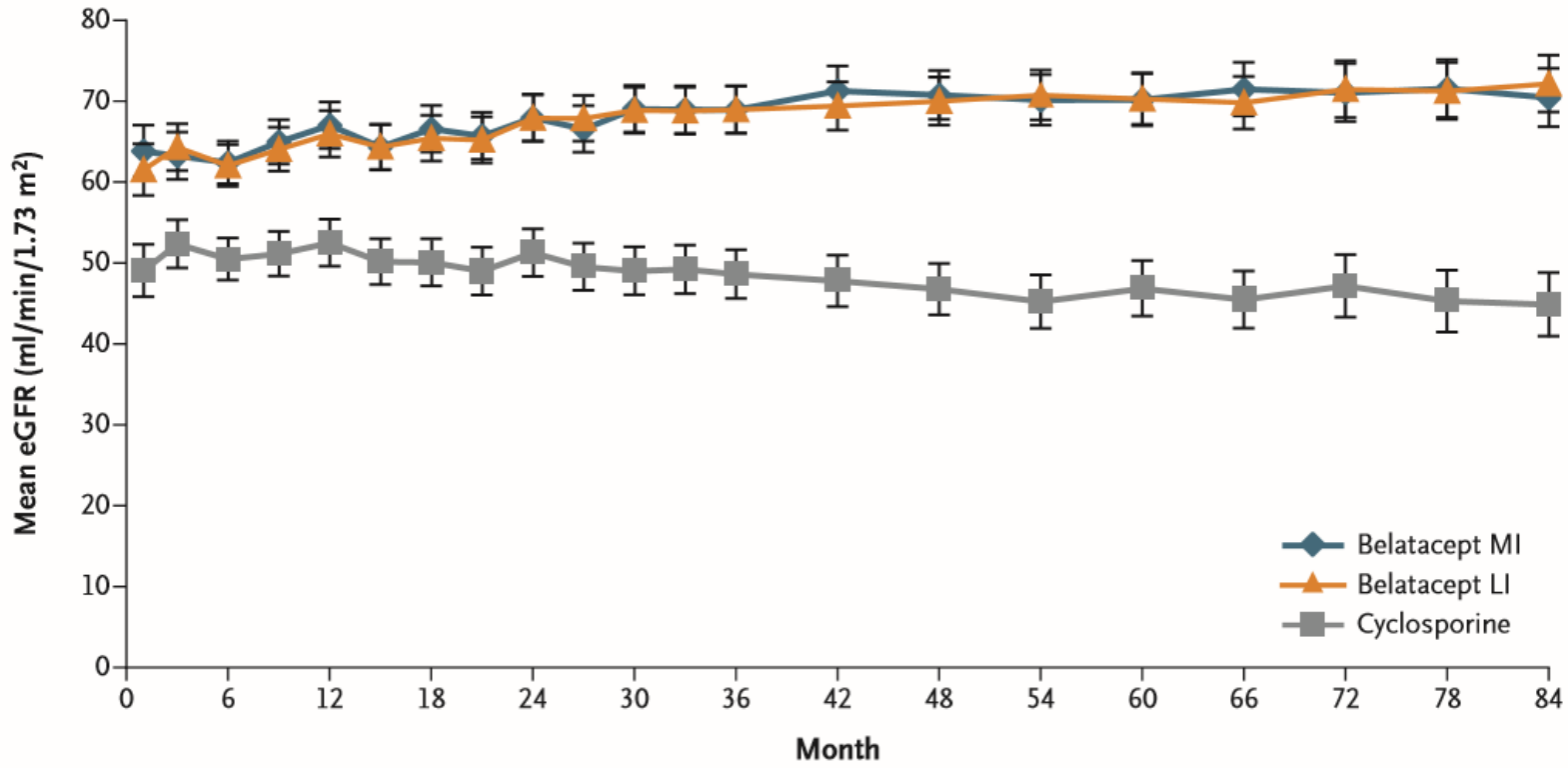


Figure 3. Glomerular Filtration Rate over the Period from Month 1 to Month 84.

The estimated glomerular filtration rate (eGFR) was determined by repeated-measures modeling, with time as a categorical variable. I bars indicate 95% confidence intervals.

Vicenti et al. NEJM 2016

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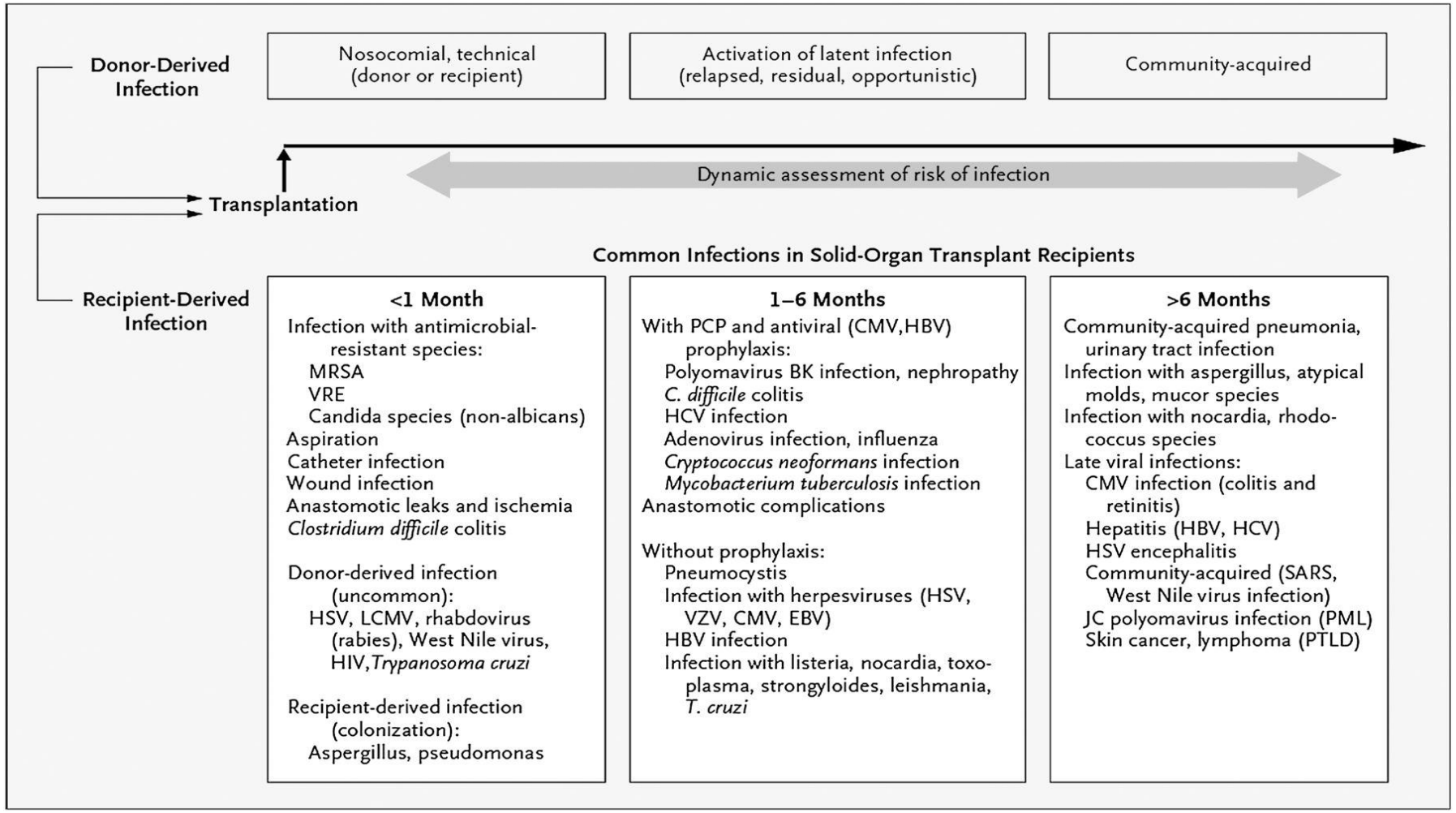
Timeline of common infections in transplant recipients



Karuthu et al. CJASN 2012

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Cancer site (ICD code[s])	Up to 5 years before RRT		During dialysis		After transplantation	
	SIR	95% CI	SIR	95% CI	SIR	95% CI
Lip (C00)	1.87	1.17–2.83	3.68	2.46–5.28	47.08	41.75–52.89
Tongue (C01–C02)	0.53	0.06–1.93	3.28	1.69–5.72	7.17	4.38–11.07
Mouth (C03–C06)	1.34	0.43–3.13	2.15	0.98–4.08	4.58	2.51–7.69
Salivary gland (C07–C08)	2.11	0.57–5.40	1.2	0.15–4.34	7.71	3.33–12.20
Esophagus (C15)	1.05	0.28–2.68	1.68	0.96–2.74	3.82	2.26–6.03
Stomach (C16)	0.81	0.35–1.60	1.52	1.01–2.19	1.84	1.07–2.94
Small intestine (C17)	1.25	0.15–4.53	3.06	1.12–6.67	1.73	0.21–6.25
Colon (C18)	1.33	1.06–1.65	1.18	0.93–1.47	2.36	1.87–2.92
Rectum (C19–C20)	1.33	0.98–1.77	1.02	0.72–1.40	0.63	0.33–1.07
Anus (C21)	0.33	0.07–0.96	0.23	0.03–0.82	2.76	1.51–4.64
Liver (C22)	2.87	0.78–7.34	2.25	1.23–3.77	3.19	1.53–5.87
Gallbladder (C23–C24)	0	-	1.55	0.67–3.05	4.34	2.16–7.76
Pancreas (C25)	2.16	0.87–4.45	1.17	0.69–1.85	1.21	0.56–2.30
Larynx (C32)	0.96	0.42–1.90	1.02	0.41–2.11	2.1	0.96–3.98
Trachea; bronchus and lung (C33–C34)	1.07	0.74–1.49	1.59	1.33–1.88	2.45	2.00–2.97
Melanoma (C43)	1.02	0.81–1.27	1.06	0.81–1.38	2.53	2.08–3.05
Mesothelioma (C45)	0.61	0.02–3.37	1.73	0.75–3.40	1.32	0.27–3.85
Kaposi sarcoma (C46) (Nalesnik et al. 2011)	19.64	4.05–57.40	57.88	21.24–125.98	207.9	113.66–348.82
Connective and other soft tissue (C47–C49)	0.49	0.06–1.78	1.26	0.41–2.93	4.13	2.13–7.21
Breast (C50) (incl. males)	0.91	0.71–1.14	1.25	0.99–1.55	1.03	0.78–1.34
Vulva (C51)	1.57	0.19–5.67	1.59	0.19–5.73	24.54	14.55–38.79
Cervix uteri (C53)	1.6	0.80–2.86	2.58	1.38–4.42	2.49	1.33–4.27
Corpus uteri (C54)	1.53	0.92–2.40	1.07	0.53–1.91	1.74	0.92–2.97
Ovary (C56)	0.78	0.25–1.82	1	0.43–1.98	1.15	0.46–2.38
Penis (C60)	1.29	0.03–7.16	4.72	0.97–13.80	15.94	5.85–34.69
Prostate (C61)	1.16	0.98–1.36	0.66	0.52–0.83	0.95	0.68–1.29
Testis (C62)	2.1	0.77–4.57	0.71	0.02–3.94	1.25	0.34–3.20
Eye (C69)	2.1	0.68–4.91	1.22	0.15–4.39	7.57	3.46–14.36
Brain (C71)	0.19	0.00–1.07	1.1	0.59–2.05	0.57	0.16–1.46
Thyroid (C73)	2.57	1.44–4.24	9.23	6.53–12.67	6.9	4.69–9.79
Hodgkin disease (C81)	1.28	0.26–3.75	2.56	0.70–6.54	3.75	1.51–7.73
Non-Hodgkin lymphoma (C82–C85)	1.51	1.05–2.10	1.36	0.94–1.90	9.86	8.37–11.54
Leukemia (91–95)	0.89	0.51–1.44	1.14	0.74–1.77	2.46	1.65–3.67

Chapman. Cold Spring Harb Persp Med 2013

Cancer

- Risk is related to duration and intensity of immunosuppression
- Non-melanoma skin cancer is most common malignancy

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Post transplant diabetes mellitus

- Incidence increasing
- Prevalence 2-53%
- Onset typically within 1-3 years
- Adverse impact on:
  - Graft survival (RR 3.72)
  - Mortality (RR 1.8)

Palepu et al. World J Diabetes 2015

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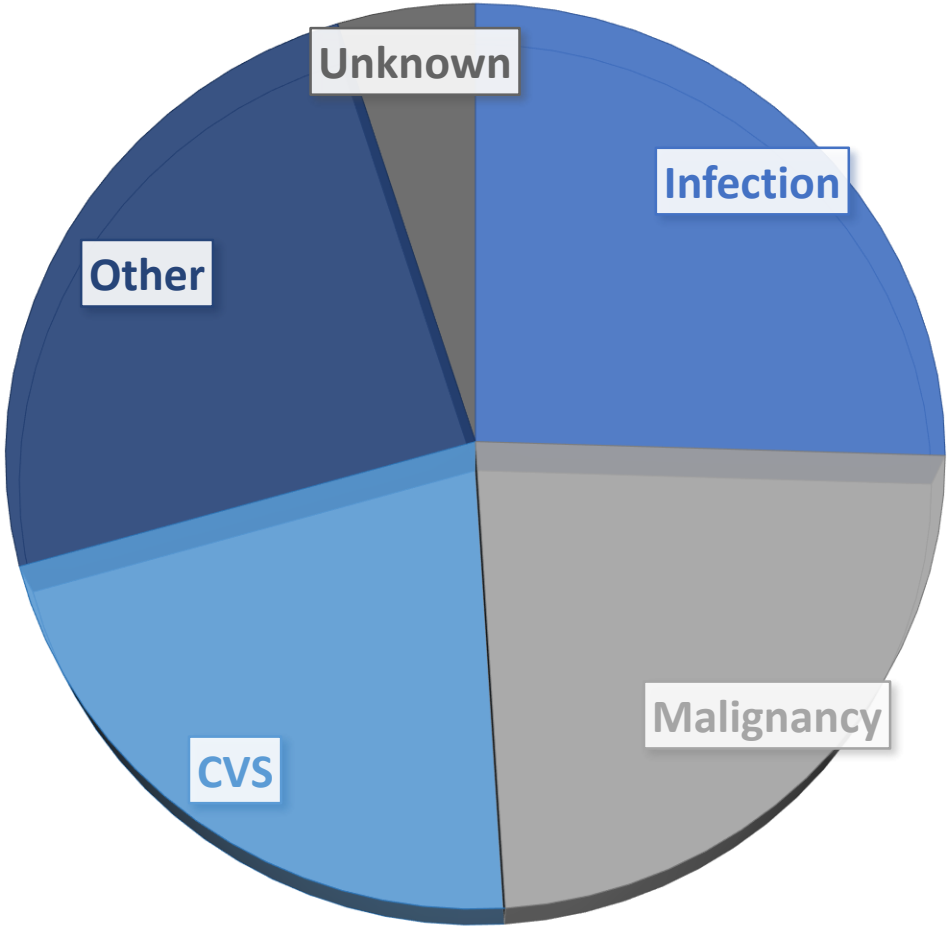
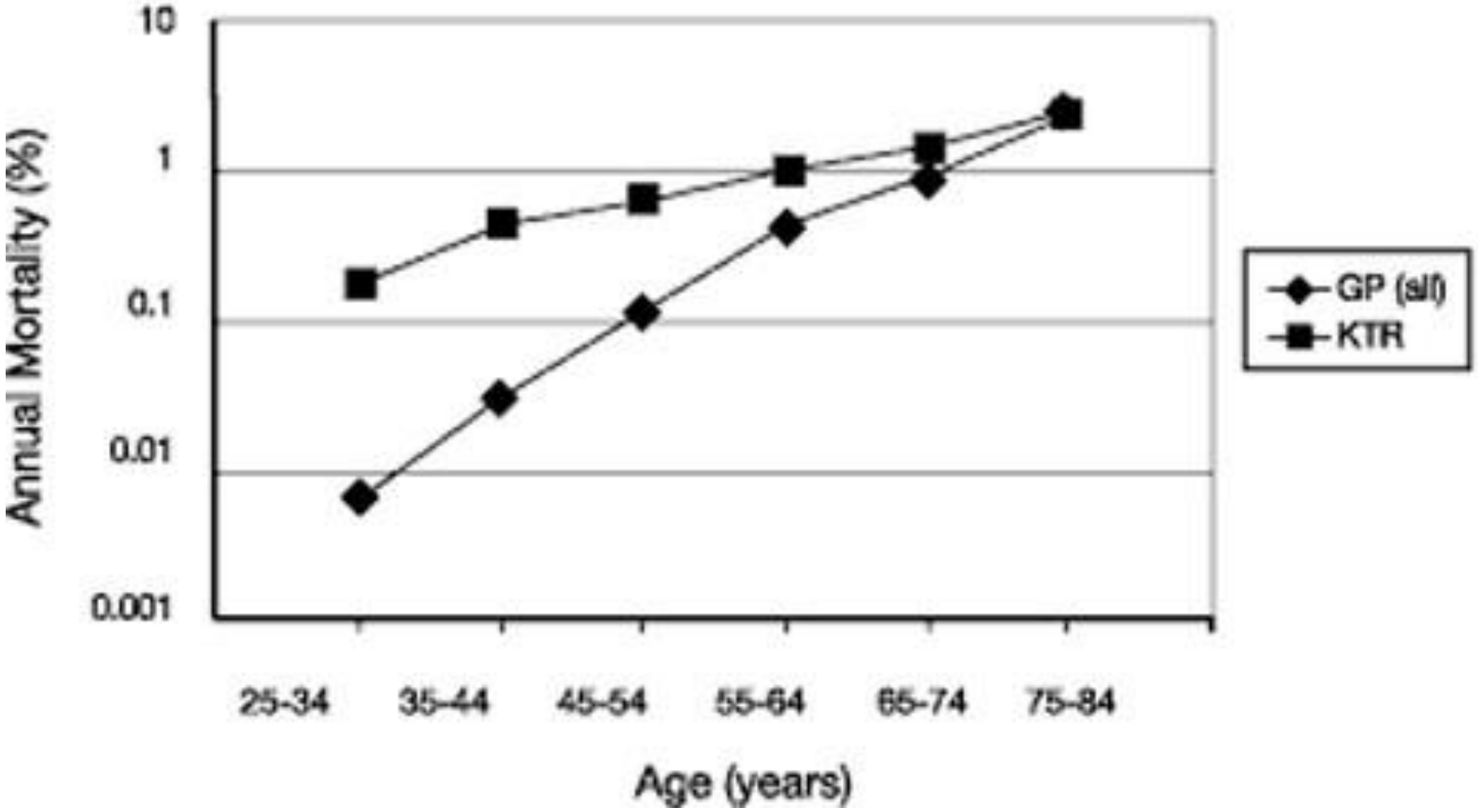
Cause of death post transplant



Mortality risk



NKF KDOQI GUIDELINES

Survival with ESRD

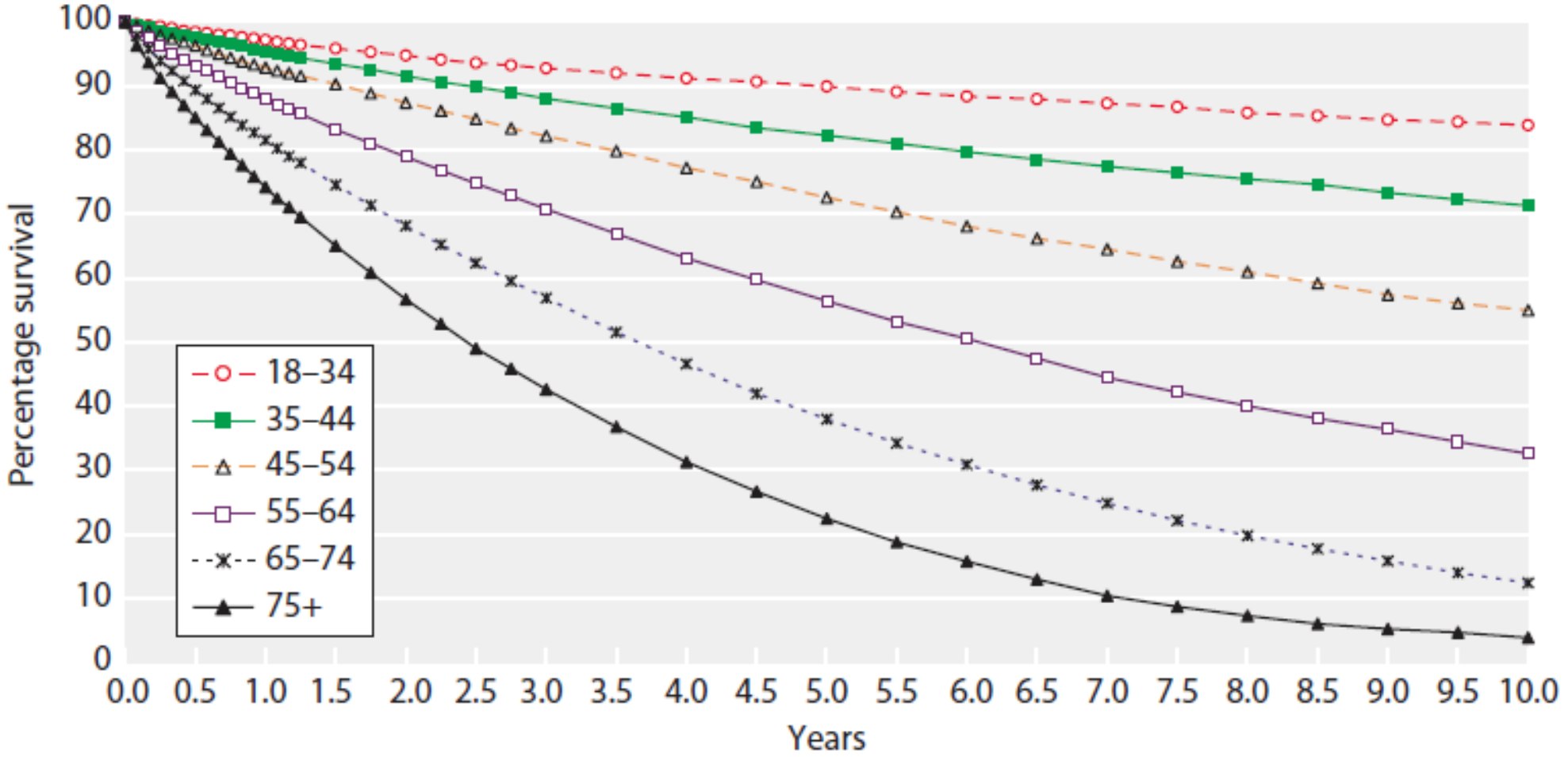


Fig. 5.5. Survival of incident patients (unadjusted), 1997–2012 cohort (from day 90), without censoring at transplantation

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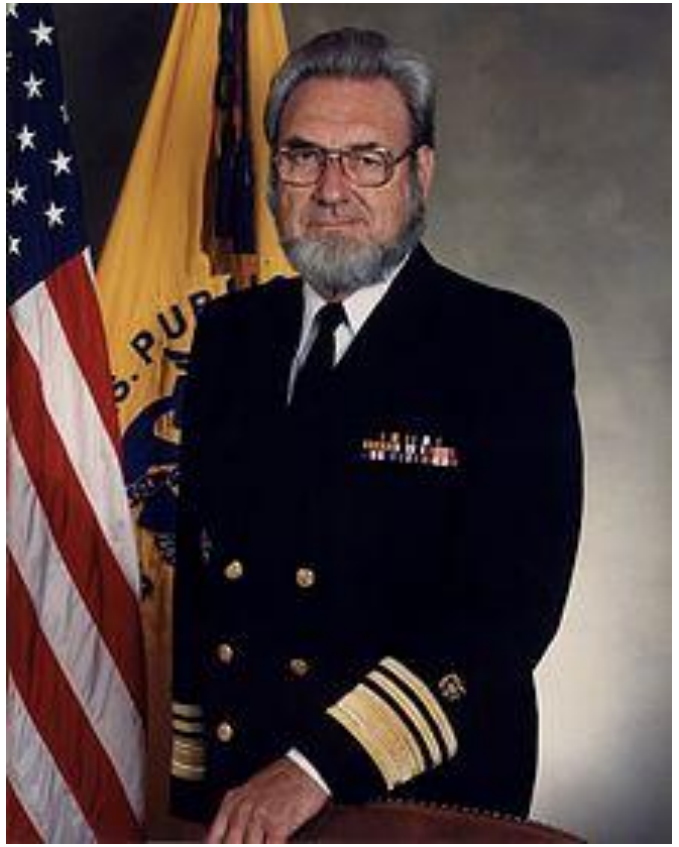


Drugs don't work in patients who don't take them.

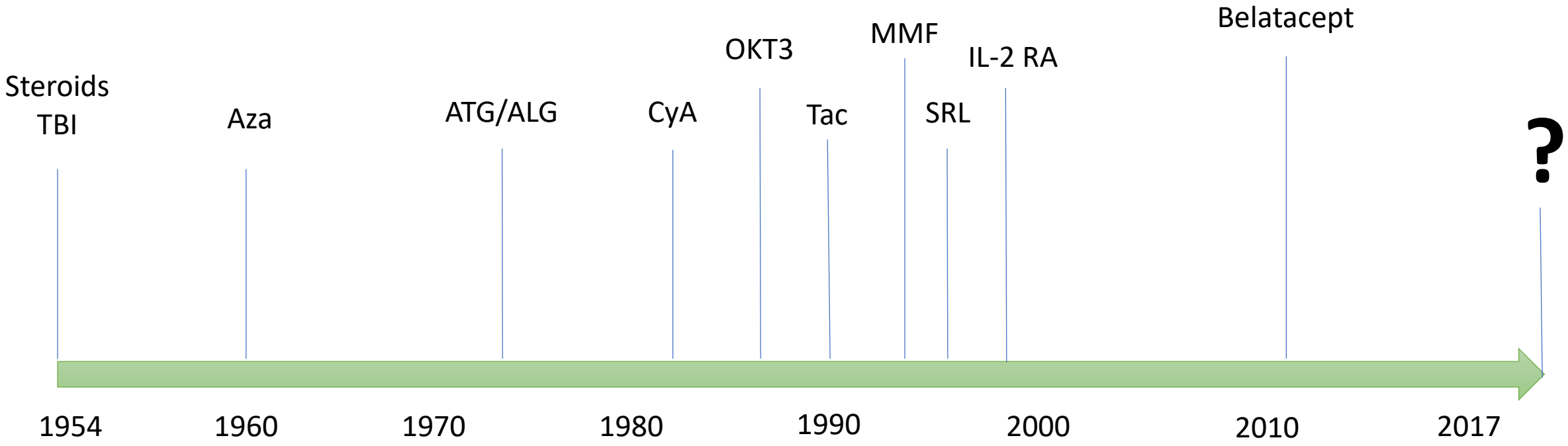
— C. Everett Koop, M.D.

Challenges

- What would the ideal immunosuppressant regimen look like?

  - Simple regimen
  - Easy to administer
  - Highly effective
  - Short term (< 6 months)
  - Non-nephrotoxic
  - Non-diabetogenic
  - Specific (avoid generalised immune suppression)
  - No impact on cardiovascular risk profile

Rising to the challenge


Steroids
TBI
Aza
ATG/ALG
CyA
OKT3
Tac
MMF
SRL
IL-2 RA
Belatacept
?
1954
1960
1970
1980
1990
2000
2010
2017

Tolerance

- “Holy grail” of transplantation

- Cell based therapies
  - Donor bone marrow
  - Peripheral blood derived stem cells/T cells

Principles

- Induction of “mixed chimerism”

- Presence of donor immune cells
  - Thymus
  - Peripheral lymphoid tissue

- Elimination of alloreactive T cell clones
  - Anergy
  - Deletion
  - Regulation

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

HLA-Mismatched Renal Transplantation without Maintenance Immunosuppression

Tatsuo Kawai, M.D., A. Benedict Cosimi, M.D., Thomas R. Spitzer, M.D., Nina Tolkoff-Rubin, M.D., Manikkam Suthanthiran, M.D., Susan L. Saidman, Ph.D., Juanita Shaffer, B.S., Frederic I. Preffer, Ph.D., Ruchuang Ding, M.D., Vijay Sharma, Ph.D., Jay A. Fishman, M.D., Bimalangshu Dey, M.D., Dicken S.C. Ko, M.D., Martin Hertl, M.D., Nelson B. Goes, M.D., Waichi Wong, M.D., Winfred W. Williams, Jr., M.D., Robert B. Colvin, M.D., Megan Sykes, M.D., and David H. Sachs, M.D.

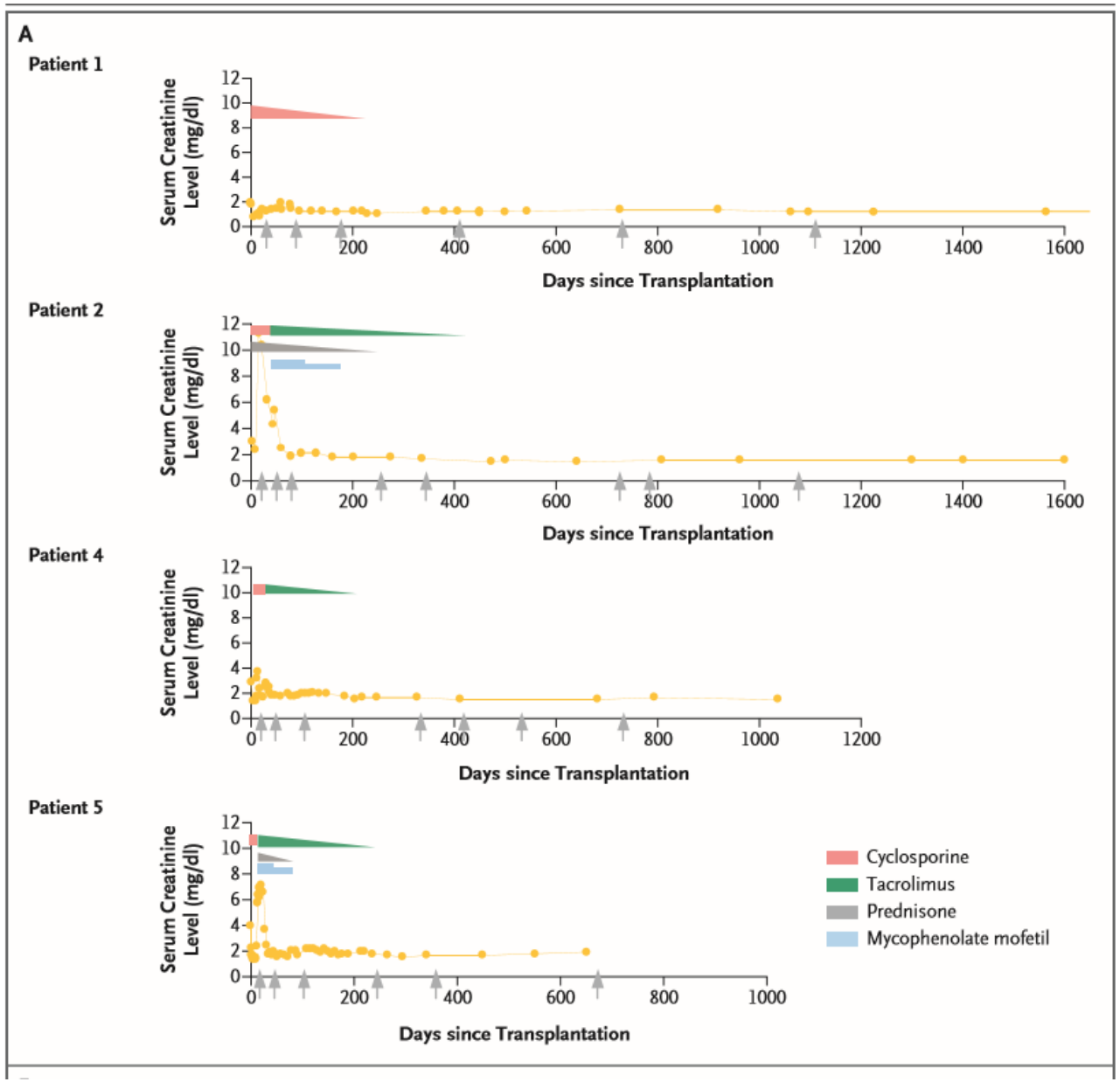
Tolerance regimen

- Cyclophosphamide
  - 60mg/kg x 2 doses (4.2g IV for 70kg man)
- Anti-CD2 antibody
  - Targets T cells/NK cells
- Thymic irradiation (700cGy)
- Rituximab
  - 375mg/kg x 2
- Steroids
  - Withdrawn at day 10
- CNI
  - Tapered off at 9 – 14 months

Kawai et al. NEJM 2008

Donor bone marrow

- 1 haplotype matched donor
  - Parent/sibling
- Bone marrow from donor iliac crest
  - 2.7×10^8 cells/kg infused on day 0
- No graft vs host disease seen
- No detectable chimerism beyond 3 weeks!



Kawai et al. NEJM 2008

Table 1. Patient Characteristics and Results of Laboratory Tests.*

Outcome and Regimen No.	Patient No.	Time to Discontinuation of Immunosuppressive Therapy after Transplantation	Graft Survival	Duration without Immunosuppression	Pathologic Status	Current Serum Creatinine Level	Time to Appearance of Post-Transplantation Donor-Specific Antibodies Detected on ELISA	Current Immunosuppression
		mo				*mg/dl*		
Long-term discontinuation of immunosuppression								
1	1	9	>10.0 yr	>9.2 yr	No rejection	1.1	Not detectable	None
1	2	14	>9.4 yr	5.8 yr	No rejection; recurrence of membranoproliferative glomerulonephritis	2.1	Not detectable	Mycophenolate mofetil after 7 yr
2	4	9	>7.7 yr	4.2 yr	Chronic rejection (after 5 yr)	1.9	1.0 yr	Mycophenolate mofetil after 6 yr
2	5	9	>6.8 yr	>6.0 yr	Early transplant glomerulopathy (after 6.8 yr)	2.3	1.7 yr	None
3	6	8	>3.8 yr	>3.2 yr	No rejection	1.5	Not detectable	None
3	7	8	>3.6 yr	>3.0 yr	No rejection	0.8	Not detectable	None
3	9	8	>3.2 yr	>2.6 yr	No rejection	1.1	Not detectable	None
No discontinuation of immunosuppression								
1	3	Not applicable	10 days	Not applicable	Acute humoral rejection	1.2 after retransplantation	10 days	Mycophenolate mofetil, tacrolimus, and corticosteroids
3	8	Not applicable	0.5 yr	Not applicable	Thrombotic microangiopathy	5–7 with dialysis	Not detectable	None after reinstitution of dialysis
3	10	Not applicable	>3.1 yr	2 mo	Acute cellular rejection	4–6	Not detectable	Dactinomycin and corticosteroids

Kawai et al. NEJM 2013

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Tolerance and Chimerism after Renal and Hematopoietic-Cell Transplantation

John D. Scandling, M.D., Stephan Busque, M.D., Sussan Dejbakhsh-Jones, M.S., Claudia Benike, B.S., Maria T. Millan, M.D., Judith A. Shizuru, M.D., Ph.D., Richard T. Hoppe, M.D., Robert Lowsky, M.D., Edgar G. Engleman, M.D., and Samuel Strober, M.D.

SUMMARY

We describe a recipient of combined kidney and hematopoietic-cell transplants from an HLA-matched donor. A post-transplantation conditioning regimen of total lymphoid irradiation and antithymocyte globulin allowed engraftment of the do-

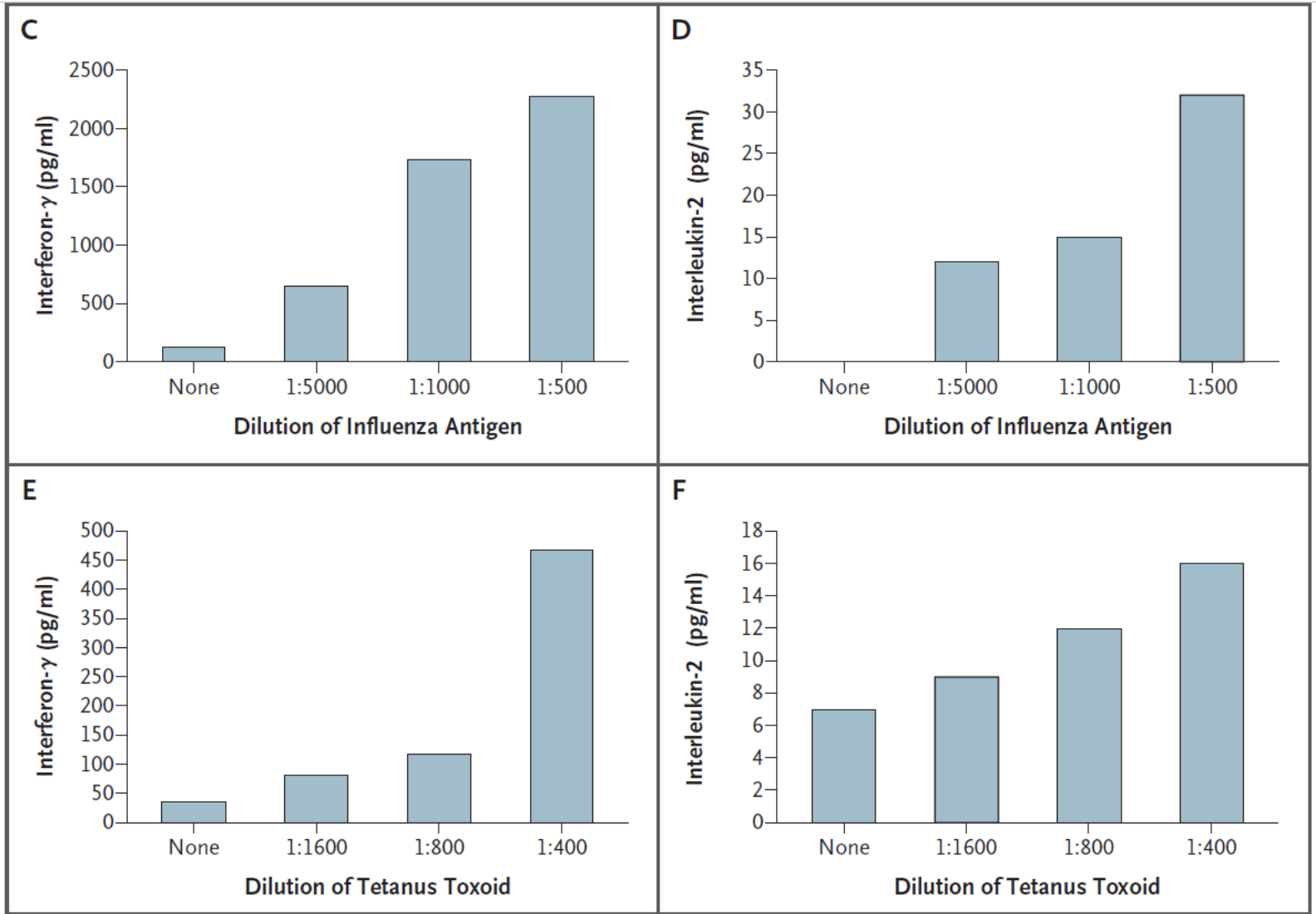


Figure 3. In Vitro Responses of the Patient's Mononuclear Cells to Stimulation by Alloantigens or Microbial Antigens, before Transplantation and 24 Months after Transplantation.

"Prediction is very difficult, especially if it's about the future."

-- Niels Bohr
Physics Nobel prize 1922