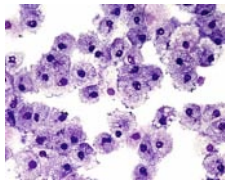
Diagnosis and Management of Acute and Chronic Humoral Rejection

Lars Pape

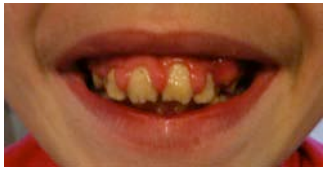
Medizinische Hochschule Hannover

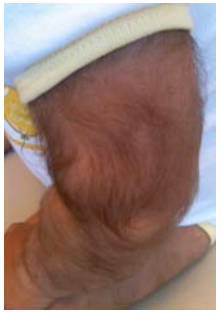
Immunosuppression

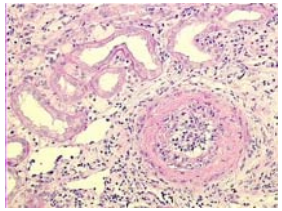


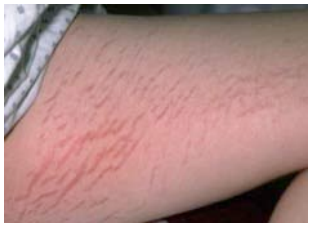
Acute rejection
Chronic rejection

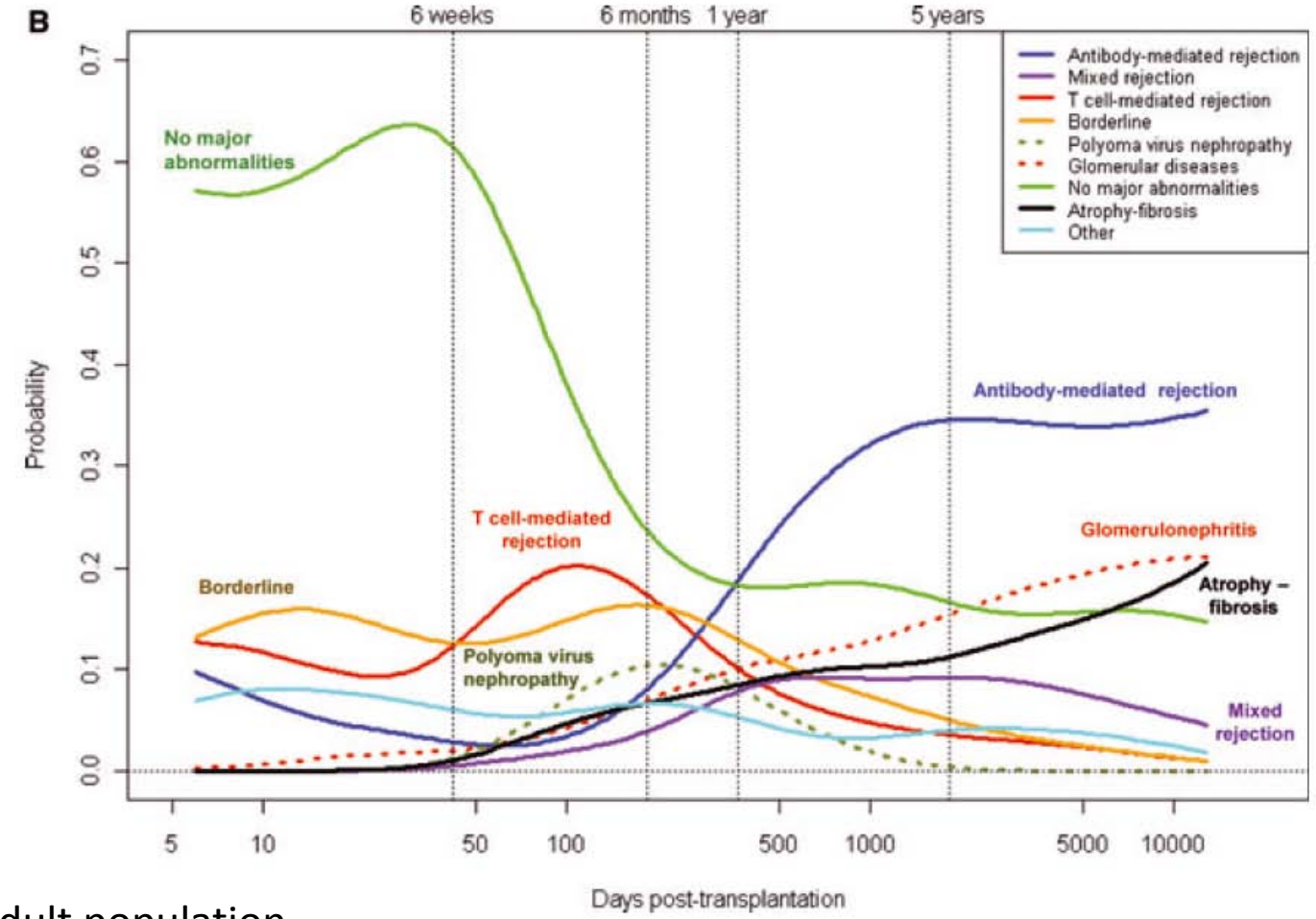
Side effects
Infections
Nephrotoxicity











Adult population

- Nearly all late rejection-related graft losses involved antibody mediated rejections *(Sellares et al., AJT 2012)*
- Younger age seems to be associated with higher risk to develop donor specific antibodies *(Everly et al., Transplantation 2013)*

Diagnosis of humoral rejection

- Transplant kidney biopsy
- Detection of Donor Specific Antibodies (DSA)
- Cross-match donor/recipient (living donation)

BANFF-Classification of transplant biopsy

Table 1: Banff 97 diagnostic categories for renal allograft biopsies—Banff '09 update

1. Normal
2. Antibody-mediated changes (may coincide with categories 3, 4 and 5 and 6)
   Due to documentation of circulating antidonor antibody, C4d,[1] and allograft pathology

C4d deposition without morphologic evidence of active rejection

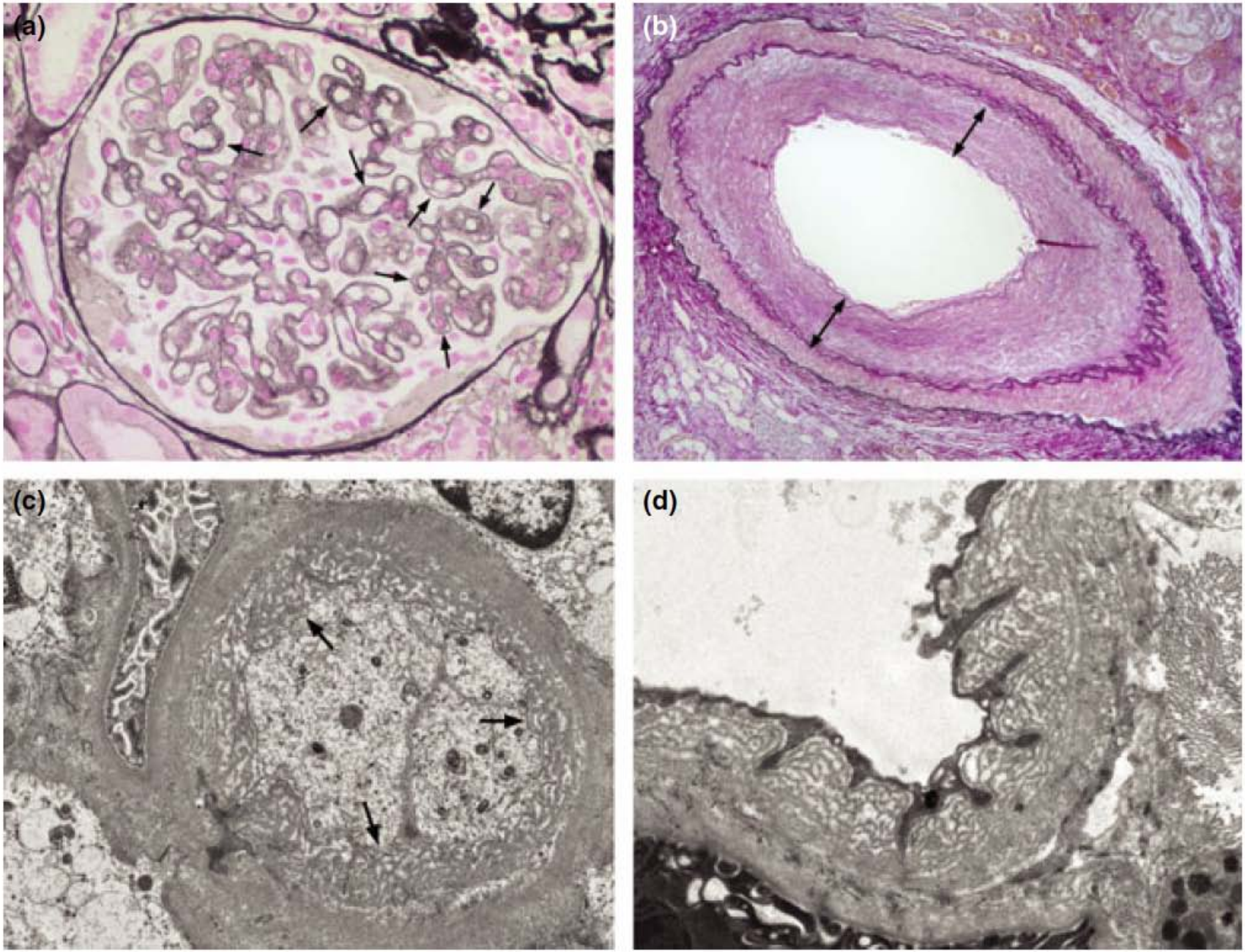
C4d+, presence of circulating antidonor antibodies, no signs of acute or chronic TCMR or ABMR (i.e. g0, cg0, ptc0, no ptc lamination (<5 layers by electron microscopy), no ATN-like minimal inflammation). Cases with simultaneous borderline changes are considered as indeterminate

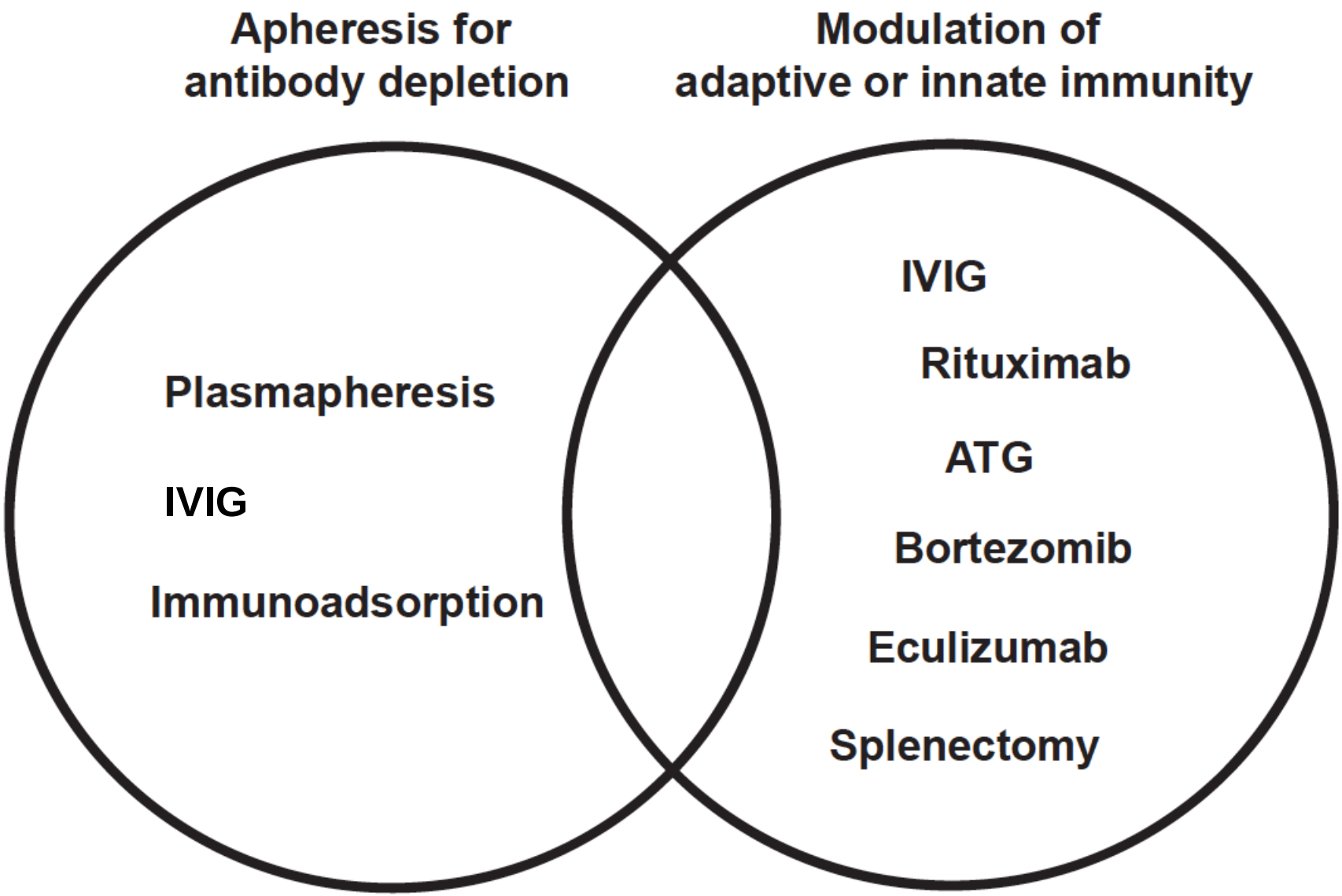
Acute antibody-mediated rejection[2]

C4d+, presence of circulating antidonor antibodies, morphologic evidence of acute tissue injury, such as (Type/Grade)
I. ATN-like minimal inflammation
II. Capillary and or glomerular inflammation (ptc/g >0) and/or thromboses
III. Arterial – v3

Chronic active antibody-mediated rejection[2]

C4d+, presence of circulating antidonor antibodies, morphologic evidence of chronic tissue injury, such as glomerular double contours and/or peritubular capillary basement membrane multilayering and/or interstitial fibrosis/tubular atrophy and/or fibrous intimal thickening in arteries


(a)
(b)
(c)
(d)


Apheresis for antibody depletion
Modulation of adaptive or innate immunity
Plasmapheresis
IVIG
Immunoadsorption
IVIG
Rituximab
ATG
Bortezomib
Eculizumab
Splenectomy

Acute humoral rejection

Therapy of acute humoral rejection

6 (?) Steroid pulses

IVIG-Administration

3-6 Plasmaphereses or Immunoadsorptions,

Discuss Ritxuimab

Increase underlying immuosuppressive therapy

Monitor DSA

Pediatr Nephrol (2011) 26:1149–1156
DOI 10.1007/s00467-011-1864-3

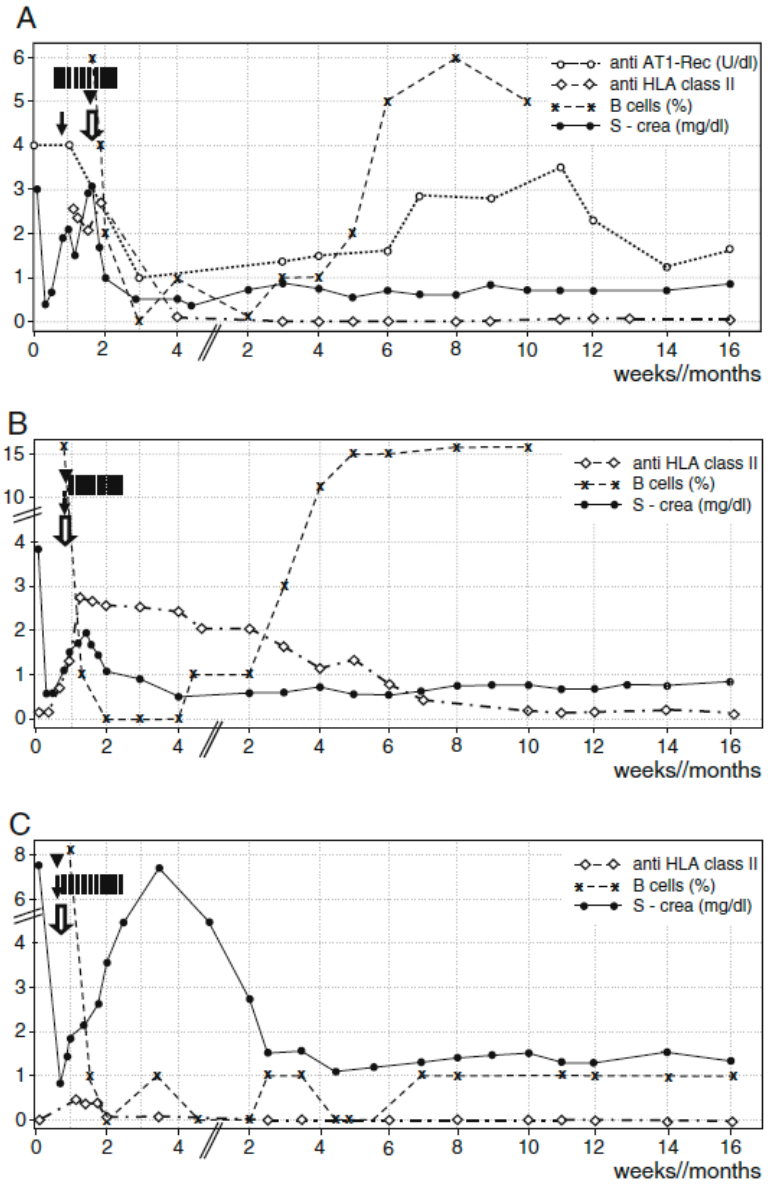
ORIGINAL ARTICLE

Acute antibody-mediated rejection in paediatric renal transplant recipients

Birgitta Kranz · Reinhard Kelsch · Eberhard Kuwertz-Bröking · Verena Bröcker · Heiner H. Wolters · Martin Konrad

In conclusion, the intense therapy with steroid pulses, TAC, MMF, plasmapheresis, IVIG and rituximab led to a favourable outcome in 3 out of 4 episodes of aAMR. In these cases a single dose of rituximab had been sufficient, although it was followed by plasmapheresis sessions starting the following day. In the episode that could not be controlled by this therapy the only obvious difference was that rituximab was administered rather late, after 10 PEs had failed. The documented B-cell depletion lasted at least 3 months, in the third patient it is still ongoing after 18 months.

Currently, it is impossible to distinguish which therapy element is the most effective and whether this multimodal therapy might be adjusted individually.


A
anti AT1-Rec (U/dl)
anti HLA class II
B cells (%)
S - crea (mg/dl)
weeks//months
B
anti HLA class II
B cells (%)
S - crea (mg/dl)
weeks//months
C
anti HLA class II
B cells (%)
S - crea (mg/dl)
weeks//months

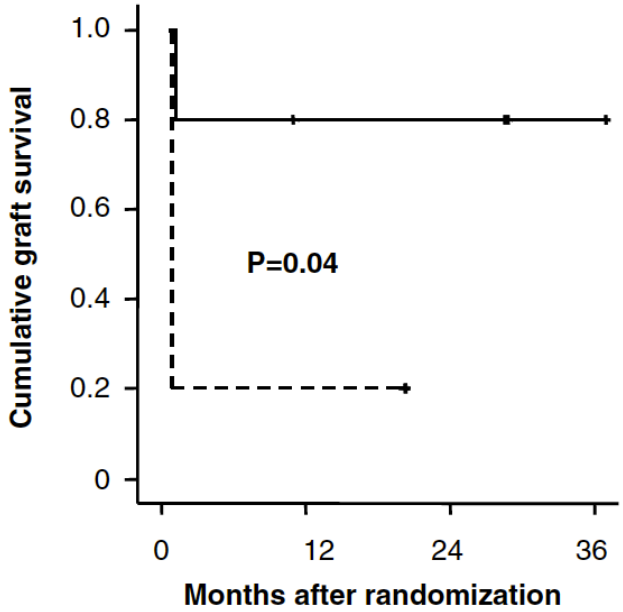
American Journal of Transplantation 2007; 7: 117–121
Blackwell Munksgaard

doi: 10.1111/j.1600-6143.2006.01613.x

Immunoadsorption in Severe C4d-Positive Acute Kidney Allograft Rejection: A Randomized Controlled Trial

G. A. Böhmig[a,*], M. Wahrmann[a], H. Regele[b], M. Exner[c], B. Robl[d], K. Derfler[a], T. Soliman[e], P. Bauer[f], M. Müllner[g] and W. Druml[a]

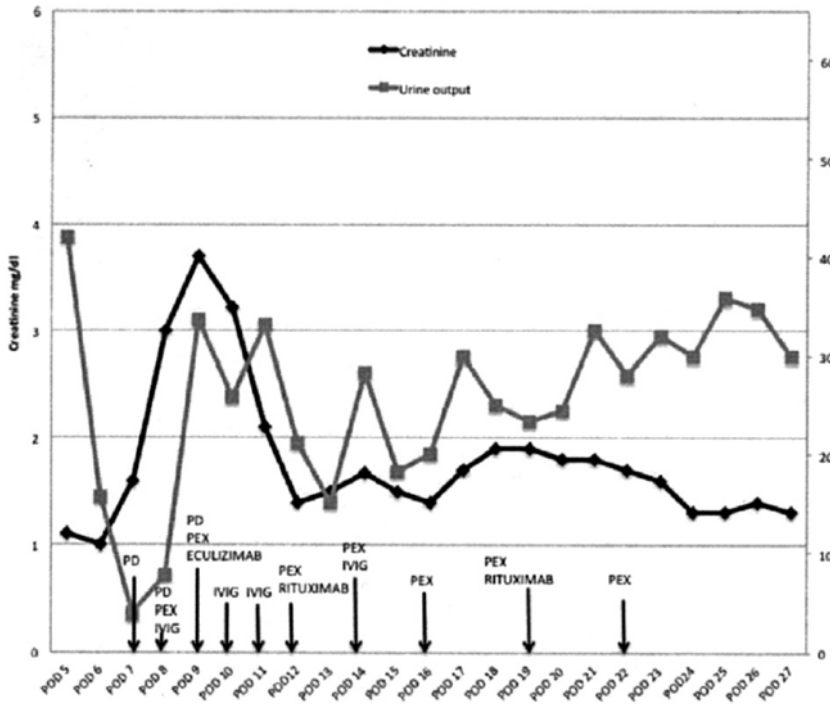
ularly poor prognosis (1–3). Mainly based on small uncontrolled series, distinctly 'anti-humoral' treatment modalities have been proposed to be effective in reversing AMR, including extracorporeal strategies for the removal of dele-

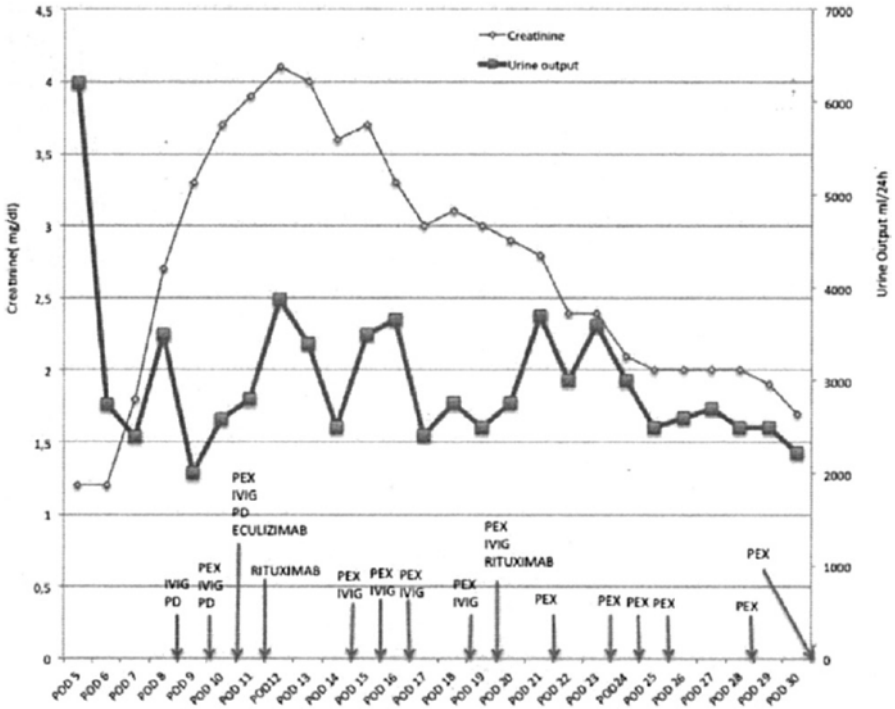


ELSEVIER

Eculizumab Treatment of Acute Antibody-Mediated Rejection in Renal Transplantation: Case Reports

F. González-Roncero, M. Suñer, G. Bernal, V. Cabello, M. Toro, P. Pereira, and M. Angel Gentil



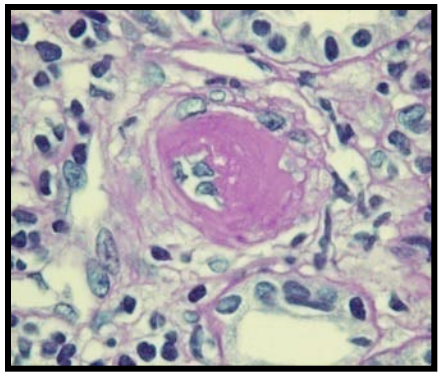


Special cases

- Transplantation against „forbidden antigens“ → desensitatation protocols (i.e. Ritxuimab /Immunoadsorption / IgG / immunosuppression prior to Tx / Induction therapy)
- High Panel reactive antibodies prior to Tx
- ABO incompatible Tx (antigen specific immunoadsorption / Rituximab / IgG / Immunosuppression before Tx)
- Non-HLA-antibodies

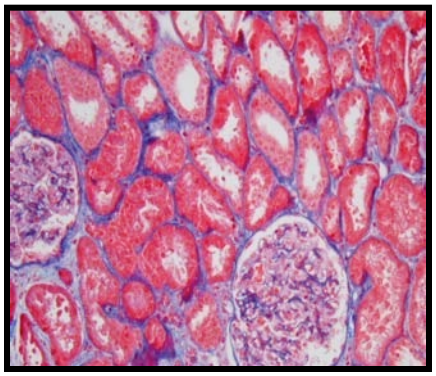
Chronic humoral rejection

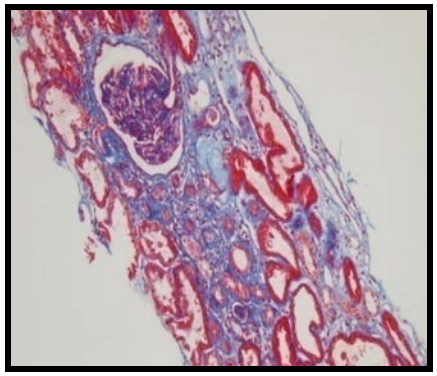
Chronic changes in protocol biopsy

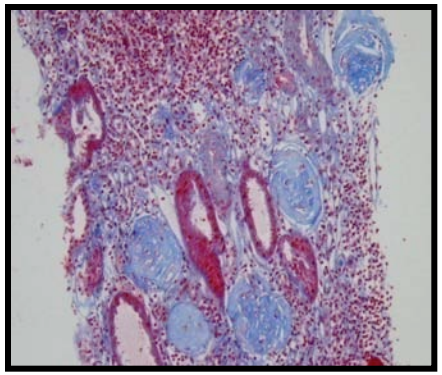


ah

IF/TA







GS

1 mo

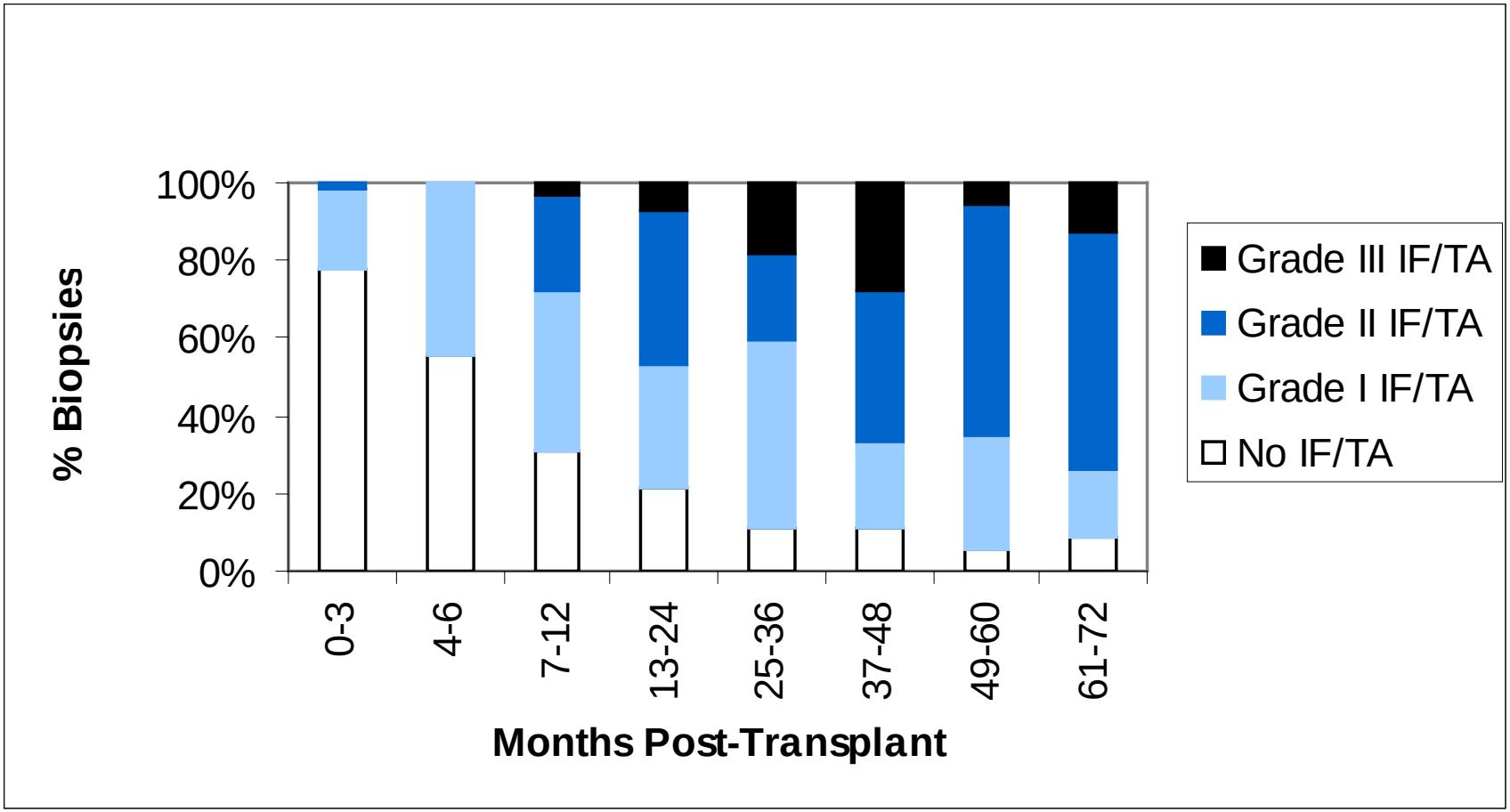
12 mo

early: tubulointersitial damage

late: microvascular / Glomerular damage

Nankivell et al, NEJM 349: 2326, 2003
Birk et al, Transplantation 15: 334, 2010

Increasing Prevalence of IF/TA
(Pediatric Recipients, Antibody/Tac/MMF/Pred)



Birk et al, Transplantation 89: 334, 2010

Meaning of fibrosis and inflammation

American Journal of Transplantation 2011; 11: 489–499
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2010.03415.x

Inflammation Lesions in Kidney Transplant Biopsies: Association with Survival Is Due to the Underlying Diseases

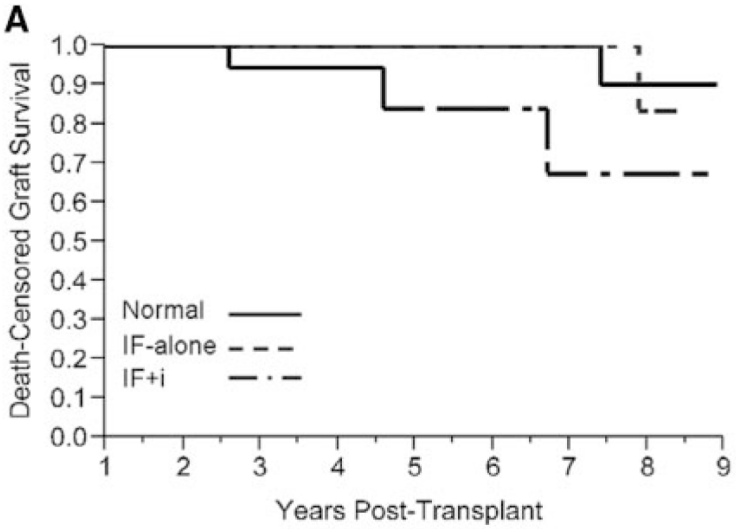
J. Sellarés[a,b], D. G. de Freitas[a,b], M. Mengel[a,c], B. Sis[a,c], L. G. Hidalgo[a,b], A. J. Matas[d], B. Kaplan[e] and P. F. Halloran[a,b,*]

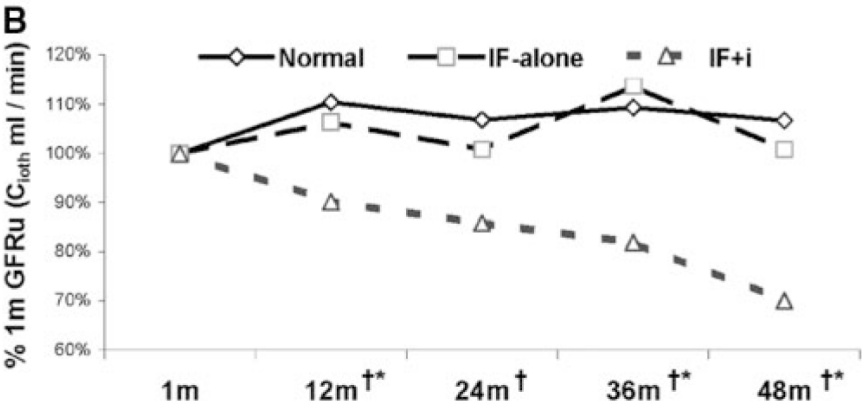
Abbreviations: ABMR, antibody-mediated rejection; ATN, acute tubular necrosis; BFC, biopsy for clinical indications; GN, glomerulonephritis; IFTA, interstitial fibrosis and tubular atrophy; TCMR, T-cell-mediated

"In late biopsies all infiltrates … were associated with increased future graft loss ….
The impact of inflammation on survival reflects the association of progressing disease with inflammation."

Sellarés et al, AJT 2011

Meaning of fibrosis and inflammation

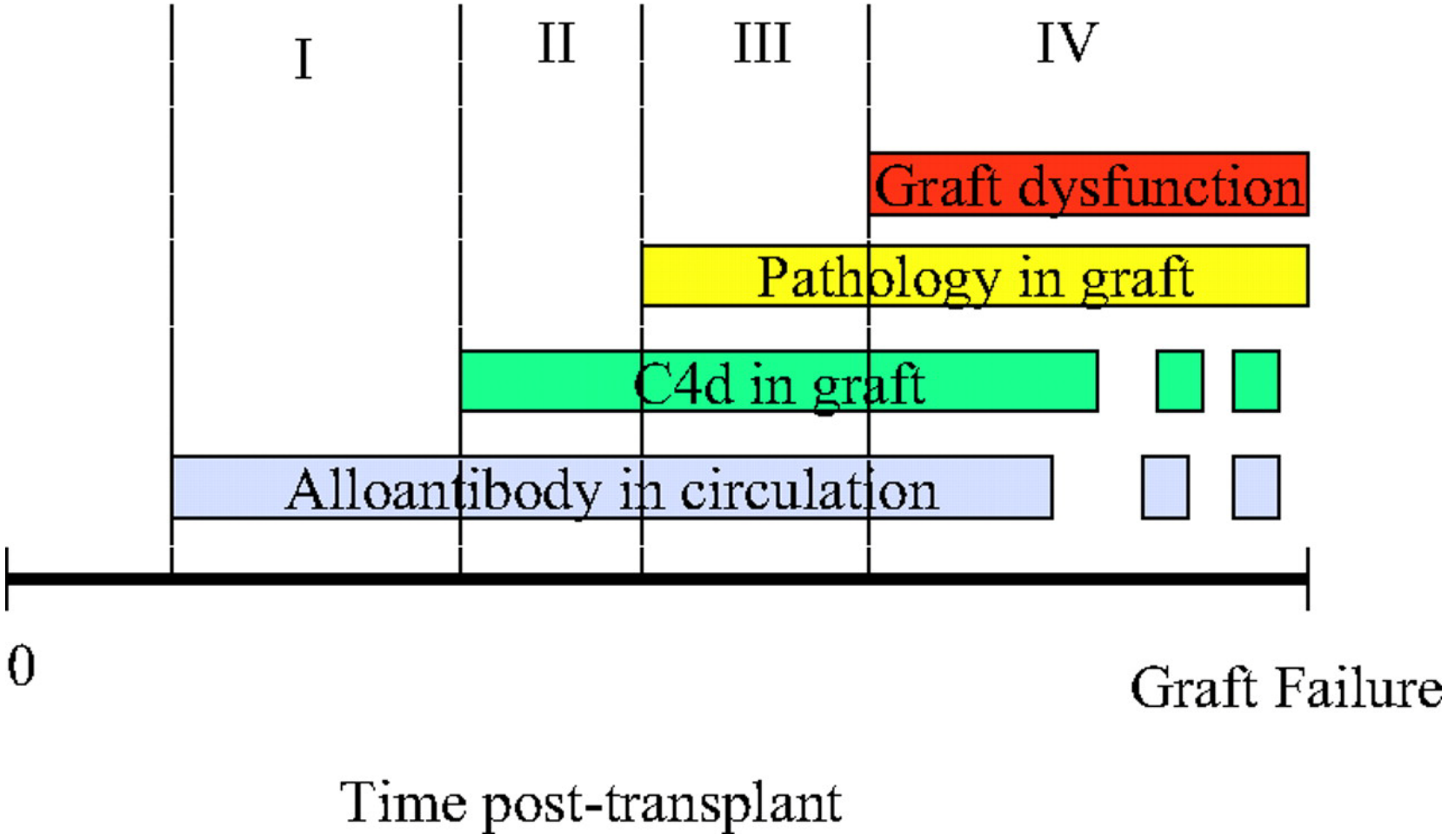




- ***1-yr protocol biopsies***
- 1.) normal histology (n=86)
- 2.) fibrosis (n=45)
- **3.) fibrosis und inflammation (n=20)**

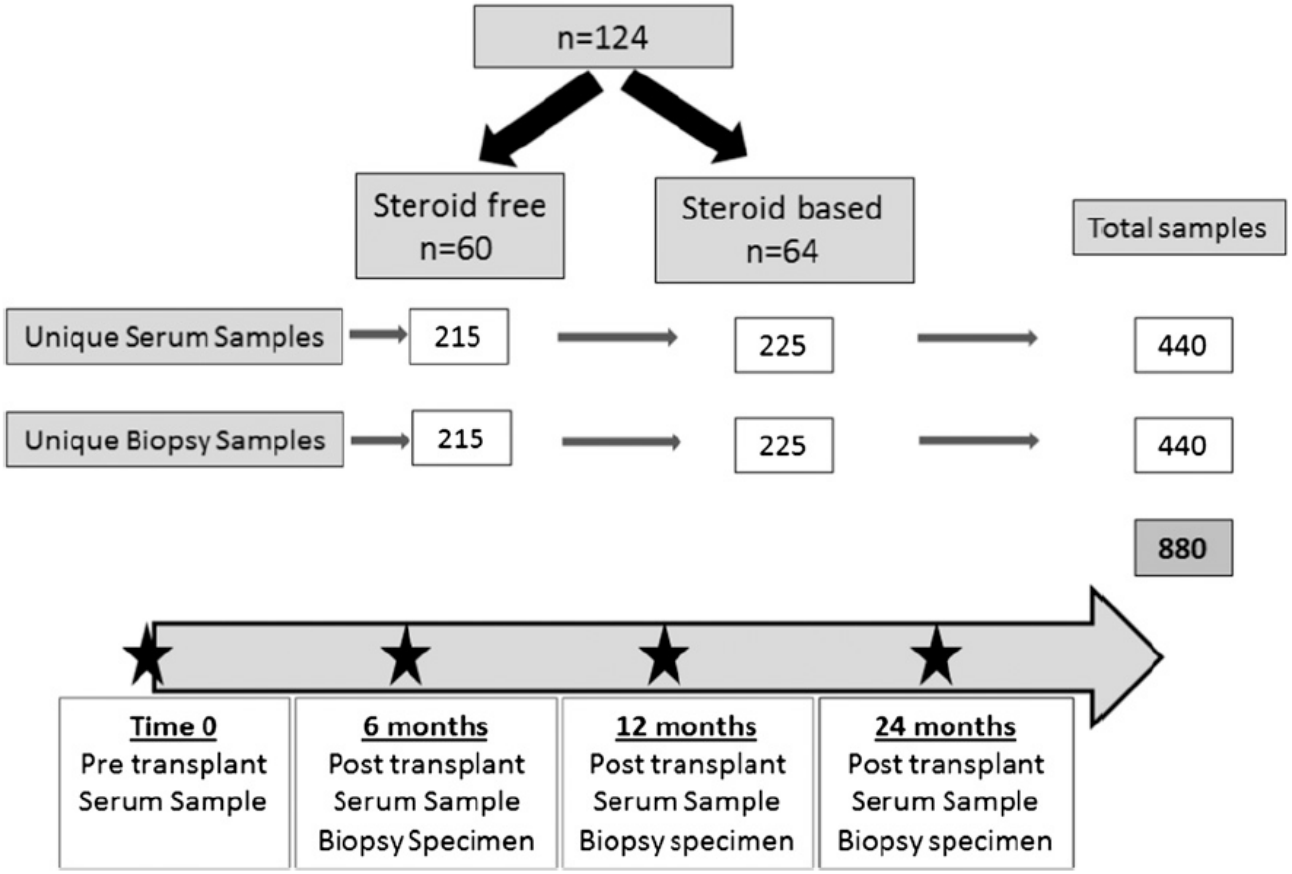
Park et al, JASN 2010

Stages of Antibody Mediated Rejection



The Clinical Impact of Humoral Immunity in Pediatric Renal Transplantation

Abanti Chaudhuri,* Mikki Ozawa,† Matthew J. Everly,† Robert Ettenger,‡ Vikas Dharnidharka,§



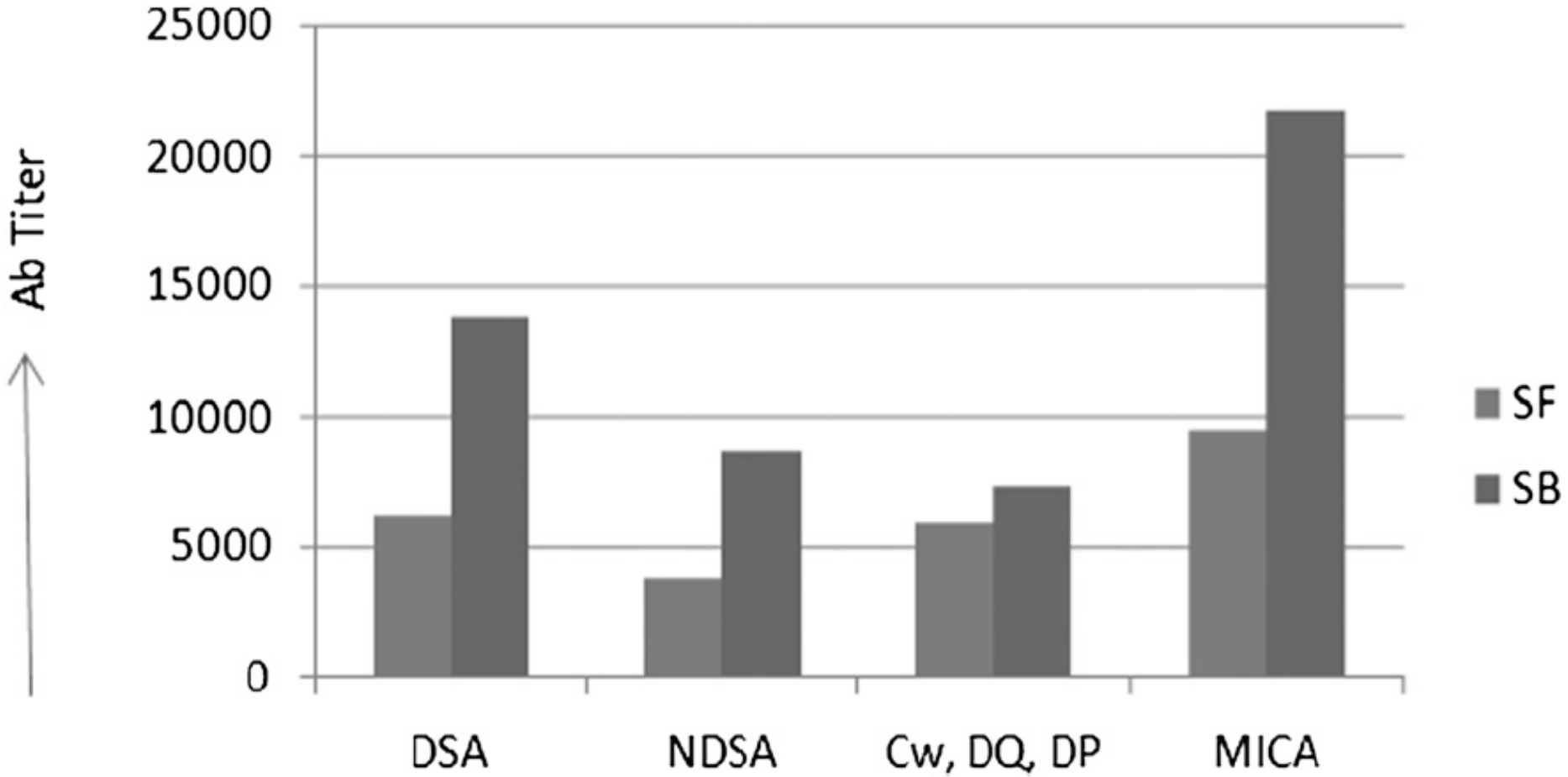


Figure 2. *De novo* antibody titers in SF versus SB immunosuppression. Antibody titers. The highest MFIs are shown for DSA, NDSA, Cw, DQ, and DP (where donor typing for these antigens were not available), and MICA antigens.

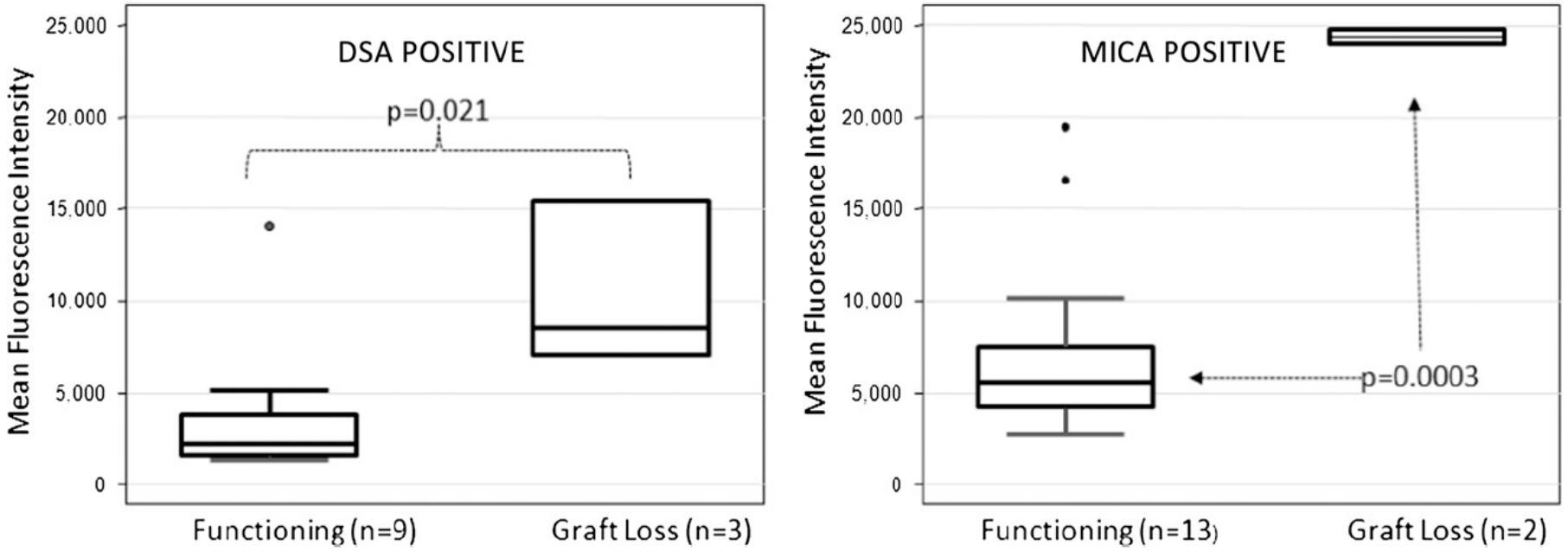


Figure 6. Significant association of Ab positivity and graft loss. Anti-HLA DSA and anti-MICA Ab positivity in patients associates with greater risk of graft loss over the course of the SNSO1 study, even in low-risk pediatric renal transplant recipients.

Association of *de novo* DSA with late graft failure

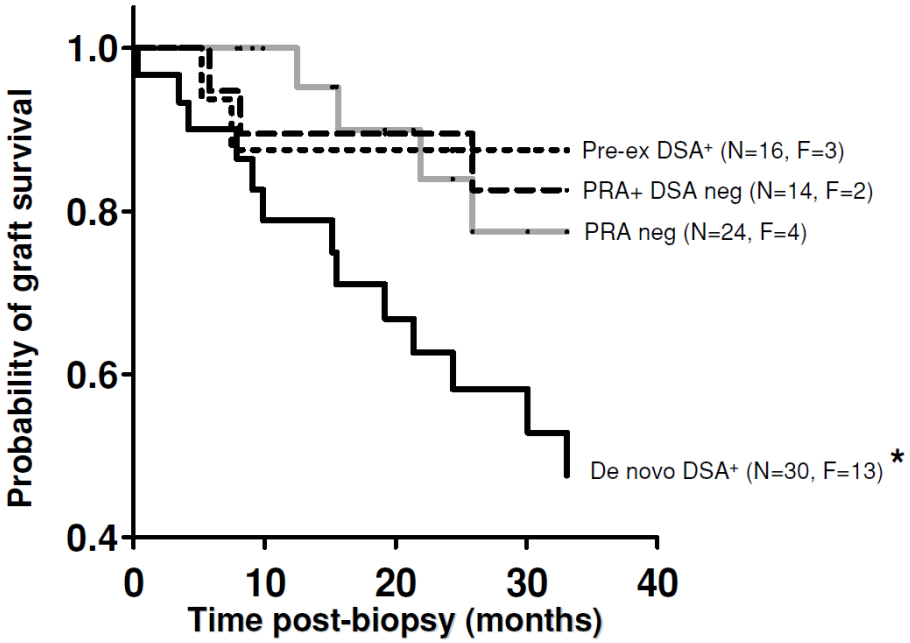
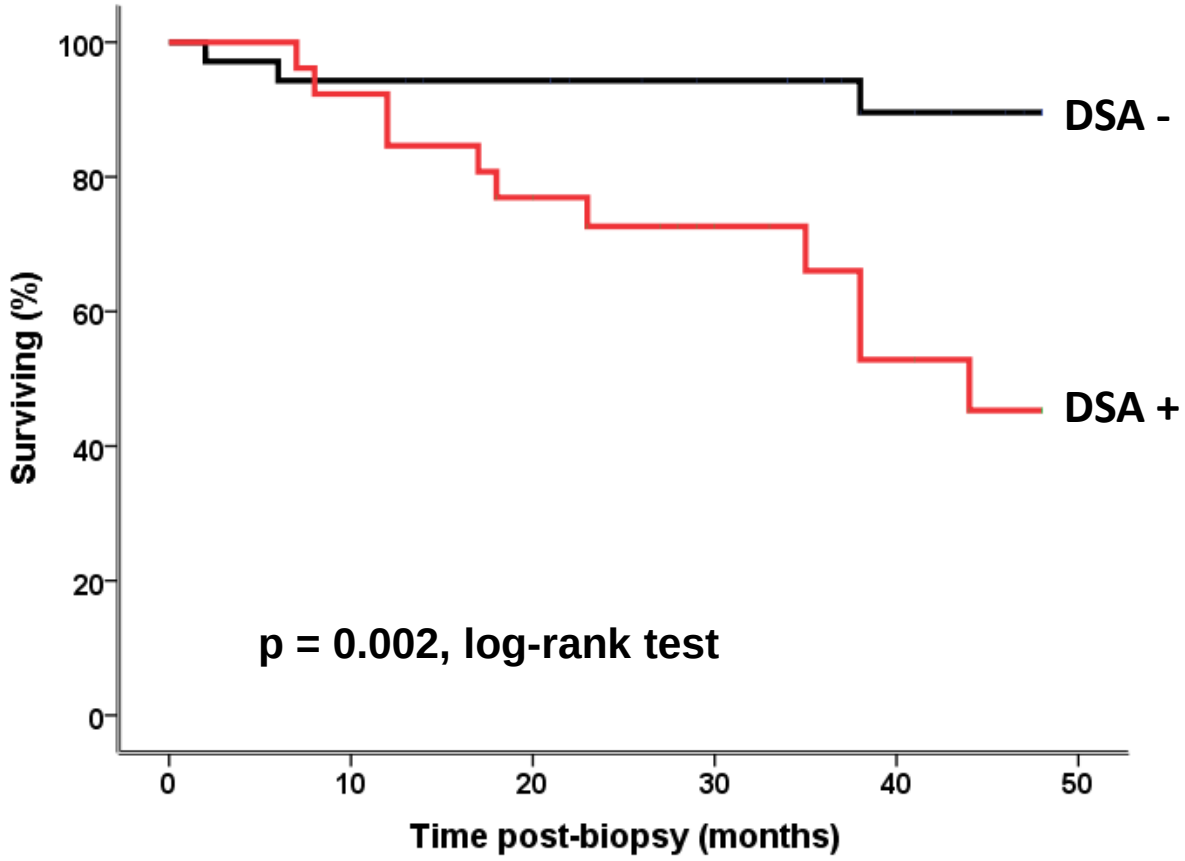


Figure 6: Probability of graft survival curves in patients who underwent a late biopsy and were assessed for DSA.

Hidalgo et al., Am J Transplant. 2009

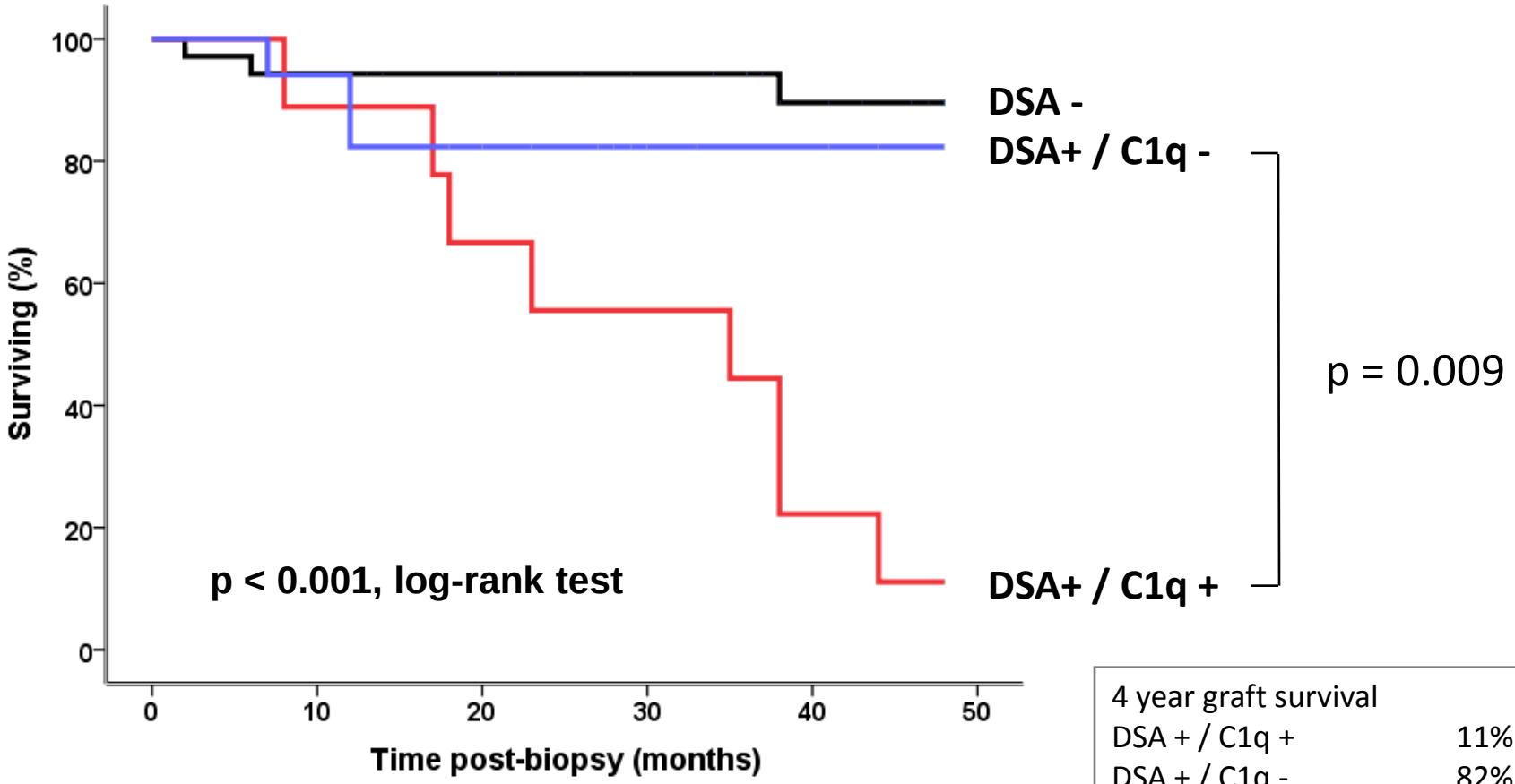
Association of DSA positivity with graft survival



4 year graft survival	
DSA +	45%
DSA -	87%

Courtesy of Alexander Fichter, Heidelberg - Germany

Association of C1q-binding DSA with graft survival



4 year graft survival	
DSA + / C1q +	11%
DSA + / C1q -	82%
DSA -	87%

BASIC RESEARCH www.jasn.org

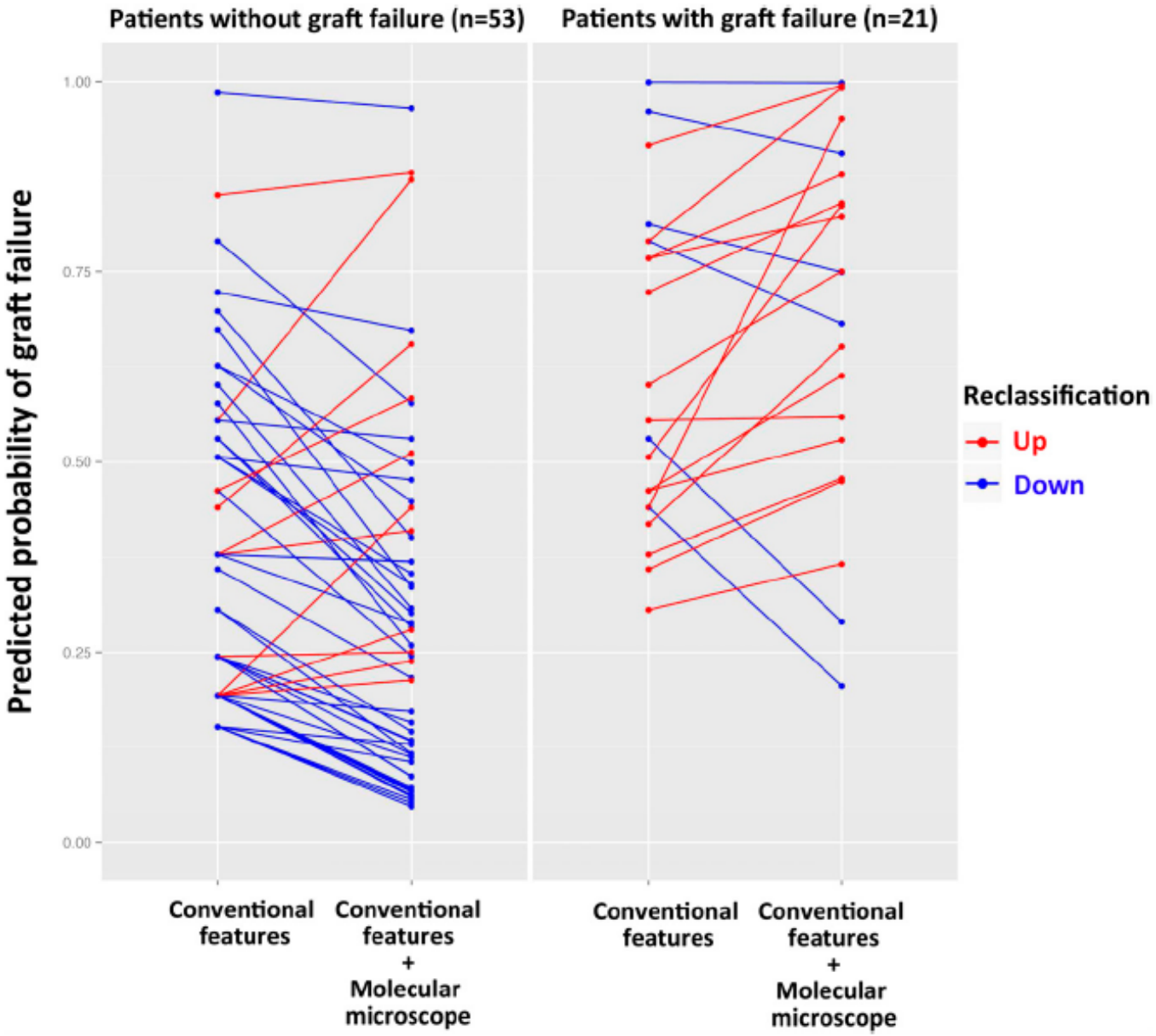
Molecular Microscope Strategy to Improve Risk Stratification in Early Antibody-Mediated Kidney Allograft Rejection

Alexandre Loupy,*† Carmen Lefaucheur,†‡ Dewi Vernerey,†§ Jessica Chang,‖ Luis G. Hidalgo,‖¶ Thibaut Beuscart,† Jerome Verine,** Olivier Aubert,† Sébastien Dubleumortier,†† Jean-Paul Duong van Huyen,*†‡‡ Xavier Jouven,† Denis Glotz,†‡ Christophe Legendre,*† and Philip F. Halloran‖§§

Table 3. Determinants of kidney transplant graft outcome after acute ABMR: univariate analysis

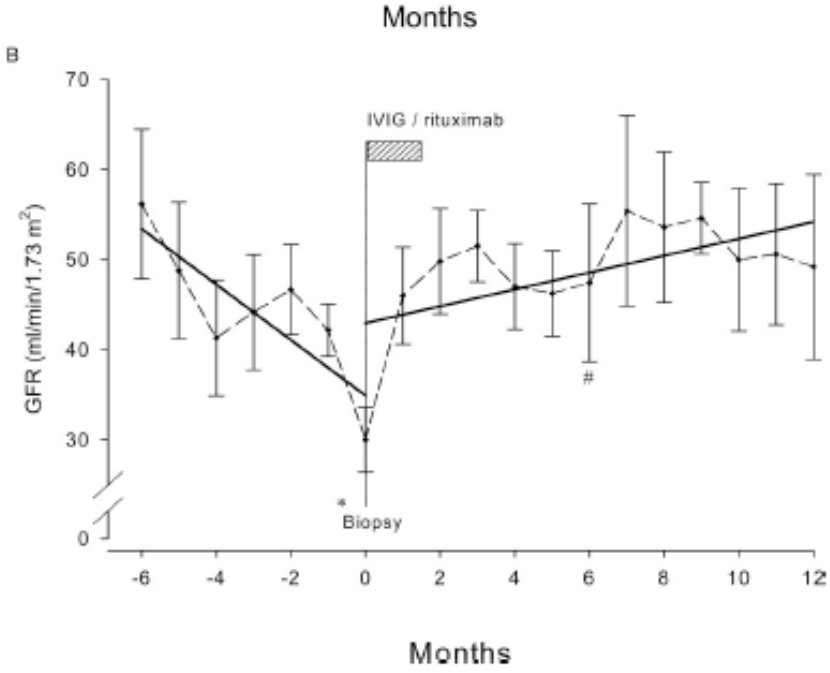
Parameters	HR	95% CI	*P* Value
Clinical parameters			
Recipient age, yr	1.02	0.98 to 1.06	0.31
Cold ischemia time, min	1.01	0.97 to 1.05	0.71
Donor age, yr			
<60	1	—	
≥60	3.58	1.45 to 8.87	0.01
Proteinuria at biopsy, g/L			
<0.15	1	—	
≥0.15	1.52	0.82 to 2.81	0.18
Immunologic parameters			
Immunodominant DSA MFI at the time of rejection	1.00	0.99 to 1.00	0.42
Functional parameters			
eGFR[a] at 1 yr			
eGFR≥30	1	—	
eGFR<30	3.04	1.28 to 7.22	0.01
Histologic parameters			
Arterial fibrous intimal thickening score	0.96	0.64 to 1.44	0.86
cg score	1.85	1.18 to 2.90	0.01
Interstitial fibrosis/tubular atrophy score	1.84	1.21 to 2.78	0.01
Interstitial inflammation score	0.75	0.45 to 1.24	0.26
Tubulitis score	0.66	0.39 to 1.11	0.12
v score[b]	1.20	0.45 to 3.08	0.13
g score	1.45	0.89 to 2.35	0.13
ptc score	1.99	0.97 to 4.07	0.06
C4d Banff score	1.47	1.03 to 2.08	0.03
Humoral histologic score[c]	1.36	1.08 to 1.71	0.01
Molecular parameters			
ABMR Molecular Score	8.82	1.82 to 42.73	0.01
Endothelial DSA-selective transcripts	2.94	1.00 to 8.69	0.05
NK transcripts	1.61	0.81 to 3.22	0.18
T-cell transcripts	0.93	0.50 to 1.73	0.83
AKI score	1.17	0.63 to 2.18	0.61

[a]eGFR using the Modification of Diet in Renal Disease formula.
[b]Note that all ABMR episodes with v lesions in the present study were treated by antibody-targeting strategies.[2]
[c]Humoral histologic score defined by g+ptc+v+cg+C4d Banff scores.


Patients without graft failure (n=53)
Patients with graft failure (n=21)
Predicted probability of graft failure
1.00
0.75
0.50
0.25
0.00
Conventional features
Conventional features + Molecular microscope
Conventional features
Conventional features + Molecular microscope
Reclassification
Up
Down

Successful Treatment of Chronic Antibody-Mediated Rejection With IVIG and Rituximab in Pediatric Renal Transplant Recipients

Heiko Billing,[1] Susanne Rieger,[1] Jörg Ovens,[2] Caner Süsal,[2] Anette Melk,[1] Rüdiger Waldherr,[3] Gerhard Opelz,[2] and Burkhard Tönshoff[1,4]



(*Transplantation* 2008;86: 1214–1221)

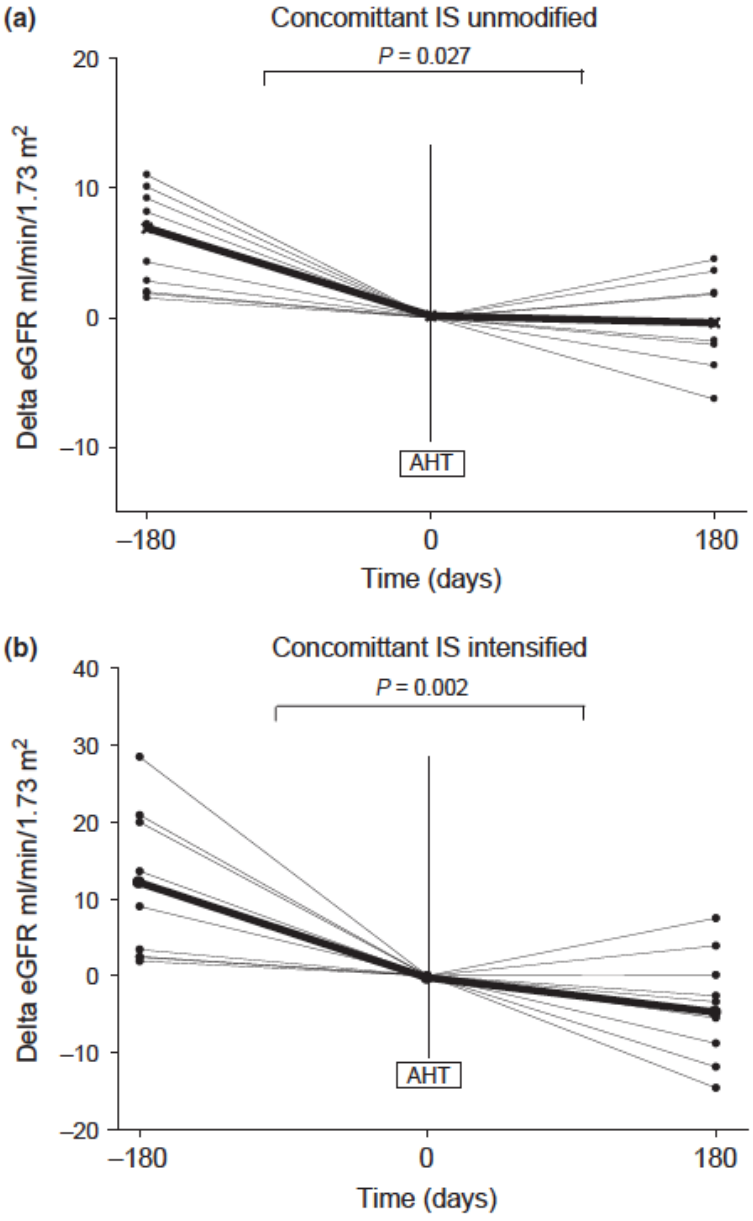
TRANSPLANT INTERNATIONAL

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

IVIG and rituximab for treatment of chronic antibody-mediated rejection: a prospective study in paediatric renal transplantation with a 2-year follow-up

Heiko Billing,[1] Susanne Rieger,[1] Caner Süsal,[2] Rüdiger Waldherr,[3] Gerhard Opelz,[2] Elke Wühl[1] and Burkhard Tönshoff[1]



American Journal of Transplantation 2010; 10: 681–686
Wiley Periodicals Inc.

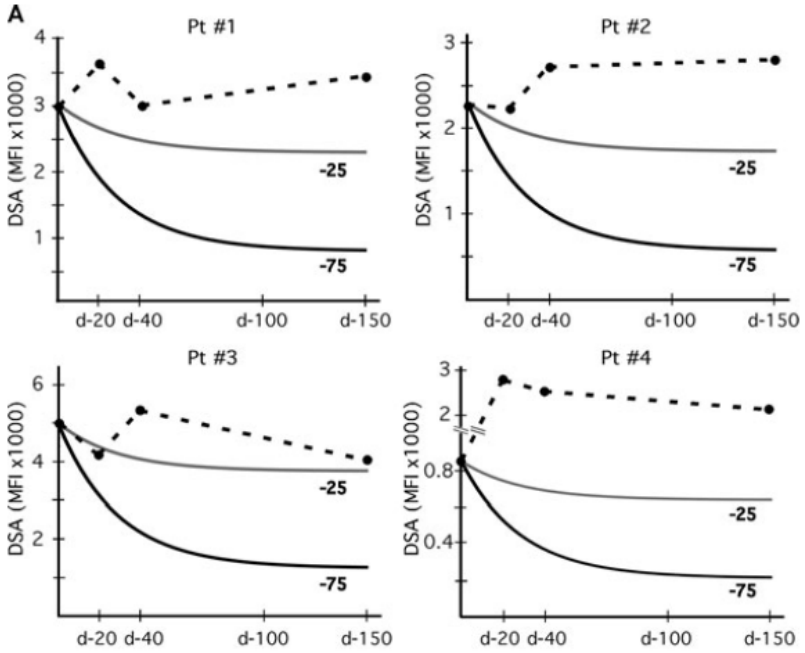
doi: 10.1111/j.1600-6143.2009.02968.x

Brief Communication

Bortezomib as the Sole Post-Renal Transplantation Desensitization Agent Does Not Decrease Donor-Specific Anti-HLA Antibodies

R. Sberro-Soussan[a,b], J. Zuber[a,b,*], C. Suberbielle-Boissel[c], S. Candon[a,d], F. Martinez[b],

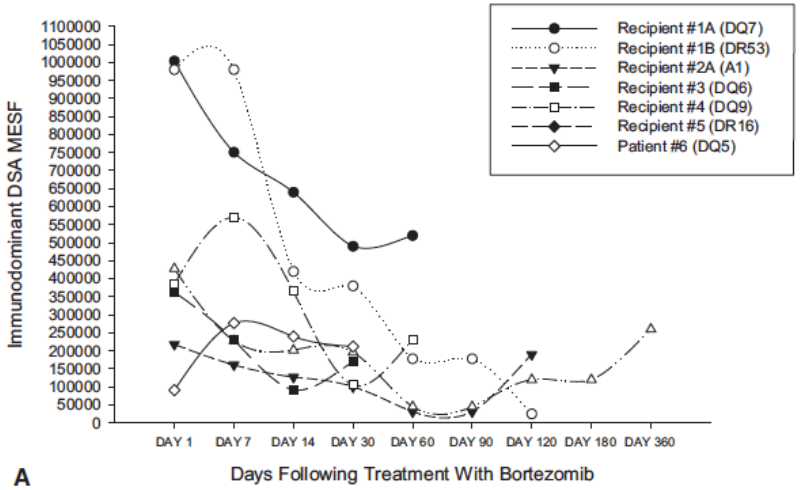
Received 07 July 2009, revised 22 October 2009 and accepted for publication 04 November 2009



Bortezomib Provides Effective Therapy for Antibody- and Cell-Mediated Acute Rejection

Matthew J. Everly,[1] Jason J. Everly,[1] Brian Susskind,[2] Paul Brailey,[2] Lois J. Arend,[3] Rita R. Alloway,[4] Prabir Roy-Chaudhury,[4] Amit Govil,[4] Gautham Mogilishetty,[4] Adele H. Rike,[1] Michael Cardi,[5] George Wadih,[5] Amit Tevar,[1] and E. Steve Woodle[1,6]

(*Transplantation* 2008;86: 1754–1761)



Immune Response of Pediatric Renal Transplant Recipients challenged by Sensitization, Vaccination or Non-Adherence: Cross-Sectional and Prospective Analyses of the International CERTAIN Registry Cohort

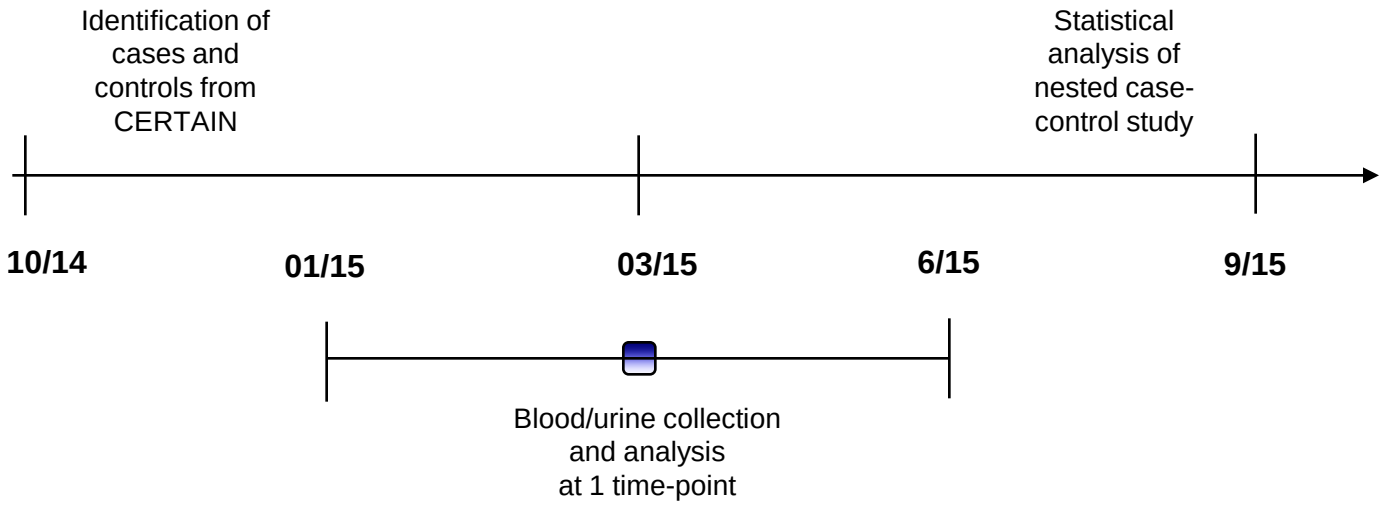
IFB Tx Integrated Research and Treatment Center Transplantation

SPONSORED BY THE Federal Ministry of Education and Research

MHH

Design

Nested case-control study



40 cases - 120 controls

Identification of controls locally and via CERTAIN registry

Design

Prospective longitudinal study

180 patients to be followed

Marker

- Cytokines (Falk)
- Senescence markers (Melk)
- Urinary Proteomics (Pape)
- Complement in Urine and Plasma (Heindl-Rusai)
- Free DNA (Schütz)
- Complement fixing DSA (Fichtner)
- Virus-specific T cells (Pape)

Conclusions I

Diagnosis of humoral rejection is a combination of detection of circulating DSA and histology. Complement fixing DSA might be the future diagnostic mean.

Acute humoral rejection is a rare condition in pediatric renal transplantation and can be treated sucesfully in most cases.

Fibrosis is a scar and stable; inflammation with fibrosis is signalling progressive disease and bad prognosis.

Conclusions II

Chronic humoral rejection is the main cause for long-term graft loss.

Chronic humoral rejection might be treated successfully if detected early enough.

Treatment consists of IgG, Rituximab, increase of underlying immunosuppression and eventually Immunoadsorption / Plasmapehresis.

The role of Bortezomib is to be determined.