# Strategie immunosoppressive e rischio infettivo nel trapianto di organo solido


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# Strategie immunosoppressive e rischio infettivo

- ✓ what we learnt
- ✓ immunosuppression and CMV
- ✓ what we would like to have

# Alexis Carrel Nobel lecture 1912

….Thus, while the problem of the transplantation of organs has been solved, from a surgical point of view……. We need a more fundamental study of the biological relationships existing between living tissues

# The Nobel Prize in Physiology or Medicine 1960

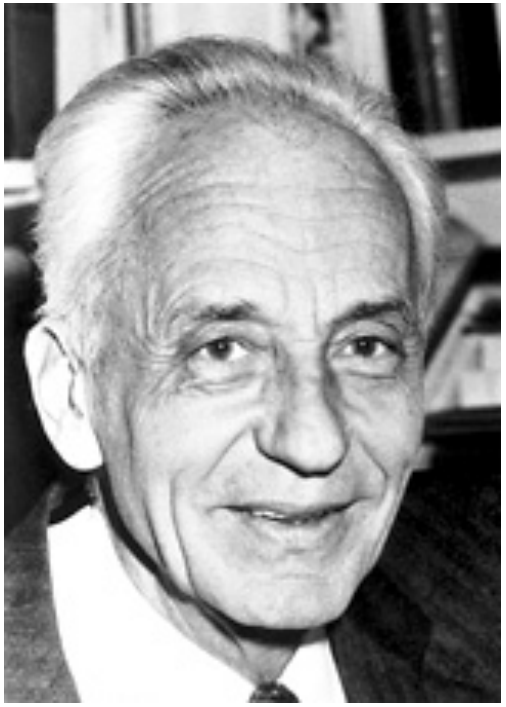
*“for discovery of acquired immunological tolerance"*

**Sir Frank Macfarlane Burnet**

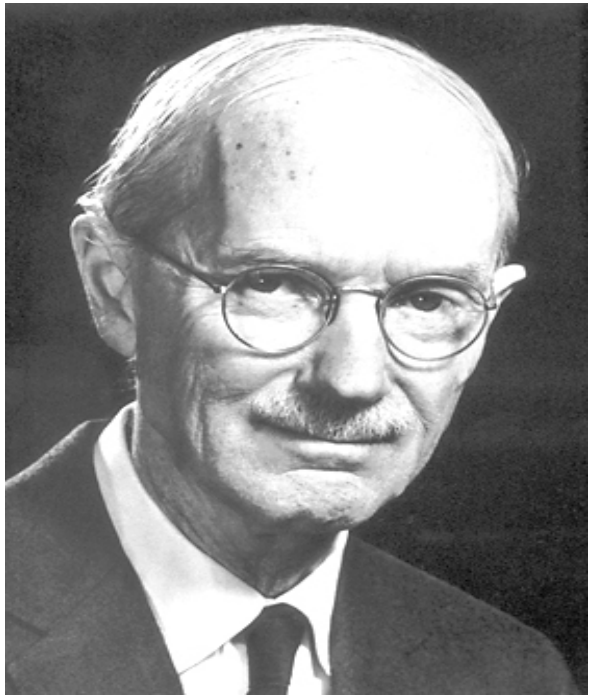
**Sir Peter Brian Medawar**

# The Nobel Prize in Physiology or Medicine 1980

Baruj Benacerraf



Jean Dausset

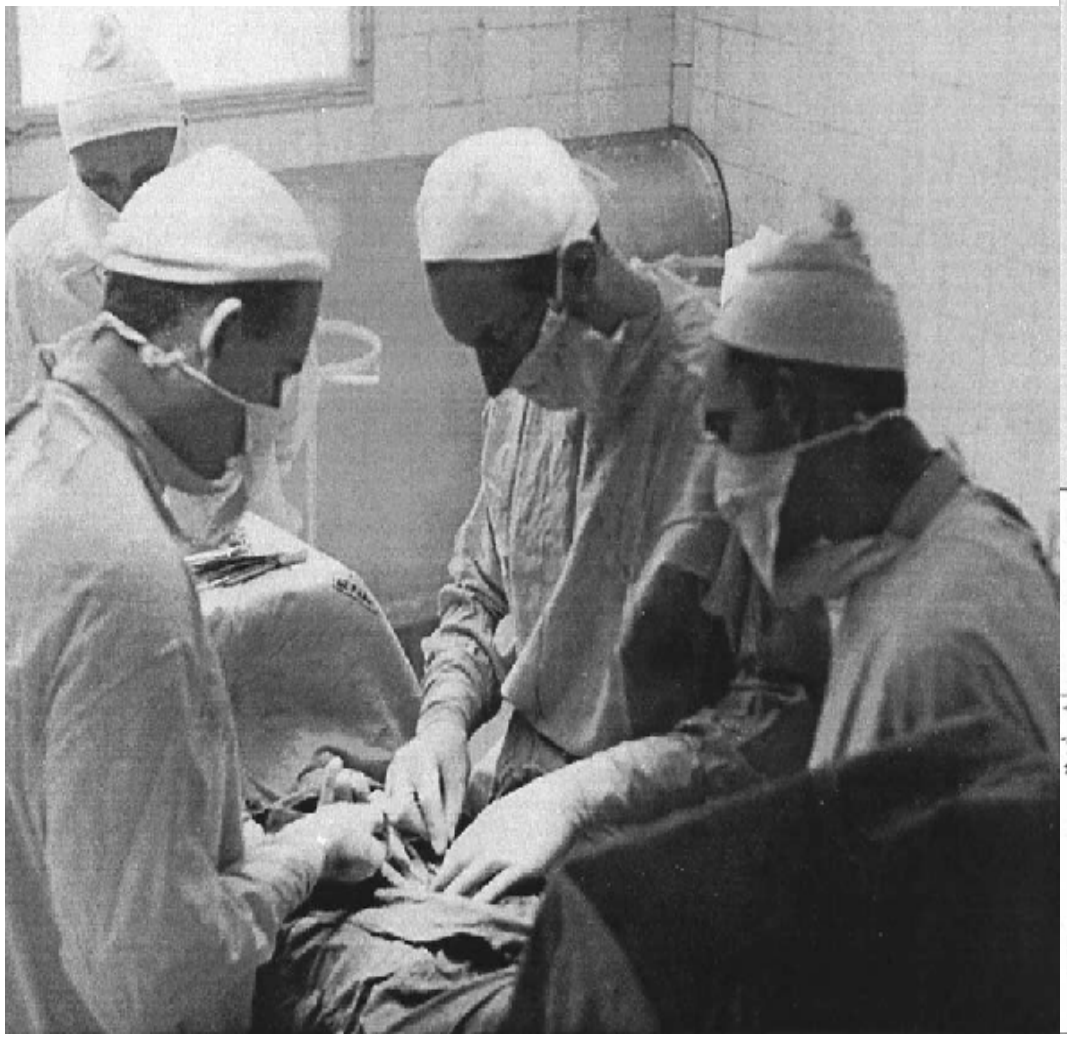


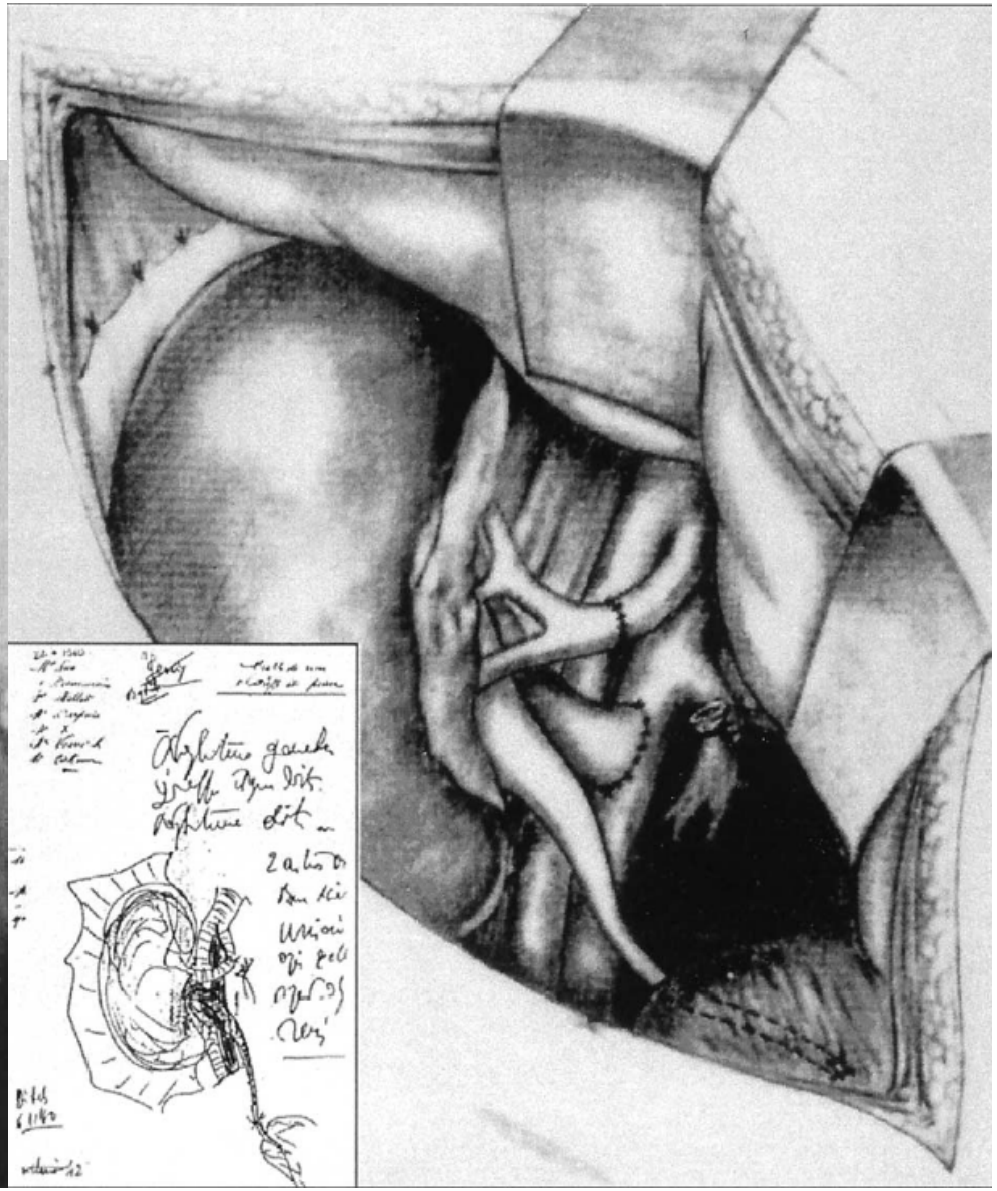
George D. Snell

***"for their discoveries concerning genetically determined structures on the cell surface that regulate immunological reactions".***

# Surgical technique for renal transplantation

## Henry Kuss





# 1950

**Surgical technique**

**Rejection / Tolerance**

**HLA differences**

**How to control the immune system ?**

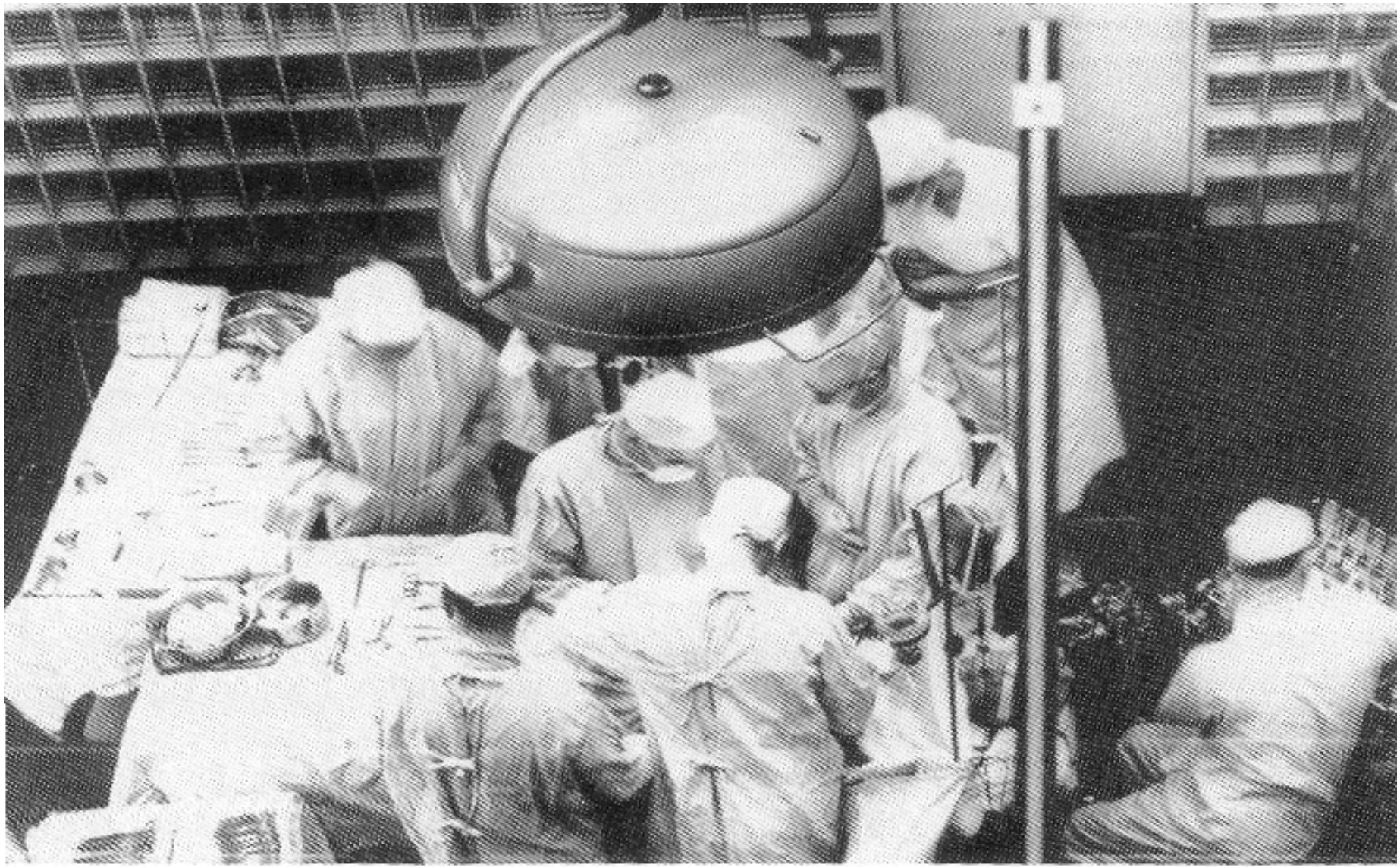
# The identical twins Herrick
# 1954 successful kidney transplant.

J. Hartwell Harrison

John P Merrill

Joseph E Murray

# 23 December 1954 : first successful kidney tx



**The identical twins Herrick leave the hospital the first participants in 1954 successful kidney transplant.**

## Joseph E. Murray

## 1954

the first successful human kidney transplant between twins in Boston.

## 1990 Nobel prize

in Physiology & Medicine

# Organ Donation

- living twins : genetic identity
- living related
- deceased cardiac death

# 1950

- Sub-lethal irradiation
- Azathioprine

1954 - 1962

# Factors in successful renal transplantation

T. E. STARZL, M.D., PH.D.*
T. L. MARCHIORO, M.D.
D. RIFKIND, M.D., PH.D.
J. H. HOLMES, M.D.
D. T. ROWLANDS, JR., M.D.
W. R. WADDELL, M.D.
DENVER, COLO.
*From the Departments of Surgery, Pathology, and Medicine, University of Colorado Medical Center and Veterans Administration Hospital*

During the interval from 15 to 2½ months ago, 45 patients were treated at the University of Colorado Medical Center with renal homografts obtained from living volunteer donors. As a consequence of this experience, many aspects of renal homotransplantation have come into focus, in-

transplantation. Furthermore, the mechanisms that caused death will be documented in the unsuccessful cases, and suggestions made for changes in management which may, in the future, help avoid the previously encountered lethal complications.

Finally, note will be made of several un-

# Factors in successful renal transplantation (1964)

- Pts Surv 6m 27/45 60 %
- Graft Surv 6m 27/45 60 %
- **Rejection** 42/45 **93 %**

- Baseline : Splenectomy + Aza
- Rejection : 6g Steroid + Actinomycin + Local Irradiation

…. to temper the vigor of the immunologic assault……. the most significant alteration to be instituted will be the use of prophylactic prednisone…. The value of this change in the immunosuppressive protocol is still highly speculative.

T. E. Starzl 1964

# 1950 - 1980

- Sub-lethal irradiation
- Azathioprine

1954 - 1959

- ALS - ATG
- Azathioprine
- Steroids

1962 - 1978

- Ciclosporine A

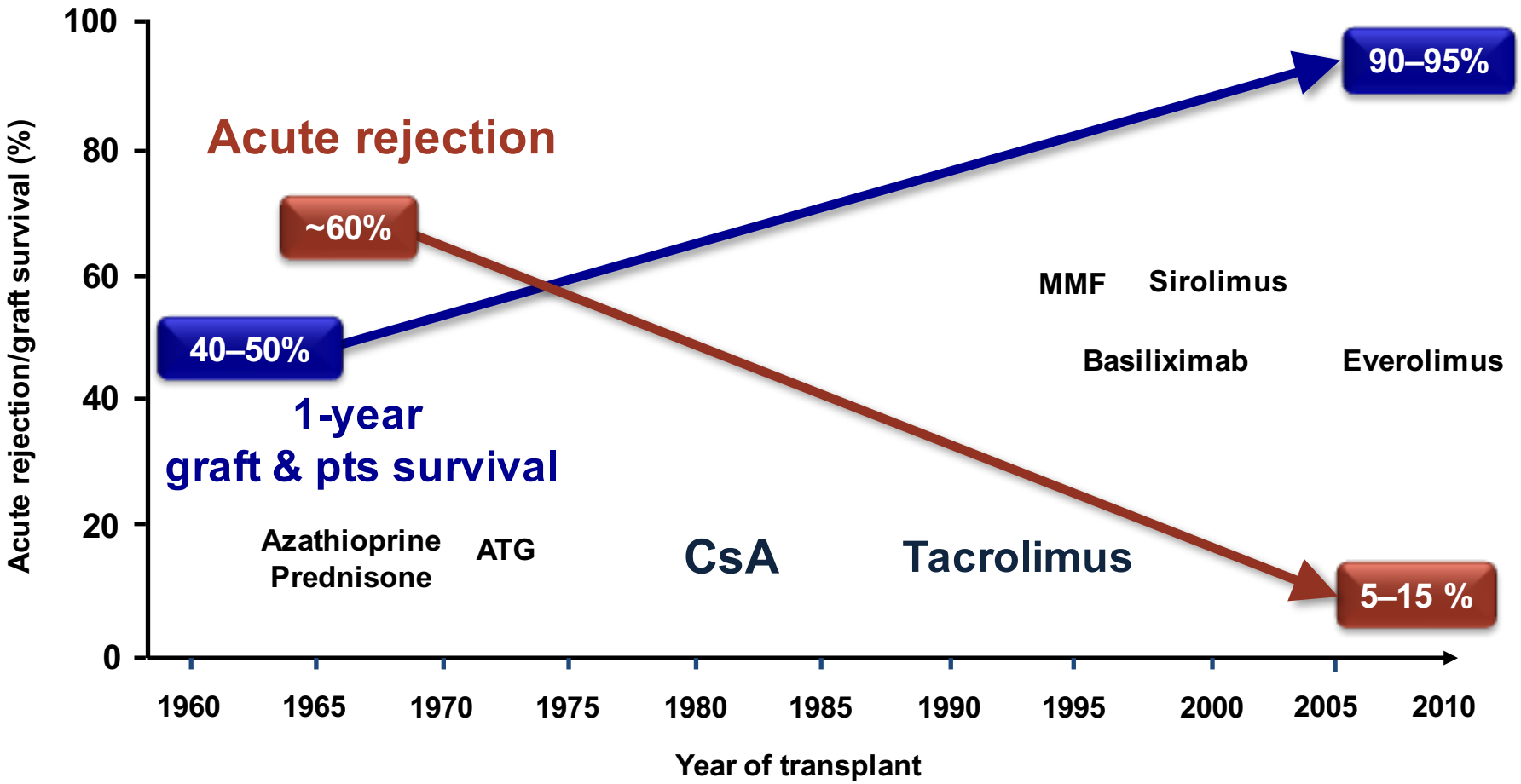
1979

# Organ Transplantation

## Evolution of immunosuppression

| | Genetics | Immunosuppression | Year |
|---|---|---|---|
| Twins | Identity | None | 1954 |
| Related | Compatibility | Sublethal X ray + BM | 1956 |
| | | Steroids | 1959 |
| Unrelated | Incompatibility | Azathioprine | 1960 |
| Deceased | Incompatibility | AZA + ster + ALS | 1962 |

# Considerable improvements have been made in the last 60 years in renal transplantation



# Renal Transplantation 2017

- Standard donor
- Old for Old
- Extended Criteria Donors
- Hyperimmunized pts
- Living donation
  - Standard / extended criteria donors
  - ABO incompatible
  - HLA incompatible positive crossmatch
- Deceased Cardiac Death

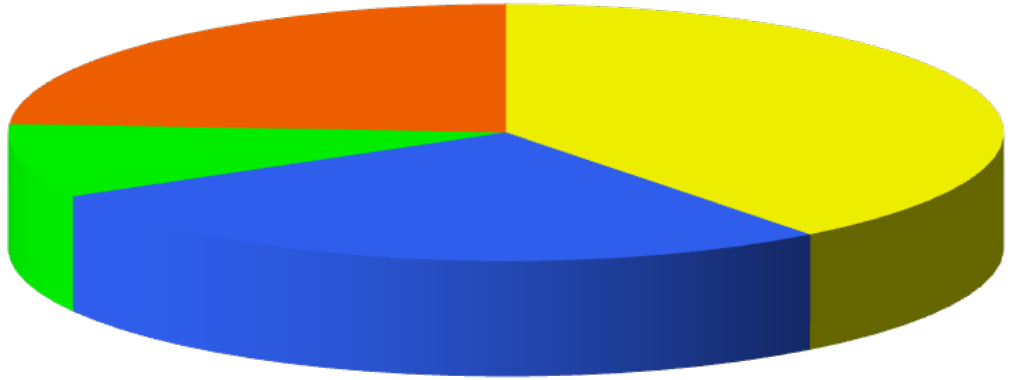
# Immunosoppressione 2017

- ✓ CNIs Cyclosporine / Tacrolimus
- ✓ MMF / MPA / Aza
- ✓ mTORi Everolimus / Sirolimus
- ✓ Basiliximab
- ✓ Thymoglobuline
- ✓ Rituximab / Bortezomib
- ✓ Eculizumab
- ✓ Belatacept

# Una soluzione per tutti i casi

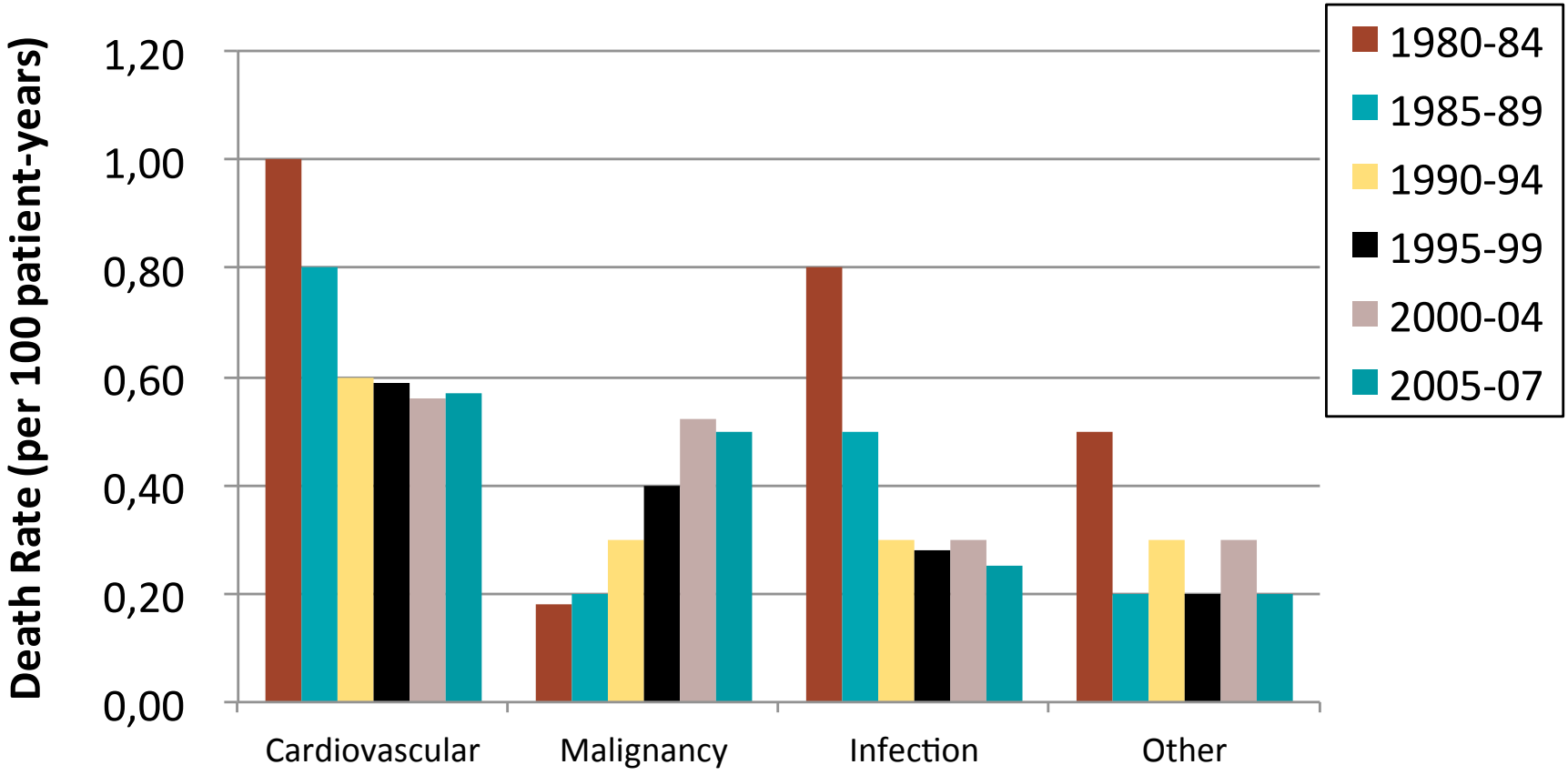
# Causes of death with a functioning graft after renal transplantation

67.874 first renal transplants, 1994–2000




USRDS = United States Renal Data System

# Adjusted death rates per 100 patient-years from cardiovascular disease, malignancy and infection reported in 5 yearly cohorts from 1980




Pilmore H, et al. *Transplantation.* 2010;89:851-857.

# ABO incompatible tx

# & Hyperimmunized pts

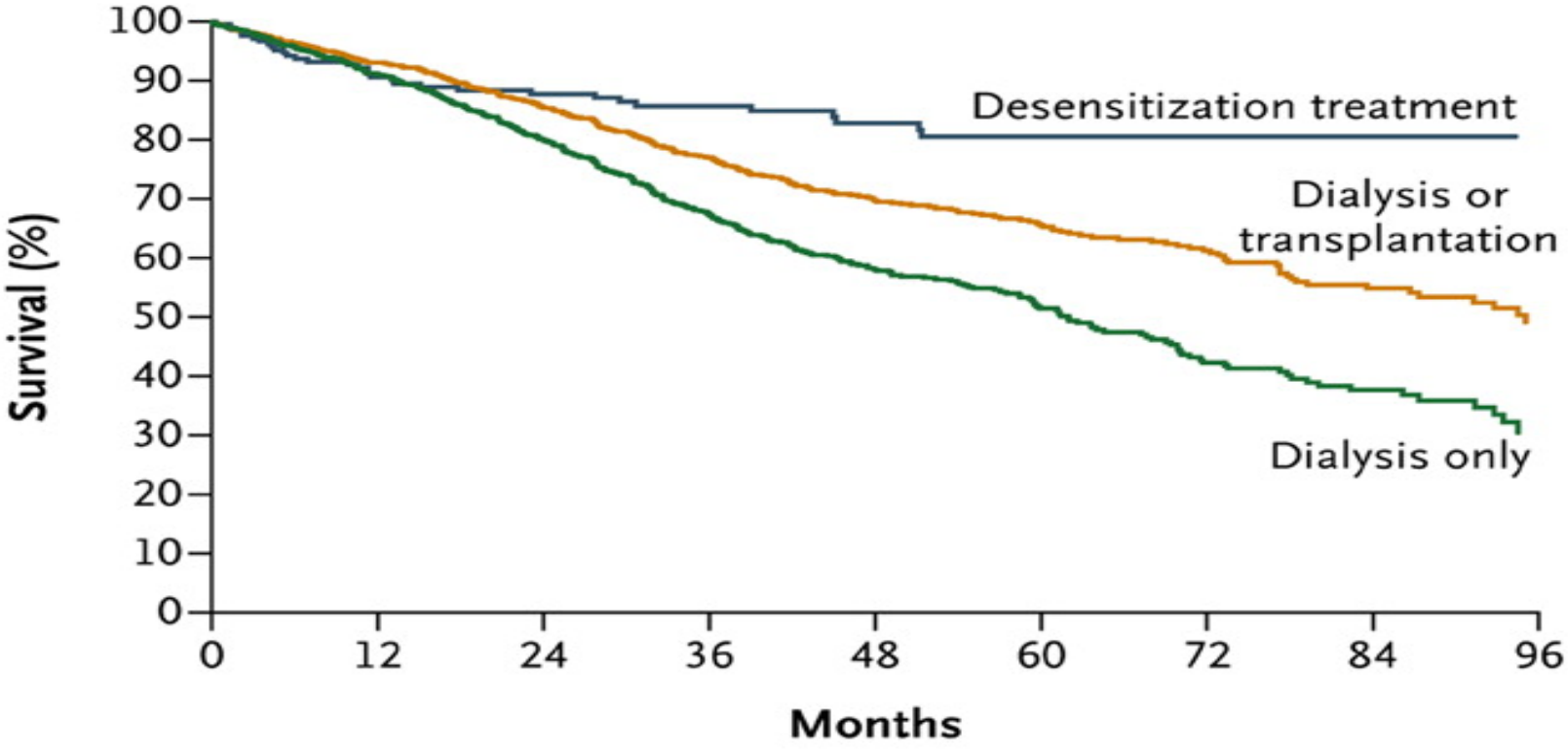
# ± positive cross-matches

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Desensitization in HLA-Incompatible Kidney Recipients and Survival

Robert A. Montgomery, M.D., D.Phil., Bonnie E. Lonze, M.D., Ph.D.,




**No. at Risk**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Desensitization treatment | 210 | 170 | 143 | 110 | 75 | 58 | 42 | 28 | 14 |
| Dual therapy | 1027 | 854 | 688 | 497 | 321 | 230 | 157 | 96 | 41 |
| Dialysis only | 1012 | 822 | 626 | 419 | 250 | 159 | 93 | 54 | 17 |

N Engl J Med 2011;365:318-26.

TRANSPLANT
INTERNATIONAL

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ORIGINAL ARTICLE

# ABO desensitization affects cellular immunity and infection control after renal transplantation

Thomas Schachtner,[1,2] Maik Stein[2] and Petra Reinke[1,2]

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2 Berlin-Brandenburg Center of Regenerative Therapies (BCRT), Berlin, Germany

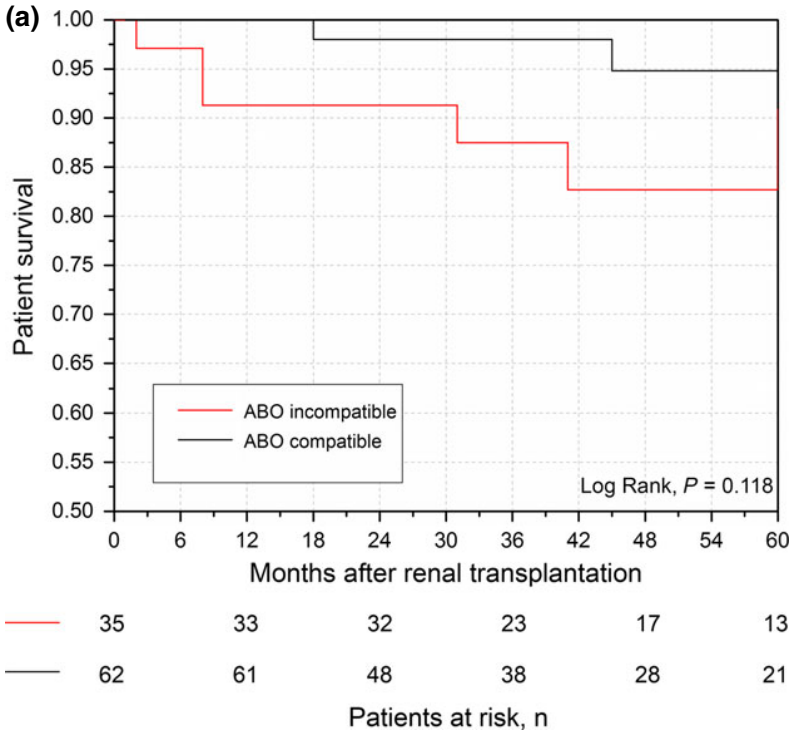
- ✓ **35 ABO-incompatible kidney transplant recipients**
- ✓ **62 ABO compatible KTRs, as controls**
- ✓ **Samples collected before, at +1, +2, +3, +6, and +12 months post-transplantation.**
- ✓ **CMV-, BKV-specific, and alloreactive T cells measured by interferon-c ELISPOT assay.**
- ✓ **immunosuppression was quantified by enumeration of lymphocyte subpopulations and cytokines.**

# Infectious complications: ABO compatible (cABO) versus ABO incompatible (iABO).

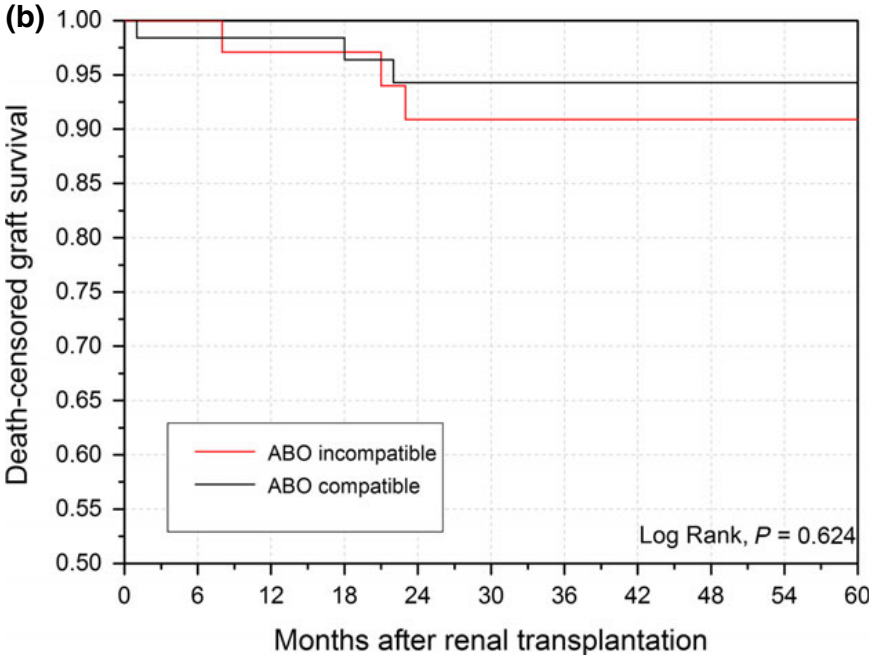
| | cABO matched ($n$ = 62) | ABO incompatible ($n$ = 35) | $P$ value |
|---|---|---|---|
| CMV seropositivity, $n$ (%) | 39 (63) | 21 (60) | 0.830 |
| CMV viremia, $n$ (%) | 13 (21) | 16 (46) | 0.020* |
| Peak CMV viremia (copies/mL)* | $4.2 \times 10^3$ ($1.3 \times 10^3$–$6.5 \times 10^5$) | $3.2 \times 10^3$ ($1.0 \times 10^3$–$5.4 \times 10^5$) | |
| CMV D+R–, $n$ (%) | 6 (10) | 5 (14) | 0.519 |
| CMV disease, $n$ (%) | 4 (6) | 6 (17) | 0.161 |
| Transplant age at CMV viremia, months* | 2 (0–9) | 1 (0–11) | 0.546 |
| BK viremia, $n$ (%) | 6 (10) | 8 (23) | 0.130 |
| Peak BK viremia (copies/mL)* | $9.2 \times 10^3$ ($4.5 \times 10^3$–$8.7 \times 10^4$) | $2.4 \times 10^4$ ($7.1 \times 10^3$–$8.4 \times 10^6$) | – |
| BK nephropathy, $n$ (%) | 0 (0) | 3 (9) | 0.044* |
| Transplant age at BK viremia, months* | 4 (2–10) | 3 (1–12) | 0.395 |
| EBV viremia, $n$ (%) | 7 (11) | 0 (0) | 0.047* |
| Peak EBV viremia (copies/mL)* | 1700 ($1.0 \times 10^3$–$5.5 \times 10^3$) | – | – |
| PTLD, $n$ (%) | 1 (2) | 0 (0) | 1 |
| Transplant age at EBV viremia, months* | 6 (3–12) | – | – |
| Septic complications, $n$ (%) | 3 (5) | 5 (14) | 0.132 |
| Severe sepsis/septic shock | 0 (0) | 4 (11) | 0.015* |
| Site of infection, $n$ (%) | | | |
| Urinary tract infection | 2 (3) | 2 (6) | 0.618 |
| Pneumonia | 1 (2) | 2 (6) | 0.295 |
| Others/unknown | 0 (0) | 1 (3) | 0.361 |
| Transplant age at sepsis, months* | 4 (2–8) | 3 (0–5) | 0.359 |
| Deaths from septic complications, $n$ (%) | 0 (0) | 3 (9) | 0.044* |
| Any infection, $n$ (%) | 18 (29) | 22 (63) | 0.001* |

*Median (range).

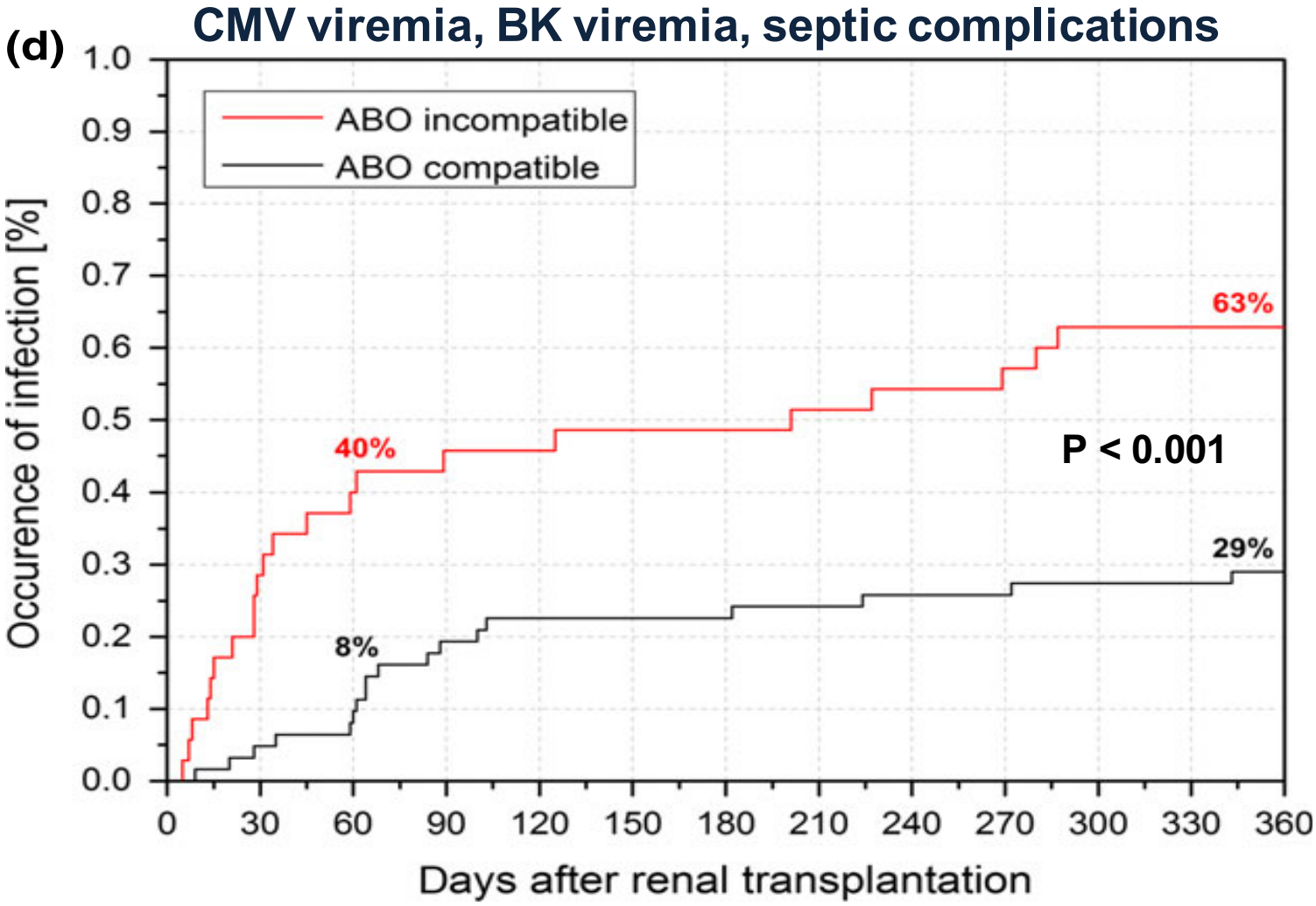
# Pts survival: ABOi vs ABOc




## Death censored graft survival



# Infections: ABOi vs ABOc



# ABO compatible (cABO) versus ABO incompatible (iABO).

**ABO-incompatible:**

- more likely to develop CMV infection, BKV- associated nephropathy, and severe sepsis ($P = 0.001$).
- poor HLA-match showed the highest rates of infections and inferior allograft function ($P < 0.05$).
- CD3+, CD4+ T-cell counts, interferon-c and IL-10 levels were lower in early post-transplantation ($P < 0.05$).
- impaired BKV and CMV-specific T-cell immunity ($P < 0.05$).
- lower frequencies of alloreactive T cells ($P < 0.05$).

- Desensitization procedures disrupt the T and B cells interaction and sinergy

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# Cancer Risk Following ABO Incompatible Living Donor Kidney Transplantation (1)

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**Eric A. Engels, MD MPH**,
Division of Cancer Epidemiology and Genetics, National Cancer Institute

**Robert A. Montgomery, MD DPhil**, and
Department of Surgery, Johns Hopkins School of Medicine

**Dorry L Segev, MD PhD**
Department of Surgery, Johns Hopkins School of Medicine

- **318 ABOi recipients in the SRTS registry**
- **7 ABOi recipients with cancers (non-Hodgkin lymphoma, Merkel cell carcinoma, gastric adenocarcinoma, hepatocellular carcinoma, thyroid cancer, pancreatic cancer, and testicular cancer)**
- **no demonstrable association between ABOi and cancer ABOi**
- **IRR 0.83, 95% CI 0.33–1.71, p=0.3**
- **ABOc matched control IRR 0.99, 95% CI 0.38–2.23, p=0.5).**

# Cancer risk after living donor kidney transplantation, comparing ABOi with ABOc matched ABO controls

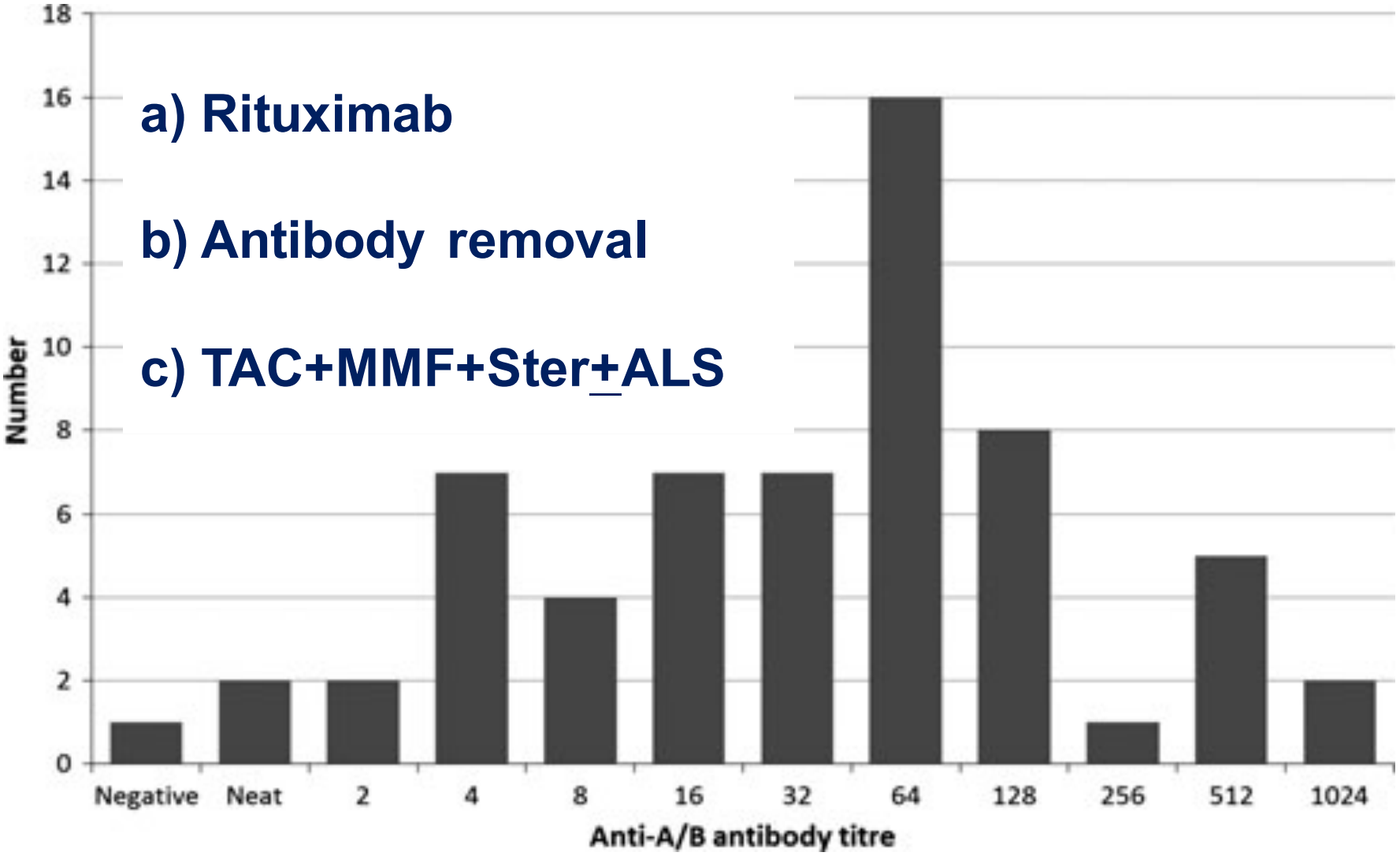
| | ABOi | ABOc (entire cohort) | ABOc (matched controls)[a] |
|---|---|---|---|
| **All Cancer** | | | |
| Rate[b] | 7.1 | 8.5 | 7.1 |
| IRR (95% CI) vs. entire cohort | 0.86 (0.02–4.85) | Reference | |
| IRR (95% CI) vs. matched controls | 0.99 (0.38–2.23) | | Reference |
| **NHL** | | | |
| Rate[b] | 1.0 | 1.2 | 1.0 |
| IRR (95% CI) vs. entire cohort | 0.76 (0.02–4.29) | Reference | |
| IRR (95% CI) vs. matched controls | 1.02 (0.02–8.38) | | Reference |

ABOi = ABO incompatible; ABOc = ABO compatible; IRR = incidence rate ratio; CI = confidence interval; NHL = non-Hodgkin lymphoma.

*a)* Matched 5 to 1 on age at transplantation, gender, race, zero HLA mismatch status, retransplantation, and year of transplant to ABOi recipients.

*b)* Per 1,000 person-years

# Tailored desensitization strategies in ABO blood group incompatible renal transplantation




Barnett et al.Transplant Iternational 27 (2014) 187–196

# Tailored desensitization strategies in ABO blood group incompatible renal transplantation

## 3y GS death censored

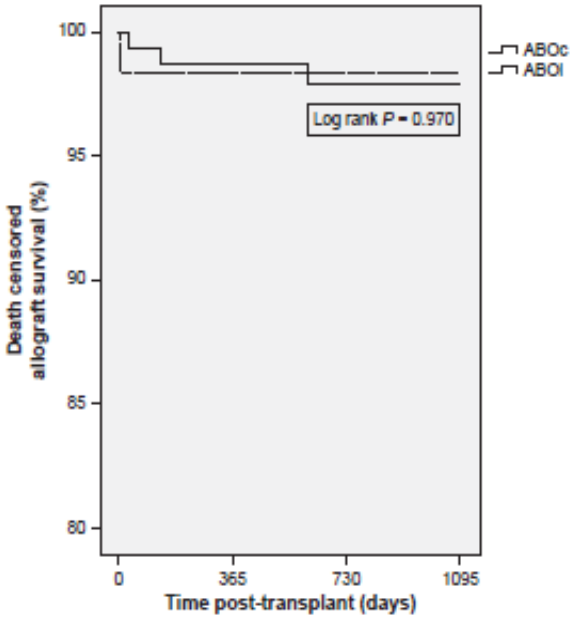



**Figure 4** Kaplan–Meier survival curve of death-censored allograft survival at 3 years post-transplant.

## 1y Rejection free surv

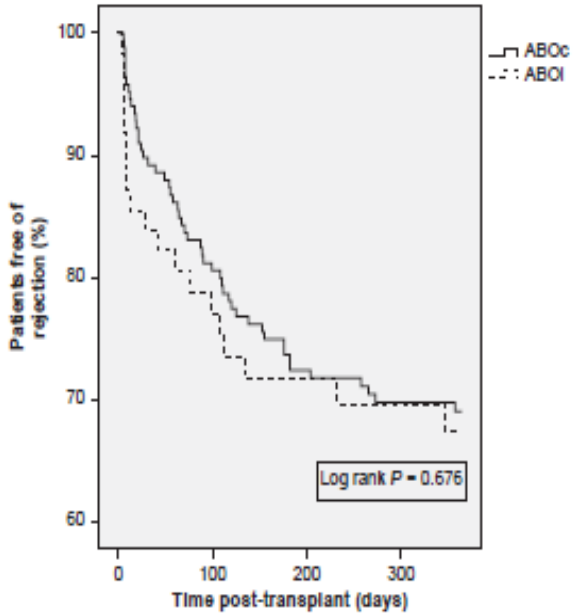



**Figure 6** Kaplan–Meier survival curve of rejection-free survival 1 year post-transplant.

## 3y PT Surv

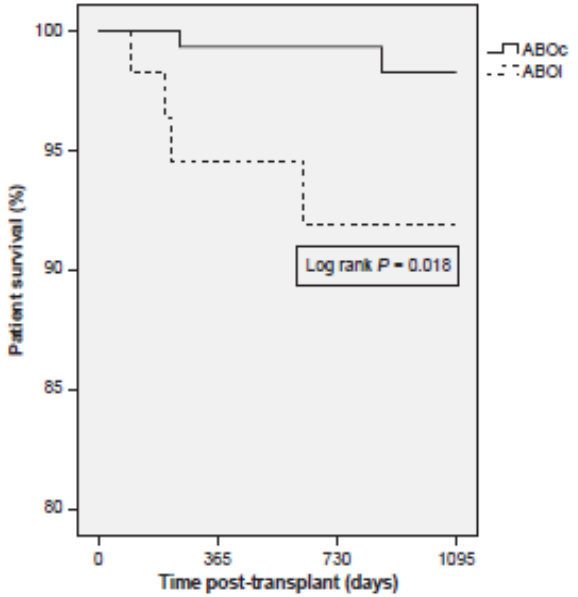



**Figure 5** Kaplan–Meier survival curve of patient survival at 3 years post-transplant.

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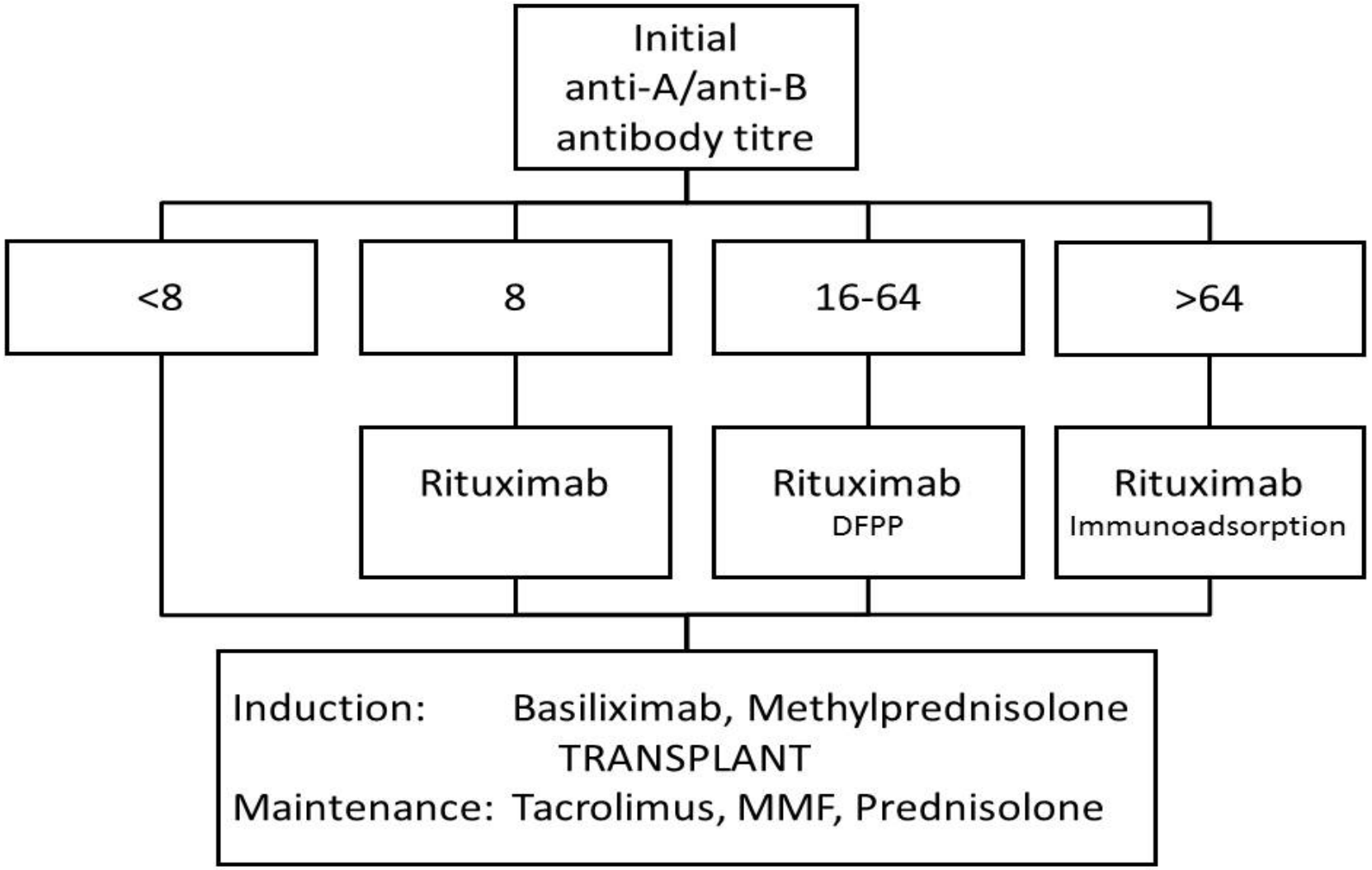
# Guy's Hospital
# tailored minimal desensitisation strategy

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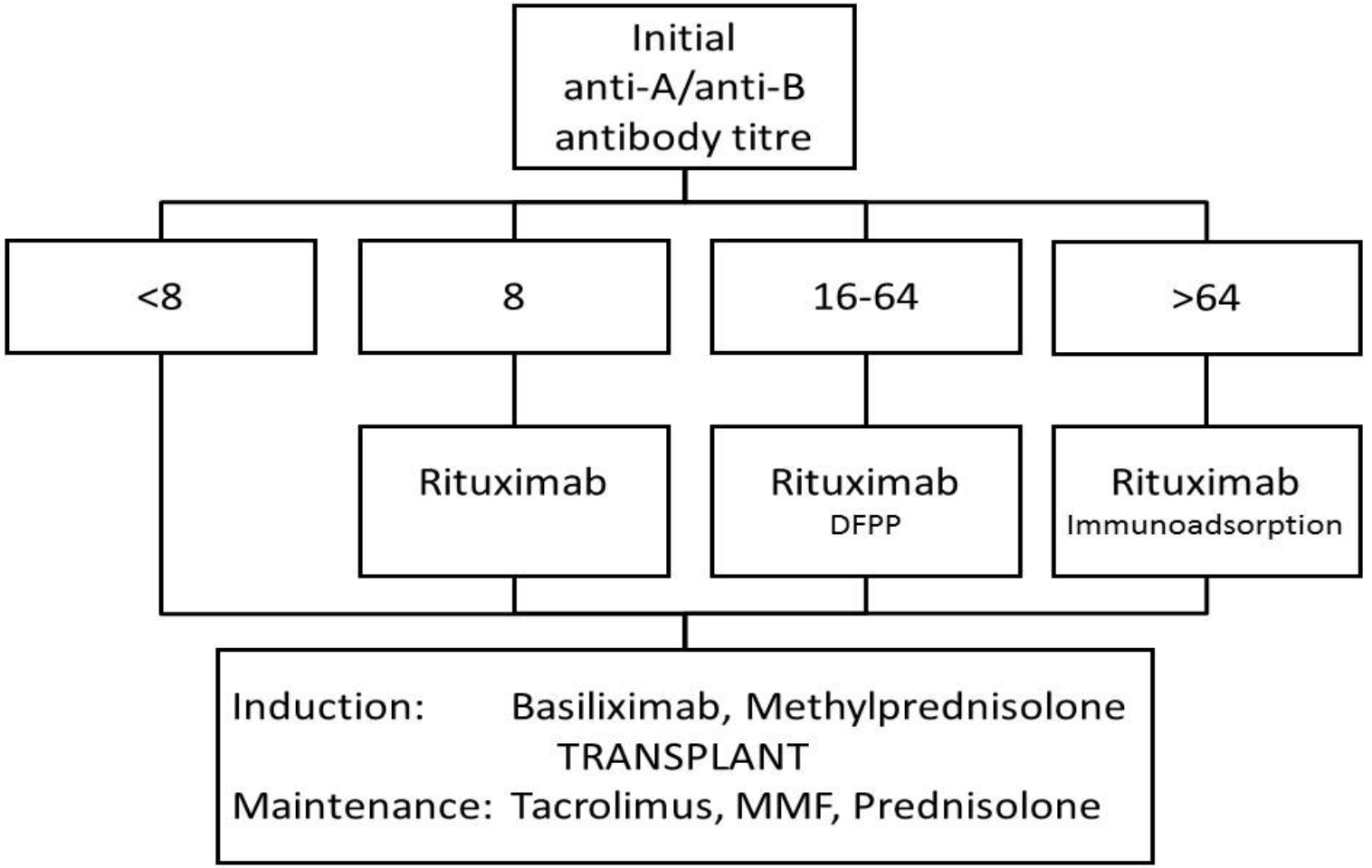
# Tailored desensitization strategies

# in ABO blood group incompatible renal transplantation




> 128 ?

Paired Kidney Exchange

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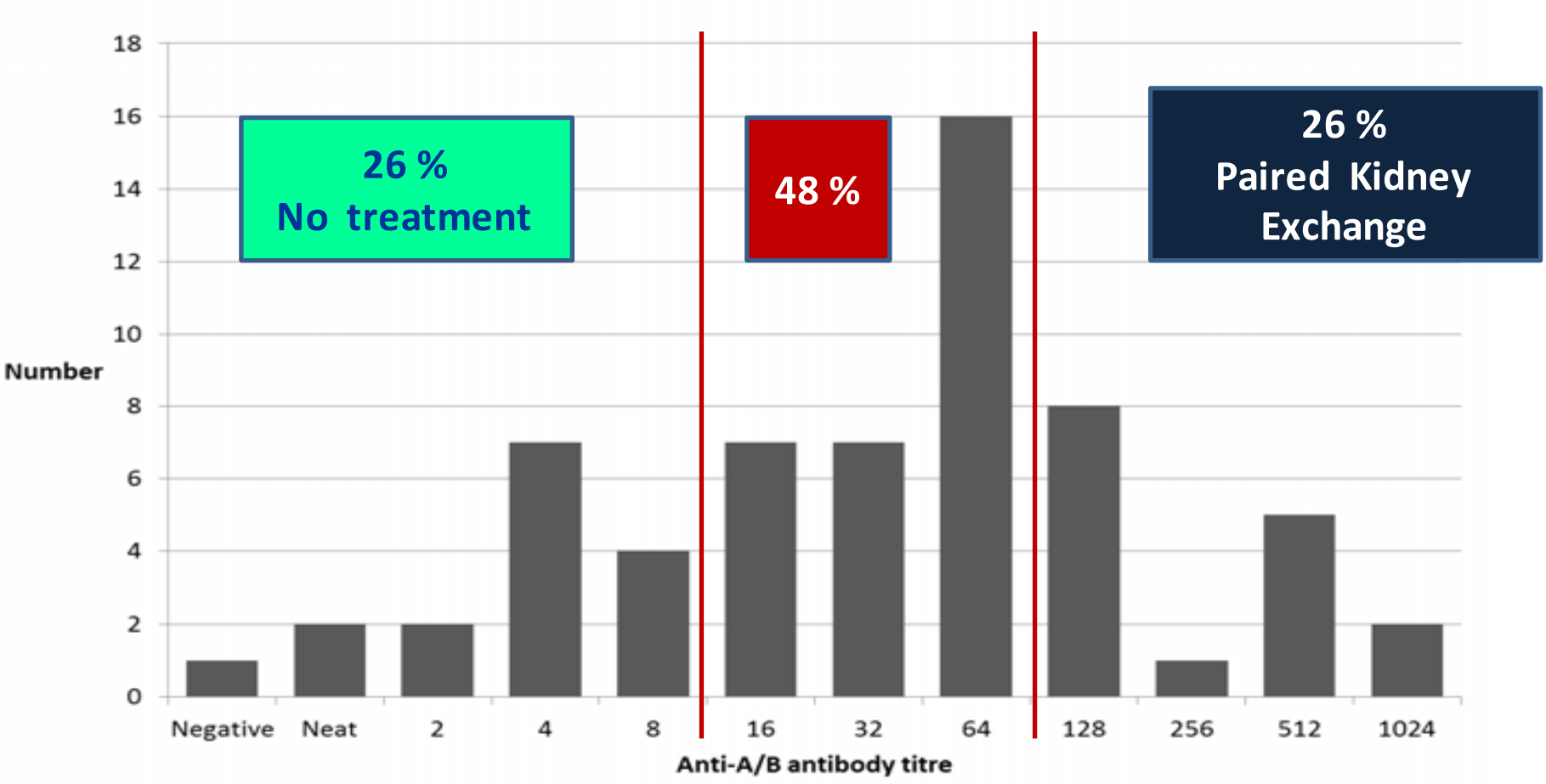
# Guy's Hospital, London
# individualized desensitisation strategy

## ABOi renal transplant recipients




N Mamode Transplant Int 2013

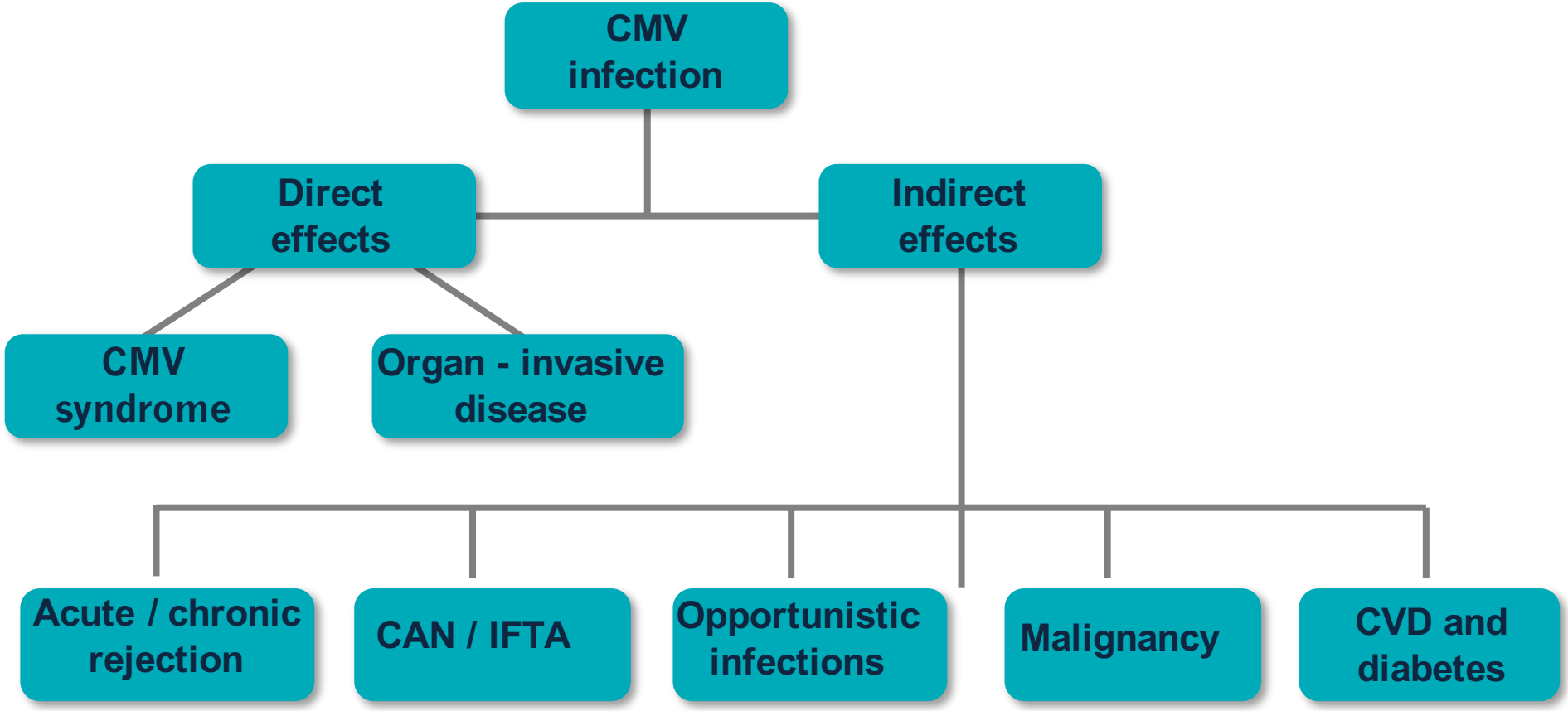
# Strategie immunosoppressive e rischio infettivo

- ✓ what we learnt
- ✓ immunosuppression and CMV
- ✓ what we would like do

# Unmet needs in CMV for the risk management of CMV infections

- CMV infection and disease
  - occur frequently after tx and are causes of CAN / IFTA, death
  - are independent risk factors for renal allograft rejection
  - CMV prophylaxis and pre-emptive antiviral therapy is addressed in recent guidelines.
- Moreover:
  - Late-onset disease is still observed
  - Antiviral resistance, although infrequent, has emerged
  - Evidence that mTOR-inhibitors may reduce replication

# CMV infection has multiple detrimental effects in organ transplant recipients



# CMV infection and renal transplantation

- **Prophylaxis vs preemptive therapy**
- **Preemptive therapy**
  - Units / copies PCR-DNA, when to treat?
  - Should we monitor specific CMV- quantiferon?
  - Should we monitor Elispot?

# Benefits and limitations of prophylaxis versus preemptive therapy

| Effect | Prophylaxis | Preemptive |
|---|---|---|
| CMV disease | +++ | +++ |
| Late CMV disease | ++ | – |
| CMV Relapse/treatment failure | ++ | ++ |
| Fewer opportunistic infections | +++ | + |
| Improved graft survival | ++ | – |
| Prevention of rejection | ++ | – |
| Survival | ++ | – |
| Prevention other viruses | + | – |
| Post transplant lymphoma | + | – |
| Kaposi sarcoma | + | – |
| Safety | ++ | +++ |
| Easier logistics | +++ | + |
| Lower drug cost | + | +++ |
| Lower monitoring cost | +++ | + |
| Resistant CMV | ++ | ++ |

+ is representative of the ease of use and strength of the evidence, +++ is the strongest evidence or favors the approach listed, a—means no evidence exists. Modified from Kotton et al. [2].

*C. Kotton American Journal of Transplantation 2013; 13: 24–40*

# Several recent studies have reported reduced post-transplant CMV incidence with mTORis

| Study | Duration, months | Immunosuppression | Patients, n | CMV incidence at 12 months, % |
|---|---|---|---|---|
| Tedesco-Silva *et al* 2007 | 12 | Everolimus + low CsA + steroids | 112 | 0.9 |
| | | Everolimus + low CsA + steroids + Bas | 117 | 2.6 |
| | 36 | Everolimus + SD CsA + steroids + Bas | 53 | 1.9 |
| Nashan *et al* 2004 | | Everolimus + low CsA + steroids + Bas | 58 | 0 |
| | 12 | SD CsA + MMF + steroids | 410 | 14.3 |
| Ekberg *et al* 2007 | | Low CsA + MMF + steroids + Dac | 413 | 11.0 |
| ELITE-Symphony | | Low tacrolimus + MMF + steroids + Dac | 411 | 9.7 |
| study | | Low sirolimus + MMF + steroids + Dac | 411 | 6.1 |
| | 12 | MMF + steroids + Dac | 179 | 12.8 |
| | | Low CsA + MMF + steroids +Dac | 183 | 10.9 |
| Ekberg *et al* 2007 | | SD CsA + MMF + steroids | 173 | 13.9 |
| CAESAR study | 24 | CsA + azathioprine + ATG | 80 | 41 |
| | | CsA + MMF + Bas | 80 | 20 |
| Hernandez *et al* 2007 | | Tacrolimus + MMF + Bas | 80 | 25 |
| | 12 | Sirolimus + MMF + prednisone | 81 | 3 |
| | | Tacrolimus + MMF + prednisone | 84 | 12 |
| Larson *et al* 2006 | | | | |

CMV, cytomegalovirus; mTORi, mammalian target of rapamycin inhibitor; CsA, cyclosporin; Bas, basiliximab; SD, standard dose; MMF, mycophenolate mofetil; Dac, daclizumab; EC-MPS, enteric-coated mycophenolate sodium; ATG, anti-thymocyte globulin

# The SYMPHONY study

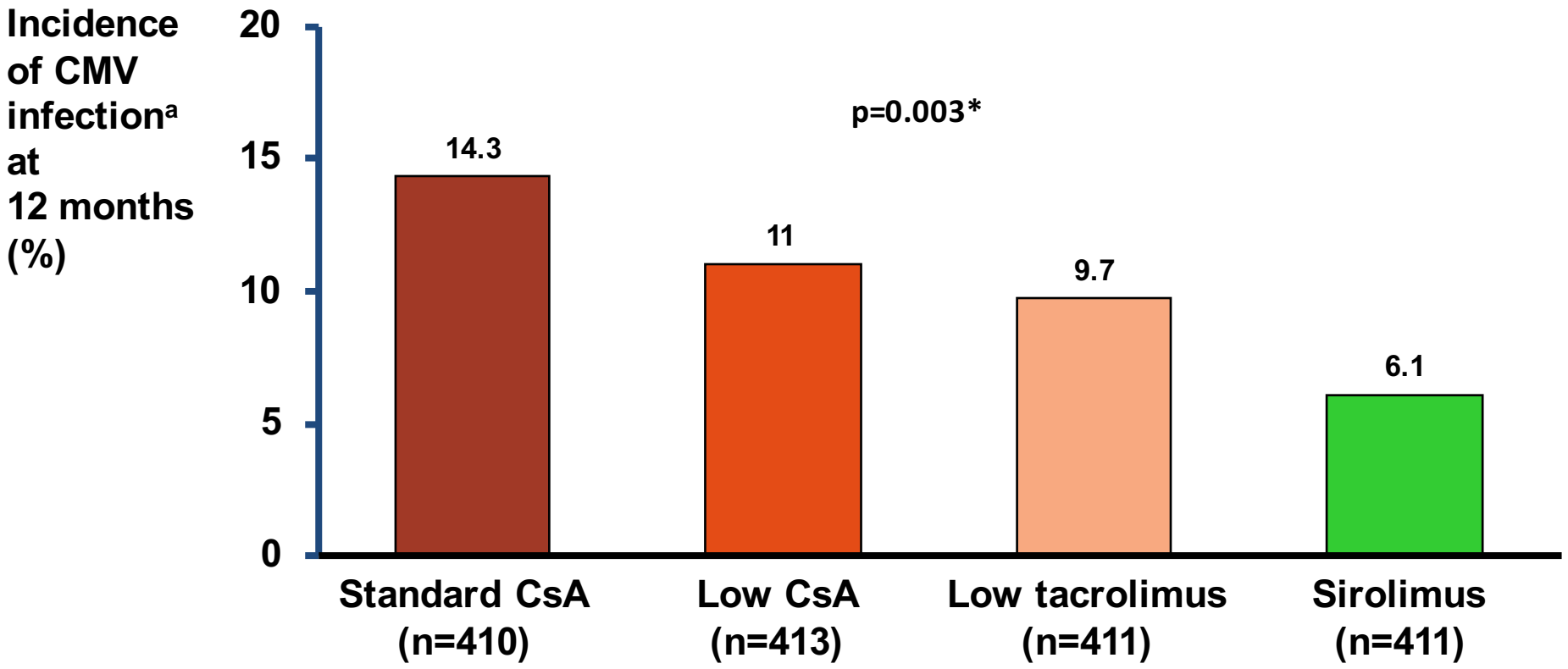
## Reduced Exposure to Calcineurin Inhibitors in Renal Transplantation

The NEW ENGLAND JOURNAL of MEDICINE

| Regimen tested | n | eGFR (C-G) | BPAR (%) | Allograft Survival (%) |
|---|---|---|---|---|
| Standard-dose CSA (100-200 ng/mL thereafter) | 390 | 57 ± 25 | 30.1 | 91.9 |
| Low-dose CSA (50-100 ng/mL) | 399 | 59 ± 25 | 27.2 | 94.3 |
| Low-dose TAC (3-7 ng/mL) | 401 | 65 ± 27 | 15.4 | 96.4 |
| Low-dose SRL | 399 | 57 ± 27 | 40.2 | 91.7 |

BPAR, biopsy proven acute rejection; CsA, cyclosporine A; eGFR, estimated glomerular filtration rate; SRL, sirolimus; TAC, tacrolimus.
Ekberg, et al, *New Eng J Med* 2007;357:2562-2575.

# Symphony: significantly lower incidence of CMV infection with an mTORi than CNIs



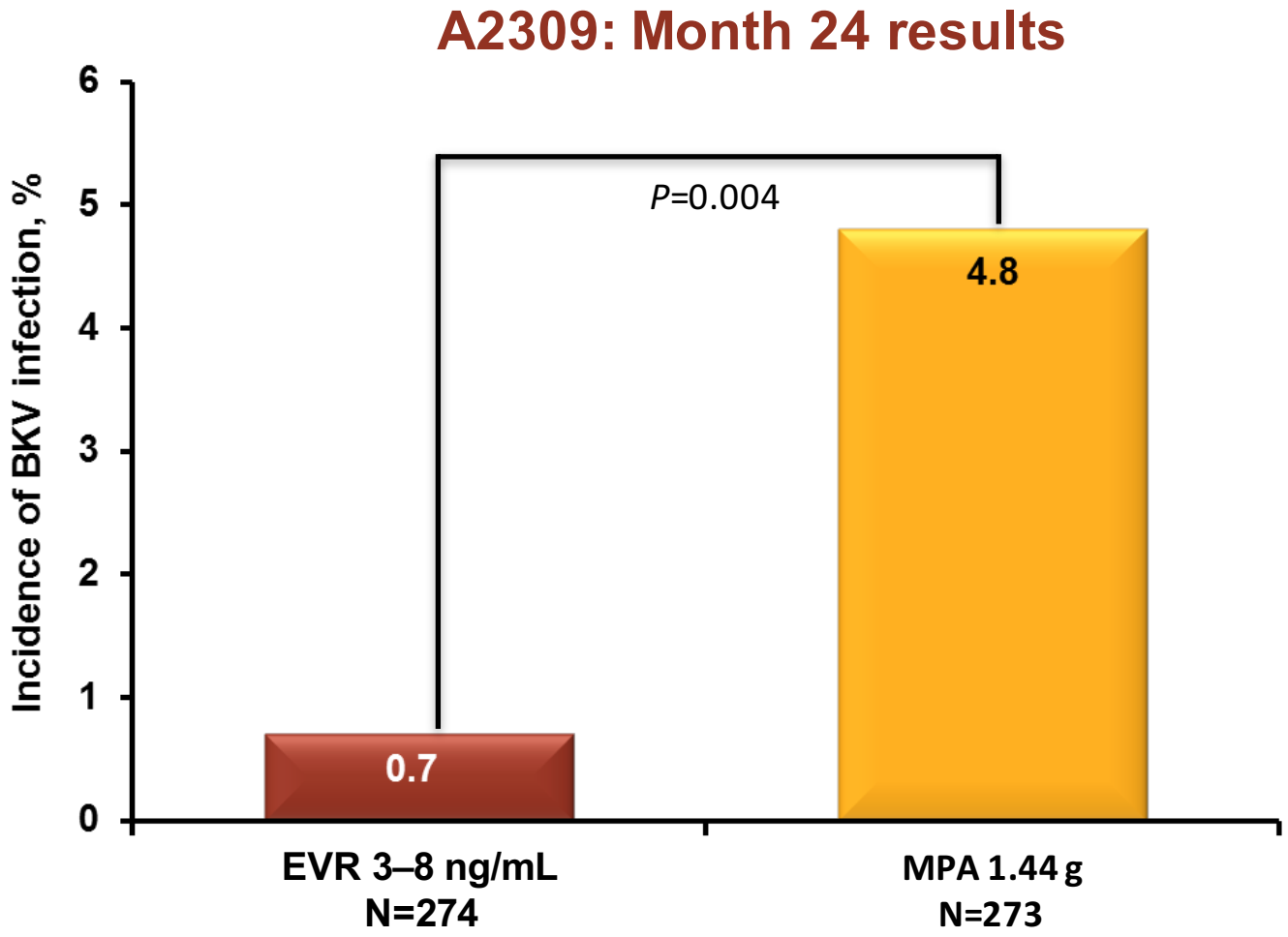

*p value across all arms; significant between-group difference

[a]Determined from reported adverse events

CMV, cytomegalovirus; mTORi, mammalian target of rapamycin inhibitor; CsA, cyclosporin; CNI, calcineurin inhibitor

Ekberg H *et al*. *N Engl J Med* 2007;357:2562–75

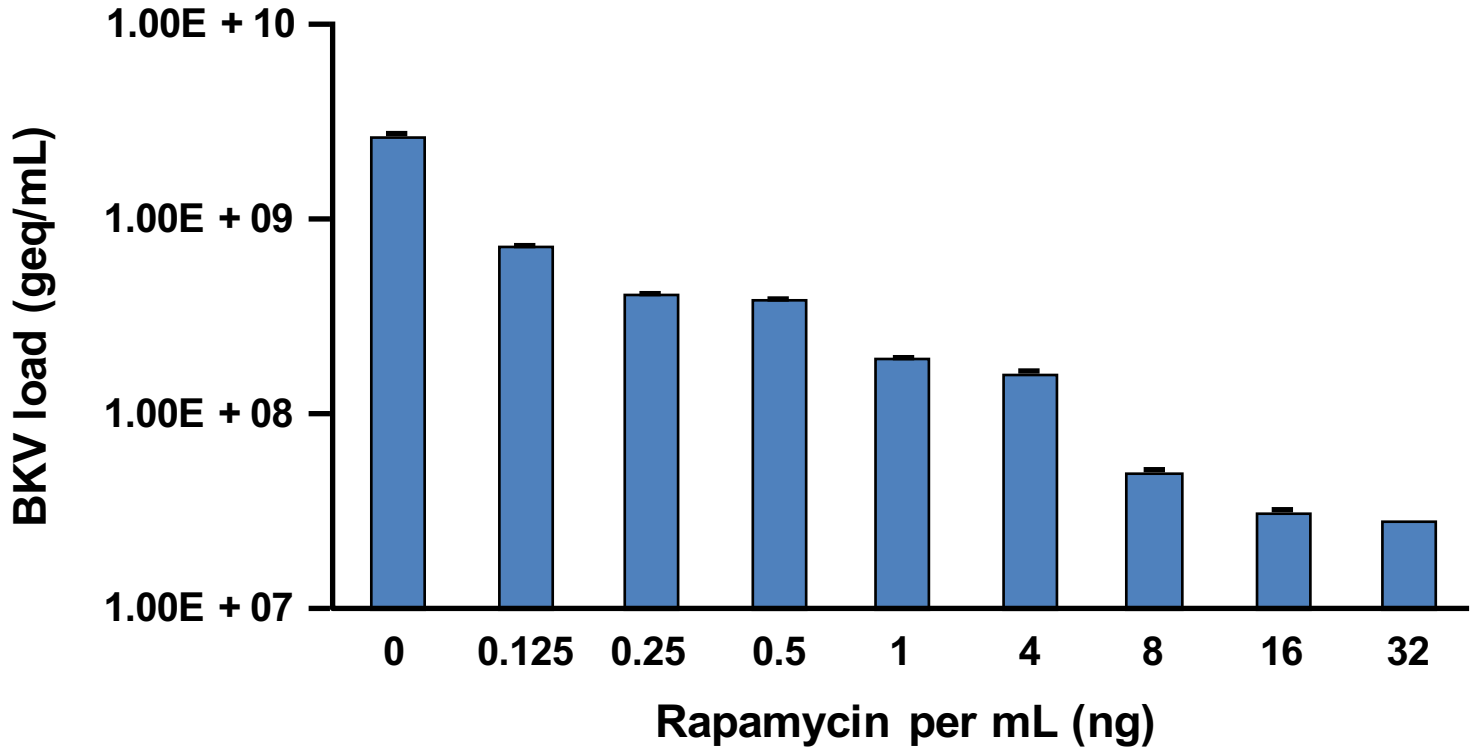
# BKV infections are less frequent with *de novo* everolimus + low CNI at 24 months




BKV, BK virus; EVR, everolimus; MPA, mycophenolic acid

Cibrik D, et al. *Transplantation.* 2013;95(7):933-942.

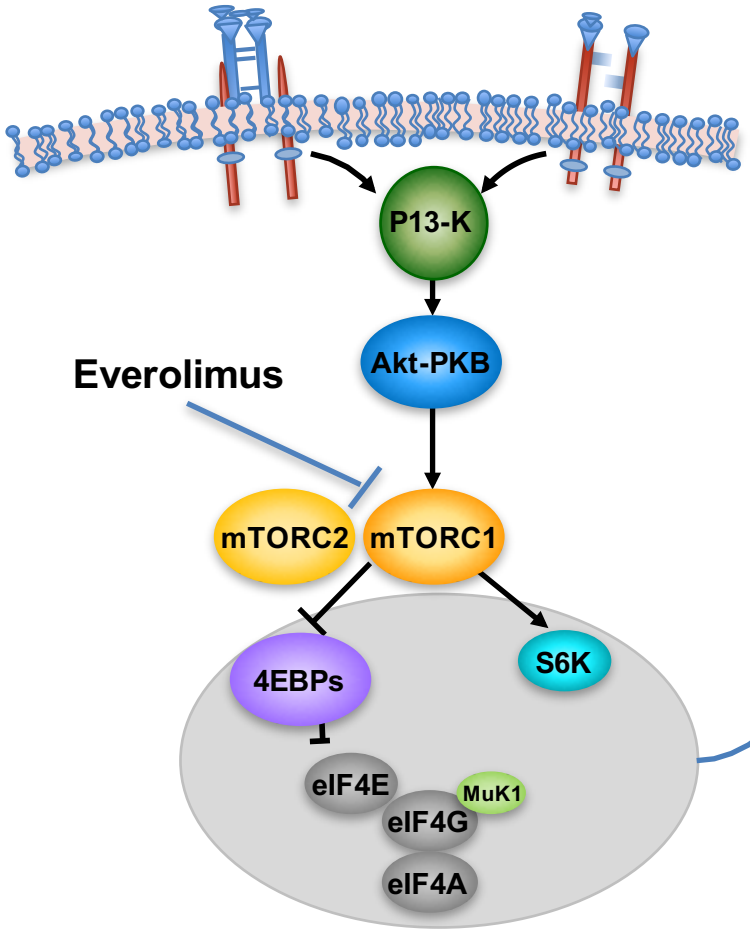
# BKV replication in human renal tubular epithelial cells is inhibited by mTORi




BKV, BK virus; mTORi, mammalian target of rapamycin inhibitor
Hirsch, Ming. Unpublished data

## Potential mechanisms for antiviral action of mTORis

# Everolimus has a central role in several pathways related to proliferation




Control of gene expression

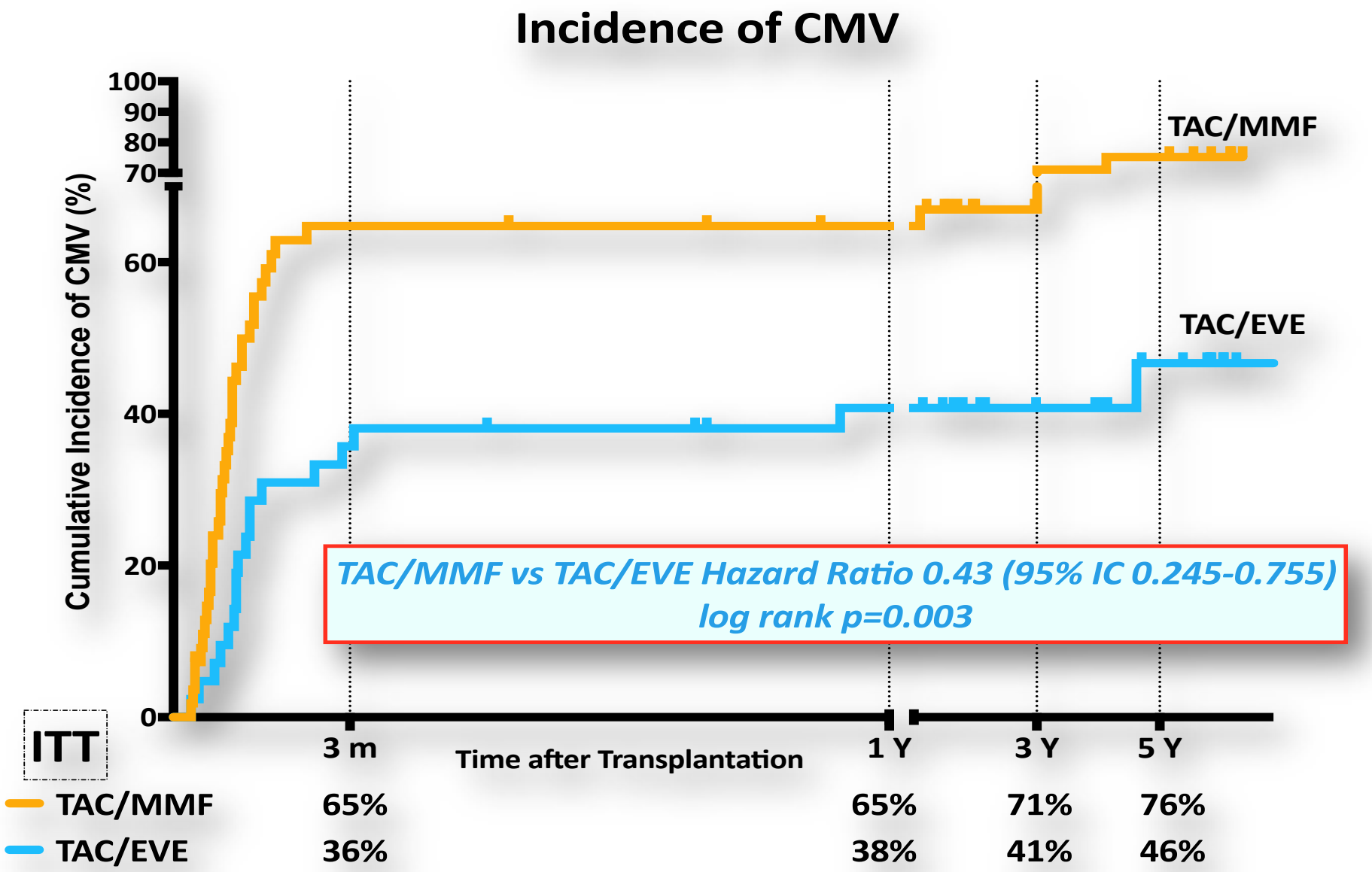
- Cell growth
- Proliferation
- Cell survival

| Physiological processes mediated by mTOR activation | |
|---|---|
| Normal growth | Immunosuppression |
| Reparative process | Tumor cell proliferation |
| Angiogenesis | Viral replication |

AKT/PKB, protein kinase B; eIF4, eukaryotic translation initiation factor; mTOR, mammalian target of rapamycin; mTORC, mammalian target of rapamycin complex; PI3K, phosphatidylinositol 3-kinase; S6K, S6 kinase.

Populo H, et al. *Int J Mol Sci* 2012;13:1886–1918; Buchkovich NJ, et al. *Nature Reviews Microbiology* 2008; 6:266–75.

# UCSC CMV preemptive therapy



# Is Cytomegalovirus Prophylaxis Dispensable in Patients Receiving an mTOR Inhibitor–Based Immunosuppression? A Systematic Review and Meta-Analysis

*Joachim Andrassy,[1,5] Verena S. Hoffmann,[2] Markus Rentsch,[1] Manfred Stangl,[1] Antje Habicht,[3] Bruno Meiser,[3] Michael Fischereder,[4] Karl-Walter Jauch,[1] and Markus Guba[1]*

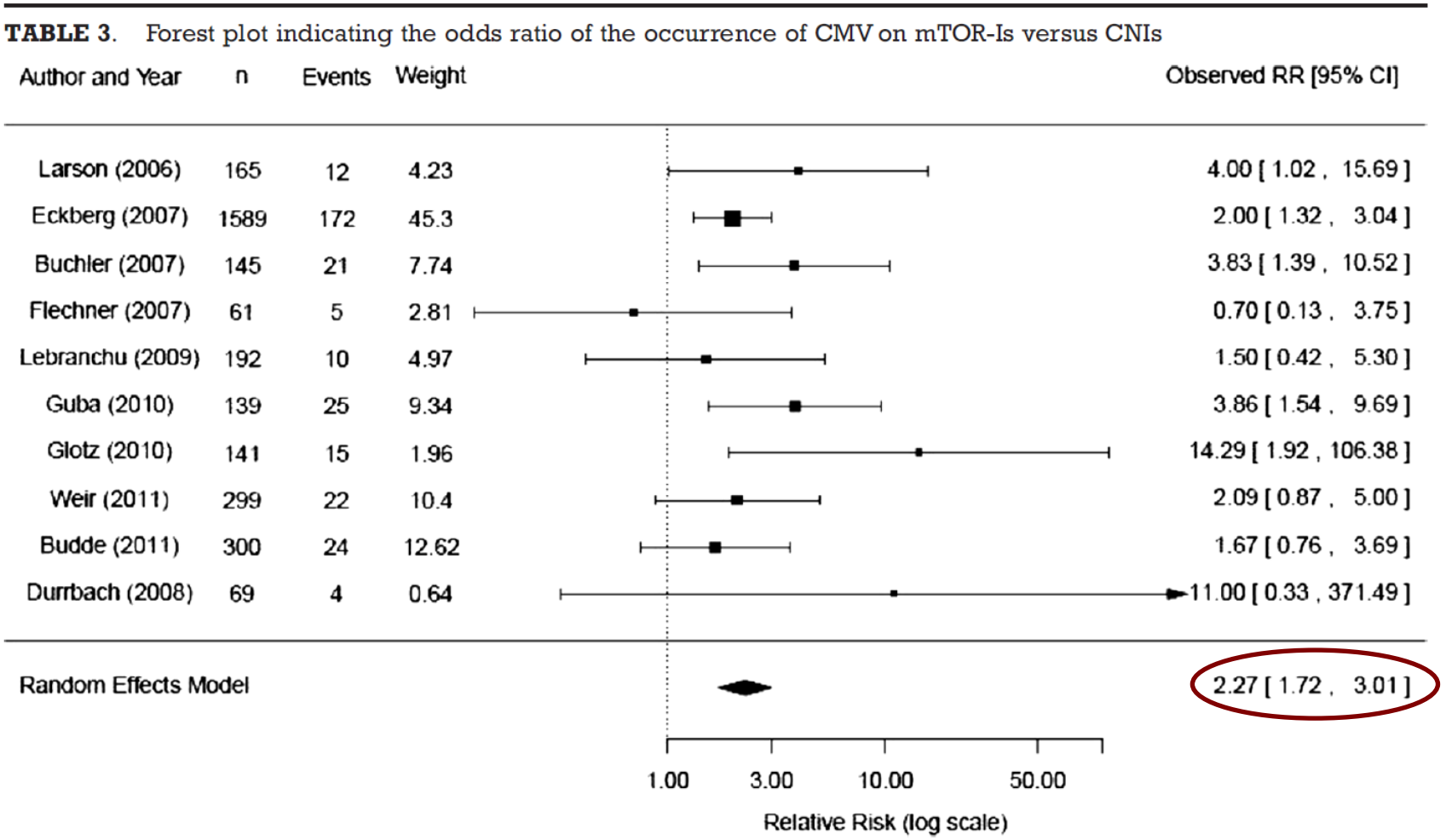
**University Hospital Grosshadern, Ludwig Maximilian's University, Munich D**

- ✓ **The current literature reviewed for RCTs in SOT comparing mTOR-I with a non-mTOR-I, CNI based treatment.**
- ✓ **Cytomegalovirus incidence was assessed in studies comparing**
  - ❖ **mTOR-In based vs a CNI based therapy: 10 trials, n=3,100 pts**
  - ❖ **mTOR-I + CNI based vs a CNI-based therapy 15 trials, n=7,100 pts**

(*Transplantation* 2012;94: 1208–1217)

# CMV occurrence mTORsi vs CNIs

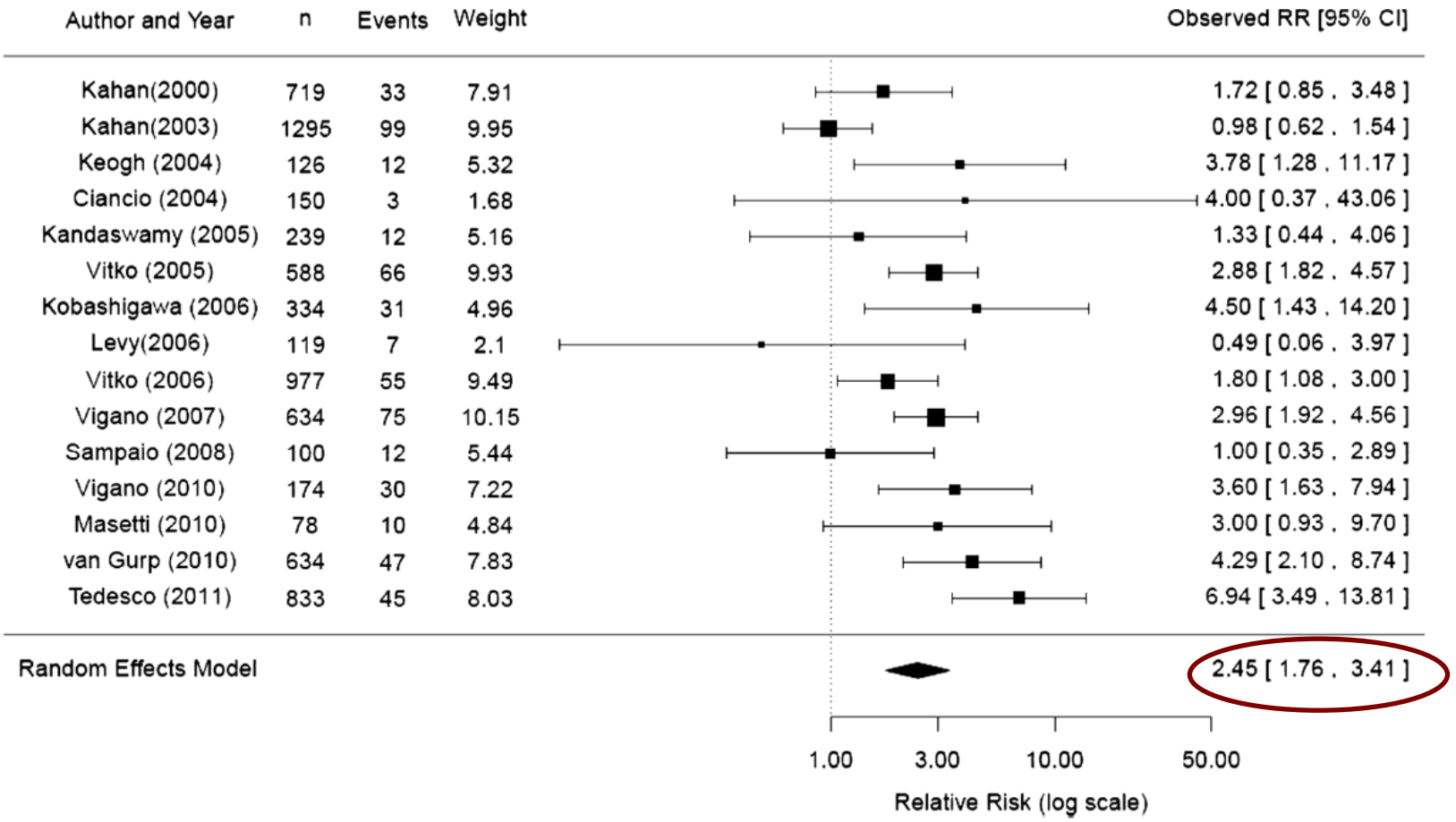
**TABLE 3.** Forest plot indicating the odds ratio of the occurrence of CMV on mTOR-Is versus CNIs



# CMV occurrence mTORsi + CNIs vs CNIs



**TABLE 4.** Forest plot indicating the odds ratio of the occurrence of CMV on a combination of mTOR-Is and CNIs versus CNIs



# Conclusions

## Unmet need in CMV for the risk management of CMV infections

- **CMV infection, syndrome and disease are reduced with Everolimus vs standard CNIs therapy**
- **CMV prophylaxis may become dispensable in pts receiving mTORsi ?**
- **Need for a clinical trial : CMV standard prophylaxis vs preemptive therapy vs no prophylaxis**

# Strategie immunosoppressive e rischio infettivo

- ✓ what we learnt
- ✓ immunosuppression and CMV
- ✓ what we would like to have

# Our Goal is

# immunosuppression-free state (IFS) post-transplantation

American Journal of Transplantation 2014; 14: 1599–1611
Wiley Periodicals Inc.



doi: 10.1111/ajt.12731

# Long-Term Results in Recipients of Combined HLA-Mismatched Kidney and Bone Marrow Transplantation Without Maintenance Immunosuppression

**T. Kawai[1,*], D. H. Sachs[2], B. Sprangers[3], T. R. Spitzer[4], S. L. Saidman[5], E. Zorn[1], N. Tolkoff-Rubin[1], F. Preffer[5], K. Crisalli[1], B. Gao[1], W. Wong[3], H. Morris[3], S. A. LoCascio[3], P. Sayre[6], B. Shonts[3], W. W. Williams Jr.[1], R.-N. Smith[5], R. B. Colvin[5], M. Sykes[3] and A. B. Cosimi[1]**

**to improve consistency of the results, this study shows that long-term stable kidney allograft survival without maintenance IS can be achieved following transient mixed chimerism induction.**

**Keywords: Chimerism, immunobiology, kidney transplantation, living donors, tolerance**

**Abbreviations: AKI, acute kidney injury; BAFF, B cell**

# Posttransplant complications

A. Conventional immunosuppression

| No. | Age at Tx | Sex | Survival | Creat | HTN | Hyper-lipid | *De novo* DM | Malignancy | Infection[1] | No. of drug IS + others |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 33 | F | >11.6 years | 1.1 | − | + | − | − | + | 3+5 |
| 2 | 42 | F | >11 years | 1 | + | + | + | − | + | 3+7 |
| 3 | 36 | F | >10.8 years | 1.4 | + | + | + | − | − | 2+12 |
| 4 | 38 | F | >10.8 years | 2.3 | + | + | − | − | + | 2+8 |
| 5 | 40 | F | >10.7 years | 1.2 | + | + | − | − | + | 3+5 |
| 6 | 42 | F | >10.6 years | 1 | + | − | − | SCC BCC | − | 2+1 |
| 7 | 26 | M | >10.3 years | 2 | + | + | + | − | − | 2+6 |
| 8 | 23 | M | >9.7 years | 1.3 | + | − | − | − | − | 3+2 |
| 9 | 27 | M | >9.5 years | 1.5 | + | + | + | Melanoma, SCC | − | 2+3 |
| 10 | 40 | M | >9.2 years | 1.9 | + | + | + | − | − | 3+9 |
| 11 | 20 | F | >8.5 years | 1.1 | − | − | − | − | − | 3+4 |
| 12 | 42 | M | >8.4 years | 2.1 | + | − | − | − | − | 2+2 |
| 13 | 32 | M | >8.3 years | 1.3 | + | + | + | − | − | 3+8 |
| 14 | 26 | M | >8.2 years | 0.95 | + | + | + | − | + | 2+9 |
| 15 | 42 | F | >8.1 years | 1.4 | − | − | − | − | − | 3+3 |
| 16 | 43 | M | >7.9 years | 1.2 | + | + | − | − | − | 3+5 |
| 17 | 31 | M | >7.7 years | 1.6 | + | + | − | − | − | 3+5 |
| Graft loss | | | | | | | | | | |
| 18 | 37 | F | 29 days | reTx | NA | NA | NA | NA | NA | NA |
| 19 | 44 | M | 3.9 years | On HD | + | − | − | − | − | 2+5[3] |
| 20 | 45 | M | 6.3 years | On HD | + | + | − | − | − | 2+12[3] |
| 21 | 22 | M | 7.1 years | On HD | + | − | − | − | − | 3+3[3] |
| Incidence of complication (p-value[4]) | | | | | 85% (p = 0.04) | 65% (p = 0.005) | 35% (ns[5]) | 10% (ns) | 25% (ns) | |

# Posttransplant complications in tolerance

B. Tolerance protocol

| No.[6] | Age at Tx | Sex | Survival | Creat | HTN | Hyper-lipid | *De novo* DM | Malignancy | Infection | No. of drugs IS + others |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 22 | F | >11 years | 1.1 | – | – | – | – | – | 0+1 |
| 2 | 22 | F | >10.5 years | 2.2 | + | – | – | – | – | 1+1[7] |
| 4 | 28 | F | >8.8 years | 2.0 | + | – | – | – | – | 2+2[8] |
| 5 | 46 | F | >7.8 years | 2.5 | + | – | – | – | – | 1+1[9] |
| 6 | 35 | F | >4.8 years | 1.5 | – | – | – | – | – | 0+1 |
| 7 | 37 | F | >4.6 years | 0.8 | – | – | – | – | – | 0 |
| 9 | 22 | M | >4.2 years | 1.1 | – | – | – | – | – | 0 |
| Graft loss | | | | | | | | | | |
| 3 | 39 | M | 10 days | | | | NA | | | |
| 8 | 36 | F | 6 months | | | | NA | | | |
| 10 | 26 | M | 3 years | | | | NA (on IS after 10 months) | | | |
| Incidence of complication | | | | | 43% | 0% | 0% | 0% | 0% | |

# Posttransplant complications in tolerance

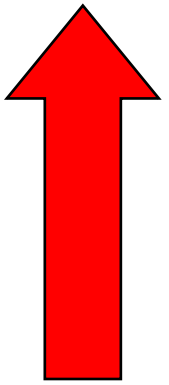
B. Tolerance protocol

| No.[6] | Age at Tx | Sex | Survival | Creat | HTN | Hyper-lipid | *De novo* DM | Malignancy | Infection | No. of drugs IS + others |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 22 | F | >11 years | 1.1 | – | – | – | – | – | 0+1 |
| 2 | 22 | F | >10.5 years | 2.2 | + | – | – | – | – | 1+1[7] |
| 4 | 28 | F | >8.8 years | 2.0 | + | – | – | – | – | 2+2[8] |
| 5 | 46 | F | >7.8 years | 2.5 | + | – | – | – | – | 1+1[9] |
| 6 | 35 | F | >4.8 years | 1.5 | – | – | – | – | – | 0+1 |
| 7 | 37 | F | >4.6 years | 0.8 | – | – | – | – | – | 0 |
| 9 | 22 | M | >4.2 years | 1.1 | – | – | – | – | – | 0 |
| Graft loss | | | | | | | | | | |
| 3 | 39 | M | 10 days | | | | NA | | | |
| 8 | 36 | F | 6 months | | | | NA | | | |
| 10 | 26 | M | 3 years | | | | NA (on IS after 10 months) | | | |

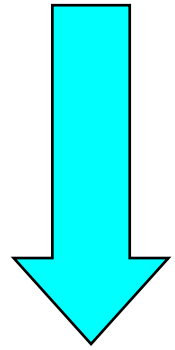
| | | | | | | |
|---|---|---|---|---|---|---|
| | tolerance | 43 | 0 | 0 | 0 | 0 % |
| ***Complications*** | no tolerance | 85 | 65 | 35 | 10 | 25 % |

# BALANCED

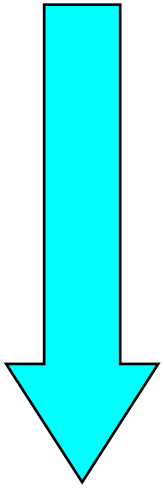
## Immunosuppression



rejection



infections



neoplasia