Herzlichen Glückwunsch

III. Medizinische Klinik und Poliklinik &
Universitäres Transplantations – Centrum UTC
ZENTRUM INNERE MEDIZIN

(Immunologische) Risikobeurteilung:

Der Schlüssel zur (individuell) angepassten Immunsuppression nach Nierentransplantation

Friedrich Thaiss

Universitätsklinikum Hamburg-Eppendorf

Risikobeurteilung:

Transplantation Reviews 30 (2016) 77–84

Contents lists available at ScienceDirect

Transplantation Reviews

journal homepage: www.elsevier.com/locate/trre

Immunological risk assessment: The key to individualized immunosuppression after kidney transplantation

Johann Pratschke [a,*], Duska Dragun [b], Ingeborg A. Hauser [c], Sabine Horn [d], Thomas F. Mueller [e], Peter Schemmer [f], Friedrich Thaiss [g]

[a] Department of General, Visceral and Transplantation Surgery, Charité University Hospital, Berlin, Germany
[b] Department of Nephrology and Intensive Care Medicine, Charite Campus Virchow Clinic, Berlin, Germany
[c] Department of Nephrology, University Hospital Frankfurt, Goethe University Frankfurt, Frankfurt am Main, Germany
[d] Division of Nephrology, Medical University of Graz, Graz, Austria
[e] Division of Nephrology, University Hospital Zürich, Zürich, Switzerland
[f] Department of General, Visceral and Transplant Surgery, Heidelberg University Hospital, Heidelberg, Germany
[g] Department Internal Medicine, Division of Nephrology & University Transplant Center, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany

Risikobeurteilung:

Nierentransplantation oder Dialysebehandlung

Dauer der Dialyse – Nierentransplantation

präemptiv – lange Wartezeit

Spender – Alter

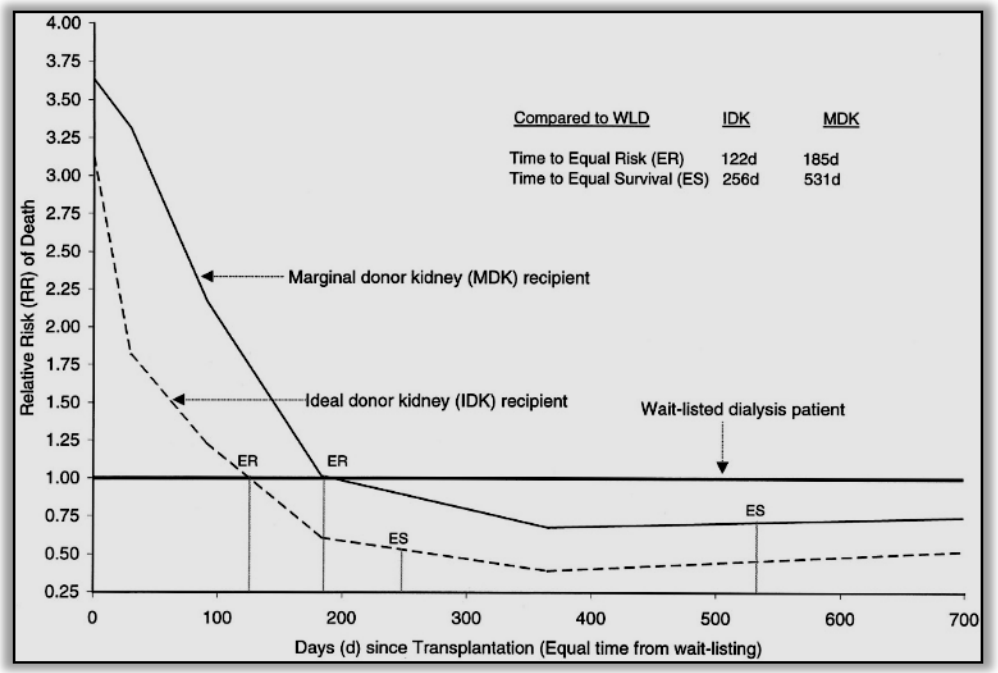
Organqualität

Empfänger – Alter

Co-Morbidität:

kardiovaskulär

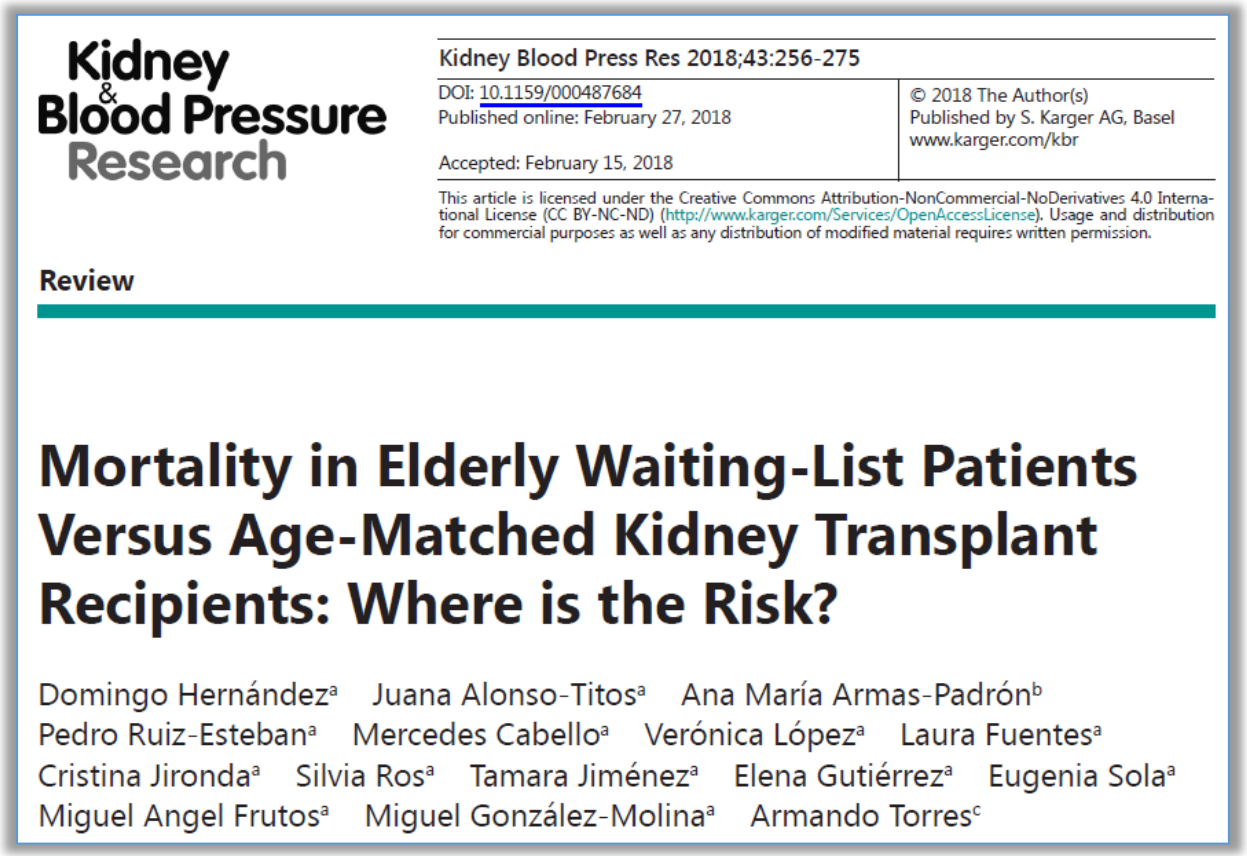
Diabetes mellitus



OJO, A. O. et al. J Am Soc Nephrol 2001;12:589-597

Risikobeurteilung:

Dialyse auf Dauer – Nierentransplantation



Kidney & Blood Pressure Research

Kidney Blood Press Res 2018;43:256-275

DOI: 10.1159/000487684

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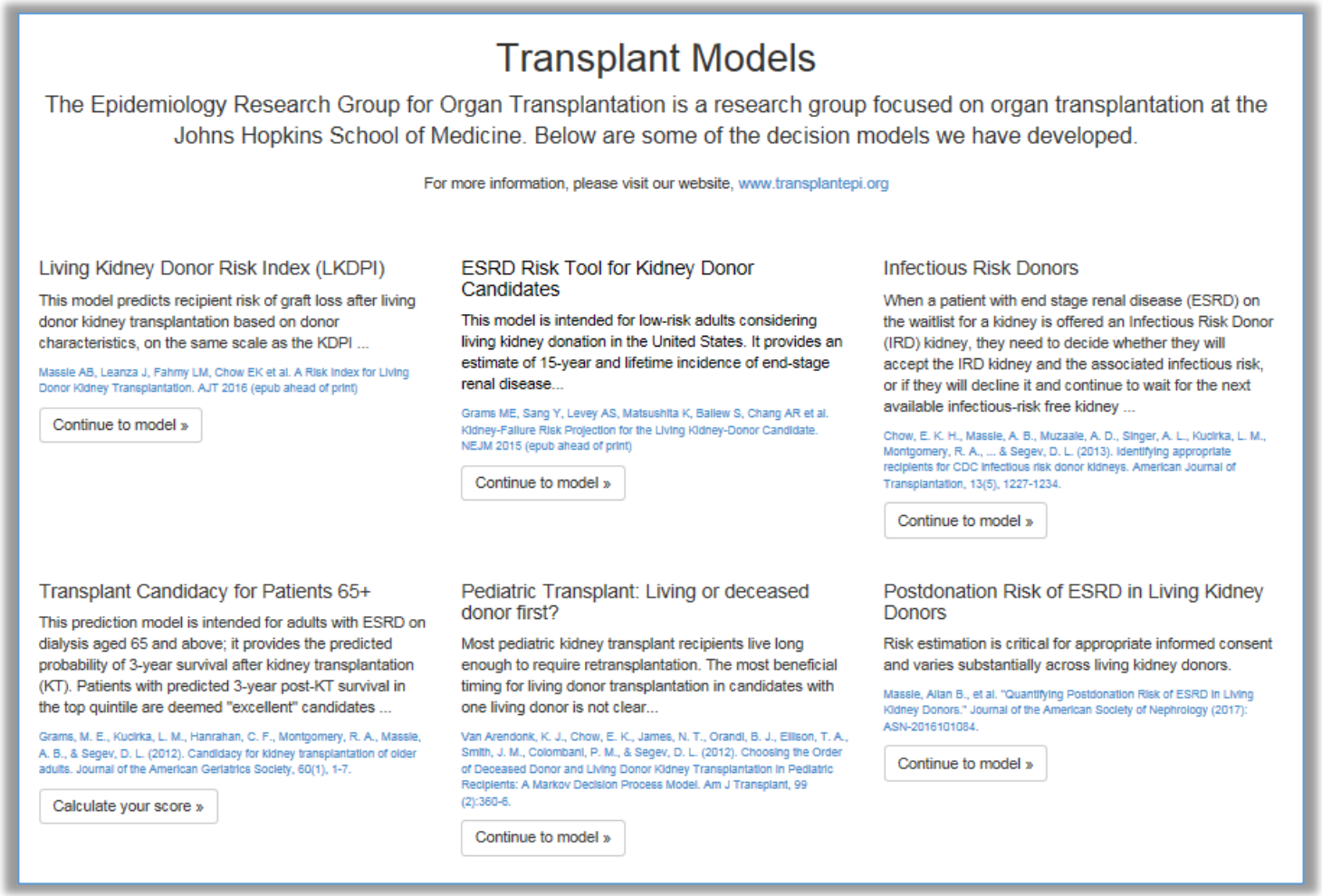
Review

Mortality in Elderly Waiting-List Patients Versus Age-Matched Kidney Transplant Recipients: Where is the Risk?

Domingo Hernández[a] Juana Alonso-Titos[a] Ana María Armas-Padrón[b]
Pedro Ruiz-Esteban[a] Mercedes Cabello[a] Verónica López[a] Laura Fuentes[a]
Cristina Jironda[a] Silvia Ros[a] Tamara Jiménez[a] Elena Gutiérrez[a] Eugenia Sola[a]
Miguel Angel Frutos[a] Miguel González-Molina[a] Armando Torres[c]

Risikobeurteilung:

www.transplantmodels.com



Transplant Models

The Epidemiology Research Group for Organ Transplantation is a research group focused on organ transplantation at the Johns Hopkins School of Medicine. Below are some of the decision models we have developed.

For more information, please visit our website, www.transplantepi.org

Living Kidney Donor Risk Index (LKDPI)

This model predicts recipient risk of graft loss after living donor kidney transplantation based on donor characteristics, on the same scale as the KDPI ...

Massie AB, Leanza J, Fahmy LM, Chow EK et al. A Risk Index for Living Donor Kidney Transplantation. AJT 2016 (epub ahead of print)

Continue to model »

ESRD Risk Tool for Kidney Donor Candidates

This model is intended for low-risk adults considering living kidney donation in the United States. It provides an estimate of 15-year and lifetime incidence of end-stage renal disease...

Grams ME, Sang Y, Levey AS, Matsushita K, Ballew S, Chang AR et al. Kidney-Failure Risk Projection for the Living Kidney-Donor Candidate. NEJM 2015 (epub ahead of print)

Continue to model »

Infectious Risk Donors

When a patient with end stage renal disease (ESRD) on the waitlist for a kidney is offered an Infectious Risk Donor (IRD) kidney, they need to decide whether they will accept the IRD kidney and the associated infectious risk, or if they will decline it and continue to wait for the next available infectious-risk free kidney ...

Chow, E. K. H., Massie, A. B., Muzaale, A. D., Singer, A. L., Kucirka, L. M., Montgomery, R. A., ... & Segev, D. L. (2013). Identifying appropriate recipients for CDC infectious risk donor kidneys. American Journal of Transplantation, 13(5), 1227-1234.

Continue to model »

Transplant Candidacy for Patients 65+

This prediction model is intended for adults with ESRD on dialysis aged 65 and above; it provides the predicted probability of 3-year survival after kidney transplantation (KT). Patients with predicted 3-year post-KT survival in the top quintile are deemed "excellent" candidates ...

Grams, M. E., Kucirka, L. M., Hanrahan, C. F., Montgomery, R. A., Massie, A. B., & Segev, D. L. (2012). Candidacy for kidney transplantation of older adults. Journal of the American Geriatrics Society, 60(1), 1-7.

Calculate your score »

Pediatric Transplant: Living or deceased donor first?

Most pediatric kidney transplant recipients live long enough to require retransplantation. The most beneficial timing for living donor transplantation in candidates with one living donor is not clear...

Van Arendonk, K. J., Chow, E. K., James, N. T., Orandi, B. J., Ellison, T. A., Smith, J. M., Colombani, P. M., & Segev, D. L. (2012). Choosing the Order of Deceased Donor and Living Donor Kidney Transplantation in Pediatric Recipients: A Markov Decision Process Model. Am J Transplant, 99 (2):360-6.

Continue to model »

Postdonation Risk of ESRD in Living Kidney Donors

Risk estimation is critical for appropriate informed consent and varies substantially across living kidney donors.

Massie, Allan B., et al. "Quantifying Postdonation Risk of ESRD in Living Kidney Donors." Journal of the American Society of Nephrology (2017): ASN-2016101084.

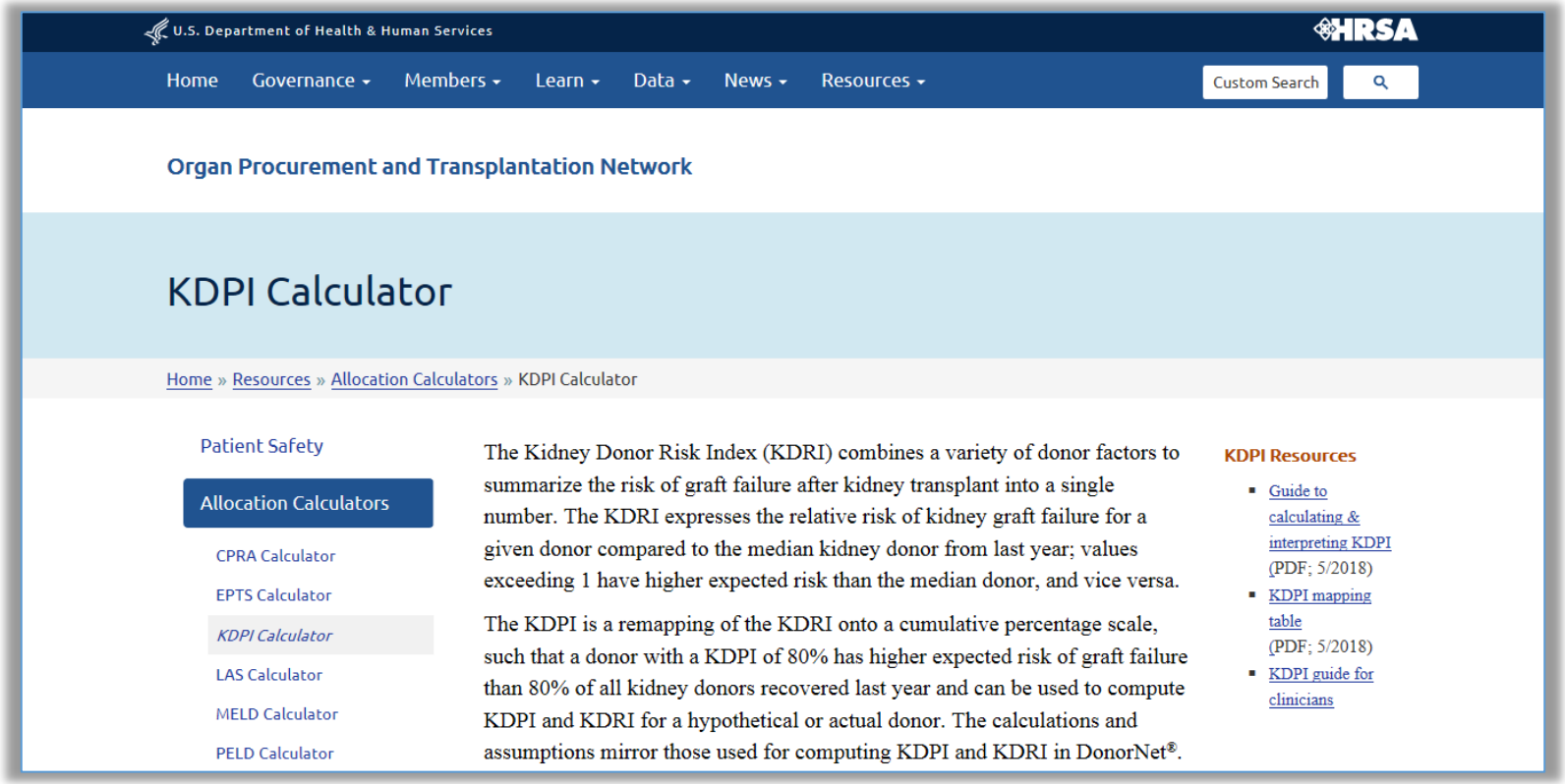
Continue to model »

Risikobeurteilung:

Kidney Donor Profile Index (KDPI)

Kidney Donor Risk Index (KDRI)

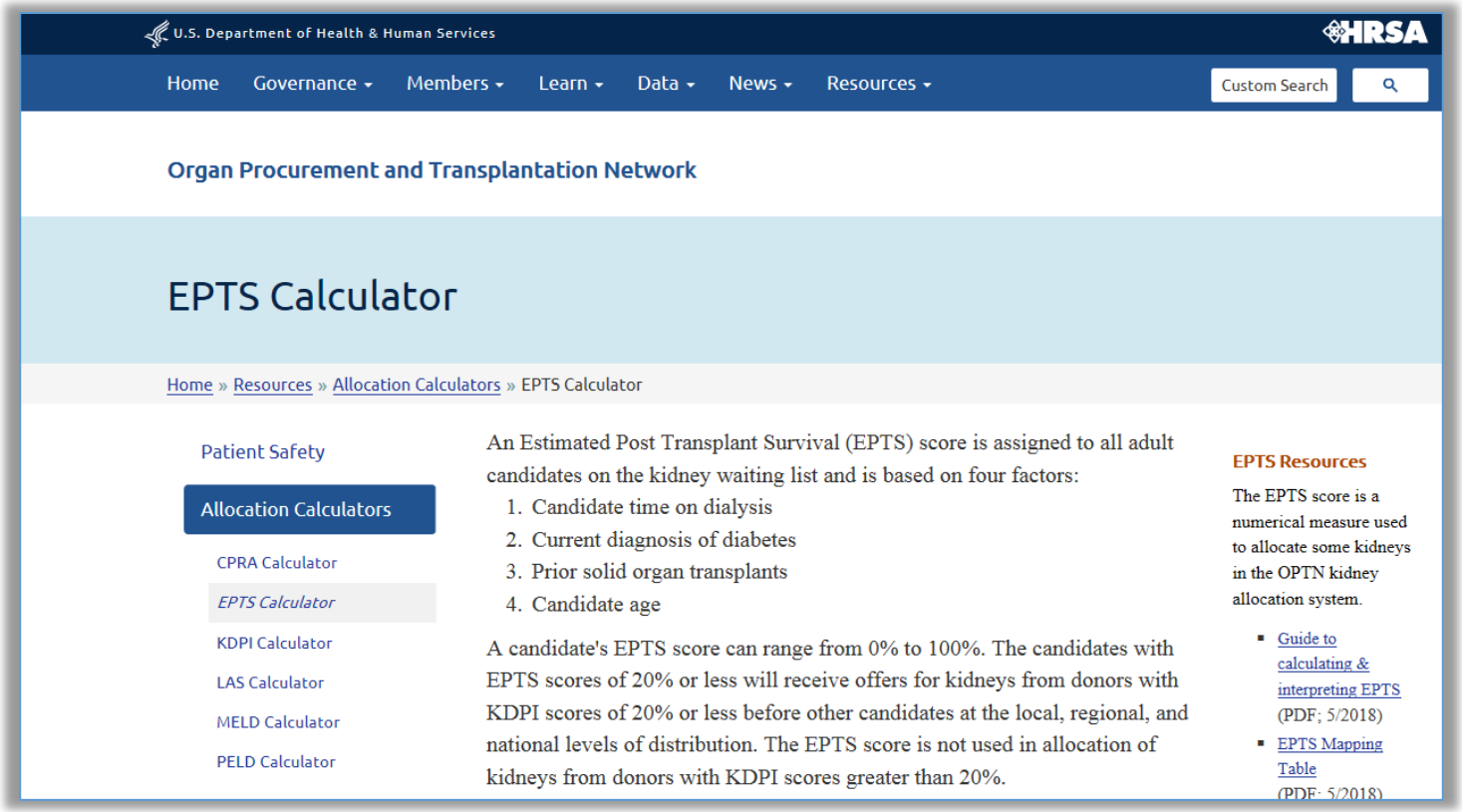
https://optn.transplant.hrsa.gov/resources/allocation-calculators/kdpi-calculator/



Risikobeurteilung:

Estimated Post Transplant Survival (EPTS) score

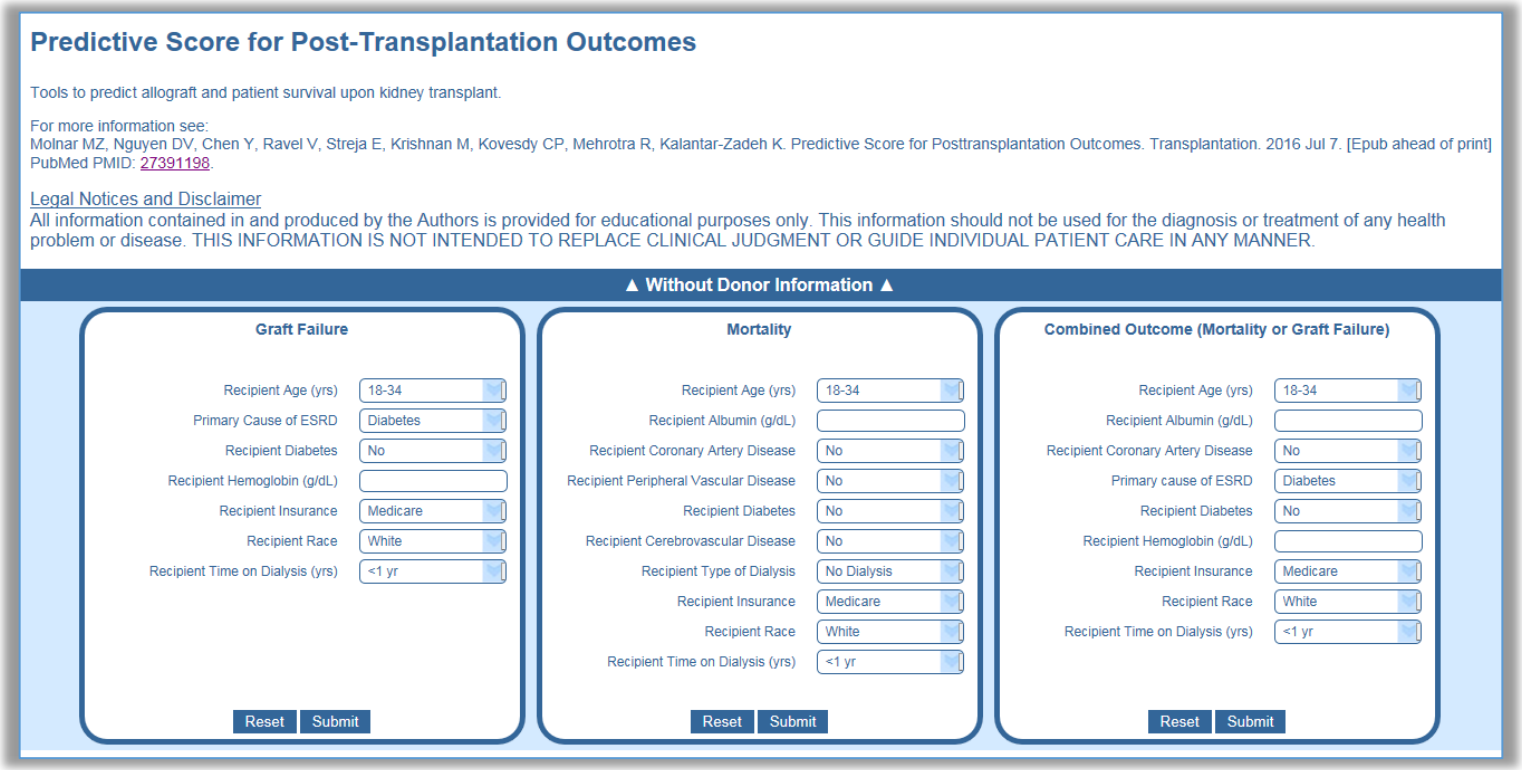
https://optn.transplant.hrsa.gov/resources/allocation-calculators/epts-calculator/



Risikobeurteilung:

Predictive Score for Post-Transplantation Outcome

www.transplantscore.com



Predictive Score for Post-Transplantation Outcomes

Tools to predict allograft and patient survival upon kidney transplant.

For more information see:
Molnar MZ, Nguyen DV, Chen Y, Ravel V, Streja E, Krishnan M, Kovesdy CP, Mehrotra R, Kalantar-Zadeh K. Predictive Score for Posttransplantation Outcomes. Transplantation. 2016 Jul 7. [Epub ahead of print]
PubMed PMID: 27391198.

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▲ Without Donor Information ▲

Graft Failure

Recipient Age (yrs)	18-34
Primary Cause of ESRD	Diabetes
Recipient Diabetes	No
Recipient Hemoglobin (g/dL)	
Recipient Insurance	Medicare
Recipient Race	White
Recipient Time on Dialysis (yrs)	<1 yr

Reset Submit

Mortality

Recipient Age (yrs)	18-34
Recipient Albumin (g/dL)	
Recipient Coronary Artery Disease	No
Recipient Peripheral Vascular Disease	No
Recipient Diabetes	No
Recipient Cerebrovascular Disease	No
Recipient Type of Dialysis	No Dialysis
Recipient Insurance	Medicare
Recipient Race	White
Recipient Time on Dialysis (yrs)	<1 yr

Reset Submit

Combined Outcome (Mortality or Graft Failure)

Recipient Age (yrs)	18-34
Recipient Albumin (g/dL)	
Recipient Coronary Artery Disease	No
Primary cause of ESRD	Diabetes
Recipient Diabetes	No
Recipient Hemoglobin (g/dL)	
Recipient Insurance	Medicare
Recipient Race	White
Recipient Time on Dialysis (yrs)	<1 yr

Reset Submit

Risikobeurteilung:

Donor – Organqualität

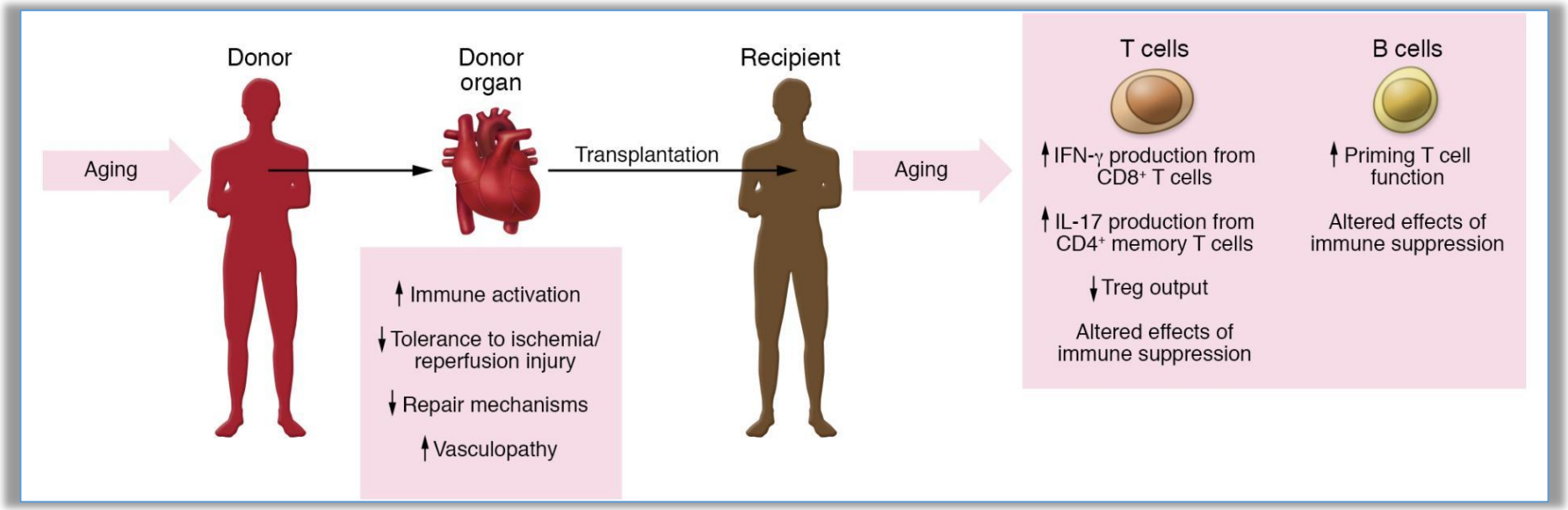
Spender – Empfänger – Alter

JCI The Journal of Clinical Investigation

Aging and the immune response to organ transplantation

Monica M. Colvin, … , Stefan G. Tullius, Daniel R. Goldstein

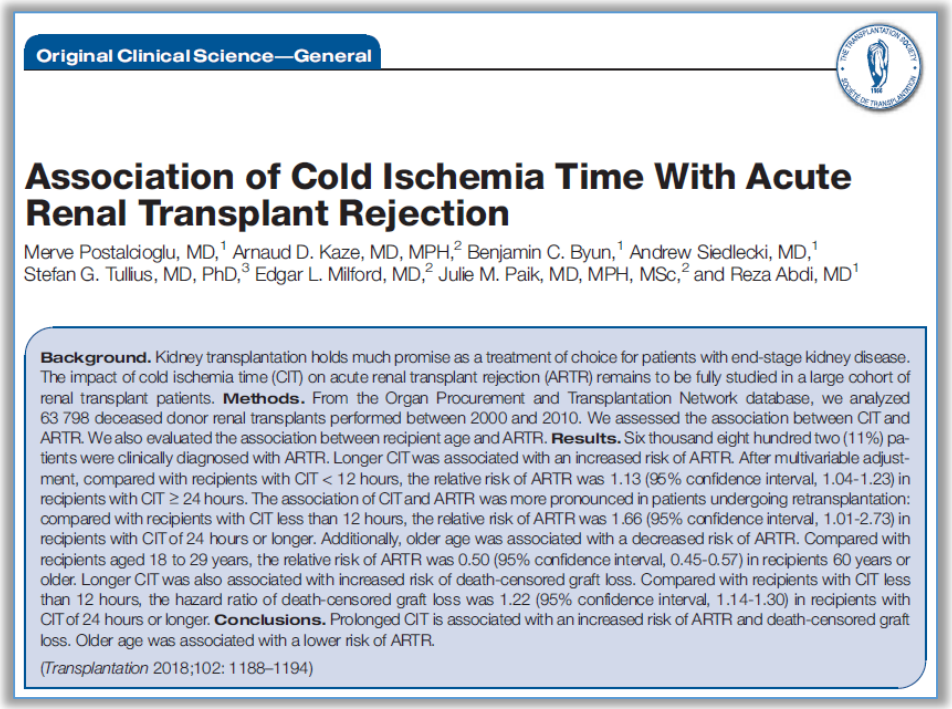
J Clin Invest. 2017;127(7):2523-2529. https://doi.org/10.1172/JCI90601.



Risikobeurteilung:

Donor – Organqualität

Ischämie – Dauer



Original Clinical Science—General

Association of Cold Ischemia Time With Acute Renal Transplant Rejection

Merve Postalcioglu, MD,[1] Arnaud D. Kaze, MD, MPH,[2] Benjamin C. Byun,[1] Andrew Siedlecki, MD,[1] Stefan G. Tullius, MD, PhD,[3] Edgar L. Milford, MD,[2] Julie M. Paik, MD, MPH, MSc,[2] and Reza Abdi, MD[1]

Background. Kidney transplantation holds much promise as a treatment of choice for patients with end-stage kidney disease. The impact of cold ischemia time (CIT) on acute renal transplant rejection (ARTR) remains to be fully studied in a large cohort of renal transplant patients. **Methods.** From the Organ Procurement and Transplantation Network database, we analyzed 63 798 deceased donor renal transplants performed between 2000 and 2010. We assessed the association between CIT and ARTR. We also evaluated the association between recipient age and ARTR. **Results.** Six thousand eight hundred two (11%) patients were clinically diagnosed with ARTR. Longer CIT was associated with an increased risk of ARTR. After multivariable adjustment, compared with recipients with CIT < 12 hours, the relative risk of ARTR was 1.13 (95% confidence interval, 1.04-1.23) in recipients with CIT ≥ 24 hours. The association of CIT and ARTR was more pronounced in patients undergoing retransplantation: compared with recipients with CIT less than 12 hours, the relative risk of ARTR was 1.66 (95% confidence interval, 1.01-2.73) in recipients with CIT of 24 hours or longer. Additionally, older age was associated with a decreased risk of ARTR. Compared with recipients aged 18 to 29 years, the relative risk of ARTR was 0.50 (95% confidence interval, 0.45-0.57) in recipients 60 years or older. Longer CIT was also associated with increased risk of death-censored graft loss. Compared with recipients with CIT less than 12 hours, the hazard ratio of death-censored graft loss was 1.22 (95% confidence interval, 1.14-1.30) in recipients with CIT of 24 hours or longer. **Conclusions.** Prolonged CIT is associated with an increased risk of ARTR and death-censored graft loss. Older age was associated with a lower risk of ARTR.

(*Transplantation* 2018;102: 1188–1194)

Spender – Konditionierung

Maschinenperfusion

Risikobeurteilung:

Dopamin – Therapie des Spenders

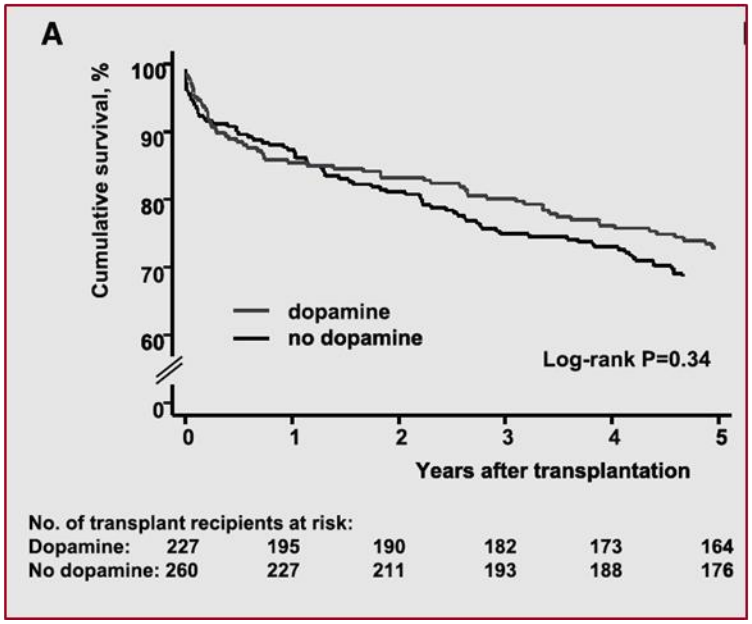
Effects of Dopamine Donor Pretreatment on Graft Survival after Kidney Transplantation: A Randomized Trial

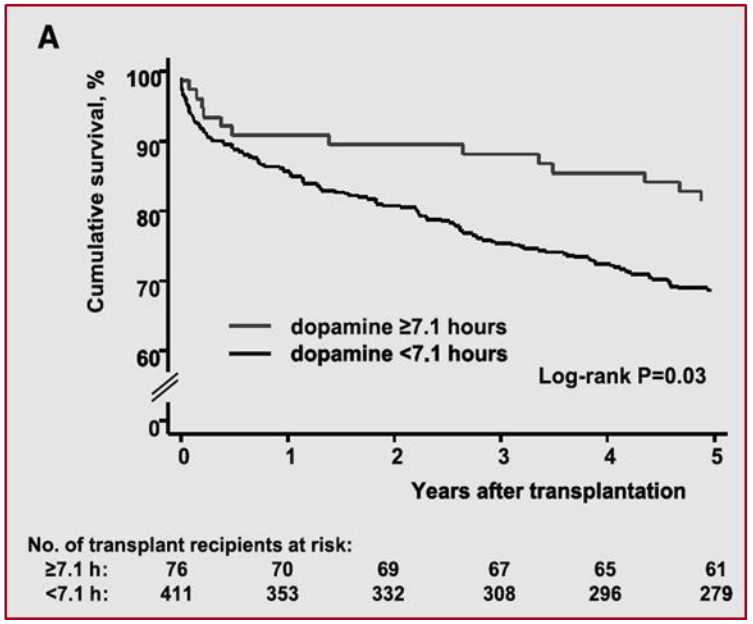
Clin J Am Soc Nephrol 12: 493–501, 2017.

Peter Schnuelle, Wilhelm H. Schmitt, Christel Weiss, Antje Habicht, Lutz Renders, Martin Zeier, Felix Drüschler, Katharina Heller, Przemyslaw Pisarski, Bernhard Banas, Bernhard K. Krämer, Matthias Jung, Kai Lopau, Christoph J. Olbricht, Horst Weihprecht, Peter Schenker, Johan W. De Fijter, Benito A. Yard, and Urs Benck

265 Organspender – 5-Jahresdaten

Dopamin-Infusionsrate: 4 mg/kg pro Minute





Maschinen-Perfusion

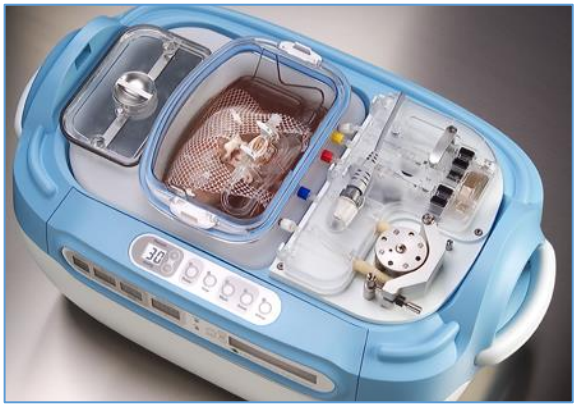
Hypothermie: hypothermic oxygenation perfusion (HOPE)
verbessert Organerhalt

Normothermie: erlaubt Rückschlüsse auf Funktion
technisch aufwendig

- Erlaubt Verwendung marginaler Organe
- reduziert IRI / DGF
  (reduziert Dauer Klinikaufenthalt und Gesamtkosten)
- **Ausblick:** Therapie während Perfusion
  anti-inflammatorisch
  anti-Lipidoxygenation
  Gabe von mesenchymalen Stromazellen

Welche Organe profitieren von der Perfusion?

Niere - Hypothermie



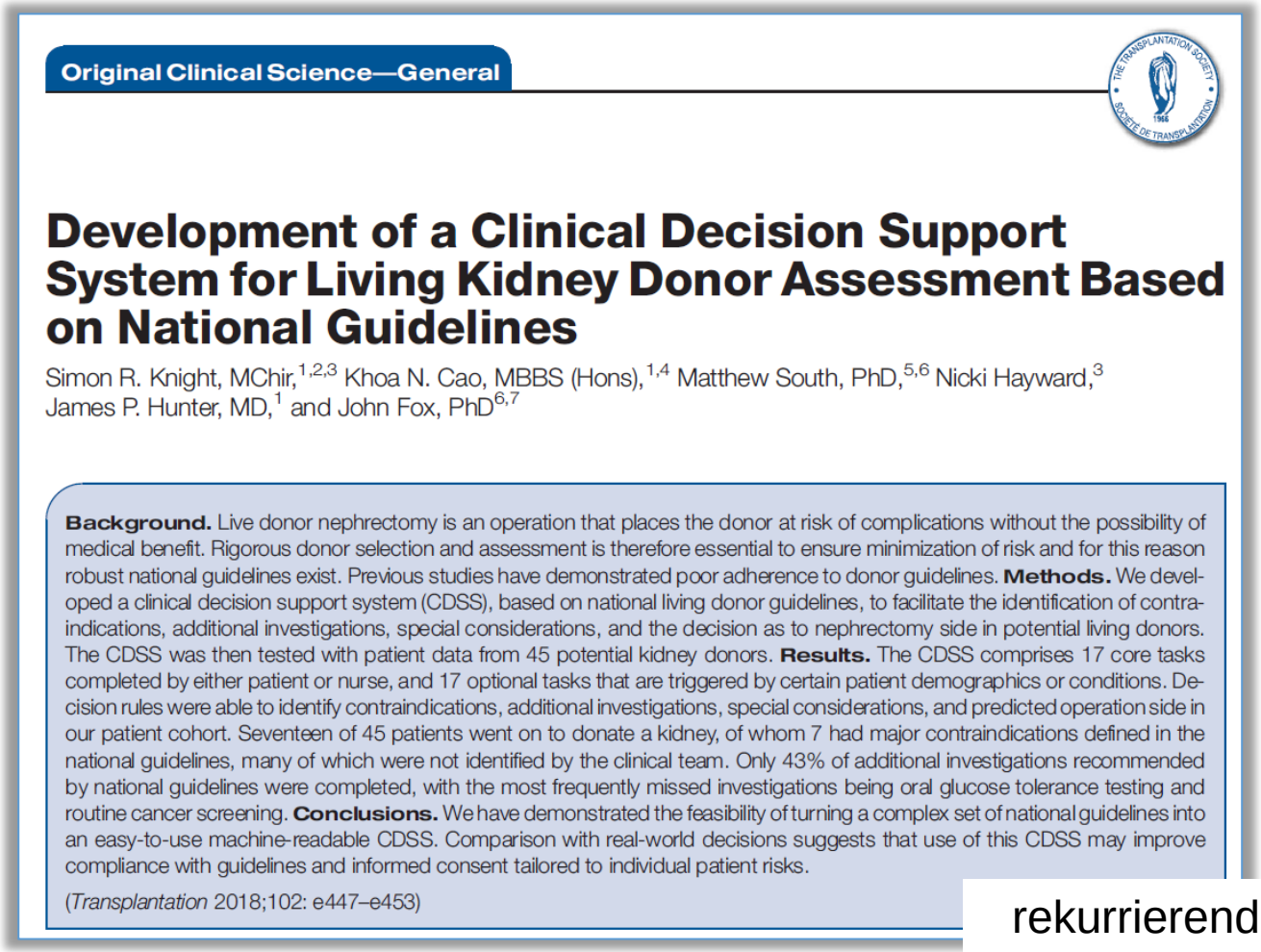
LifePort (Organ Recovery Systems, Chicago, IL)

Lunge - Normothermie

XPS (XVIVO Perfusion, Sweden)

Risikobeurteilung:

Lebendspende – Nierentransplantation



Original Clinical Science—General

Development of a Clinical Decision Support System for Living Kidney Donor Assessment Based on National Guidelines

Simon R. Knight, MChir,[1,2,3] Khoa N. Cao, MBBS (Hons),[1,4] Matthew South, PhD,[5,6] Nicki Hayward,[3] James P. Hunter, MD,[1] and John Fox, PhD[6,7]

Background. Live donor nephrectomy is an operation that places the donor at risk of complications without the possibility of medical benefit. Rigorous donor selection and assessment is therefore essential to ensure minimization of risk and for this reason robust national guidelines exist. Previous studies have demonstrated poor adherence to donor guidelines. **Methods.** We developed a clinical decision support system (CDSS), based on national living donor guidelines, to facilitate the identification of contraindications, additional investigations, special considerations, and the decision as to nephrectomy side in potential living donors. The CDSS was then tested with patient data from 45 potential kidney donors. **Results.** The CDSS comprises 17 core tasks completed by either patient or nurse, and 17 optional tasks that are triggered by certain patient demographics or conditions. Decision rules were able to identify contraindications, additional investigations, special considerations, and predicted operation side in our patient cohort. Seventeen of 45 patients went on to donate a kidney, of whom 7 had major contraindications defined in the national guidelines, many of which were not identified by the clinical team. Only 43% of additional investigations recommended by national guidelines were completed, with the most frequently missed investigations being oral glucose tolerance testing and routine cancer screening. **Conclusions.** We have demonstrated the feasibility of turning a complex set of national guidelines into an easy-to-use machine-readable CDSS. Comparison with real-world decisions suggests that use of this CDSS may improve compliance with guidelines and informed consent tailored to individual patient risks.

(*Transplantation* 2018;102: e447–e453)

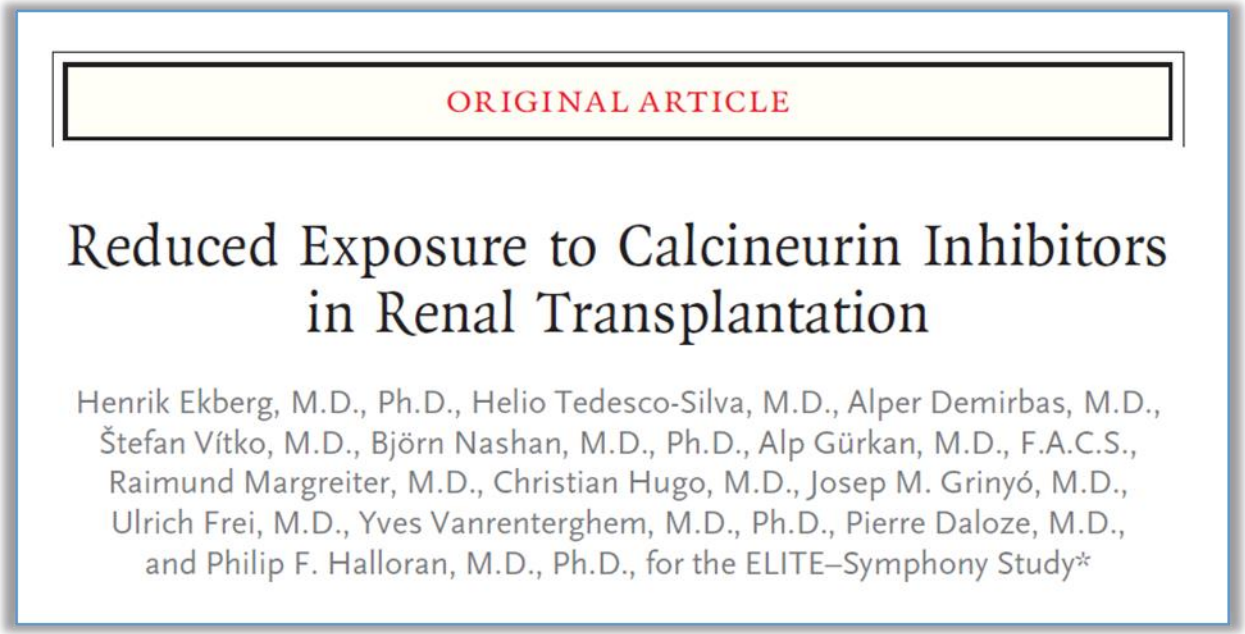
clinical decision support system (CDSS)

rekurrierende Grunderkrankung

Risikobeurteilung:

Immunsuppression

ELITE – Symphony study



ORIGINAL ARTICLE

Reduced Exposure to Calcineurin Inhibitors in Renal Transplantation

Henrik Ekberg, M.D., Ph.D., Helio Tedesco-Silva, M.D., Alper Demirbas, M.D., Štefan Vítko, M.D., Björn Nashan, M.D., Ph.D., Alp Gürkan, M.D., F.A.C.S., Raimund Margreiter, M.D., Christian Hugo, M.D., Josep M. Grinyó, M.D., Ulrich Frei, M.D., Yves Vanrenterghem, M.D., Ph.D., Pierre Daloze, M.D., and Philip F. Halloran, M.D., Ph.D., for the ELITE–Symphony Study*

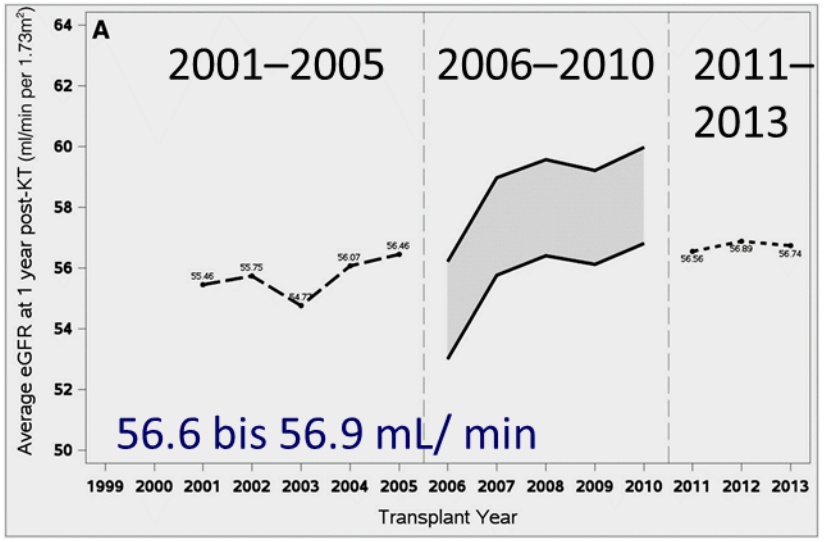
N Engl J Med 2007;357:2562-75.

Currently more than 80% of the patients after kidney transplantation are treated with low dose tacrolimus + MMF/MPA + steroids.

Risikobeurteilung:

Long Term Outcome did not Improve

Average eGFR **at 1 year** post-kidney transplant has remained essentially unchanged for both deceased donor kidney transplant and living donor kidney transplant recipients between 2001 and 2013.



Yihung Huang et al. JASN 2017;28:2498-2510

American Journal of Transplantation 2017; XX: 1–9

Renal Allograft Histology at 10 Years After Transplantation in the Tacrolimus Era: Evidence of Pervasive Chronic Injury

M. D. Stegall[1,*], L. D. Cornell[2], W. D. Park[1], B. H. Smith[3] and F. G. Cosio[4]

Almost all renal allografts sustained major histologic injury by 10 years after transplantation.

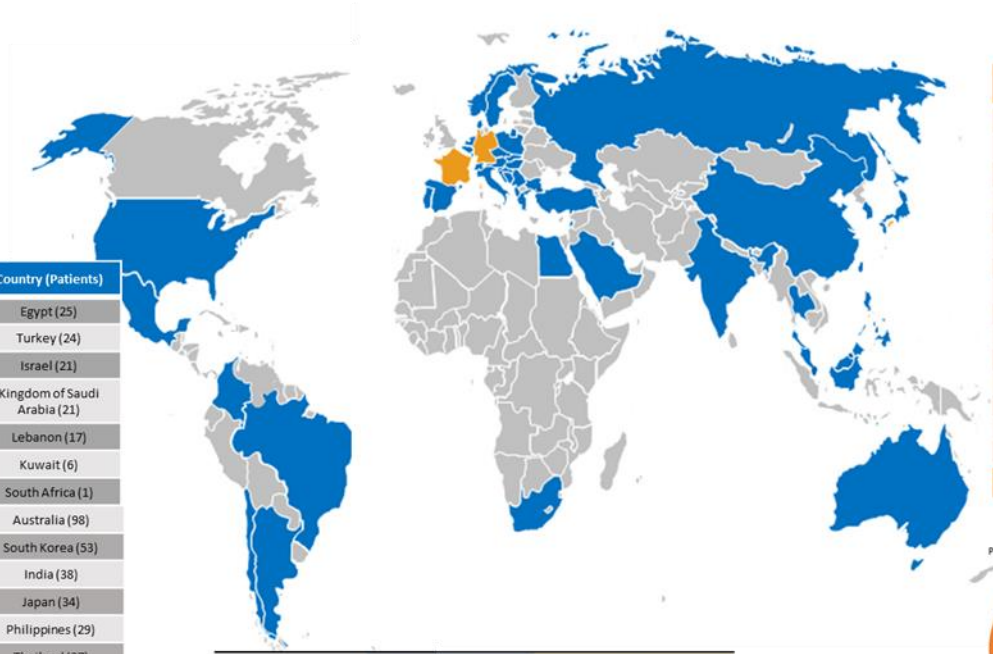
Much damage appeared non-immunologic, suggesting that new approaches are needed to decrease late injury.

Risikobeurteilung:

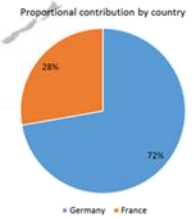
„Transplantation in TRANSFORMation“

Country (Patients)
USA (352)
Brasil (86)
Argentina (77)
Columbia (22)
Chile (8)
Mexico (2)
Germany (168)
Spain (159)
Netherlands (143)
Italy (93)
France (85)
Belgium (56)
Russia (47)
Sweden (38)
Croatia (35)
Slovakia (35)
Austria (34)
Czech Republic (30)
Poland (25)
Greece (24)
Switzerland (22)
Portugal (19)
Norway (15)
Serbia (14)
Bulgaria (12)
Slovenia (9)

Country (Patients)
Egypt (25)
Turkey (24)
Israel (21)
Kingdom of Saudi Arabia (21)
Lebanon (17)
Kuwait (6)
South Africa (1)
Australia (98)
South Korea (53)
India (38)
Japan (34)
Philippines (29)
Thailand (27)
Taiwan (23)
Malaysia (5)
Singapore (5)



Germany (15)
Essen (100)
Hamburg (64)
Heidelberg (61)
Dresden (57)
Münster (46)
Hannover (27)
Berlin (25)
Frankfurt (16)
Bochum (16)
Erlangen (16)
Aachen (13)
Kiel(11)
Tübingen (9)
Freiburg (9)
Mainz (3)
France (12)



Sites	**186**	**27**
Countries	42	2
Patients	2037	612

Risikobeurteilung:

Immunsuppression

Der „sensibilisierte Patient“ zur Nierentransplantation

ABMR prognostic score

iBox

http://www.paristransplantgroup.org/

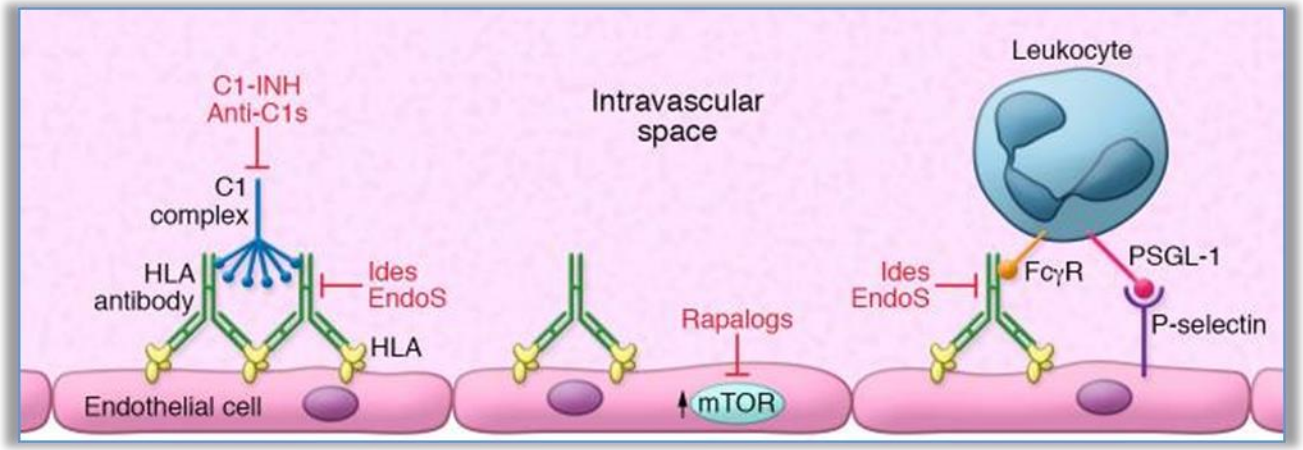
https://clinicaltrials.gov/ct2/show/NCT03474003

Risikobeurteilung:

***de novo* DSA:**

nach 5 Jahren 7%
nach 10 Jahren 20% (- 40%)

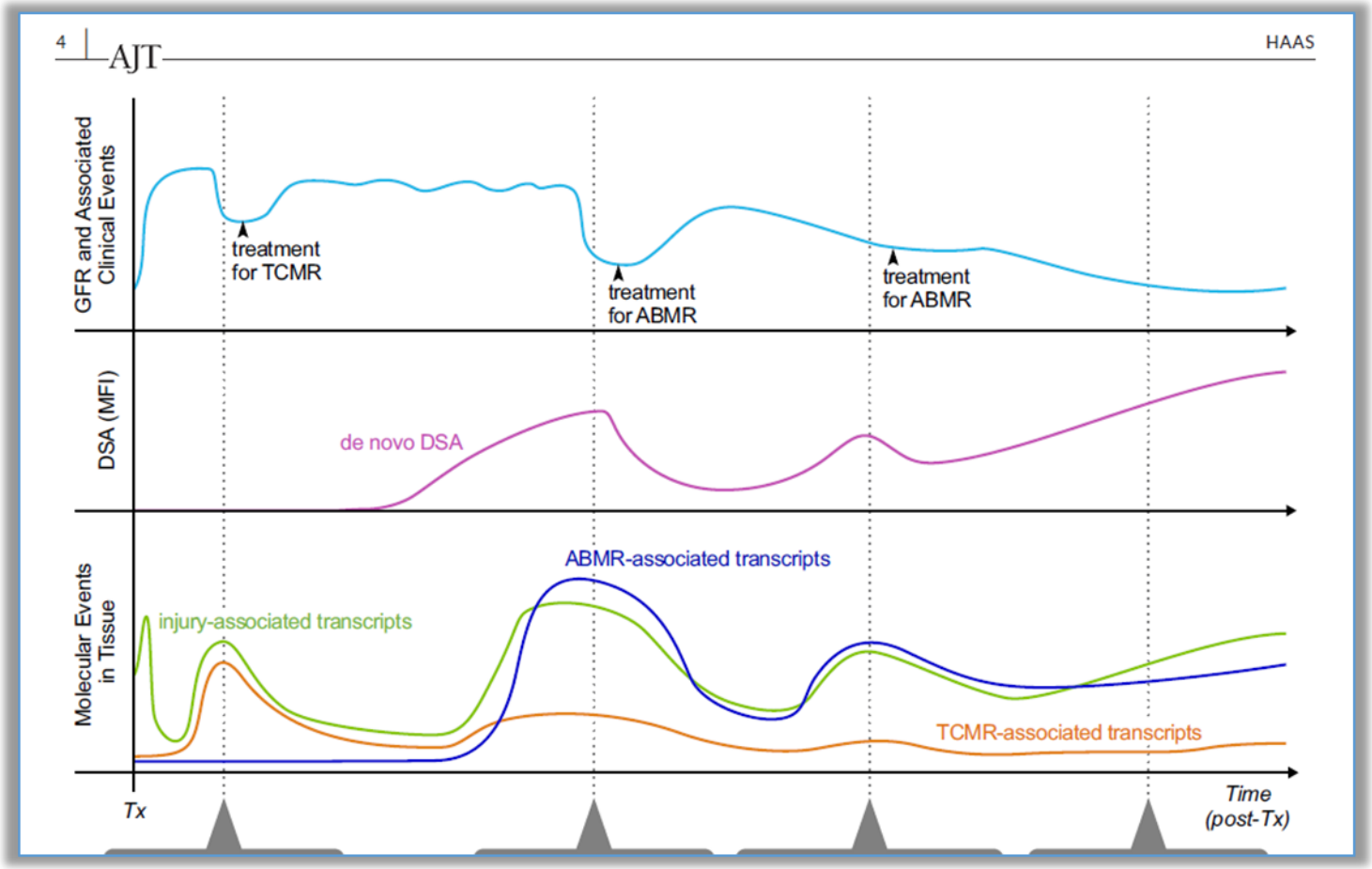
5 Jahre nach *de novo* DSA:
40% Transplantatverlust



Valenzuela NM, Reed EF. J Clin Invest. 2017 Jun 30;127(7):2492-2504.

Risikobeurteilung:

Kaskade der Abstoßung nach Nierentransplantation



Haas M. Am J Transplant. 2018 Dec;18(12):2849-2856.

Risikobeurteilung:

Review

OPEN

Summary of 2017 FDA Public Workshop: Antibody-mediated Rejection in Kidney Transplantation

Ergun Velidedeoglu, MD,[1] Marc W. Cavaillé-Coll, MD, PhD,[1] Shukal Bala, PhD,[1] Ozlem A. Belen, MD, MPH,[1] Yan Wang, PhD,[2] and Renata Albrecht, MD[1]

Abstract. Despite major advances in understanding the pathophysiology of antibody-mediated rejection (AMR); prevention, diagnosis and treatment remain unmet medical needs. It appears that early T cell–mediated rejection, de novo donor-specific antibody (dnDSA) formation and AMR result from patient or physician initiated suboptimal immunosuppression, and represent landmarks in an ongoing process rather than separate events. On April 12 and 13, 2017, the Food and Drug Administration sponsored a public workshop on AMR in kidney transplantation to discuss new advances, importance of immunosuppressive medication nonadherence in dnDSA formation, associations between AMR, cellular rejection, changes in glomerular filtration rate, and challenges of clinical trial design for the prevention and treatment of AMR. Key messages from the workshop are included in this summary. Distinction between type 1 (due to preexisting DSA) and type 2 (due to dnDSA) phenotypes of AMR needs to be considered in patient management and clinical trial design. Standardization and more widespread adoption of routine posttransplant DSA monitoring may permit timely diagnosis and understanding of the natural course of type 2 and chronic AMR. Clinical trial design, especially as related to type 2 and chronic AMR, has specific challenges, including the high prevalence of nonadherence in the population at risk, indolent nature of the process until the appearance of graft dysfunction, and the absence of accepted surrogate endpoints. Other challenges include sample size and study duration, which could be mitigated by enrichment strategies.

(*Transplantation* 2018;102: e257–e264)

Risikobeurteilung:

Review

The Treatment of Antibody-Mediated Rejection in Kidney Transplantation: An Updated Systematic Review and Meta-Analysis

Susan S. Wan, MMed (Clin Epi), FRACP,[1,2] Tracey D. Ying, MMed (Clin Epi), FRACP,[1,2] Kate Wyburn, FRACP, PhD,[1,2] Darren M. Roberts, FRACP, PhD,[3,4] Melanie Wyld, MBA, MPH,[1,5] and Steven J. Chadban, FRACP, PhD[1,2]

Background. Current treatments for antibody-mediated rejection (AMR) in kidney transplantation are based on low-quality data from a small number of controlled trials. Novel agents targeting B cells, plasma cells, and the complement system have featured in recent studies of AMR. **Methods.** We conducted a systematic review and meta-analysis of controlled trials in kidney transplant recipients using Medline, EMBASE, and CENTRAL from inception to February 2017. **Results.** Of 14 380 citations, we identified 21 studies, including 10 randomized controlled trials, involving 751 participants. Since the last systematic review conducted in 2011, we found nine additional studies evaluating plasmapheresis + intravenous immunoglobulin (IVIG) (two), rituximab (two), bortezomib (two), C1 inhibitor (two), and eculizumab (one). Risk of bias was serious or unclear overall and evidence quality was low for the majority of treatment strategies. Sufficient RCTs for pooled analysis were available only for antibody removal, and here there was no significant difference between groups for graft survival (HR 0.76; 95% CI 0.35-1.63; $P = 0.475$). Studies showed important heterogeneity in treatments, definition of AMR, quality, and follow-up. Plasmapheresis and IVIG were used as standard-of-care in recent studies, and to this combination, rituximab seemed to add little or no benefit. Insufficient data are available to assess the efficacy of bortezomib and complement inhibitors. **Conclusion.** Newer studies evaluating rituximab showed little or no difference to early graft survival, and the efficacy of bortezomib and complement inhibitors for the treatment of AMR remains unclear. Despite the evidence uncertainty, plasmapheresis and IVIG have become standard-of-care for the treatment of acute AMR.

(*Transplantation* 2018;102: 557–568)

Risikobeurteilung:

Therapie der akuten ABMR:

Plasmapherese:	5 – 7 Behandlungen
Ivlg:	1-2 g/ kg KG
	Frequenz? (alle 3-4 Wochen)
Steroidboli:	

ATG:	
Rituximab:	

Tac:	6-10 ng/ mL
MMF/ MPA:	ausdosiert
	Leukopenie, Infekte
Steroide:	5-10 mg täglich

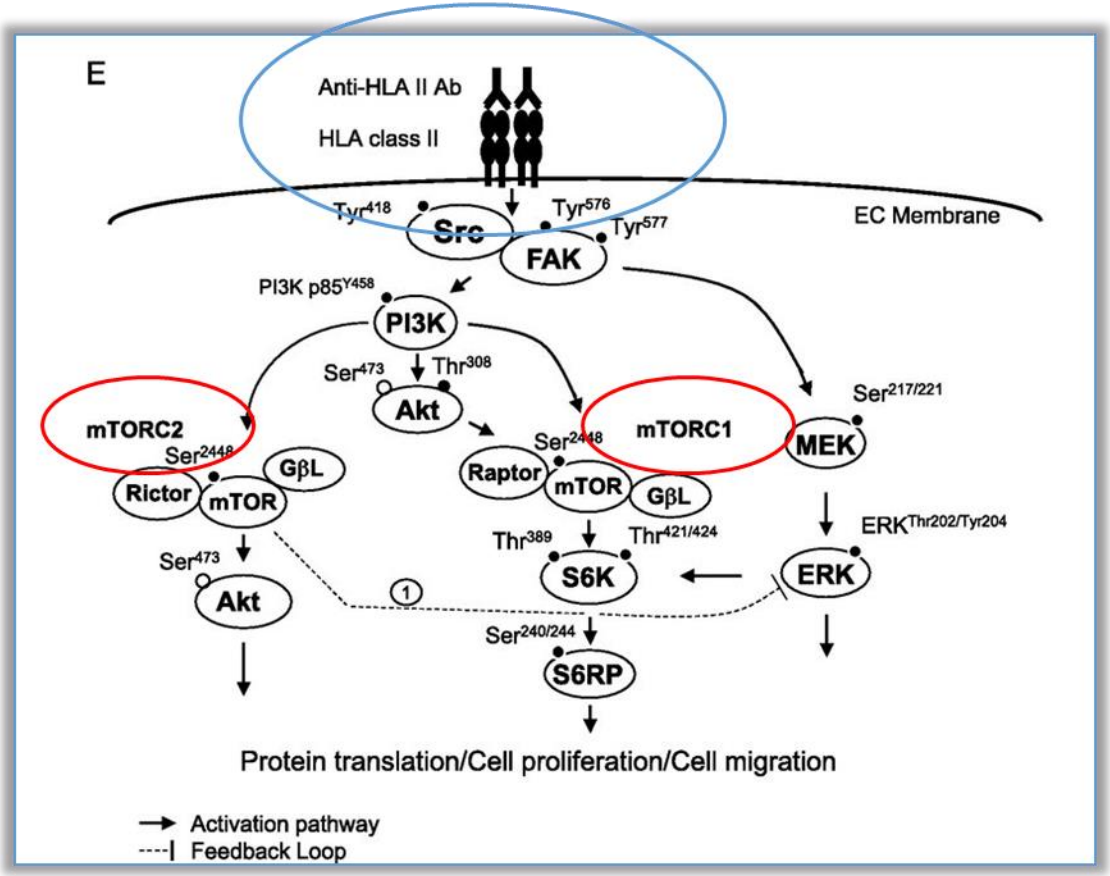
Complement – Inhibition

IL-6 Rezeptor-Blocker / Antikörper

IdeS

Risikobeurteilung:

HLA Class II–Triggered Signaling Cascades Cause Endothelial Cell Proliferation and Migration: Relevance to Antibody-Mediated Transplant Rejection

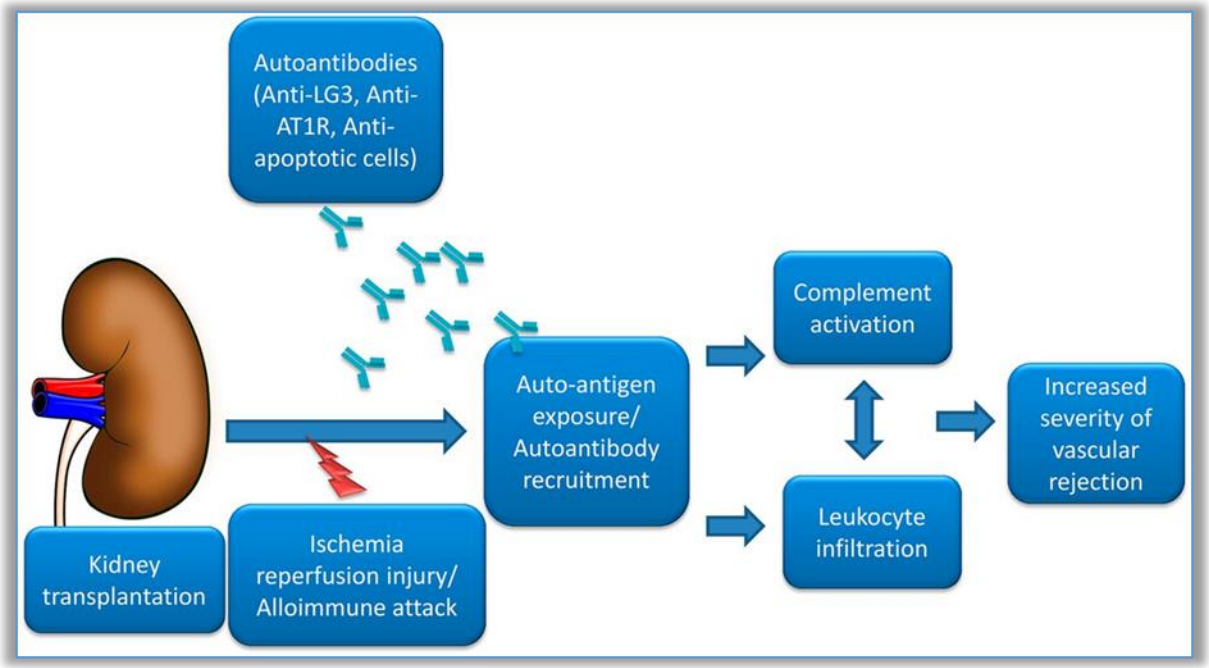


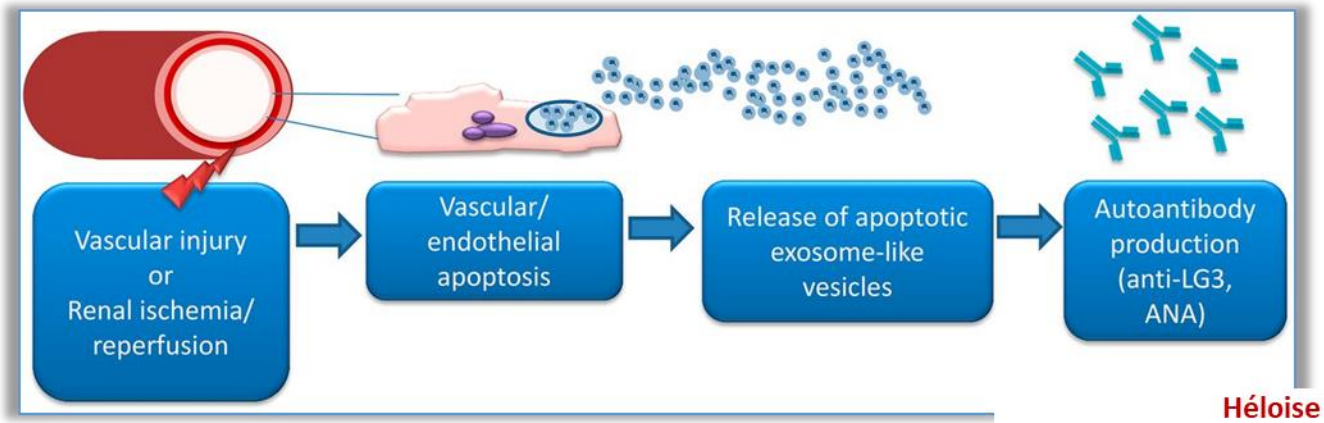
Yi-Ping Jin et al. J Immunol 2018;200:2372-2390

Risikobeurteilung:

non-HLA Antikörper

Auto – Antikörper



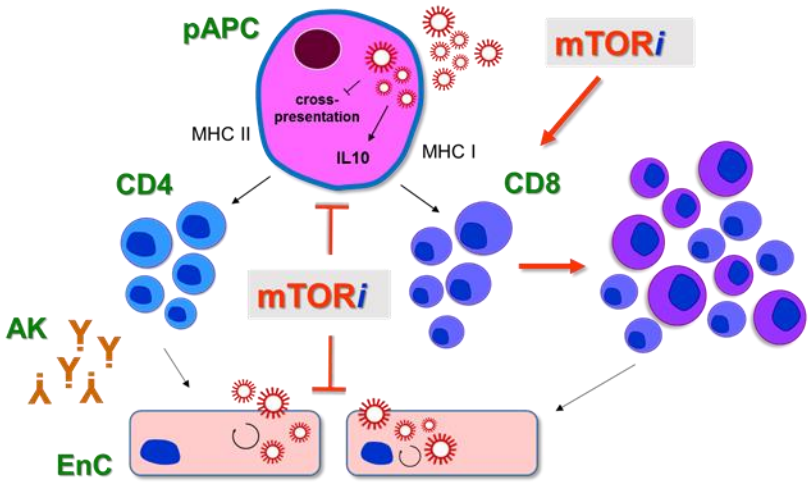


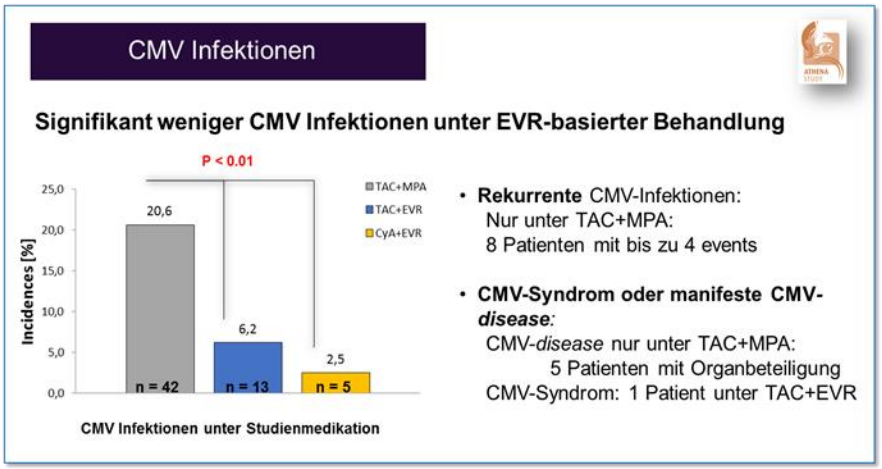
JASN

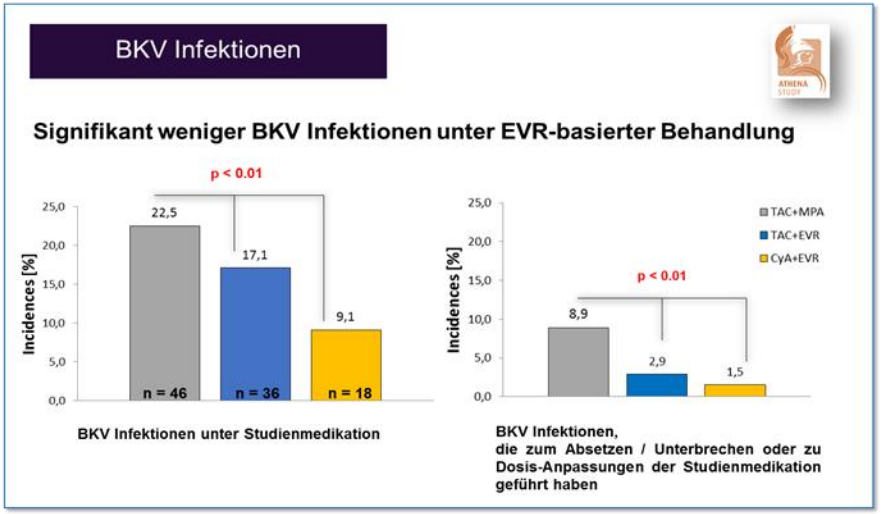
Héloise Cardinal et al. JASN 2017;28:400-406

Risikobeurteilung:

Virusinfektionen







Risikobeurteilung:

Adhärenz

Telemedizin

(Immunologische) Risikobeurteilung:

Der Schlüssel zur (individuell) angepassten Immunsuppression nach Nierentransplantation

Carpe diem—Time to transition from ***empiric*** to ***precision*** medicine in kidney transplantation

Wiebe C, Ho J, Gibson IW, Rush DN, Nickerson PW. Am J Transplant. 2018 Jul;18(7):1615-1625.

Risikobeurteilung:

What are the best immunosuppression targets for the patient in front of me?

How aggressively can I decrease the immunosuppression in a patient with BK virus nephropathy without causing a rejection?

Can I minimize the immunosuppression in a patient who has been stable for months or years?

Wiebe C, Ho J, Gibson IW, Rush DN, Nickerson PW. Am J Transplant. 2018 Jul;18(7):1615-1625.

Risikobeurteilung:

Immunsuppressiva

Rekurrenz Grunderkrankung

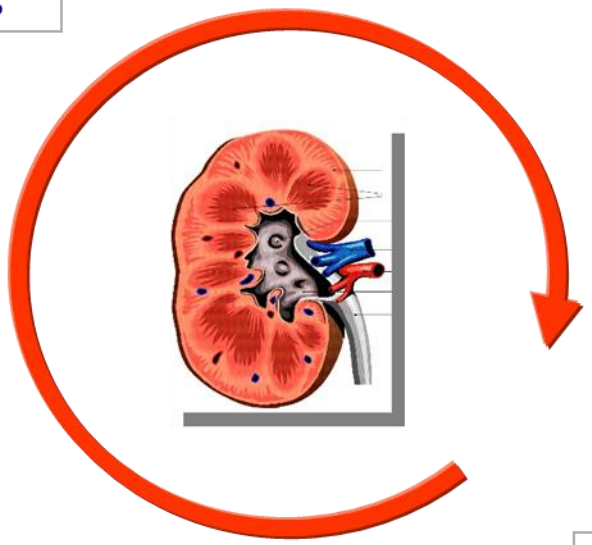
Infektionen

Humorale Abstoßung

Environment

Subklinische Abstoßung

Bluthochdruck



Akute Abstoßung

Diabetes

Nierenmasse

Mikrobiom

Organqualität

Fettstoffwechselstörung

Bewegung - Ernährung

Zeitpunkt der Transplantation

Patientenzuverlässigkeit

Grunderkrankung

Zusammenarbeit: Zuweiser - Zentrum

UKE
HAMBURG



thaiss@uke.de