Nuovi farmaci nella gestione del trapianto renale

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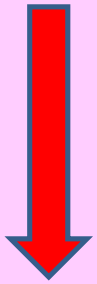
Nuovi farmaci nella gestione del trapianto renale

- La terapia immunosoppressiva dopo trapianto d'organo e' un problema molto complesso
- Negli ultimi 50 anni, sono stati fatti incredibili progressi nel trattamento e nella cura dei pazienti con migliorata sopravvivenza del paziente e dell'organo trapiantato
- Tuttavia gli effetti collaterali ed i rischi correlati alla terapia immunosoppressiva a lungo-termine, richiedono una personalizzazione del trattamento per rispondere alle caratteristiche individuali

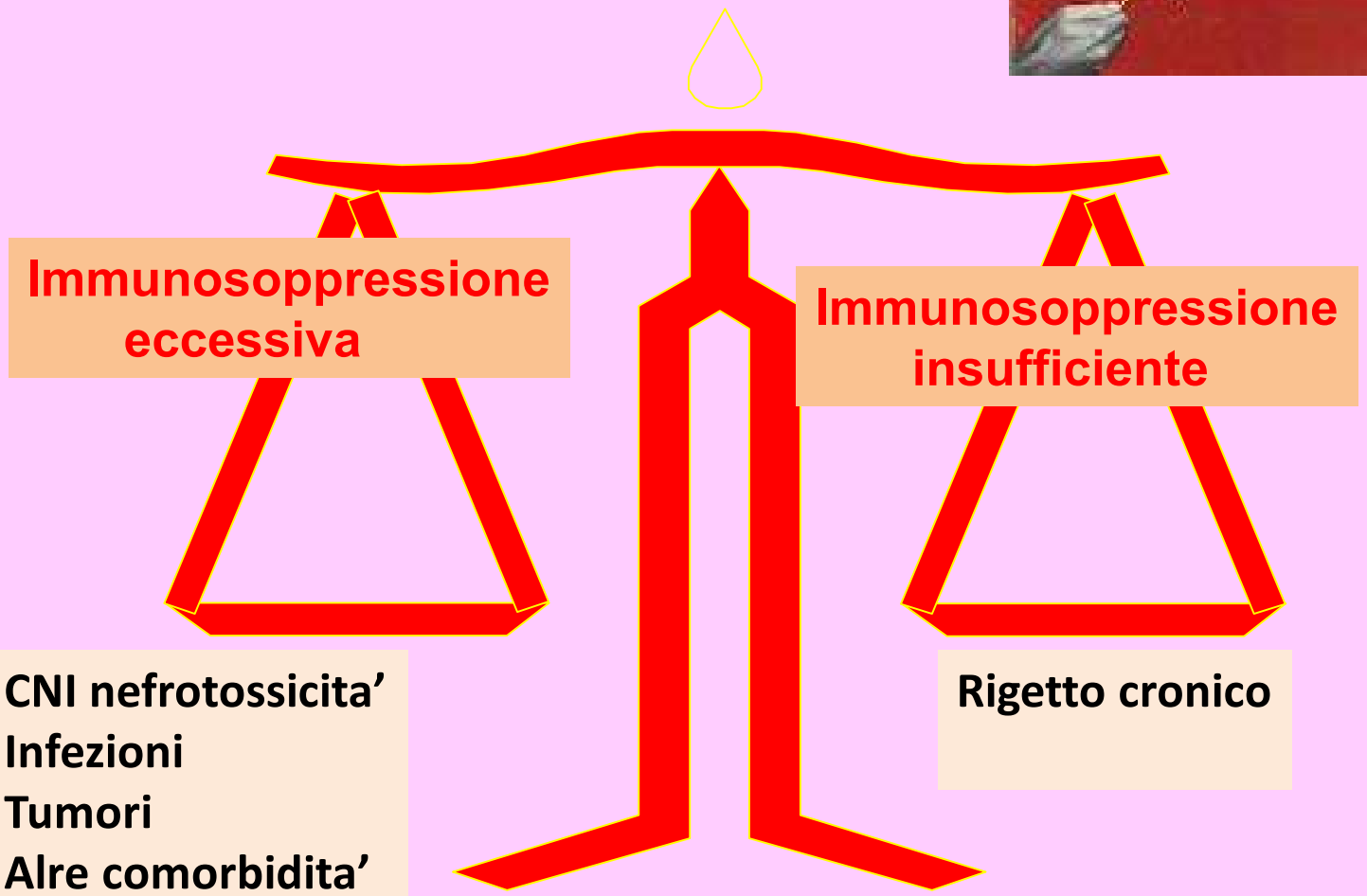
Immunosoppressione convenzionale :

- Ottimi risultati a breve termine
- Mancanza di risultati soddisfacenti a lungo termine



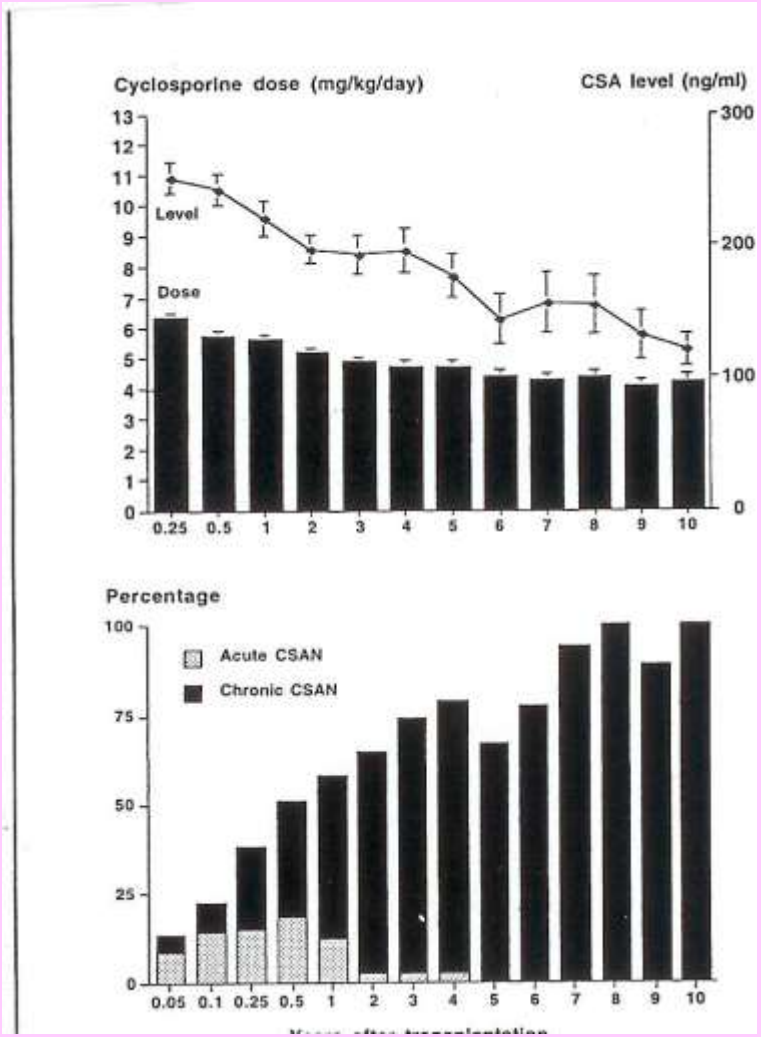
Strategie per prolungare la sopravvivenza del rene trapiantato

Immunosuppressione adeguata ed approppriata: rischi e benefici



Calcineurin Inhibitor Nephrotoxicity: Longitudinal Assessment by Protocol Histology

Nankivell BJ et al. Transplantation 78: 557-65, 2004



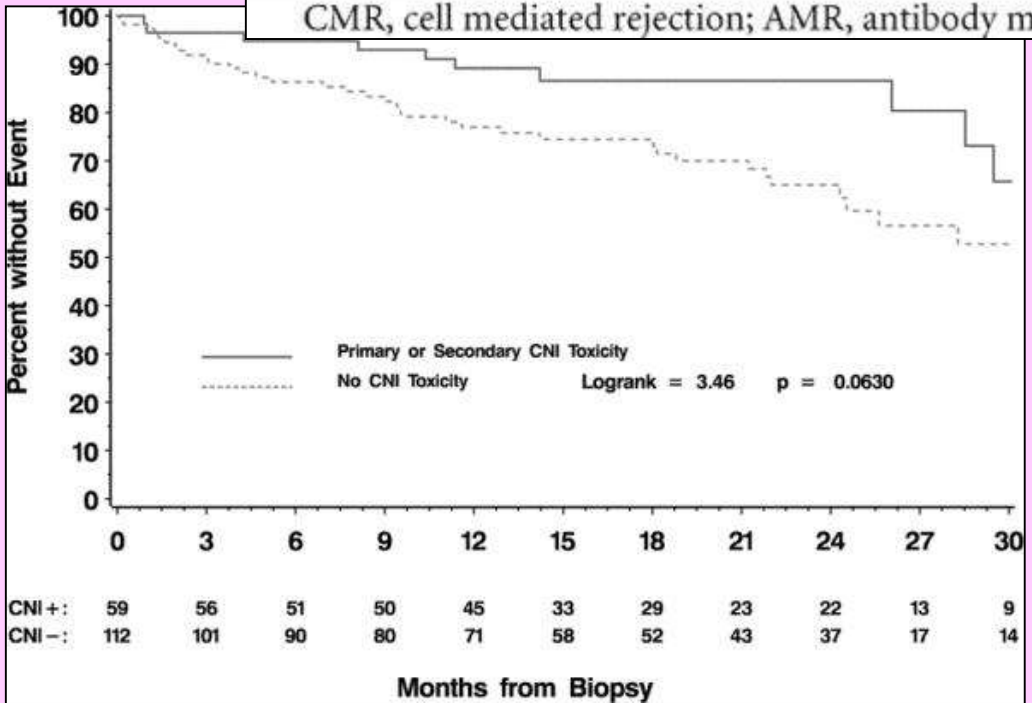
Evidence for Antibody-Mediated Injury as a Major Determinant of Late Kidney Allograft Failure

Gaston R. et al. Transplantation 90(1):68-74, 2010

TABLE 2. Local primary and secondary diagnoses at entry biopsy, by % of patients with each diagnosis

Chronic allograft nephropathy	49%
Calcineurin inhibitor nephrotoxicity	35%
Acute rejection (CMR and AMR)	27%
Other (e.g., pyelonephritis)	23%
Transplant glomerulopathy	21%
Recurrent disease	9%

CMR, cell mediated rejection; AMR, antibody mediated rejection.



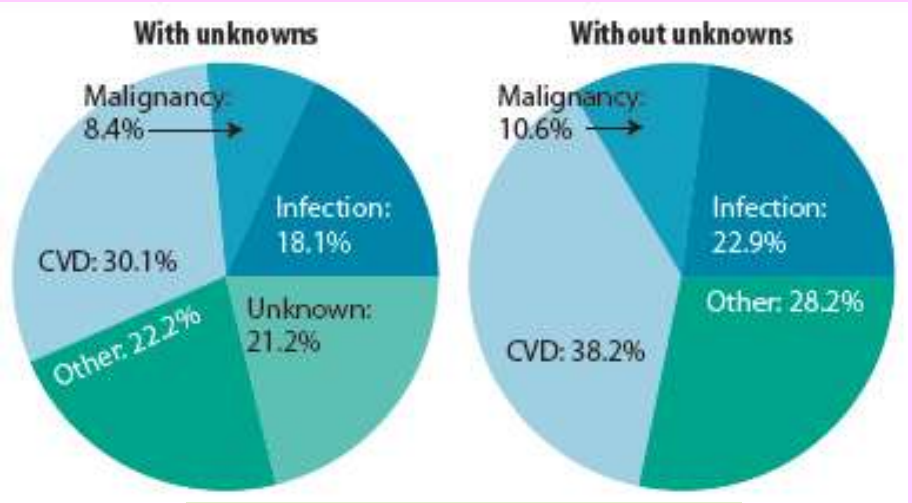
Kaplan-Meier analysis of the impact of primary or secondary local diagnosis of calcineurin inhibitor (CNI) nephrotoxicity on kidney allograft survival after for-cause biopsy.

Sopravvivenza del rene trapiantato e' multifattoriale

Causes of late Kidney Allograft Loss

50%
Death with graft function

50%
Chronic alloraft failure



Alloantigen dipendent

40-80%

Alloantigen indipendent

20-40%

Acute rejection
Histocompatibility mismatch
Suboptimal immunosup.
Prior sensitization
Medication noncompliance
Ongoing humoral injury

Brain death cytokine release
Ischemic injury and DGF
CNI nephrotoxicity
Older donor age
Hypertension
Hyperlipidemia
Proteinuria
Infection

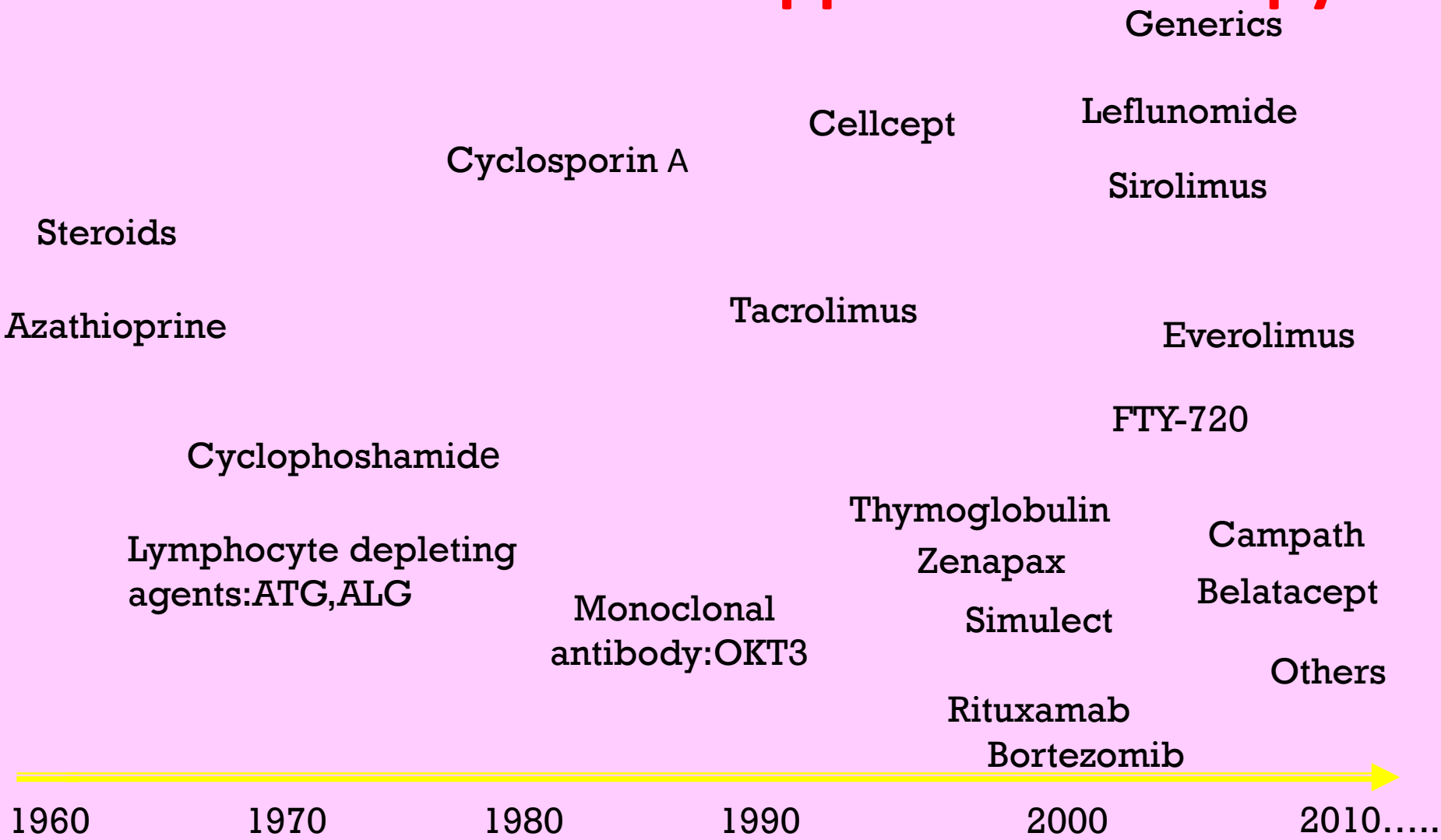
Drugs toxicity
Recurrent disease
New disease

US Renal ystem 2008

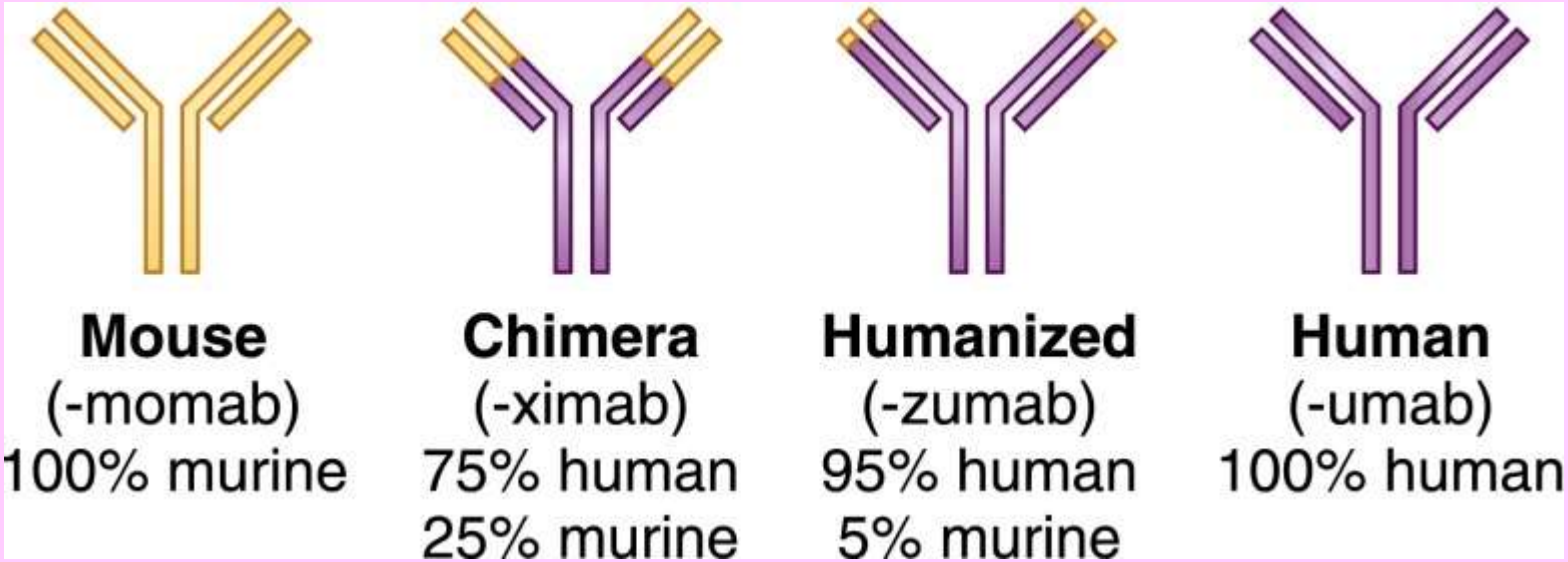
History of Immunosuppressive Therapy

- 1959- “Total body radiation” con trapianto tra gemelli eterozigoti.Sopravvivenza >20 anni: J.Murray, J. Hamburger
- Mercaptopurina prolunga la sopravvivenza nel trapianto di cane :R.Calne, C. Zukwoski , Inghilterra
- 1961- Impiego dell’Azatioprina nell’uomo: J.Murray (Nobel 1990)
- 1983- Ciclosporina A viene approvata come immunosoppressore nell’uomo

Evolution of Immunosuppressive Therapy



Anticorpi Monoclonali



Growing Shortage for Organ Supply

Deceased donors:

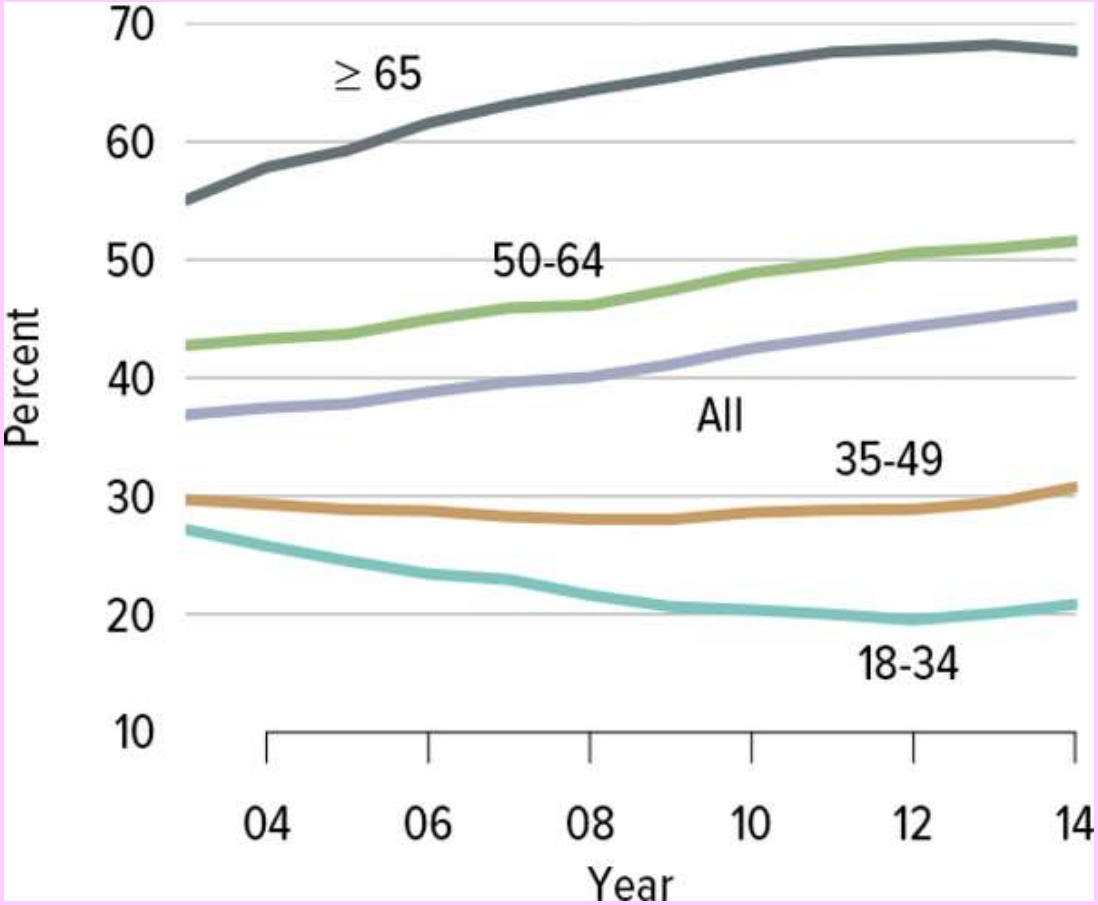
- **Expanded Criteria Donor Kidneys**
- **(ECD)**
- **Non heart beating donors (NHBD)= Donation after circulatory death (DCD)**
- **Dual kidneys**

Living Donors

Immunological barriers

Which is the appropriate IS?

Adults willing to accept an ECD kidney, by age



American Journal of Transplantation 2016

Subgroups with significant survival benefits after ECD transplantation

Patients older than 40 yr

Long median waiting time (> 4 yr)

Patients with diabetes or hypertension

Dialysis patients with vascular access problems

Dialysis patients whose life expectancy in dialysis is lower than the estimated waiting time for kidney transplantation

World J Transplant 2016

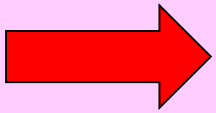
Expanded criteria donor kidney transplantation: Maximizing benefits

Modifying allocation rules for ECD kidneys in an effort to match the appropriate kidney to the appropriate recipient

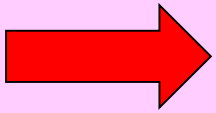
Minimizing risk factors for DGF: Lowering CIT, pulsatile perfusion preservation

Preimplantation renal biopsy for ECD kidney recipients

Simultaneous dual ECD kidney transplantation



Restricting the use of ECD kidneys to patients of low immunological risk



Applying individualized immunosuppressive regimens

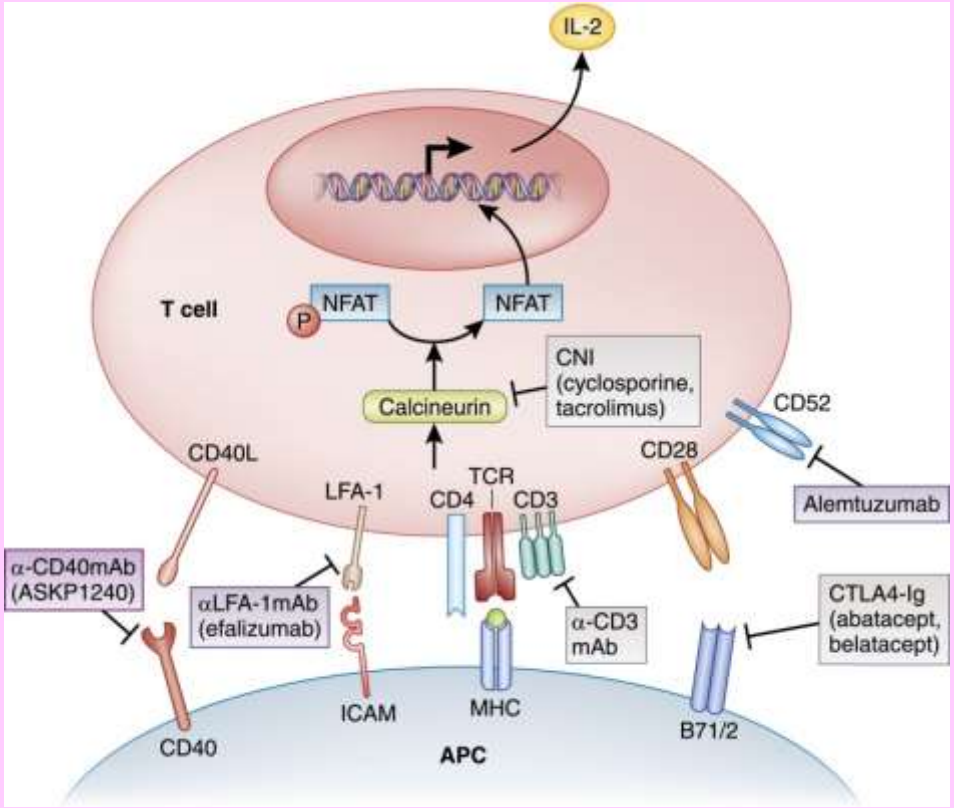
Fasi e Ruoli
Terapia Immunosoppressiva

- Induzione
- Mantenimento
- Trattamento rigetto acuto

Prevenzione e trattamento

- rigetto cronico
(anticorpo mediato)
- CAI
(Chronic allograft injury)

T Cell-Directed Therapy



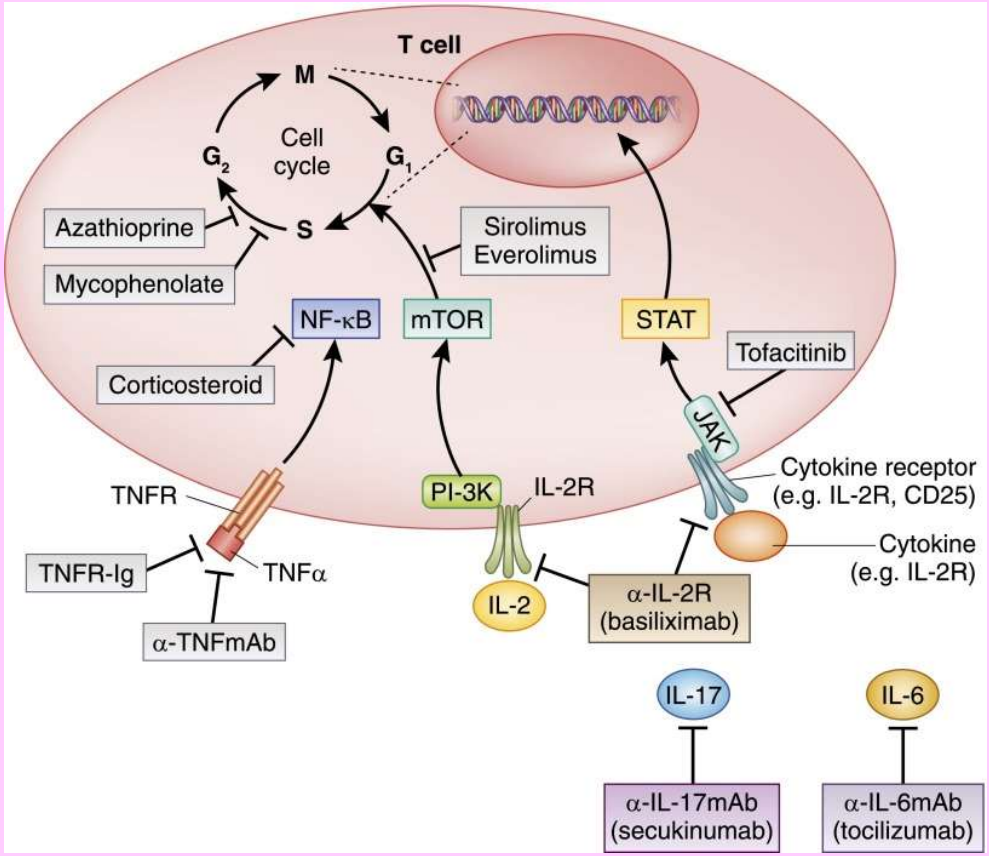
❑Agent targeting signal 1
Interaction of T cell receptor (TCR)
with antigen presenting cell (APC)

Calcineurin Inhibitors:
Cyclosporine*
Tacrolimus*

❑Agent targeting signal 2
Costimulation by additional T cell/APC

Abatacept
Belatacept*
Anti-CD40 mAb

***Maintenance IS**



Antiproliferative agents

mTOR inhibitors
Sirolimus*
Everolimus*

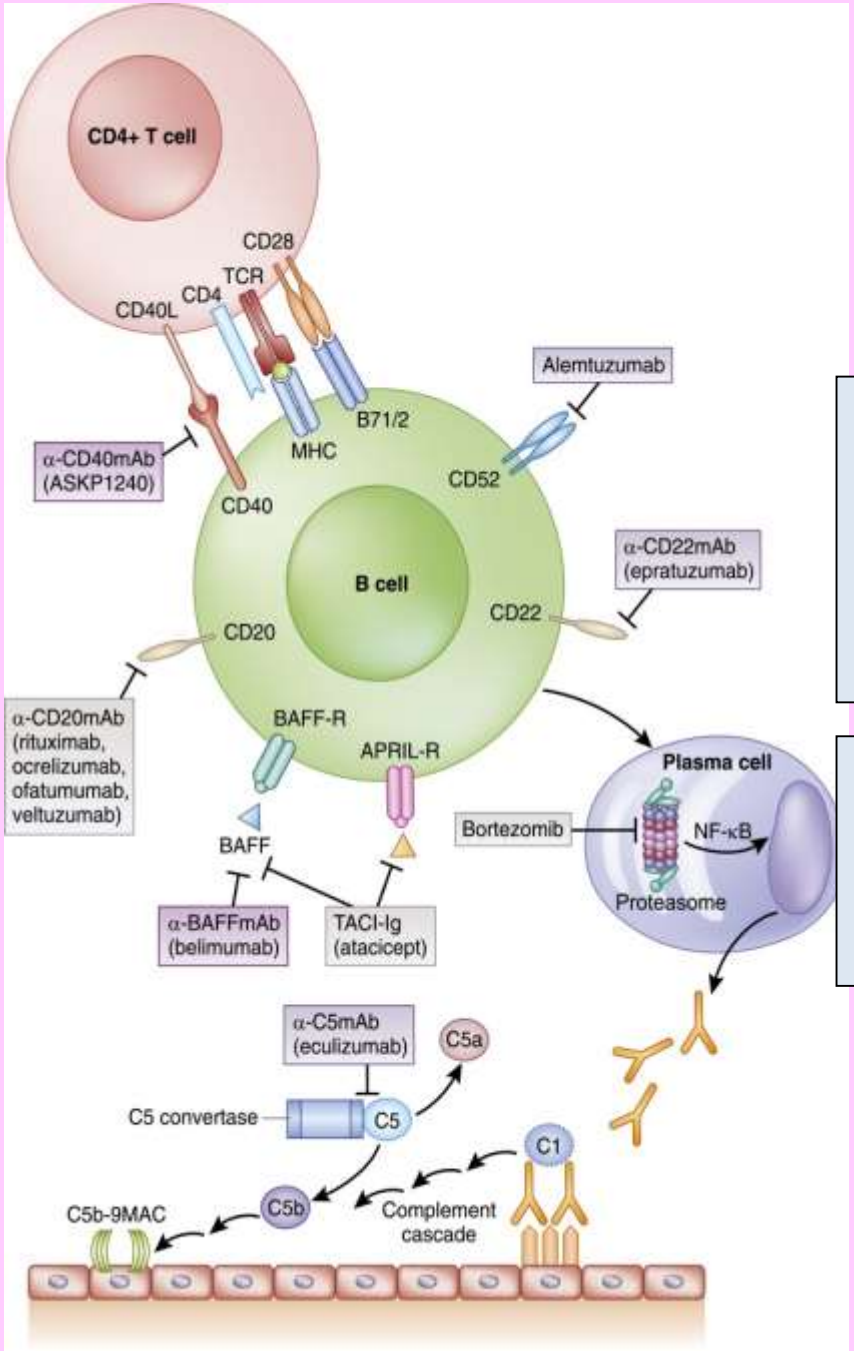
Antimetabolite agents

Azathioprine
Mycophenolate*
Leflunomide

***Maintenance IS**

B Cell-Directed Therapy

Inhibition of:
humoral response to auto-or alloantigen
APC function
B/T cell interaction
Plasma Cell function (Ab production)



Anti –CD20 targeting:
Rituximab*
Ocrelizumab
Ofatumubab
Anti-CD22 targeting:
Epratuzumab

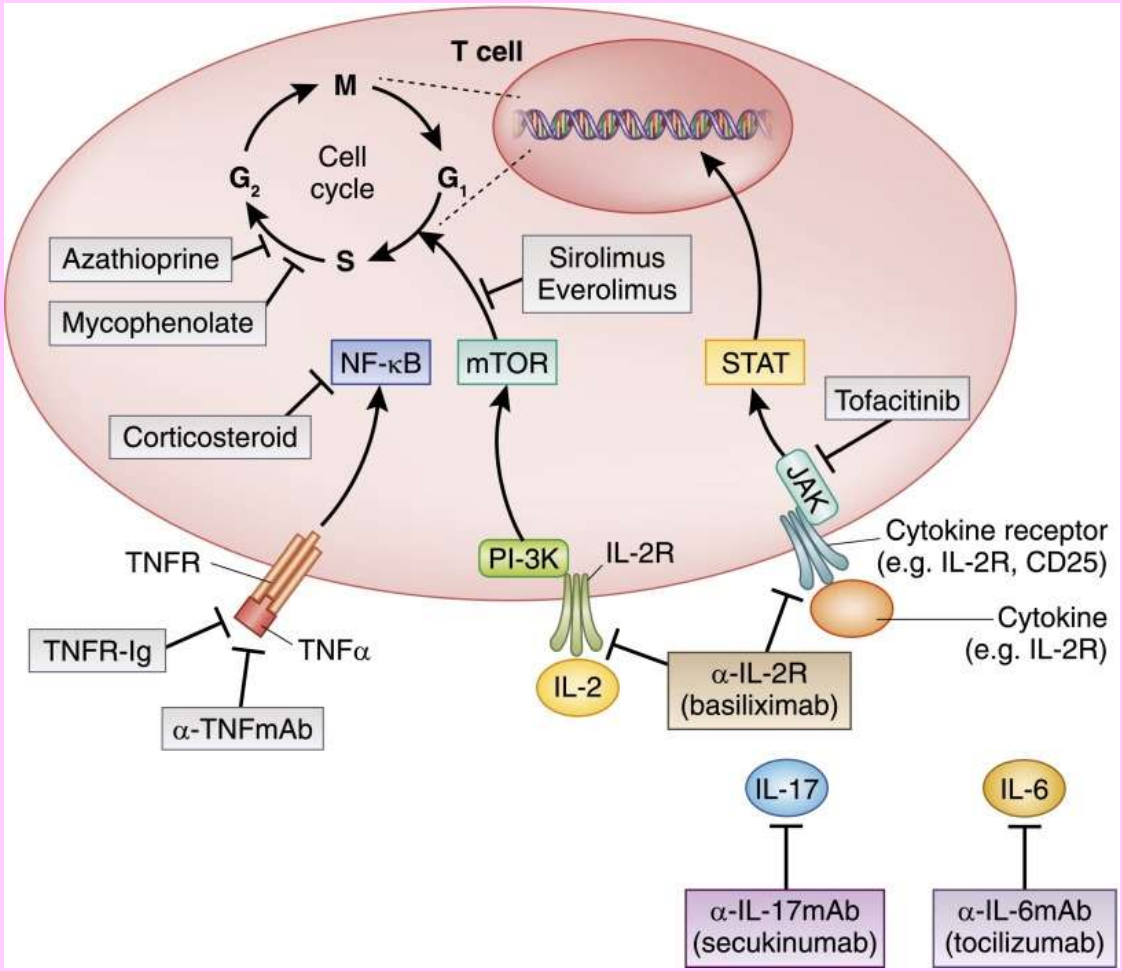
Plasma Cell targeting:
Bortezomib*

B Cell differentation:
targeting:
Belimumab
Atacicept

Complement Inhibition:
Eculizumab*

***-Desensitization protocols**
- Ab mediated rejection
-DSA removal

Agents targeting cytokines

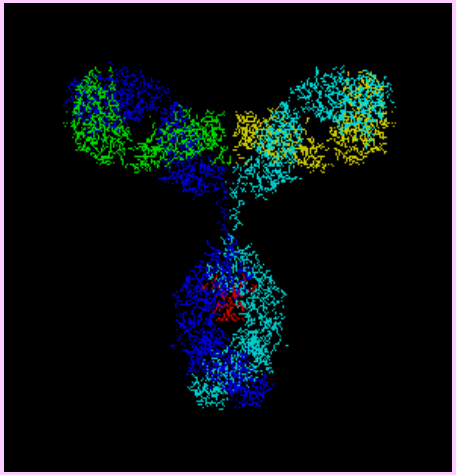


Janus Kinase Inhibition
(Tofacitinib)
IL-2 receptor antagonist
Basiliximab*
Anti TNF-α
IL-1, 6.17

***Induction agents**

“Induction” Agents

Campath-1H

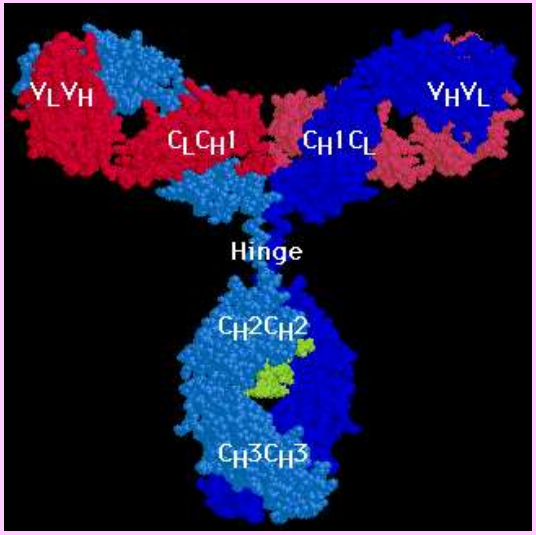


Rituximab

Basiliximab

Daclizumab

Thymoglobulin



OKT3

MALG

ATGAM

Thymoglobulin: Benefits

- Decrease and delay onset of acute rejection
- Delay introduction of calcineurin inhibitors
- Useful in high risk population/ situations such as delayed graft function
- Predictable suppression of T cells
- Repeat courses possible
- <u>New Clinical Trends:</u>
  - Pre-transplant administration/Role in the ischemia-reperfusion injury
  - Desensitization protocol
  - Impact on *de novo* DSA
  - Tolerance induction

Pros and Cons of Depleting and Nondepleting Antibodies

Depleting Antibodies	Nondepleting antibodies
•Rejection rare during use •Calcineurin inhibitors can be used sequentially (ie, delayed) •Acute side effects with administration •Associated with increased infection and malignancy	•Rejection occurs during use •Calcineurin inhibitors should not be delayed •No acute side effects •Very safe, not associated with complications of over-immunosuppression

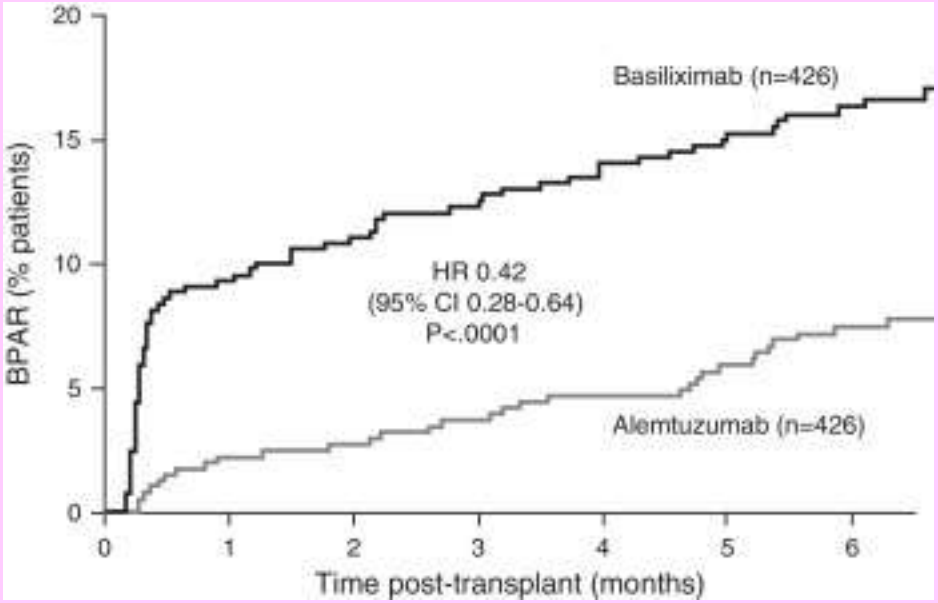
Induction therapy should be individualized based on immunologic and nonimmunologic risk factors

- The majority of patients can be induced by anti-IL-2R antagonist mAbs

- T-cells depleting agents should be considered for
  - -Sensitized patients (PRA, DSA, retransplants)
  - -Patients with DGF
  - -African-American young recipients
  - -Patients who will receive sparing regimens

CAMPATH-1H

- Humanized anti-CD 52 antibody
- Lympholytic antibody against both T and B cells
- Risk of cytokine release syndrome, prevented with intra-operative methyprednisolone



Incidence of biopsy-proven acute rejection (BPAR) in 852 unselected kidney transplant patents randomized to alemtuzumab induction with low-exposure tacrolimus, low-dose mycophenolic acid and no steroids, or to basiliximab induction with standard tacrolimus

Lymphocyte-depleting induction and steroid minimization after kidney transplantation: A review
Naesens M et al. Nefrologia 2016

“Maintenance” Agents

FTY720

Everolimus

Mycophenolate sodium

Sirolimus

Generic cyclosporine

Mycophenolate Mofetil

Microemulsion CsA

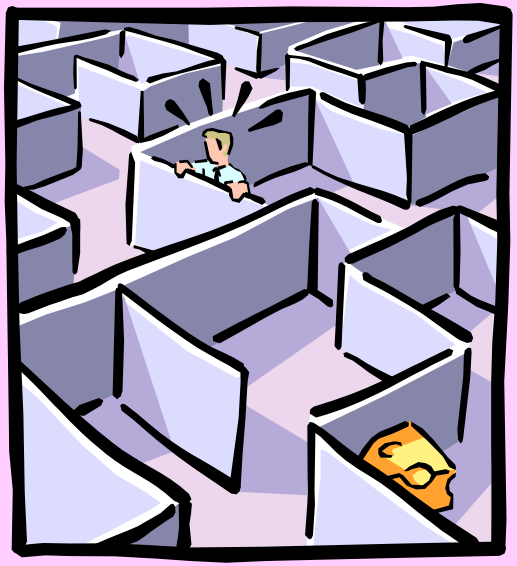
Tacrolimus

Cyclosporine

Azathioprine

Cyclophosphamide

Corticosteroids



Corticosteroids

- Cornerstone of immunosuppression since the earliest days of clinical transplantation
- Precise mechanisms of action are unknown

Inhibit function of dendritic cells

Inhibit translocation to nucleus to NF-kB

Promote lymphocyte death by apoptosis

Suppress production of IL-1,2,3,6 , TNF-α, γ-IFN

Inhibit expression of adhesion molecule

Reduce inflammatory cell migration

Corticosteroids

- Steroid-sparing strategies have been attempted in recent decades to avoid morbidity from long-term steroid intake among kidney transplant recipients

- Most protocols use low dose prednisone indefinitely

- Steroid-free maintenance immunosuppression protocols

- **Challenge:**

  -to identify the subset of KTX recipients who may not benefit from steroid- free regimen

  -to identify the subset of KTX who may benefit from steroid –free regimen

Corticosteroid Withdrawal

Initial randomized studies showed that complete withdrawal of CS from an immunosuppressive regimen including CsA led to increases in acute rejection and the relative risk for graft failure

Hricik DE et al. JASN 1993;4:1300

Schulak JA et al. Clin Transplant. 1994;8: 211

Ahsan et al. Transplantation 1999;68:1865

Luan F et al. Kidney Int. (2009), 76, 825-830

Steroid avoidance or withdrawal for kidney transplant recipients.

Haller M et al.Cochrane Database Syst Rev. 2016

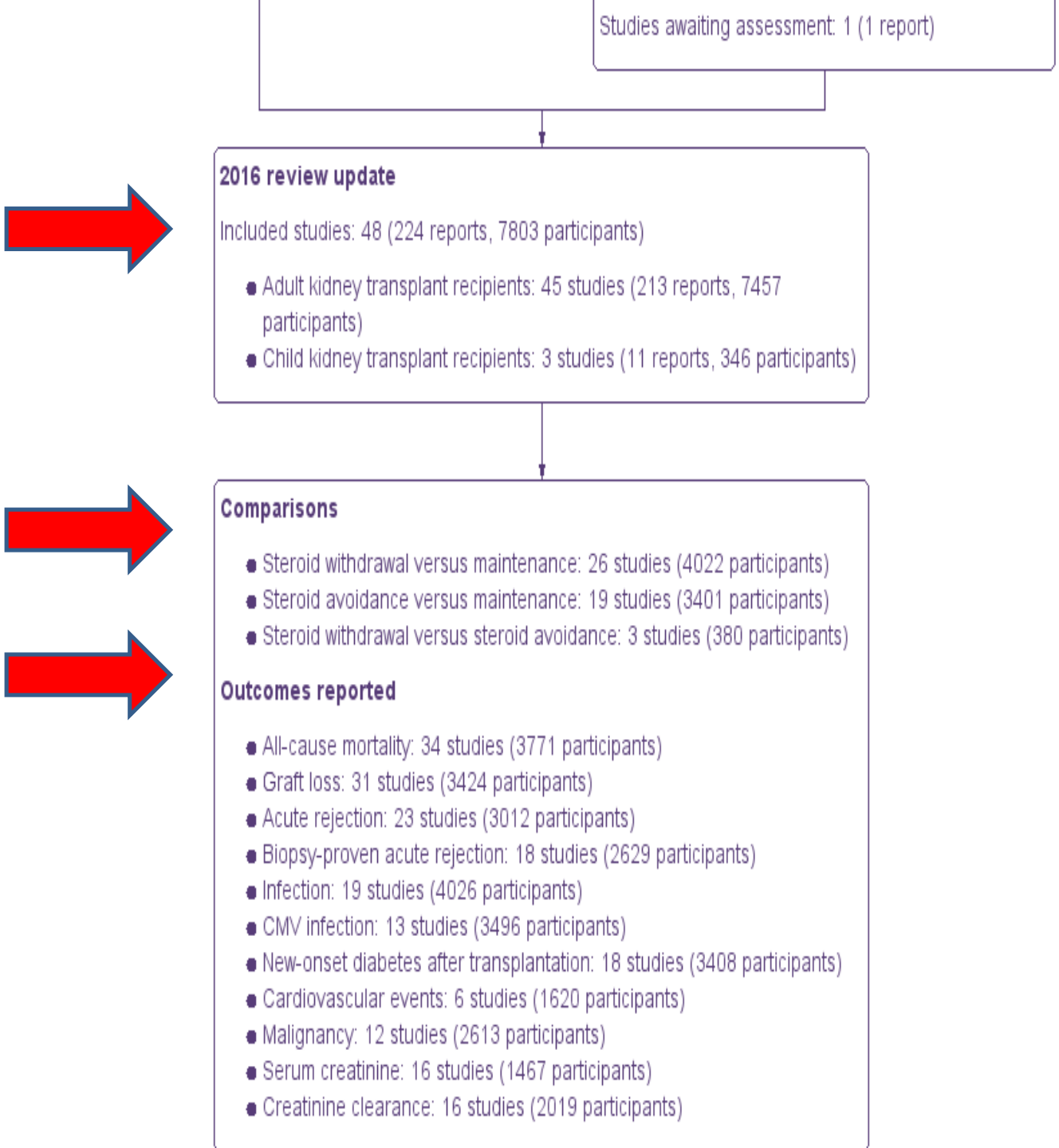
OBJECTIVES:

To evaluate the benefits and harms of steroid withdrawal or avoidance for kidney transplant recipients.

SELECTION CRITERIA:

All randomized and quasi-randomized controlled trials (RCTs) in which steroids were avoided or withdrawn at any time point after kidney transplantation were included.

Cochrane Database of Systematic Reviews
22 AUG 2016



Conclusions

Cochrane Database of Systematic Reviews

22 AUG 2016

- No significant difference in patient mortality in studies comparing steroid withdrawal vs maintenance
- No significant difference in graft loss @1 year after TX
- Incresead risk for acute rejection in patients treated with steroid for less than 14 days after TX and for patients who were withdrawn from steroid @any later time point after TX

Steroids : Yes/Not?

- ↑risk for acute rejection
- Probable less risk for acute rejection with TAC, MMF, T-cell depleting agents (Thymoglobulin, Alemtusumab)
- Steroid avoidance may be inadvisable in pts with high immunological risk or at risk of recurrent glomerular disease (patients with autoimmune diseases?)
- Better to avoid steroid for <1 week rather than later W/D (↑risk for rej. if steroid discontinued after 8 days?)
- Rapid steroid W/D → less risk for several complications (cataract, vascular necrosis, CMV etc.).
- CV benefits are not completely esthablished

  Positive effects for lipid profile, weight gain, NODAT

Steroids : Yes/Not?

- ↑ risk for *de novo* DSA (probably not with Thymo induction?)
- Role of protocol biopsies (↑fibrosis?)
- CNI and steroid free regimens Belatacept+MMF, Belatacept +Sirolimus

Conventional Immunosuppressive Protocols

1.Cyclosporine/MMF/Steroids

2.Tacrolimus/MMF/Steroids

3.Cyclosporine/Sirolimus/Steroids

4.Tacrolimus/Sirolimus/Steroids

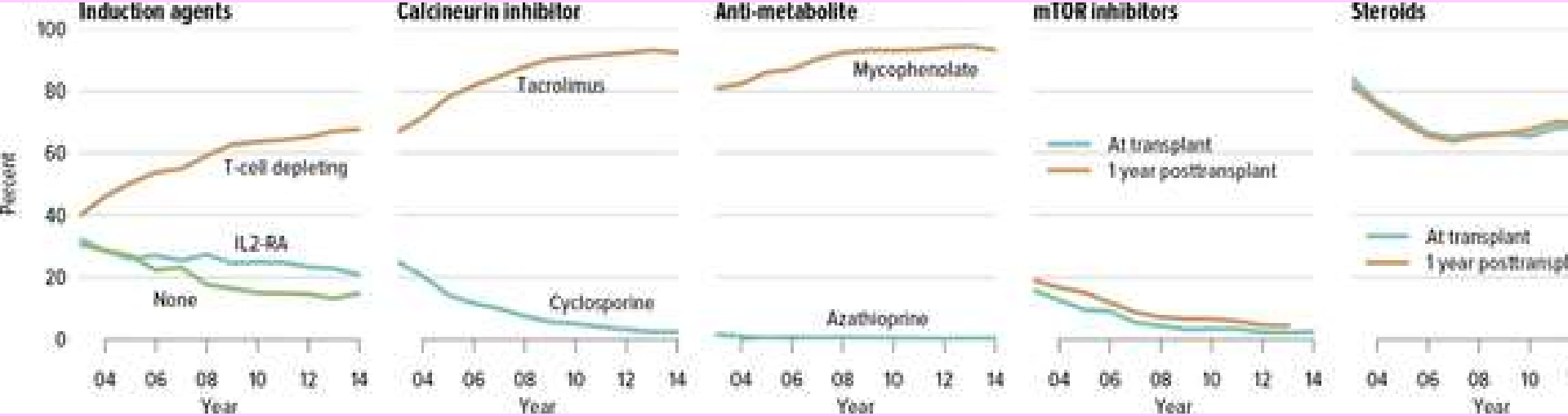
5.Cyclosporine/Everolimus/Steroids

6.Tacrolimus/Everolimus/Steroids

7.Sirolimus/MMF/Steroids

8.Everolimus/MMF/Steroids

Immunosuppression in adult kidney transplant recipients

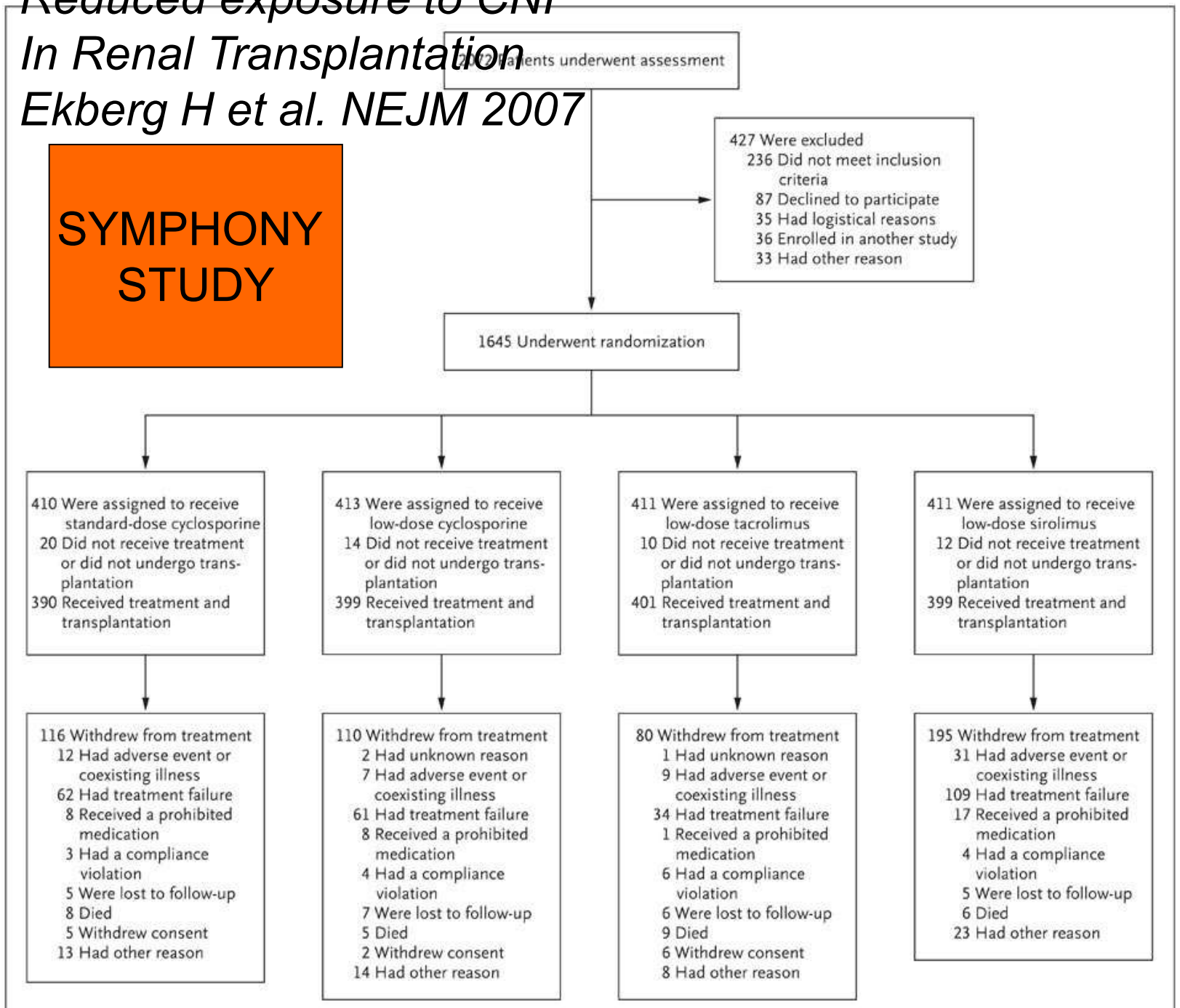


Am J Transplant, 2016

Reduced exposure to CNI In Renal Transplantation

Ekberg H et al. NEJM 2007

SYMPHONY STUDY



SYMPHONY STUDY

Table 2. Primary End Point and Selected Secondary End Points.*

End Point	Standard-Dose Cyclosporine (N=390)	Low-Dose Cyclosporine (N=399)	Low-Dose Tacrolimus (N=401)	Low-Dose Sirolimus (N=399)
Primary end point				
Mean calculated GFR — ml/min‡	57.1±25.1	59.4±25.1	65.4±27.0	56.7±26.9
P value for comparison with tacrolimus	<0.001	0.001	Reference	<0.001
Secondary end points				
Mean measured GFR — ml/min§	63.5±25.4	65.3±26.6	69.6±27.9	64.4±28.5
P value for comparison with tacrolimus	0.01	0.10	Reference	0.02
Mean calculated GFR — ml/min¶	46.2±23.1	50.2±23.1	54.3±23.9	47.5±26.1
P value for comparison with tacrolimus	<0.001	0.007	Reference	<0.001
Acute rejection‖				
At 6 mo				
Biopsy-proven (excluding borderline values) — %	24.0	21.9	11.3	35.3
P value for comparison with tacrolimus	<0.001	<0.001	Reference	<0.001
At 12 mo				
Suspected and treated — %	32.8	29.5	17.2	43.5
P value for comparison with tacrolimus	<0.001	<0.001	Reference	<0.001
Biopsy-proven (including borderline values) — %	30.1	27.2	15.4	40.2
P value for comparison with tacrolimus	<0.001	<0.001	Reference	<0.001
Biopsy-proven (excluding borderline values) — %	25.8	24.0	12.3	37.2
P value for comparison with tacrolimus	<0.001	<0.001	Reference	<0.001
Antibody treated — %	6.3	4.7	2.3	6.6
P value for comparison with tacrolimus	0.006	0.08	Reference	0.005
Allograft survival‖				
Censored for death of patients with functioning allograft — %	91.9	94.3	96.4	91.7
P value for comparison with tacrolimus	0.007	0.18	Reference	0.007
Uncensored for death of patients with functioning allograft — %	89.3	93.1	94.2	89.3
P value for comparison with tacrolimus	0.01	0.56	Reference	0.01

SYMPHONY STUDY

Daclizumab+MMF+Steroids

with

Low-dose Tacrolimus

May be advantageous for renal function, graft survival, acute rejection rates

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Effect of different IS regimens on the evolution of distinct metabolic parameters: evidence from the Symphony study

Claes K et al NDT 2012

CyA: highest uric acid values and BP

SIR: worst lipid control

TAC: " a possible NODAT could not be excluded

BELATACEPT

- Fusion protein composed of the Fc fragment of human IgG1 linked to the extracellular domain of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4)
- Inhibits T-cell activation through costimulation blockade
- Approved by U.S FDA and EMA 2011

Vincenti F, et al. A Phase III Study of Belatacept-based Immunosuppression Regimens versus Cyclosporine in Renal Transplant Recipients (BENEFIT Study). Am J Transplant 2010

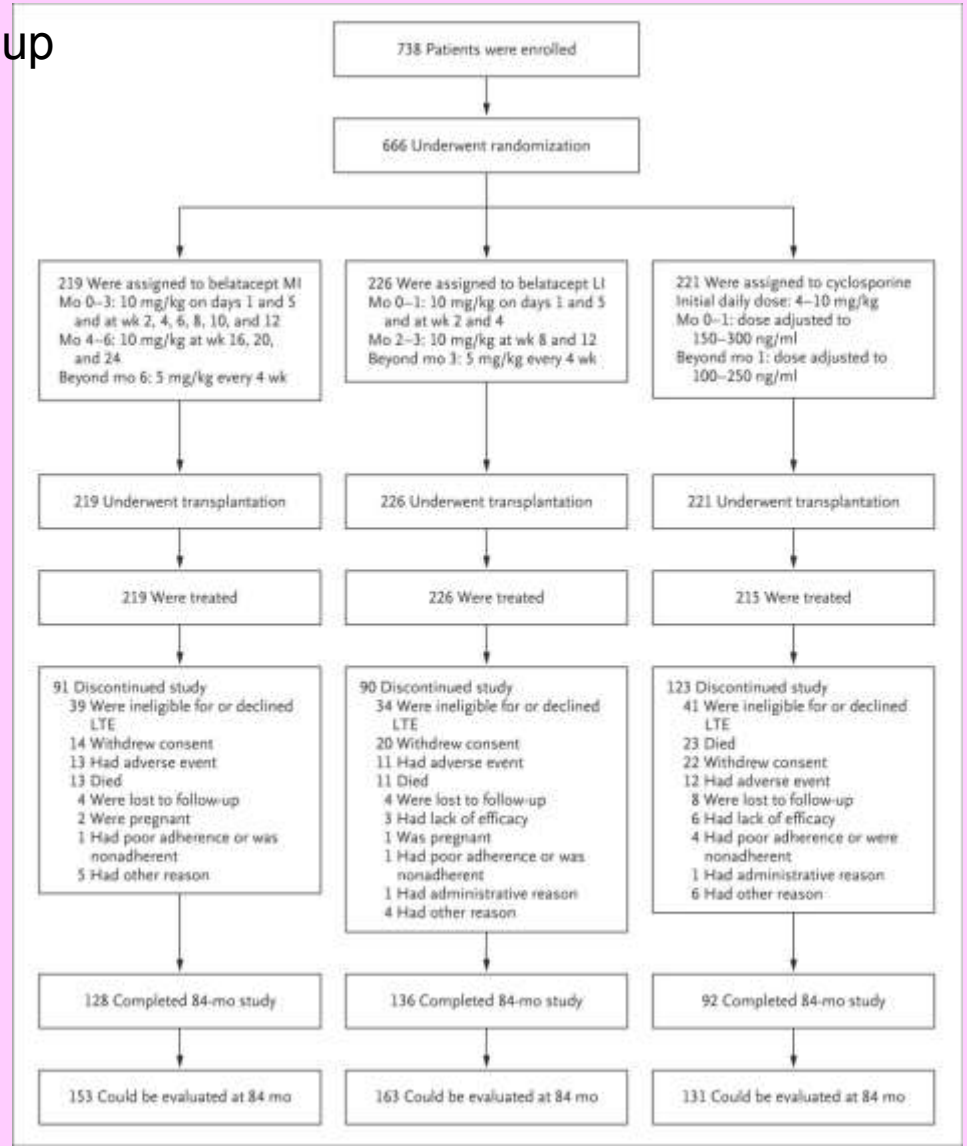
Durrbach A. et al. A Phase III Study of Belatacept Versus Cyclosporine in Kidney Transplants from Extended Criteria Donors (BENEFIT-EXT Study). Am J Transplant. 2010

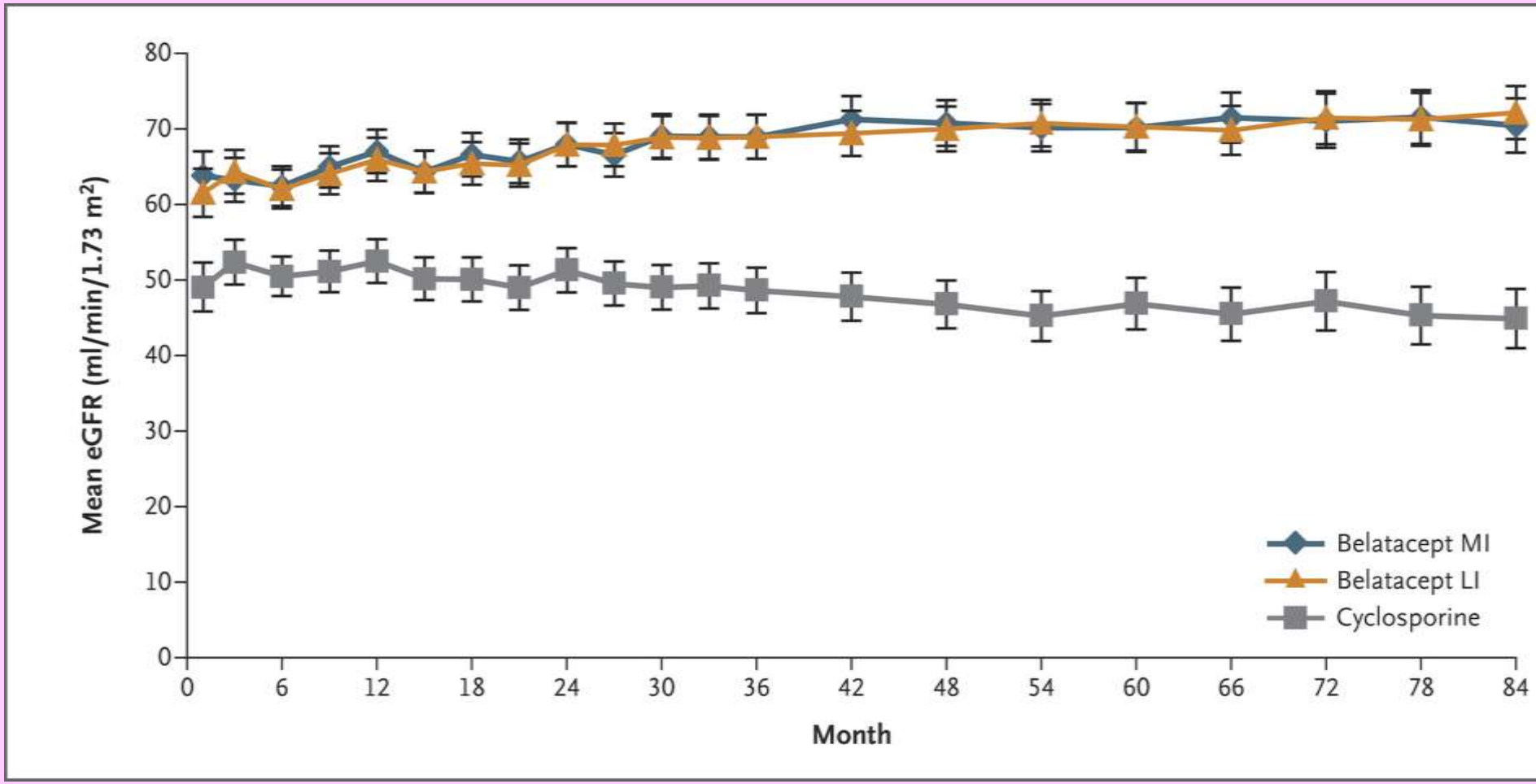
Belatacept and Long-Term Outcomes in Kidney Transplantation *Vincenti F. et al. NEJM 2016*

Randomized, single-blind,parallel-group study with an active control
Cadaver (Standard Criteria) or LD recipients TX
1:1:1 Ratio
Basiliximab Induction,MMF, Steroids

- ❑Primary objective @12 months:
  Pt and graft survival
  Renal function (eGFR)
  Incidence of acute rejection

- ❑Outcomes @ 84 months





Vincenti F. et al. NEJM

Vincenti F. et al. NEJM

- Patients assigned to more –intensive or less-intensive belatacept regimens @ 7 years had 43% (38%-45%) reduction in the risk of death and graft loss (44%-41%) as compared with control CyA group
- Improvement in renal function with belatacept sustained @ 7 years
- DSA development significant lower in both belatacept groups than in CyA group
- Trial was with CyA and not with Tacrolimus!

Trapianto da donatore vivente

Aspetti:
Etici
Psicologici
Educativi
Legali

Controindicazioni assolute e relative

Percorso di idoneita' alla donazione

Donatore idoneo

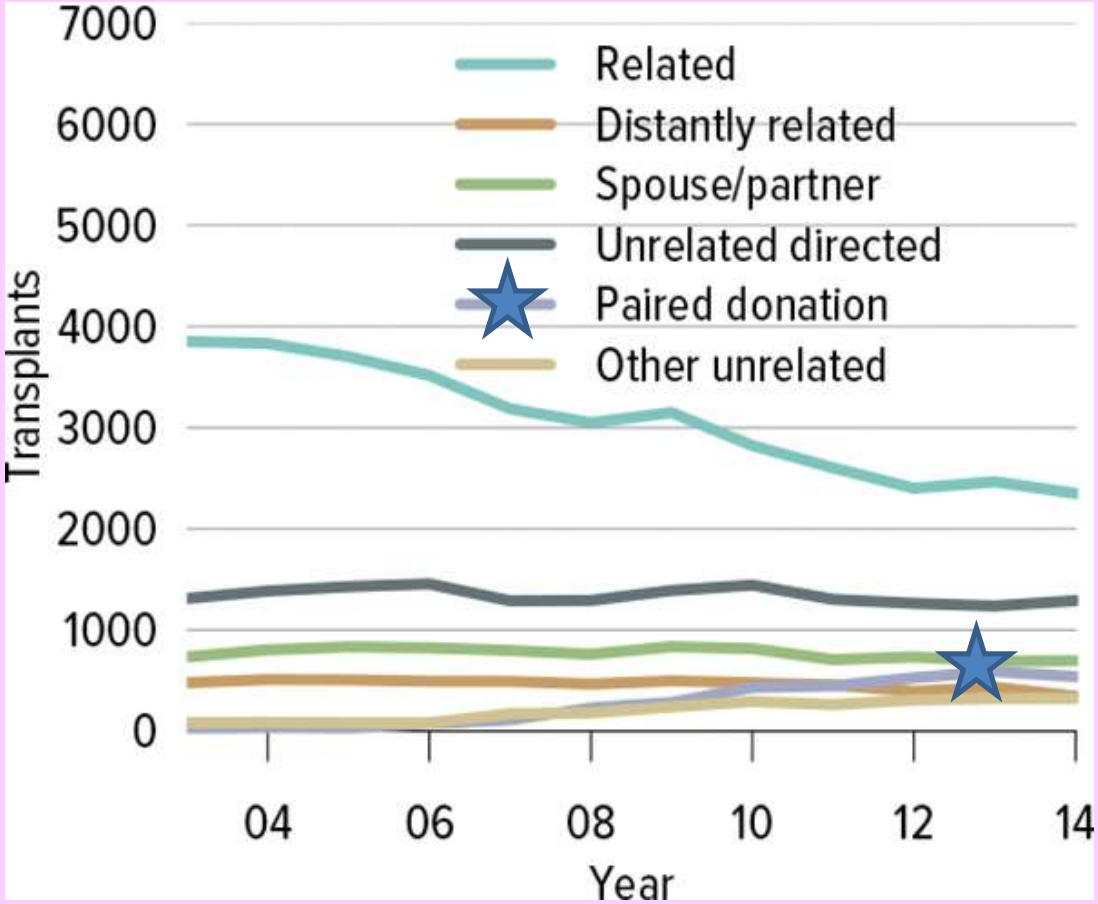
•Problematiche
• del ricevente:
•mediche
•immunologiche
•psicologiche

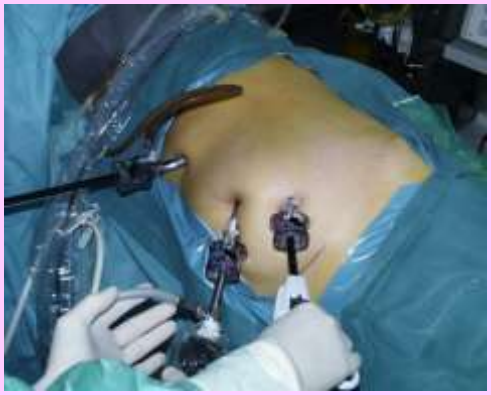
Donatore non idoneo

Altri donatori?

Immunosoppressione

Kidney transplants from living by donor relation





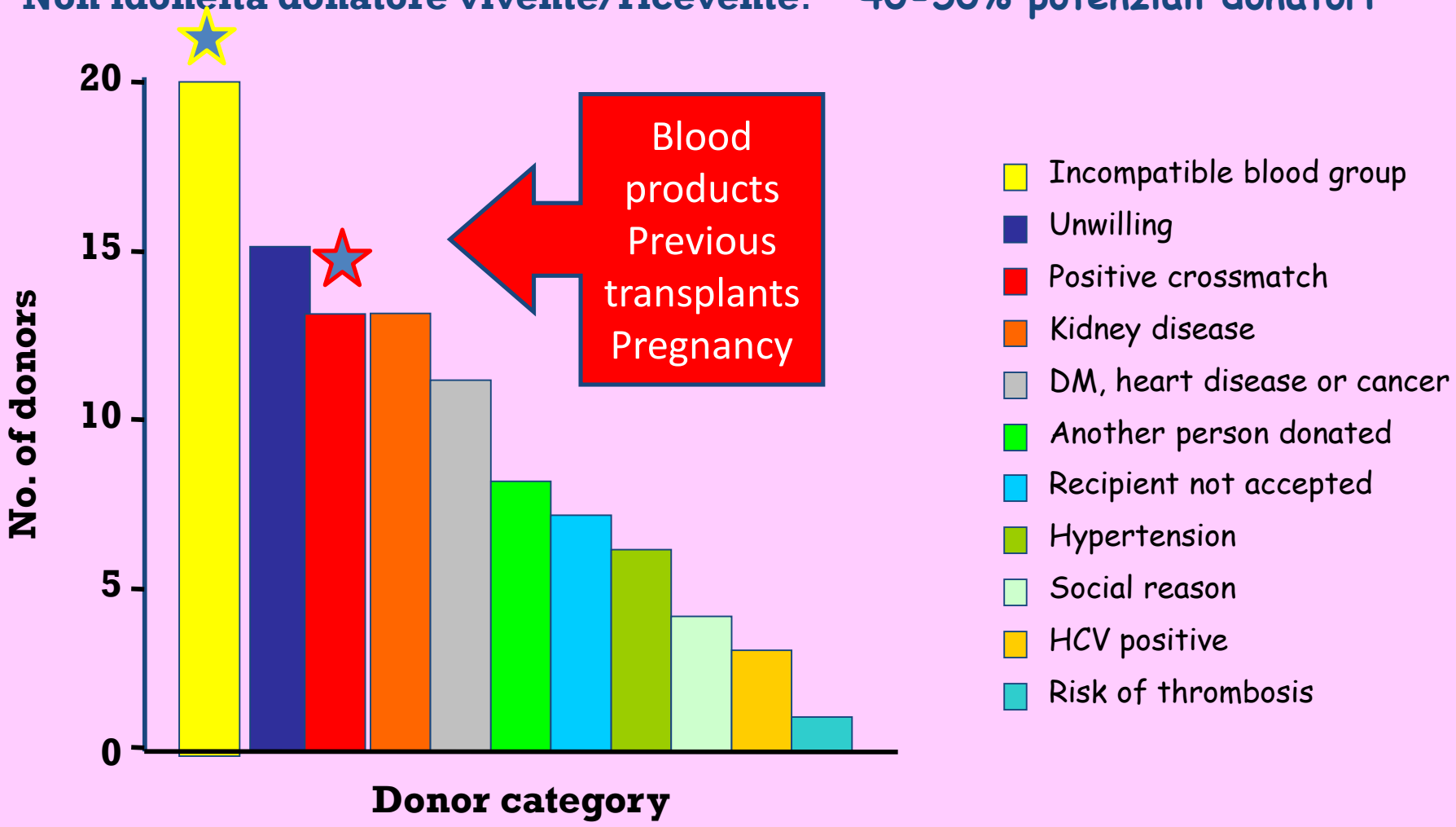
Prelievo laparoscopico

Prelievo robotico

American Journal of Transplantation, 2016

Il trapianto di rene da donatore vivente: il superamento delle barriere di incompatibilità biologica

Non idoneità donatore vivente/ricevente: ~ 40-50% potenziali donatori



Come rimuovere questi anticorpi?

1. Immunoadsorption (IA)
    1. on protein A columns (IgG only)
    2. on donor tissue (all isotypes sink):
        1. Irradiated donor lymphocytes
        2. auxiliary liver graft (high regenerative index)

2. Plasmapheresis

3. High-dose (2 g/kg per 2 doses) intravenous immune globulins (IVIg)

4. Rituximab (375 mg/m^2 – 1 g per 2 doses)

5. Various combinations of these
    - **plasmapheresis** (1-1.5 volumes) + (splenectomy) + **low-dose** (100 mg/kg of body weight per dose) **IVIg** [the day of infusion] and 30) +**rituximab** (1 g regardless of weight [or, in children, 375 mg/m^2 of body-surface area] on days 7 and 22)

Esperienza di PISA

Trapianti di Rene Immunologicamente Incompatibili (Lug. 2009 - Dic. 2016)

22 coppie solo AB0i

6 coppie AB0i + DSA

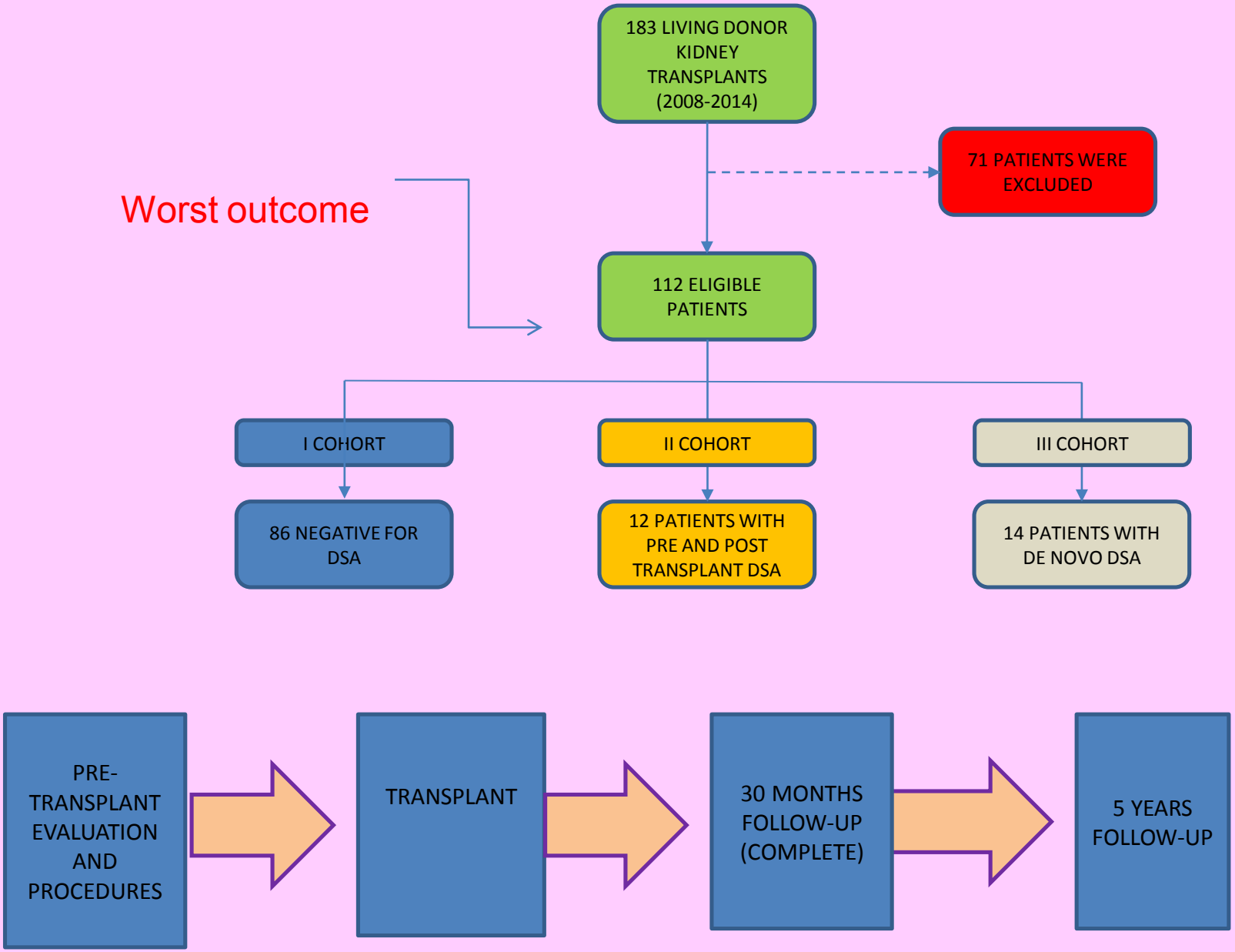
ABOi Titolo Agglutinine da 1:8 a 1:4096

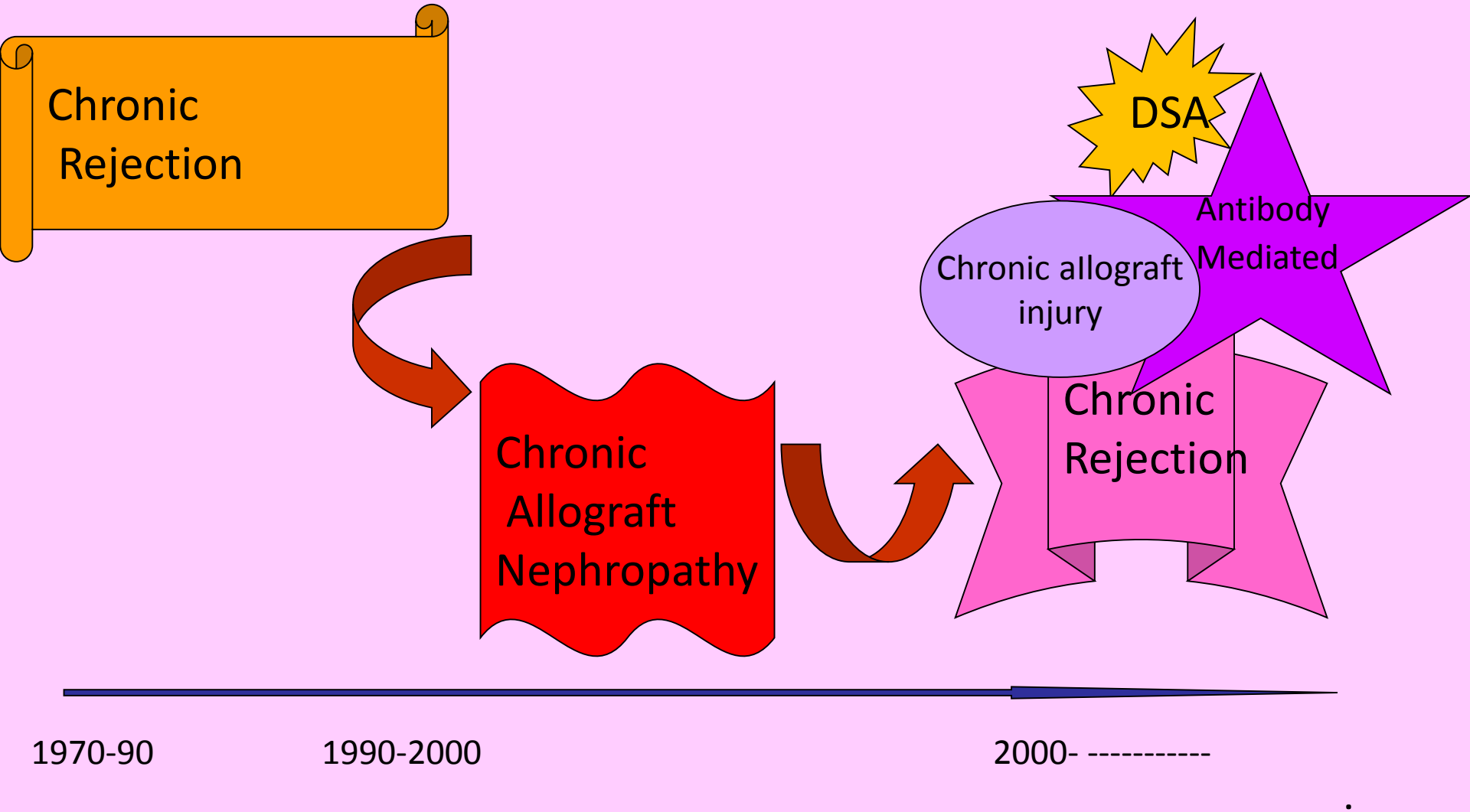
UNIVERSITY OF PISA

CLINICAL IMPACT OF DONOR SPECIFIC ANTIBODIES IN LIVING DONOR KIDNEY TRANSPLANTATION

D Giannese, D Moriconi, A Mazzoni, S Gabbriellini, L Mariotti, U Boggi, MF Egidi

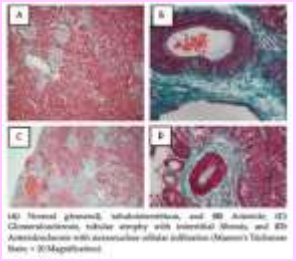
Submitted to AJT 2016

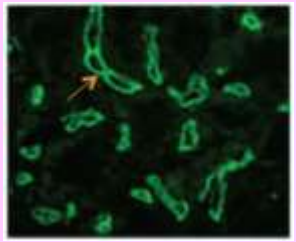

183 LIVING DONOR KIDNEY TRANSPLANTS (2008-2014)
71 PATIENTS WERE EXCLUDED
Worst outcome
112 ELIGIBLE PATIENTS
I COHORT
II COHORT
III COHORT
86 NEGATIVE FOR DSA
12 PATIENTS WITH PRE AND POST TRANSPLANT DSA
14 PATIENTS WITH DE NOVO DSA
PRE-TRANSPLANT EVALUATION AND PROCEDURES
TRANSPLANT
30 MONTHS FOLLOW-UP (COMPLETE)
5 YEARS FOLLOW-UP

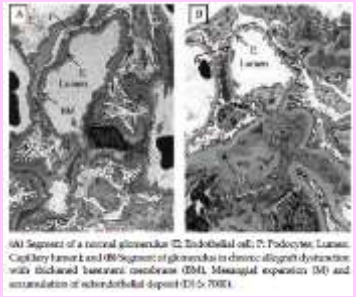

Chronic
Rejection
Chronic
Allograft
Nephropathy
DSA
Antibody
Mediated
Chronic allograft
injury
Chronic
Rejection
1970-90
1990-2000
2000- ----------
anni

Chronic Allograft Injury (CAI)

- Seconda causa di perdita del rene trapiantato (la prima è la morte del paziente con rene funzionante)
- Le biopsie renali effettuate per protocollo ad un anno mostrano CAI nel 40-50% dei casi







Chronic allograft injury (CAI)

Immunological factors:

Acute and sub-acute rejection
HLA mismatches
Donor specific antibodies (DSA)→
Chronic rejection

Non immunological factors

Ischemia /reperfusion injury
Delayed graft function
Donor factors (age)

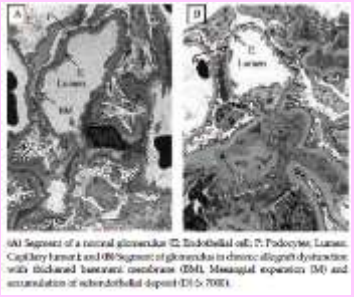
CNI toxicity
Viral nephritis (CMV, Polyomavirus)
Hypertension
Hyperlipidemia

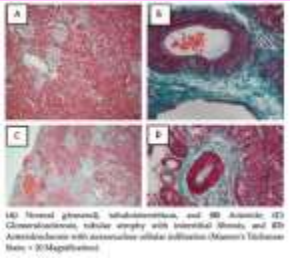
Inflammation
Injury

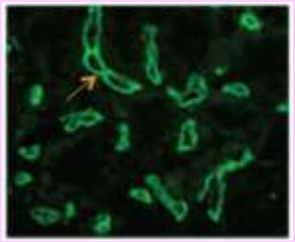
Adhesion molecules
Cytokines
Growth factors

Accelerated senescence

Interstitial fibrosis
Transplant glomerulopathy
Tubular athrophy
Fibrous intimal tickening of arteries







Donor Specific Antibodies (DSAs)

- ↑ risk for antibody-mediated rejection (AMR)
- Allograft dysfunction and proteinuria
- First appearance may be months to years before graft dysfunction

Major cause of allograft failure

- *Everly MJ, Terasaki PI. Seminars in Immunology 2012;24:143*
- *Lachmann N et al. Transplantation 2009; 87 (10):1505*
- *Worthington JE et al. Transplantation 2003;75 (7): 1034*

Donor Specific Antibodies (DSA)

- **Pre-existing DSA**
  restimulation of previously sensitized memory population
  early and specific cooperation of T-B cells
- ***de novo* DSA**
  in previously non-sensitized patients
- **Other antibodies**
  autoantibodies to cryptic antigens:
  antiperlecan/LG3, anti-endothelium,
  anti- angiotensin II receptor,
  against minor histocompatibility Ag *

Cardinal et al. JASN, 2016

HLA-incompatible transplantation (DSA)

Sources of allosensitization

1. blood transfusion (even leucodepleted units => prefer epoetins)

HLA and RBC immunization after filtered and buffy coat-depleted blood transfusion in cardiac surgery: a randomized controlled trial

Volume 43, June 2003 **TRANSFUSION** 765

Leo van de Watering, Jo Hermans, Marian Witvliet, Michel Versteegh, and Anneke Brand

CONCLUSION: Buffy coat removal, and additional WBC reduction by filtration, either before or after storage, result in similar posttransfusion alloimmunization frequencies after a single transfusion event with multiple RBCs.

= 16.1%

Vox Sang 1997;72:238–241

Received: November 11, 1995
Revised manuscript received: November 19, 1996
Accepted: November 27, 1996

Ellen Toaning [a,c]
Anne Catrine Simonsen [c]
Erik Hjelms [d]
Arne Svejgaard [c]
Niels Morling [b]

Platelet Alloimmunization after Transfusion

A Prospective Study in 117 Heart Surgery Patients

They received mostly saline-adenine-glucose + mannitol red blood cell components (poor in leukocytes and platelets) in connection with cardiac surgery.

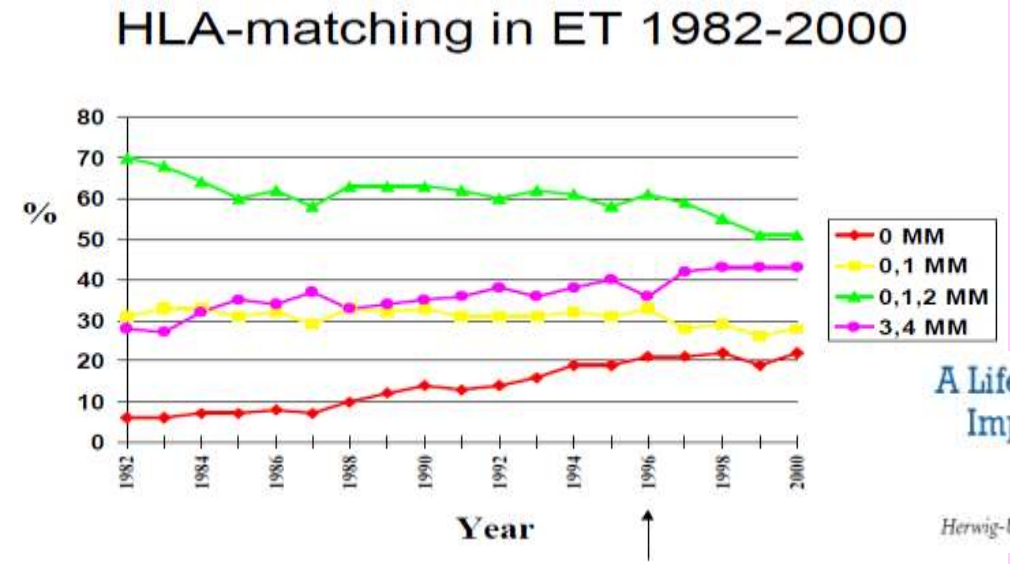
HLA antibodies were detected by the standard lymphocyte cytotoxicity techniques.

We detected lymphocytotoxic HLA antibodies in 21 patients (17.9%), of whom 18 (15.4%) had had no detectable antibodies before transfusion.

HLA-incompatible transplantation (DSA)

Sources of allosensitization

2. pregnancy (F vs. M = 33% vs. 17%)
3. prior allotransplantation (2nd vs 1st 52% vs. 15%; PBHSCT > BMHSCT; Lapierre, 2002)



Introduction of the Acceptable Mismatch program

A Lifetime Versus a Graft Life Approach Redefines the Importance of HLA Matching in Kidney Transplant Patients

Herwig-Ulf Meier-Kriesche,[1,4] Juan C. Scornik,[2] Brian Susskind,[3] Shehzad Rehman,[1] and Jesse D. Schold[3]

Transplantation • Volume 88, Number 1, July 15, 2009 www.transplantjournal.com | 23

Results. There was no appreciable change in PRA for patients receiving a first 0 HLA-A, -B, -DR, or 0 HLA-A, -B–mismatched kidney transplant; contrariwise, there was a significant increase in PRA by increasing HLA mismatch of the first transplant. Only 10% of patients became sensitized after a 0 HLA-A, -B–mismatched transplant, whereas the proportion rose up to 37% with increasing HLA mismatches. Other factors, notably younger age and African American race, also contributed to a higher PRA at relisting.

Conclusions. Although there might be a limited impact of HLA matching on acute rejection and graft survival, many patients might be negatively impacted from poor HLA matching of their first kidney transplant when needing a second transplant. This might be particularly important in patients with a long life expectancy because of the high likelihood of needing a second transplant during their lifetime.

Does *de novo* development of anti-HLA antibodies predict long-term graft failure?

American Journal of Transplantation 2009; 9: 2532–2541
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2009.02800.x

De Novo Donor-Specific Antibody at the Time of Kidney Transplant Biopsy Associates with Microvascular Pathology and Late Graft Failure

L. G. Hidalgo[a,*], P. M. Campbell[a,b], B. Sis[a], G. Einecke[c], M. Mengel[a], J. Chang[b], J. Sellares[d], J. Reeve[a] and P. F. Halloran[b]

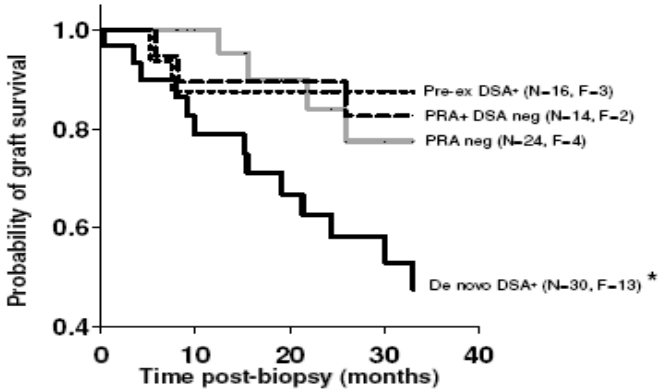
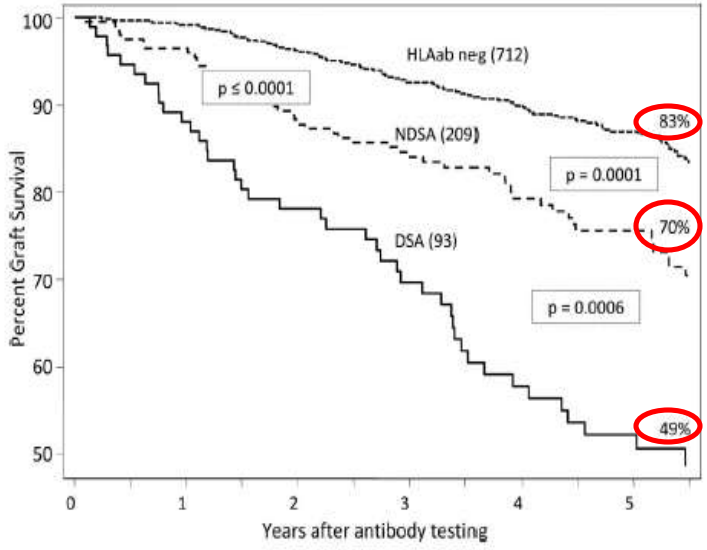


Figure 6: Probability of graft survival curves in patients who underwent a late biopsy and were assessed for DSA. Probability of graft survival in patients in each DSA subgroup was compared to patients with no detectable HLA antibodies (PRA neg). N depicts the number of patients in each group and F; the number of failed grafts. *p = 0.001 (log-rank test).

Anti-Human Leukocyte Antigen and Donor-Specific Antibodies Detected by Luminex Posttransplant Serve as Biomarkers for Chronic Rejection of Renal Allografts

Nils Lachmann,[1,2,8] Paul I. Terasaki,[2] Klemens Budde,[3] Lutz Liefeldt,[3] Andreas Kahl,[4] Petra Reinke,[4] Johann Pratschke,[5] Birgit Rudolph,[6] Danilo Schmidt,[3] Abdulgabar Salama,[7] and Constanze Schönemann[1]



Risk factors for the *de novo* development of DSA

Morath et al. Journal of Immun.Res. 2014

- Retransplantation
- HLA-antibodies before TX
- Young age (18-35 years old)
- DR, DQ mismatch
- Nonadherence
- Insufficient IS
- Inflammation (i.e infection)
- (Subclinical) T-cell-mediated rejection

Immunotherapeutic Approaches for Removal of HLAabs

- IVIG blockage of anti HLA antibody re-synthesis, modification of APC, apoptosis of mature B cells, regulation of anti-idiotipic ab to anti-HLA, expansion and effector function of CD4+/CD25+/FoxP3+Tregs
- **Rituximab** (anti cD-20) B cells depletion
- Plasmapheresis DSAs depletion
- Blocking co-stimulation pathways (CD40-40L, CD28-B7)
- **Bortezomib**, Carfilzomib
- Anti BAFF/April anti B-cell activating factor
- Anti-IL-6-receptor antibodies: Tocilizumab
- Modifiers of complement activation : Ecluzumab
- Belatacept (LEA29Y: CTLA4-Ig variant)?

Jordan ST. Discovery Medicine, 2012

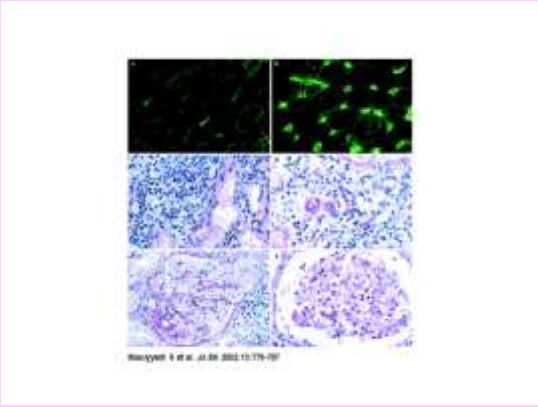
Everly MJ, Terasaki PI . Seminars in Immunology 2012; 24:142

Kahwaji L et al. Transplant Int 2016

Rostaing L et al. Ther Apher Dial 2016

Sautenet B et al. Transplantation 2016

AMR: Characterization



- Serum: Presence of DSAs

- Renal biopsy: Spectrum of lesions

  C4d deposition in the peritubular capillaries (as a marker of ab-mediated activation of the complement cascade) (C4d negative AMR!!)

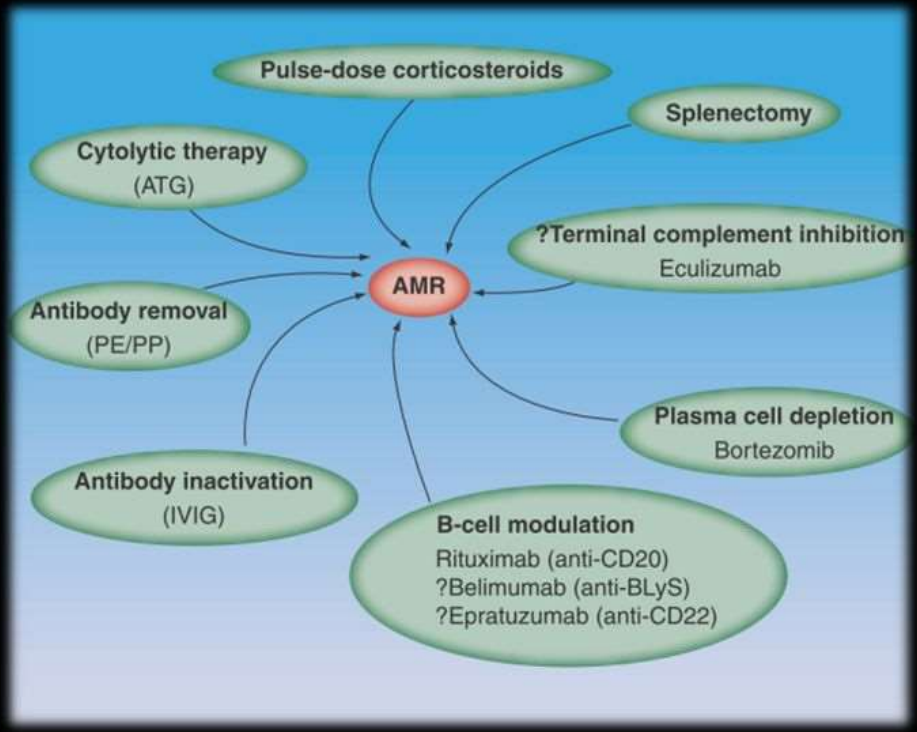
  IF, transplant glomerulopathy, intimal arteritis, microvascular injury

- Clinically : chronic allograft dysfunction
  significant proteinuria

  → **graft failure**

Hidalgo et al. 2009; Platt 2010; Jordan et al. 2011; Halloran et al. 2010; Lefaucheur et al.2009; Gaston et al. 2011, Haas 2012

Therapeutic strategies antibody-mediated rejection



Future Cardiol. (2012) 8(4)

Eculizumab

Licensed for the treatment of:

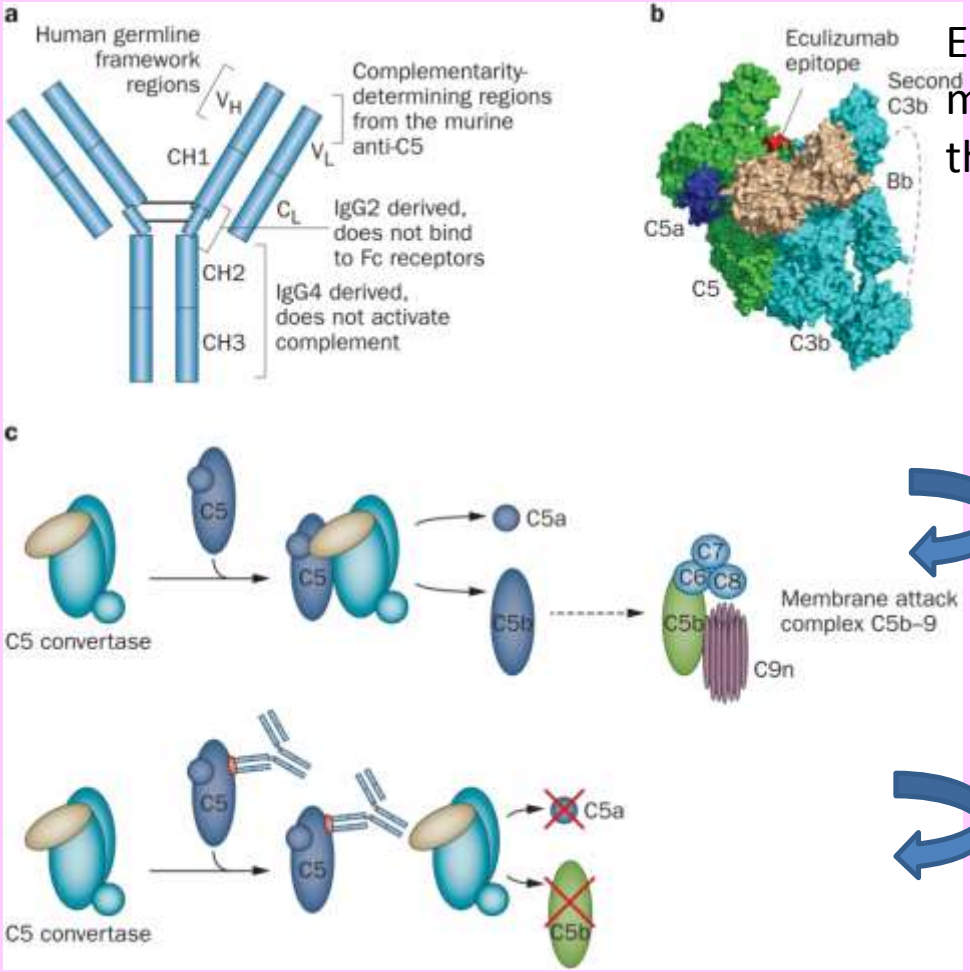
- ❑paroxysmal nocturnal hemoglobinuria
- ❑atypical hemolytic uremic syndrome

Used "off label" to treat:

- ❑refractory antibody-mediated rejection
(very limited number of patients, although with impressive efficacy)
- ❑renal transplant candidates with a genetically determined risk of post-transplantation aHUS recurrence
- ❑C3glomerulopathy

Hillmen, P. N. & Rother, R. P *N.Engl .J.Med. (2006)*
Kelly, R. J. Blood (2011)
Gruppo, RA et al. N. Engl. J. Med. (2009)
Nürnberger, J. et al. N. Engl. J. Med (2009)
Sethi, S. & Fervenza, F. C.N. Engl. J. Med. (2012)
Nester, C. *et al*. Clin. J. Am. Soc. Nephrol. (2011)

Eculizumab: molecular structure and mode of action



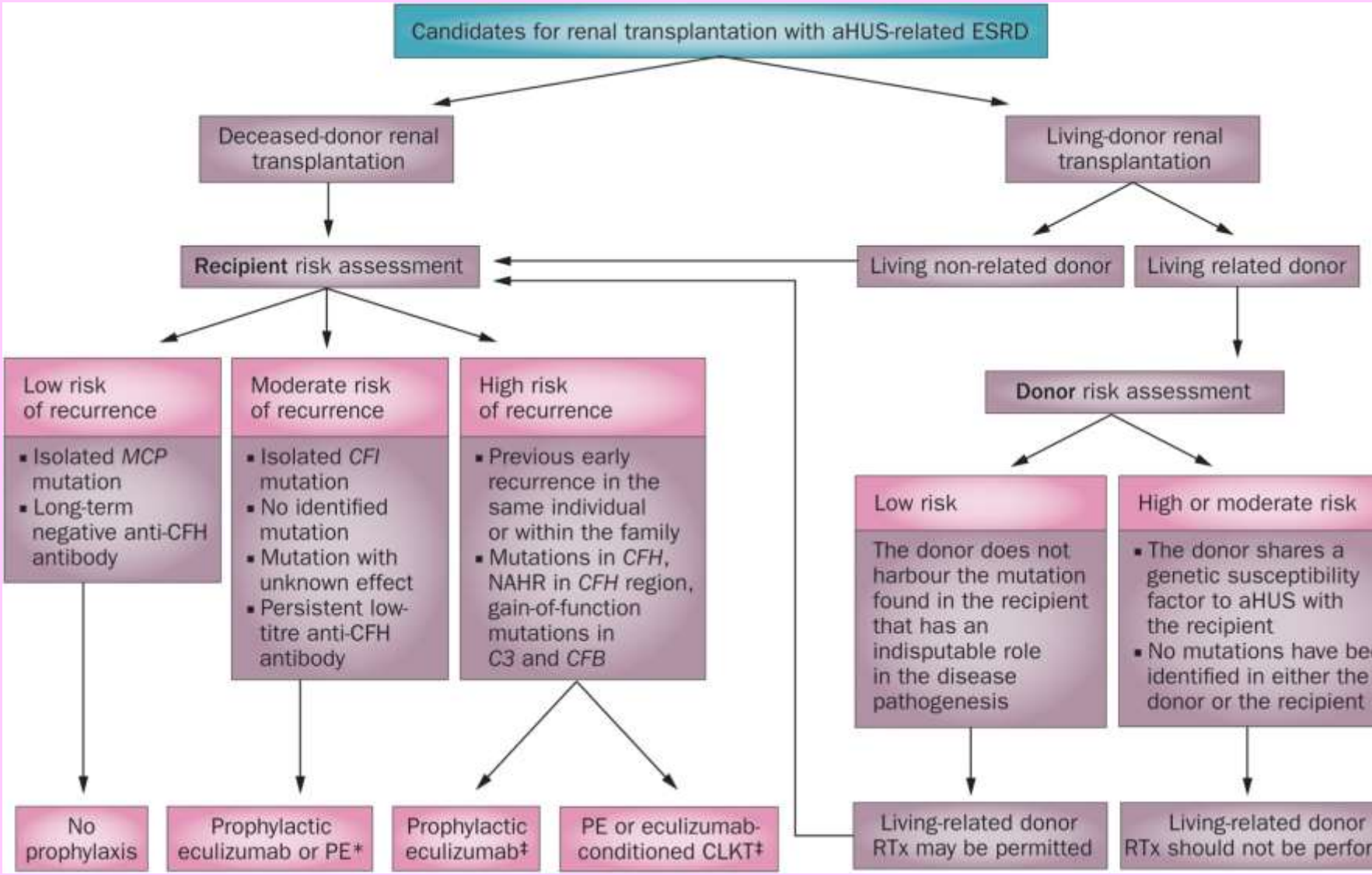
Eculizumab is a complement-inhibitory monoclonal antibody that inhibits assembly of the membrane attack complex via C5

Substrate C5 enters into the C5 convertase and is cleaved to C5a and C5b. C5b binds C6, C7, C8 and several molecules of C9 to form the membrane attack complex C5b–9

Eculizumab binds to C5 with a very high affinity, preventing its entry into th C5 convertase. This effect prevents C5 cleavage and the formation of C5a and C5b–9

Zuber, J. et al. (2012)
Nat. Rev. Nephrol.

Risk assessment for patients with aHUS who are candidates for renal transplantation



Eculizumab and Antibody Mediated Rejection

- The Use of Antibody to Complement Protein C5 for Salvage Treatment of Severe Antibody-Mediated Rejection

  J. E. Locke et al. AJT 2009

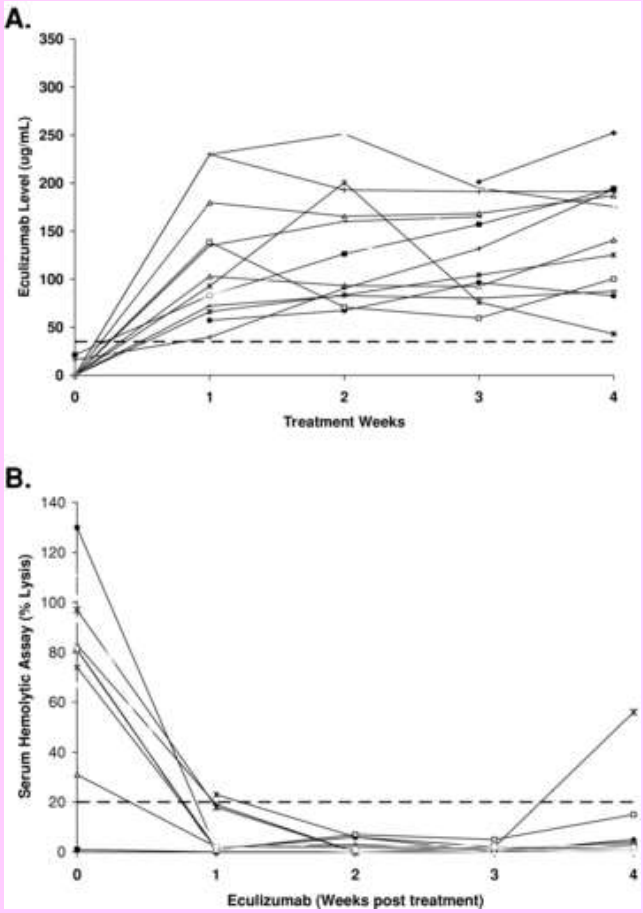
- Terminal Complement Inhibition Decreases Antibody-Mediated Rejection in Sensitized Renal Transplant Recipients

  Stegall MA et al AJT 2011

- Eculizumab for the Treatment of Severe Antibody-Mediated Rejection:a case report and a review of the literature

  Tran D e al. Case Rep Transplant 2016

Terminal Complement Inhibition Decreases Antibody-Mediated Rejection in Sensitized Renal Transplant Recipients



Eculizumab levels in the first 16 patients were therapeutic at the end of each dosing period

Hemolytic activity was blocked in all patients except one patient at week 4

AJT 2011

Bortezomib

- Protocolli di desensibilizzazione
- Rimozione DSA post-trapianto
- Trattamento rigetto anticorpo mediato

Moreno Gonzales MA et al., Transplantation 2016

Jeong JC et al.Medicine (Baltimore) 2016

Jordan SC et al. Transplant Proc 2016

Shah N. et al. Curr Opin Organ Transplan 2015

Stegal MD, Clin Transplat 2010

Trapianto di rene

Passato	Metodiche per preservazione organi e tecniche chirurgiche Terapie immunosoppressive per prevenire o ridurre gli episodi di rigetto acuto
Passato recente	Impiego di diverse combinazioni di immunosoppressori con differenti meccnismi d'azione (induzione, duplice e triplice terapia) - bilanciare il rischio di rigetto e la nefrotossicita' - migliorare la sopravvivenza del paziente e del rene
Presente	nuovi criteri di allocazione organi "donatori marginali" (ECD, DCD) trapianti ABO incompatibili, cross over cell-based immunosoppressione (www.onestudy.org) Continua revisione della classificazione Banff, espressione genica ecc.
Futuro	**Riprogrammare il sistema immunitario per indurre tolleranza**


PRENDIAMOCI A
CUORE IL RENE
NUOVE PROSPETTIVE BASATE
SU ATTUALI CERTEZZE
Milano - Hotel Michelangelo
2-3 dicembre 2016

Grazie!!