カテゴリー5　免疫抑制

既存抗体陽性症例の治療戦略

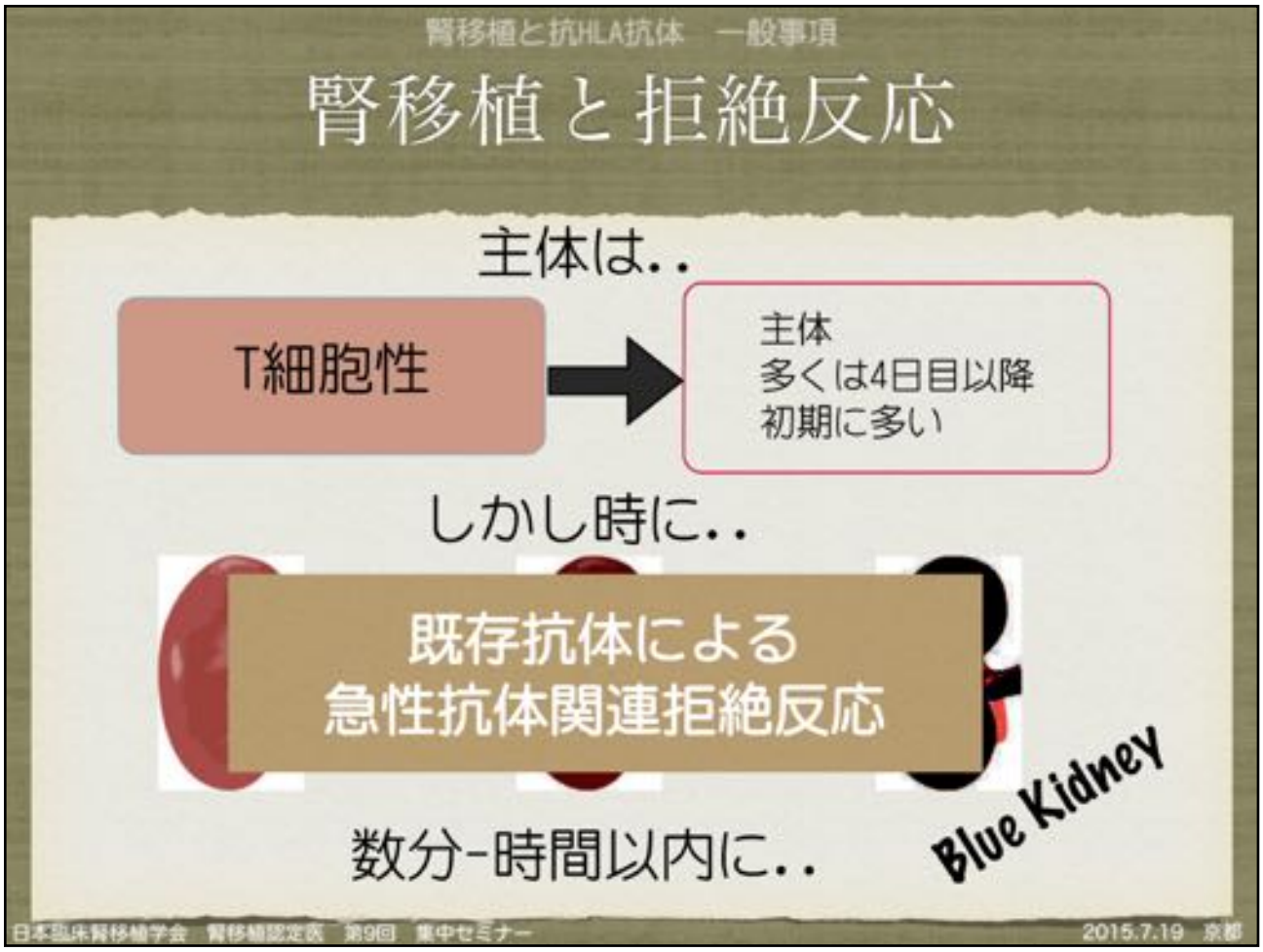
市立札幌病院　腎臓移植外科
原田　浩

2015.7.19　京都

お話する内容

- 腎移植と抗HLA抗体　一般事項
- 腎移植と抗HLA抗体　最近の話題
- 当科における既存抗体陽性例への対応
- 症例提示


腎移植と抗HLA抗体　一般事項


腎移植と抗HLA抗体　一般事項
腎移植と拒絶反応
主体は..
T細胞性
主体
多くは4日目以降
初期に多い
しかし時に..
既存抗体による
急性抗体関連拒絶反応
Blue Kidney
数分-時間以内に..
日本臨床腎移植学会　腎移植認定医　第9回　集中セミナー
2015.7.19　京都

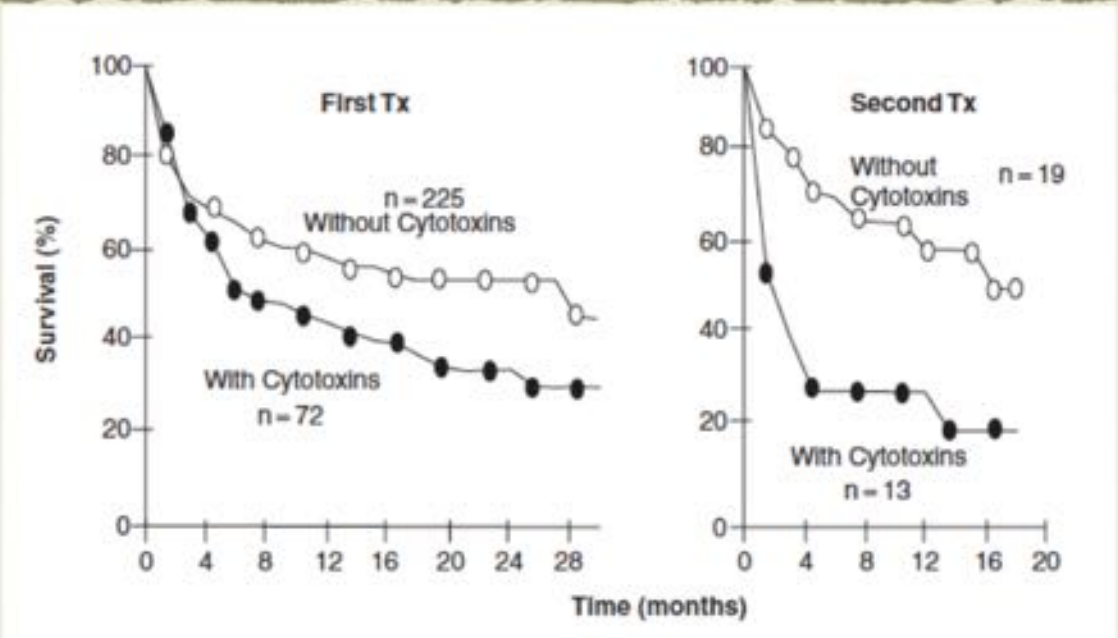
腎移植と抗HLA抗体　一般事項

腎移植と拒絶反応

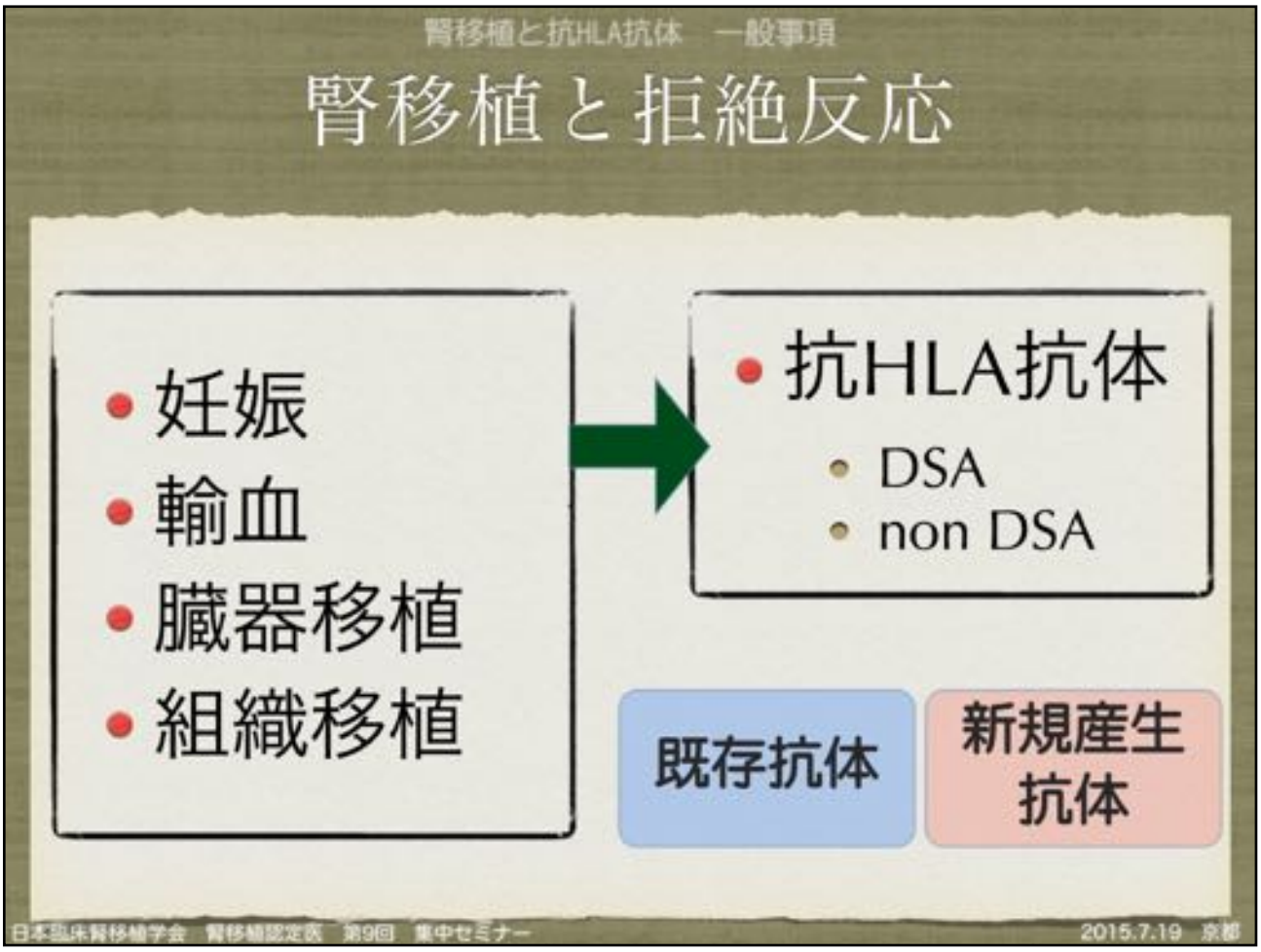
T細胞性 →	主体 多くは4日目以降 初期に多い
抗体関連 →	最近着目 直後からも発症 慢性期に問題
混合性	各々に 急性・慢性がある

腎移植と抗HLA抗体　一般事項

既感作(PRA陽性)と移植腎生着



Terasaki PI, Kreisler M, Mickey RM. Presensitization and kidney transplant failures. Postgrad Med J 1971; 47: 89–100.


腎移植と抗HLA抗体　一般事項
腎移植と拒絶反応
妊娠
輸血
臓器移植
組織移植
抗HLA抗体
DSA
non DSA
既存抗体
新規産生抗体
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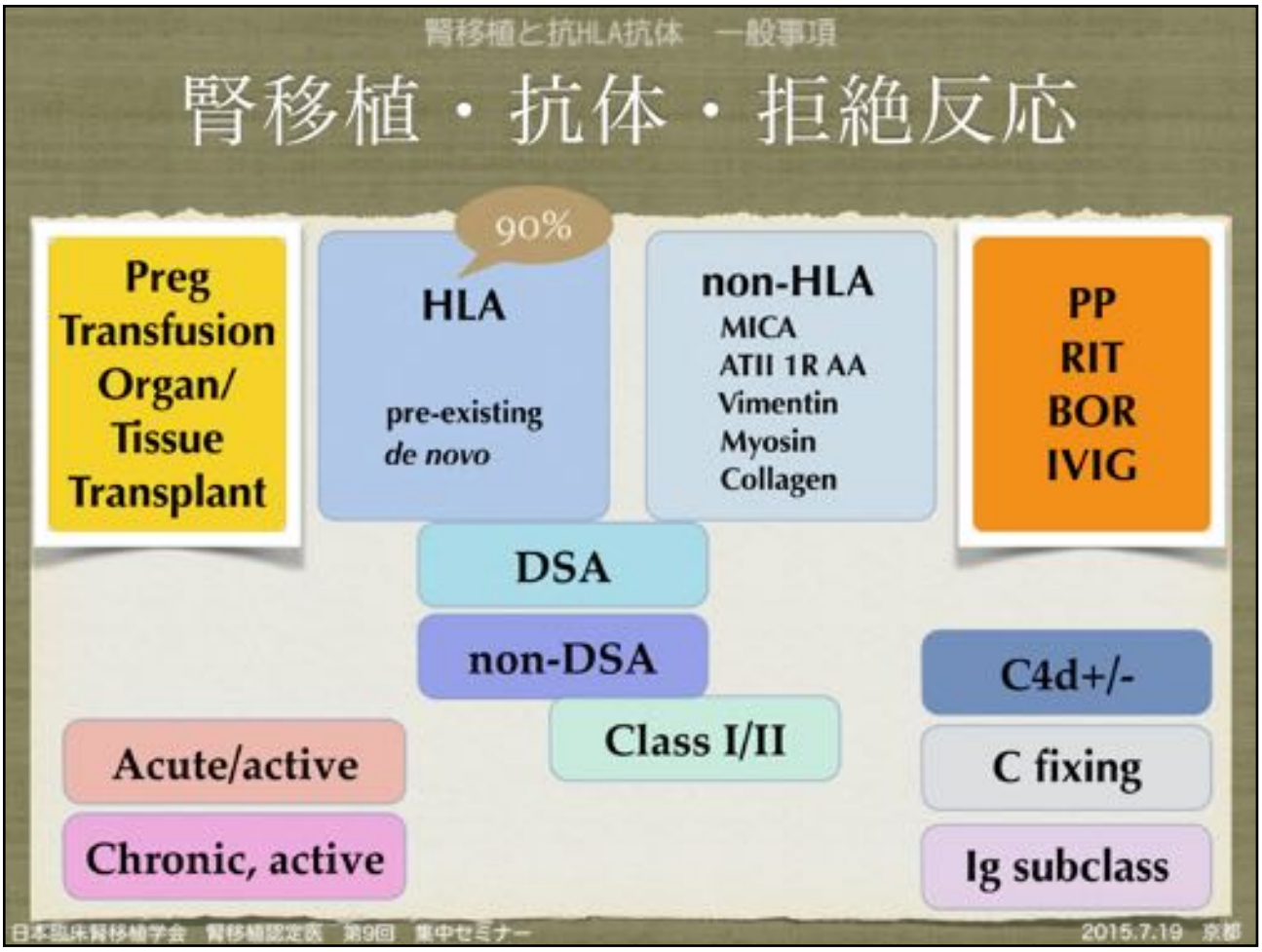
腎移植と抗HLA抗体　一般事項
腎移植・抗体・拒絶反応
Preg
Transfusion
Organ/
Tissue
Transplant
90%
HLA
pre-existing
de novo
non-HLA
MICA
ATII 1R AA
Vimentin
Myosin
Collagen
PP
RIT
BOR
IVIG
DSA
non-DSA
Class I/II
C4d+/-
C fixing
Ig subclass
Acute/active
Chronic, active
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腎移植と抗HLA抗体　一般事項

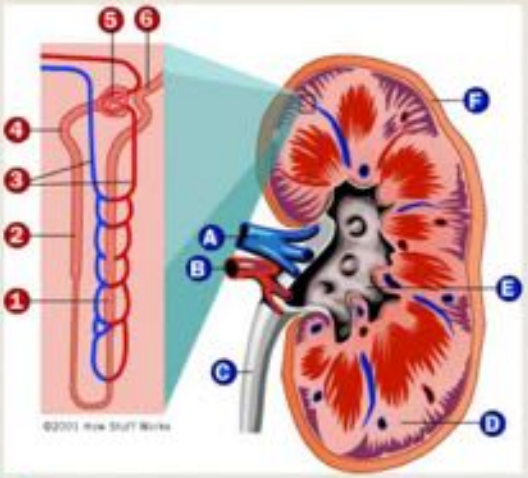
Phenotype of ABMR

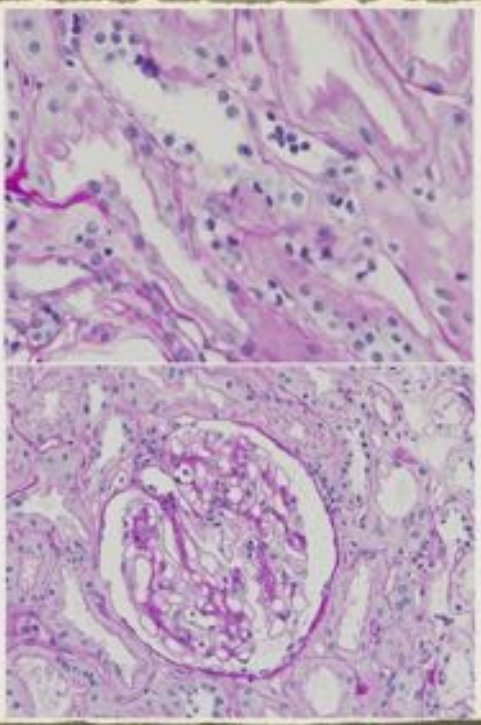
- Phenotype 1: Due to pre-existing Abs

Phenotype 2: Due to de-novo Abs

腎移植と抗HLA抗体　一般事項

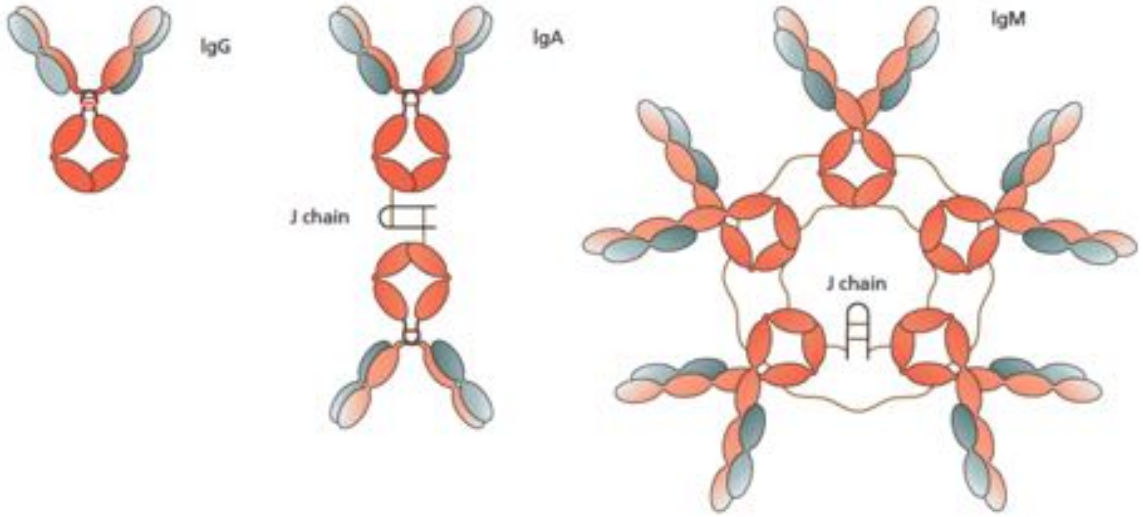
ABMR とMVI





腎移植と抗HLA抗体　一般事項

Ig classes



腎移植と抗HLA抗体　一般事項

Character of hIgs

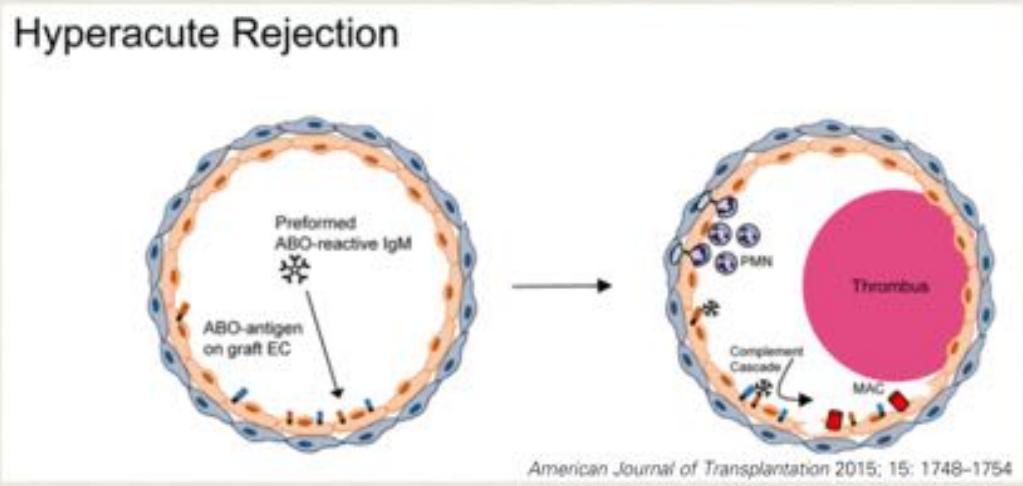
ヒト・イムノグロブリンの特性

Property	IgG				IgA		IgM	IgD	IgE
H chain class (heavy chain)	γ				α		μ	δ	ε
H Chain Subclasses	γ1	γ2	γ3	γ4	α1	α2	None	None	None
H chain MW	59 kDa	50 kDa	60 kDa	50 kDa	55 kDa	55 kDa	75 kDa	62 kDa	70 kDa
L chain MW * (light chain κ and γ)	23 kDa	23 kDa	23 kDa	23 kDa	23 kDa	23 kDa	23 kDa	23 kDa	23 kDa
Total MW	150 kDa	150 kDa	170 kDa	150 kDa	160 kDa (serum) 600 kDa (secretory)	160 kDa (serum) 600 kDa (secretory)	970 kDa	180 kDa	180 kDa
Normal Serum Concentration (mg/mL	5–9.5	2.2–4.8	0.4–1.0	0.1–0.6	0.4–3	0.1–0.5	0.2–2.8	<1	<1
Ext. Coeff. 0.1% @ 280 nm	1.4	1.4	1.4	1.4	1.32	1.32	1.18	1.7	1.53
Complement fixation	weak 2	weak 3	strong 1	no 4	no	no	strong	no	no
Fc receptor binding	strong	weak	strong	weak	yes	yes	yes	no	yes
Mast cell/basophil degranulation	no	no	no	no	no	no	no	no	yes
Placental transfer	strong	weak	strong	strong	no	no	no	no	no

*Light chains are present on all immunoglobulin classes. In humans, κ chains are found 67% of the time, and λ chains are found 33% of the time. For ratios in other species, see Table Immunoglobulin Light Chain Ratios.

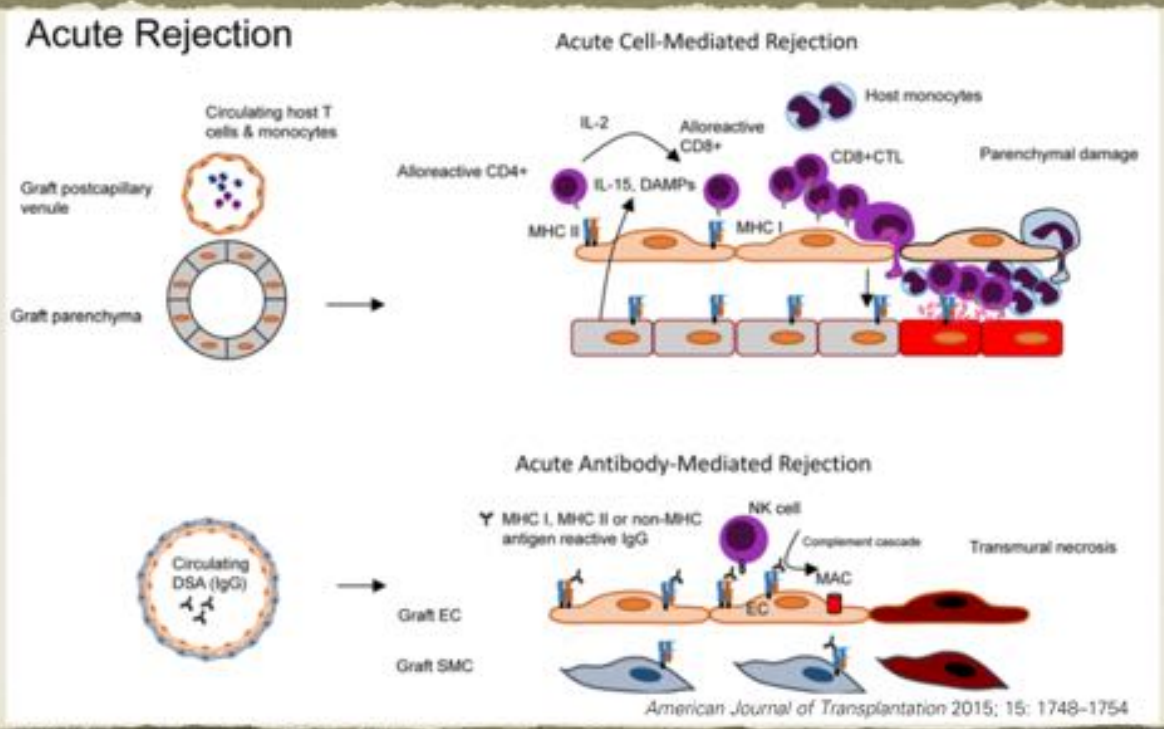
腎移植と抗HLA抗体　一般事項

Hyperacute Rejection



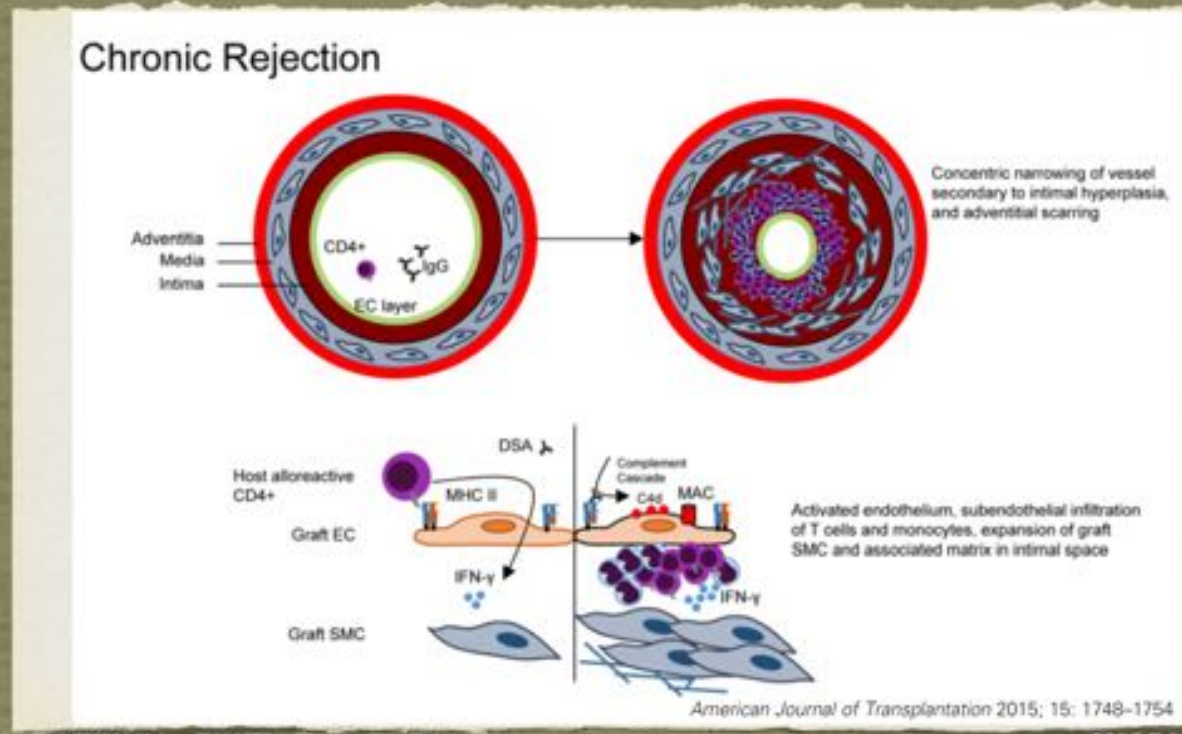
腎移植と抗HLA抗体　一般事項

Acute Rejection



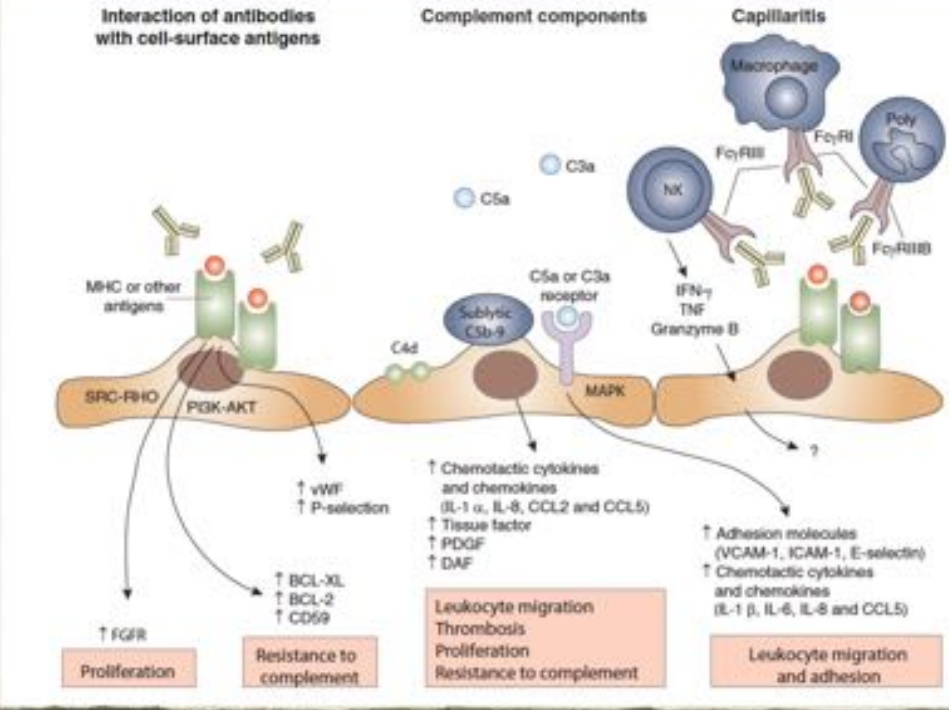
腎移植と抗HLA抗体　一般事項

Chronic Rejection



腎移植と抗HLA抗体　一般事項

抗体による細胞障害



腎移植と抗HLA抗体　一般事項

ABMR 最新バンフ分類

American Journal of Transplantation 2014; 14: 272–283
Wiley Periodicals Inc.

doi: 10.1111/ajt.12590

Meeting Report

Banff 2013 Meeting Report: Inclusion of C4d-Negative Antibody-Mediated Rejection and Antibody-Associated Arterial Lesions

M. Haas[1,*], B. Sis[2], L. C. Racusen[3], K. Solez[2], D. Glotz[4], R. B. Colvin[5], M. C. R. Castro[6], D. S. R. David[7], E. David-Neto[6], S. M. Bagnasco[3], L. C. Cendales[8], L. D. Cornell[9], A. J. Demetris[10], C. B. Drachenberg[11], C. F. Farver[12], A. B. Farris III[13], I. W. Gibson[14], E. Kraus[15], H. Liapis[16], A. Loupy[17], V. Nickeleit[18], P. Randhawa[10], E. R. Rodriguez[12], D. Rush[19], R. N. Smith[5], C. D. Tan[12], W. D. Wallace[20] and M. Mengel[2] as the Banff meeting report writing committee

[18]*Department of Pathology and Laboratory Medicine, Division of Nephropathology, University of North Carolina at Chapel Hill, Chapel Hill, NC*
[19]*Department of Internal Medicine, University of Manitoba Health Sciences Centre, Winnipeg, Manitoba, Canada*
[20]*Department of Laboratory Medicine and Pathology, University of California, Los Angeles, CA*
* *Corresponding author: Mark Haas, mark.haas@cshs.org*

The 12th Banff Conference on Allograft Pathology was held in Comandatuba, Brazil, from August 19–23, 2013, and was preceded by a 2-day Latin American

腎移植と抗HLA抗体　一般事項

ABMR 最新バンフ分類

Table 1: Revised (Banff 2013) classification of antibody-mediated rejection (ABMR) (30)

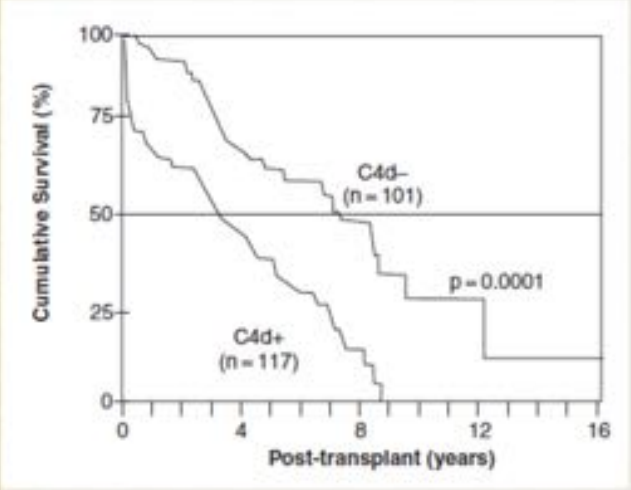
Acute/active ABMR; all three features must be present for diagnosis[1,2]
1. Histologic evidence of acute tissue injury, including one or more of the following:
   - Microvascular inflammation ($g > 0$[3] and/or $ptc > 0$)
   - Intimal or transmural arteritis ($v > 0$)[4]
   - Acute thrombotic microangiopathy (TMA), in the absence of any other cause
   - Acute tubular injury, in the absence of any other apparent cause
2. Evidence of current/recent antibody interaction with vascular endothelium, *including at least one of the following*:
   - Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections, or $C4d > 0$ by IHC on paraffin sections)
   - At least moderate microvascular inflammation ($[g + ptc] \geq 2$)[5]
   - Increased expression of endothelial activation and injury transcripts (ENDATs) or other gene expression markers of endothelial injury in the biopsy tissue, if thoroughly validated
3. Serologic evidence of donor-specific antibodies (HLA or other antigens)

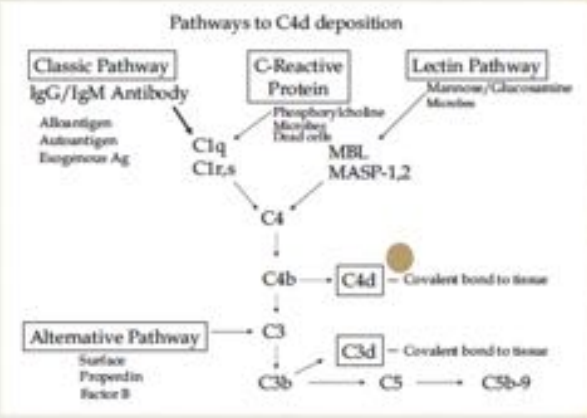
Chronic, active ABMR; all three features must be present for diagnosis[1,6]
1. Morphologic evidence of chronic tissue injury, including one or more of the following:
   - Transplant glomerulopathy ($cg > 0$),[7] if no evidence of chronic TMA
   - Severe peritubular capillary basement membrane multilayering (requires electron microscopy [EM])[8]
   - Arterial intimal fibrosis of new onset, excluding other causes[9]
2. Evidence of current/recent antibody interaction with vascular endothelium, *including at least one of the following*:
   - Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections, or $C4d > 0$ by IHC on paraffin sections)
   - At least moderate microvascular inflammation ($[g + ptc] \geq 2$)[5]
   - Increased expression of endothelial activation and injury transcripts (ENDATs) or other gene expression markers of endothelial injury in the biopsy tissue, if thoroughly validated
3. Serologic evidence of donor-specific antibodies (HLA or other antigens)

C4d staining without evidence of rejection; all three features must be present for diagnosis[10]
1. Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections, or $C4d > 0$ by IHC on paraffin sections)
2. $g = 0$, $ptc = 0$, $cg = 0$ (by light microscopy (LM) and by EM if available), $v = 0$; no TMA, no peritubular capillary basement membrane multilayering, no acute tubular injury (in the absence of another apparent cause for this)
3. No acute cell-mediated rejection (Banff 1997 type 1A or greater) or borderline changes

腎移植と抗HLA抗体　一般事項

C4d染色の差異による生着率





Feucht HE, Lederer SR, Kluth B. Humoral alloreactivity in recipients of renal allografts as a risk factor for the development of delayed graft function. Transplantation 1998; 65: 757–758.

Rotman S, Collins AB, Colvin RB: C4d deposition in allografts: Current concepts and interpretation. *Transplant Rev* 19: 65–77, 2005

腎移植と抗HLA抗体　一般事項

C4d-Positive ABMR

C4d-Negative ABMR

Proposed criteria under discussion by Banff working group

Sero
• DS

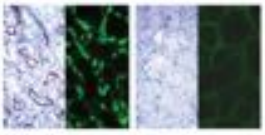
Diagnosis and Management of Antibody-Mediated Rejection: Current Status and Novel Approaches

A. Djamali[1,2,*], D. B. Kaufman[2], T. M. Ellis[3], W. Zhong[3,4], A. Matas[3] and M. Samaniego[3]

American Journal of Transplantation 2014; 14: 255–271

Evidence

Immunopathologic Evidence
• IF: Diffuse-positive C4d in PTC
• IHC: Diffuse- or focal-positive C4d in PTC



Immunopathologic Evidence
• Negative C4d staining; and
• Endothelial activation, detected by increased mRNA expression of endothelial genes, such as W/F, PECAM, SELE, etc; and/or
• Evidence for glomerular and/or capillary endothelial cycling (CD31+Ki67+ cells lining the microcirculation)

Histopathologic Evidence ACUTE
• ATN like changes, and/or
• Peritubular capillaritis, and/or
• Glomerulitis, and/or
• Arterial fibroid necrosis, and,
• No evidence for chronic capillary injury (reduction and/or multilayering of glomerular and peritubular capillary basement membranes)

Histopathologic Evidence ACUTE
• Peritubular capillaritis, and/or
• Glomerulitis, and/or
• Thrombotic microangiopathy, and/or
• Arterial fibroid necrosis, and
• No evidence for chronic capillary injury (reduction and/or multilayering of glomerular and peritubular capillary basement)

Histopathologic Evidence CHRONIC
• Transplant glomerulopathy, and/or
• PTC basement membrance multilamination, and/or
• IFTA, and/or
• Fibrous intimal thickening of arteries
• May be accompanied by glomerulitis and/or capillaritis

Histopathologic Evidence CHRONIC
• Transplant glomerulopathy, and/or
• PTC basement membrane multilamination, and/or
• Fibrous intimal thickening of arteries
• May be accompanied by glomerulitis and/or capillaritis

Diagnosis and Management of Antibody-Mediated Rejection: Current Status and Novel Approaches
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腎移植と抗HLA抗体　一般事項

ABMRの予防

Table 2: Strategies to prevent ABMR

1. Do not transplant highly sensitized patients
2. Avoid blood transfusion
3. Paired kidney exchange
4. In sensitized patients, precise characterization of their alloantibodies and exact HLA typing of the donor at the time of transplantation
5. Participation in special programs (such as the Eurotransplant Acceptable Mismatch Program)
6. Removal of DSA (plasmapheresis, immunoadsorption)
7. Direct or indirect inhibition of DSA production
   a. Anti-B cell agents (rituximab[1])
   b. Anti-plasma cell agents (proteasome inhibitors, e.g. bortezomib[1])
   c. Rabbit anti-human thymocyte immunoglobulins (e.g. thymoglobulin)?
   d. Costimulation blockade (e.g. belatacept)?
8. Inhibition of complement cascade (eculizumab[1])
9. Intravenous immunoglobulin[1]
   e. Neutralizing DSA: anti-idiotypic activity
   f. Inhibiting complement activation by binding C3b, C4b
   g. Inhibiting activation of macrophages, neutrophils by binding FcγRs
   h. Apoptosis of B cells (inhibits CD19 expression)
10. Splenectomy

ABMR, antibody-mediated rejection; DSA, donor-specific antibodies; FcγRs, Fc gamma.
[1]These drugs are used off-label in solid organ transplantations.

腎移植と抗HLA抗体　一般事項

組織適合性検査

1960～

HLA Antigen
HLA Antibody
CrossMatch

Terasaki Tray

Complement dependent
cytotoxicity; CDC

2000～

Flow Cytometer

Luminex

HLA Antigen
HLA Antibody

HLA Antibody
CrossMatch

福岡赤十字病院　検査部　横口 裕樹氏より


腎移植と抗HLA抗体　一般事項
組織適合性検査-DSA検出のため
DSA Donor Specific Antibody
ドナーに反応する抗体
抗体関連拒絶
NDSA Non Donor Specific Antibody
ドナーに反応しない抗体
Safe?
福岡赤十字病院　検査部　橋口 裕樹氏より
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腎移植と抗HLA抗体　一般事項
組織適合性検査　感度とコスト
日本人に特徴的
なアリル網羅
＋
抗原レベル網羅
抗体特異性同定
抗原レベル網羅
抗体特異性同定
LAB Screen
Supplement
スクリーニング
ELISA法
抗体検査
細胞障害性
抗体検査
sensitivity
LATトレー
Flow PRA
&
LAB Screen
PRA
LAB Screen
Single Antigen
LAB Screen
Single Antigen
Price
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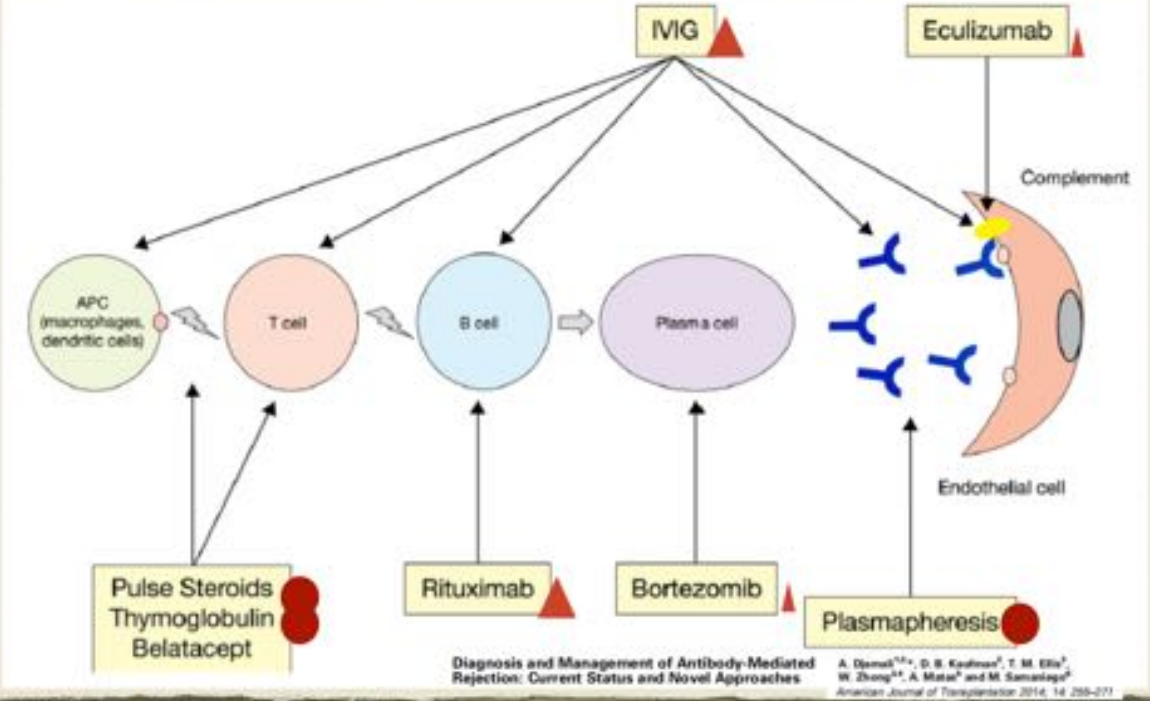
腎移植と抗HLA抗体　一般事項

ABMRの治療



Diagnosis and Management of Antibody-Mediated Rejection: Current Status and Novel Approaches

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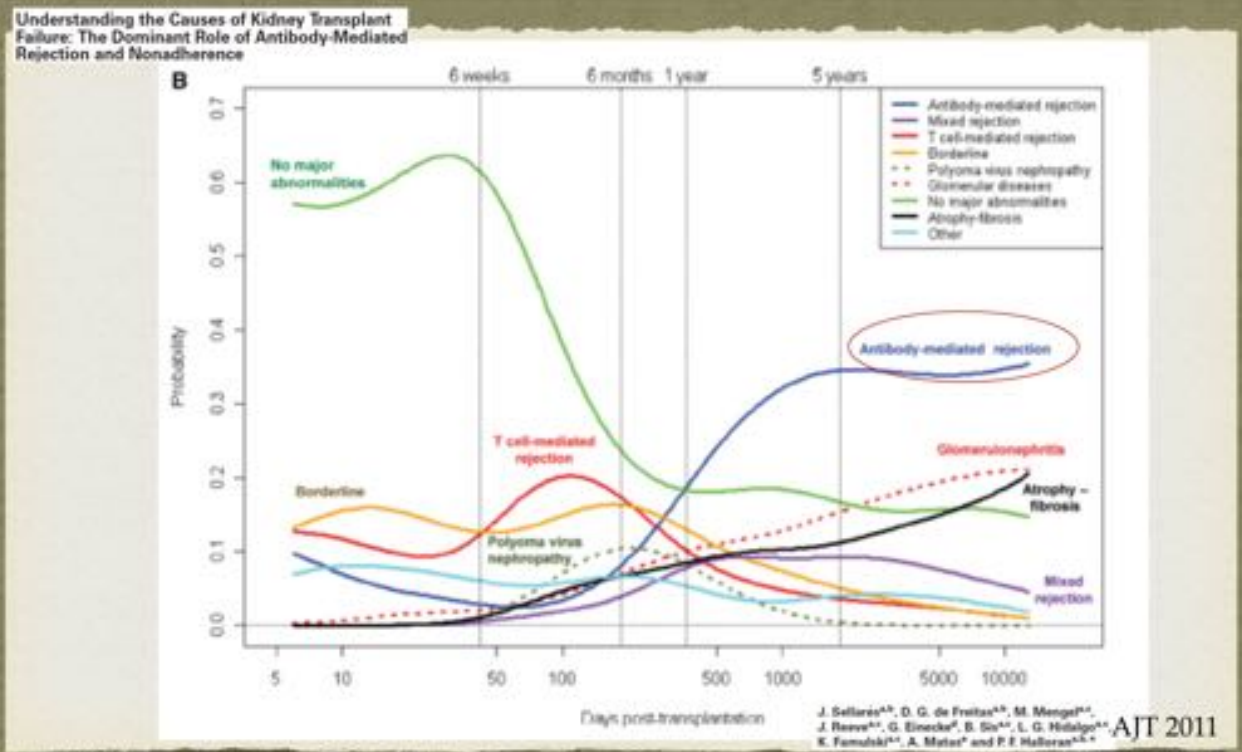
American Journal of Transplantation 2014; 14: 255–271

腎移植と抗HLA抗体　一般事項

ABMRを何とかしなくては



腎移植と抗HLA抗体　一般事項

ABMRを何とかしなくては

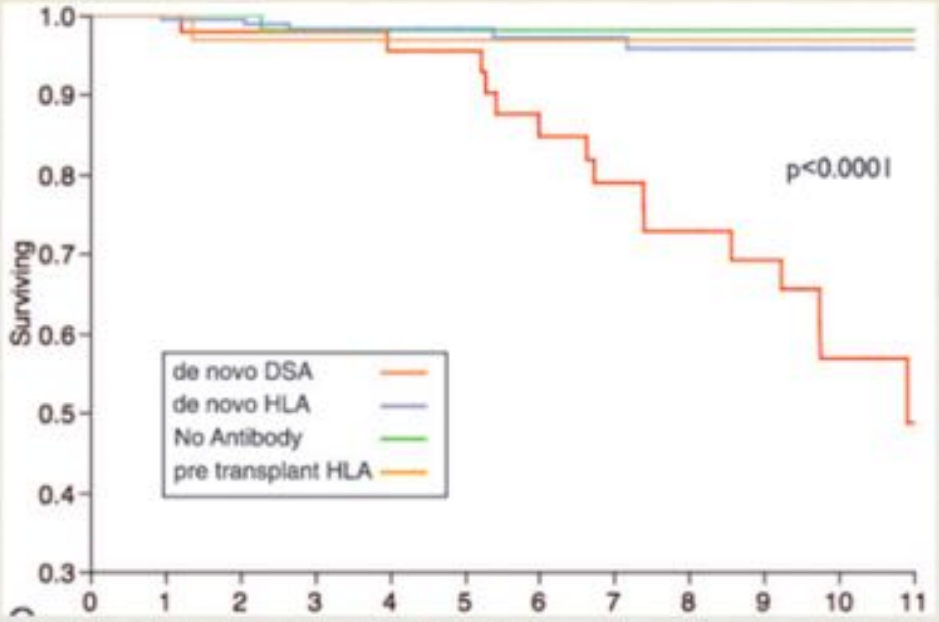
Table 1: Histological diagnosis and HLA antibody status of the transplants that failed during follow-up period versus those that did not fail, in the last biopsy available per patient

	Current status of the graft				
	Grafts that did not fail in the study period		Failed grafts		
Time of biopsy posttransplant	15.4[a] (0.2–427)[b]		50[a] (0.8–381.7)[b]		
Duration of follow-up after biopsy	31.4[a] (0–60.7)[b]		24.6[a] (0.3–36.9)[b]		
Histological diagnosis	n	%	n	%	p-Values
Antibody-mediated rejection	37	14%	28	47%	4.66E-07
Probable ABMR	9	4%	2	3%	0.26
Mixed rejection	7	3%	6	10%	0.002
T-cell–mediated rejection	17	7%	1	2%	0.13
Borderline	27	10%	1	2%	0.03
Polyoma virus nephropathy	5	2%	1	2%	0.88
Glomerular diseases	26[c]	10%	12[d]	20%	0.15
No major abnormalities	92	36%	3	5%	2.04E-06
Atrophy-fibrosis	23	9%	3	5%	0.25
Other	12	5%	3	5%	0.92
Total	255	100%	60	100%	
Patients with donor-specific antibody at time or after the biopsy	66	26%	38	63%	2.85E-08
Patients with recorded non-adherence	7	3%	19	32%	0.0001

[a]Median and [b]range shown in months.
[c]Ig A nephropathy n = 8; Diabetic nephropathy n = 4; Membrano-proliferative glomerulonephritis (GN) n = 4; Focal and segmental glomerulosclerosis n = 2; Membranous nephropathy n = 1; Immuno-complex GN n = 3; Focal proliferative GN n = 2; Mesangial GN of unknown etiology n = 1; Chronic advanced GN with double contours n = 1.
[d]Membrano-proliferative GN n = 3; Focal and segmental glomerulosclerosis n = 4; Fibrillary GN n = 1; Immune complex GN n = 1; Crescentic GN n = 1; Focal proliferative GN n = 1; Severe parenchymal atrophy and fibrosis with one crescent in one glomerulus n = 1.
ABMR = antibody-mediated rejection.

腎移植と抗HLA抗体　一般事項

既存抗体まだなんとかなる

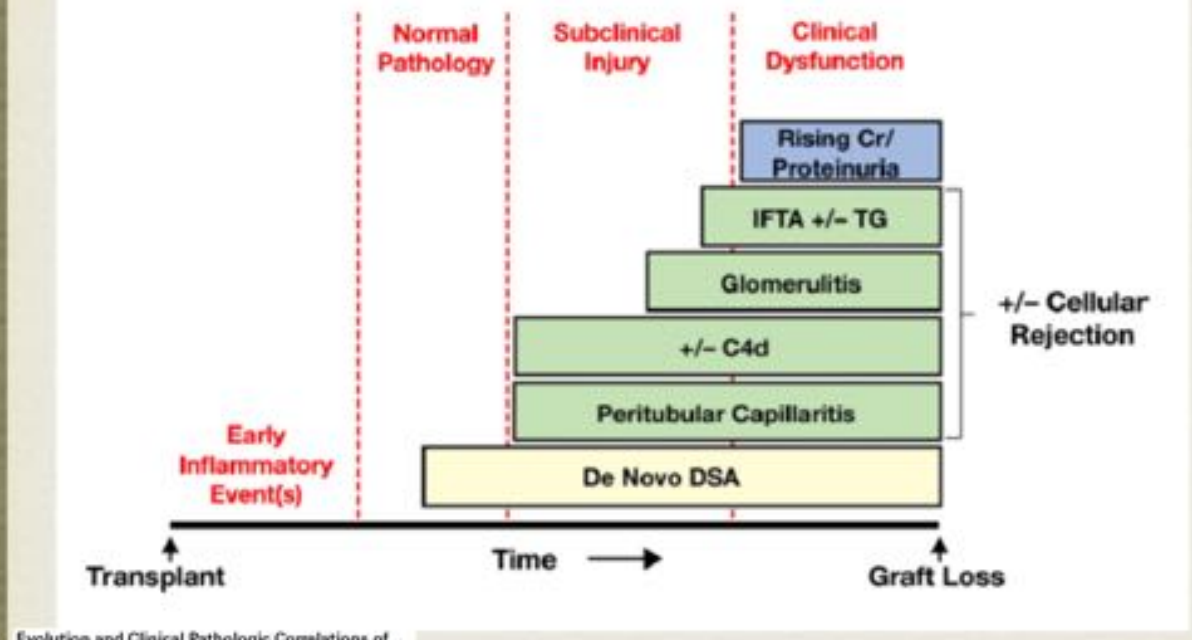


Evolution and Clinical Pathologic Correlations of *De Novo* Donor-Specific HLA Antibody Post Kidney Transplant

C. Wiebe[a,†], I. W. Gibson[b,c,†], T. D. Blydt-Hansen[d], M. Karpinski[a], J. Ho[a], L. J. Storsley[a], A. Goldberg[d], P. E. Birk[d], D. N. Rush[a] and P. W. Nickerson[a,c,*]　*American Journal of Transplantation 2012; 12: 1157–1167*

腎移植と抗HLA抗体　一般事項

Natural history of type2 ABMR



Evolution and Clinical Pathologic Correlations of *De Novo* Donor-Specific HLA Antibody Post Kidney Transplant

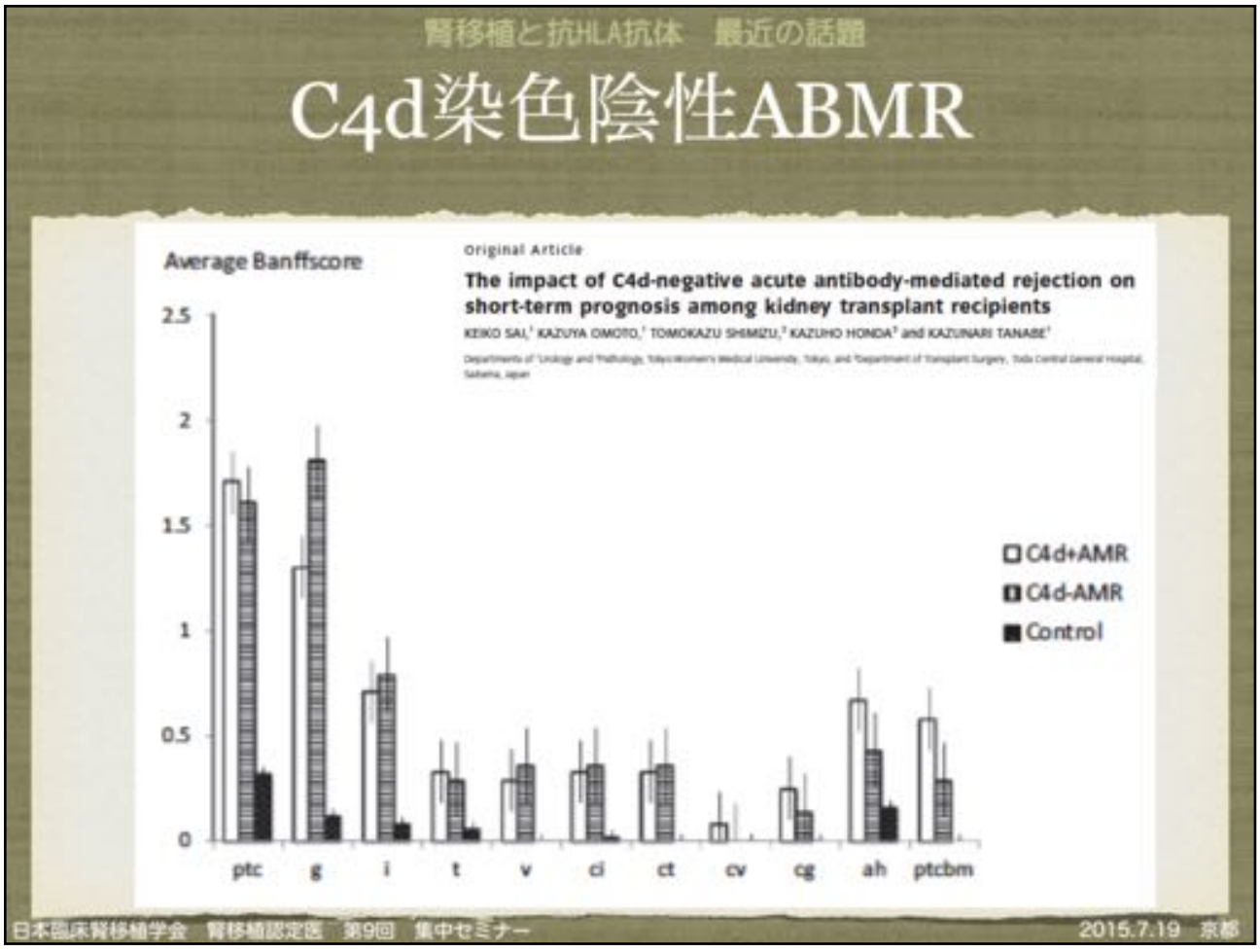
American Journal of Transplantation 2012; 12: 1157–1167

腎移植と抗HLA抗体　一般事項

既存抗体陽性の腎移植の意義

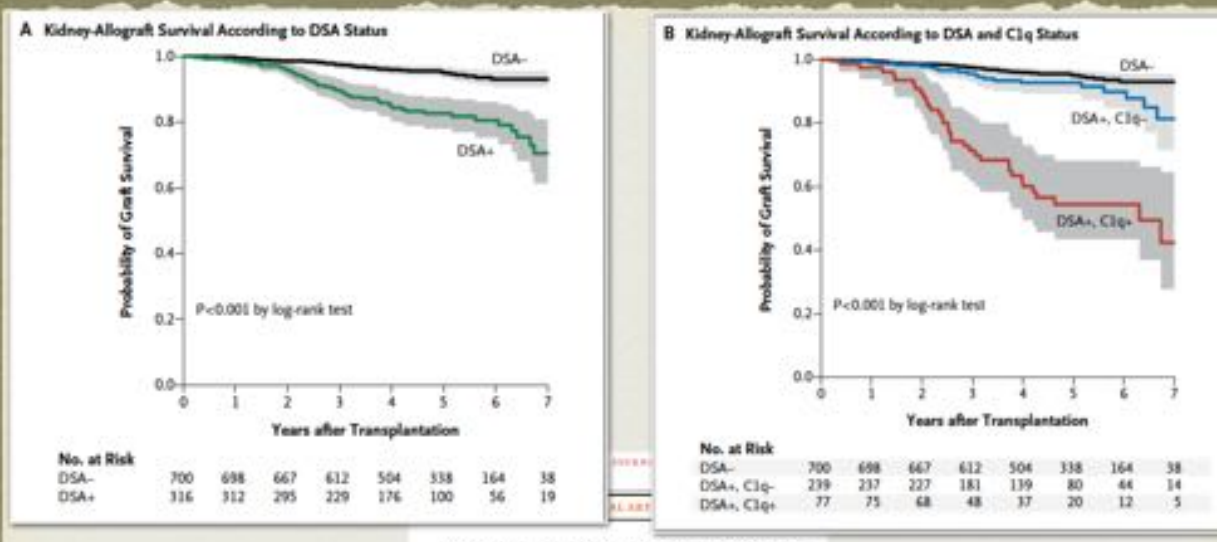
- CAABMRのリスクはあるも透析療法より
  格段によい予後、QoL
- 十分なDSAの把握により適応の決定が可能
- 理想の脱感作にてHARは避けることができる


腎移植と抗HLA抗体　最近の話題


腎移植と抗HLA抗体　最近の話題
C4d染色陰性ABMR
Average Banffscore
2.5
2
1.5
1
0.5
0
ptc
g
i
t
v
ci
ct
cv
cg
ah
ptcbm
C4d+AMR
C4d-AMR
Control
Original Article
The impact of C4d-negative acute antibody-mediated rejection on short-term prognosis among kidney transplant recipients
KEIKO SAI,[1] KAZUYA OMOTO,[1] TOMOKAZU SHIMIZU,[2] KAZUHO HONDA[2] and KAZUNARI TANABE[1]
日本臨床腎移植学会　腎移植認定医　第9回　集中セミナー
2015.7.19　京都

腎移植と抗HLA抗体　最近の話題

C1q 結合性

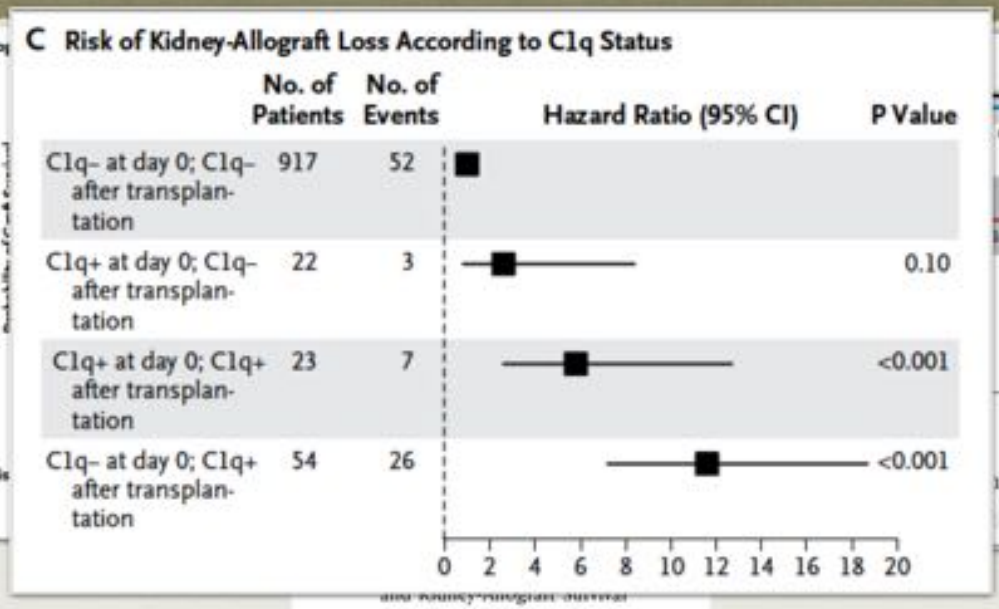


Complement-Binding Anti-HLA Antibodies and Kidney-Allograft Survival

Alexandre Loupy, M.D., Ph.D., Carmen Lefaucheur, M.D., Ph.D., Dear Vernerey, M.P.H., Christof Prugger, M.D., Jean-Paul Duong van Huyen, M.D., Ph.D., Nyala Mooney, Ph.D., Caroline Suberbielle, M.D., Ph.D., Véronique Frémeaux-Bacchi, M.D., Ph.D., Arnaud Méjean, M.D., François Desgrandchamps, M.D., Dany Anglicheau, M.D., Ph.D., Dominique Nochy, M.D., Dominique Charron, M.D., Ph.D., Jean-Philippe Empana, M.D., Ph.D., Michel Delahousse, M.D., Christophe Legendre, M.D., Denis Glotz, M.D., Ph.D., Gary S. Hill, M.D., * Adriana Zeevi, Ph.D., and Xavier Jouven, M.D., Ph.D.

腎移植と抗HLA抗体　最近の話題

C1q 結合性



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腎移植と抗HLA抗体　最近の問題

Ig subclass

subclass pattern	„biological" group	N
1	strong C-activating	32
1+3	strong C-activating	14
3	strong C-activating	2
2	weak/no C-activating	6
2+4	weak/no C-activating	2
4	weak/no C-activating	1
1+2	mixture	21
1+2+3	mixture	19
1+2+3+4	mixture	14
1+4	mixture	6
1+2+4	mixture	6
3+3	mixture	2
2+3+4	mixture	-
1+3+4	mixture	-
3+4	mixture	-
no IgG1-4	all negative	17

strong C-activating (n=48; 34%)

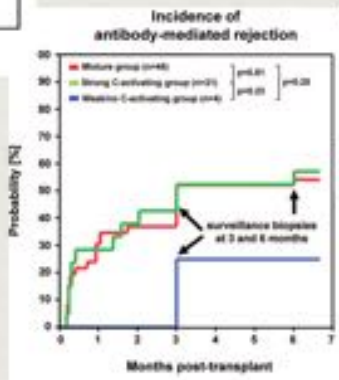
weak/no C-activating (n=9; 6%)

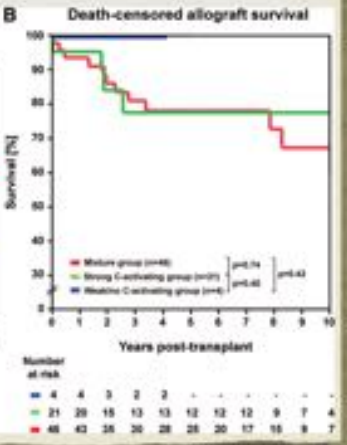
mixture (n=67; 48%)

all negative (n=17; 12%)

Pretransplant IgG Subclasses of Donor-Specific Human Leukocyte Antigen Antibodies and Development of Antibody-Mediated Rejection

Transplantation - Volume 92, Number 1, July 15, 2011





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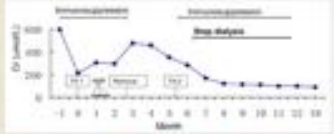
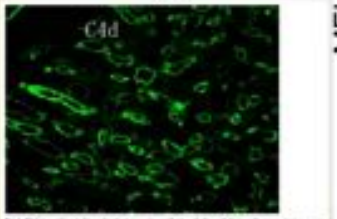
腎移植と抗HLA抗体　最近の話題

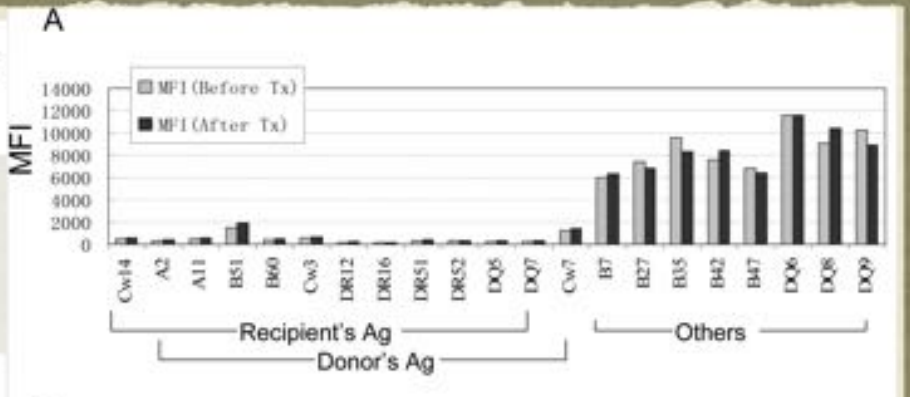
MICA Ab

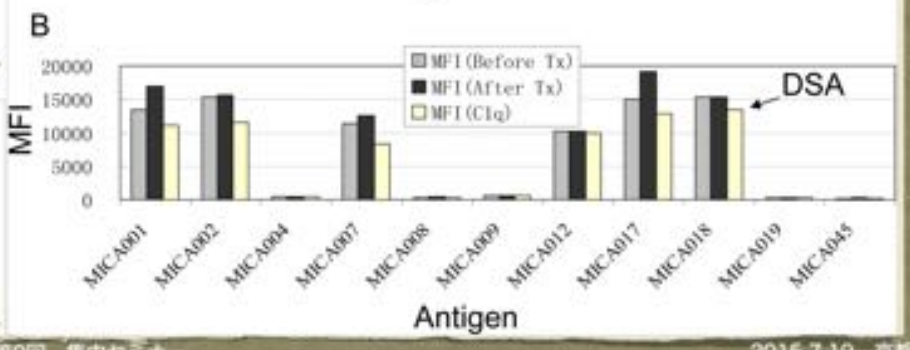
Acute Antibody-Mediated Rejection in Presence of MICA-DSA and Successful Renal Re-Transplant with Negative-MICA Virtual Crossmatch

PLOS ONE









日本臨床腎移植学会　腎移植認定医　第9回　集中セミナー　2015.7.19　京都

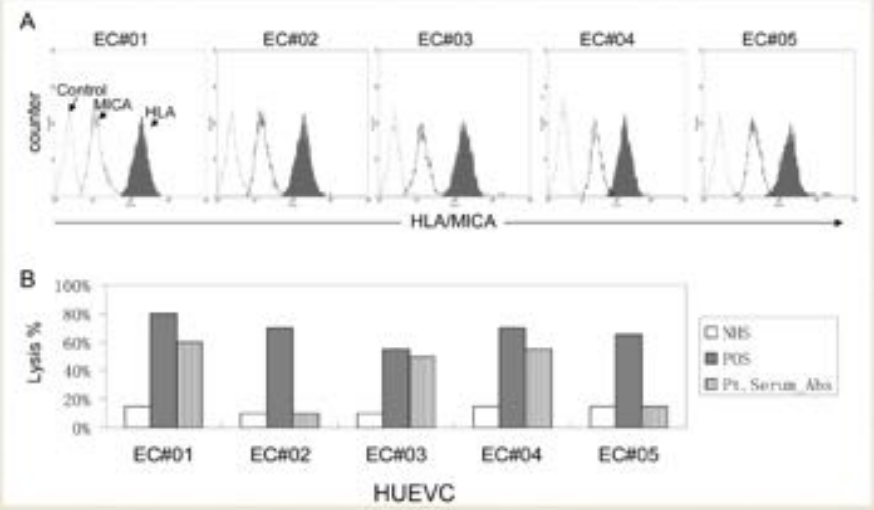
腎移植と抗HLA抗体　最近の話題

MICA Ab

Table 1. HLA/MICA typing results.

Subject	ABO	HLA-A	HLA-B	Bw	HLA-C	DRB1	DRB3/4/5	DQB1	MICA
Patient	A	A2, A1101	B51, B60	Bw4, Bw6	Cw3, C*14:02	DR12, DR16	DR52, DR51	DQ5, DQ7	*008, *009
Donor 1	A	A2, A1101	B51, B60	Bw4, Bw6	Cw3, Cw7	DR12, DR16	DR52, DR51	DQ5, DQ7	*008, *018
Donor 2	A	A2, A1101	B52, B13	Bw4	Cw3, C*12:02	DR4, DR16	DR53, DR51	DQ5, DQ4	*004, *008

doi:10.1371/journal.pone.0127961.t001

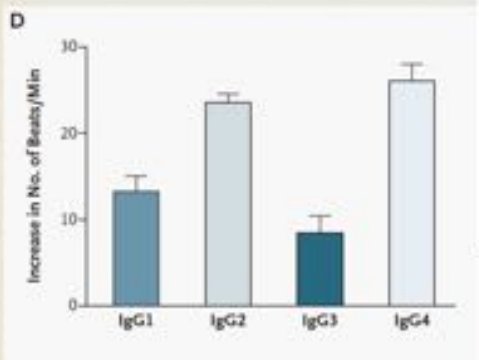


腎移植と抗HLA抗体　最近の話題

anti-ATII type1R activating Ab


ORIGINAL ARTICLE

Angiotensin II Type 1–Receptor Activating Antibodies in Renal-Allograft Rejection



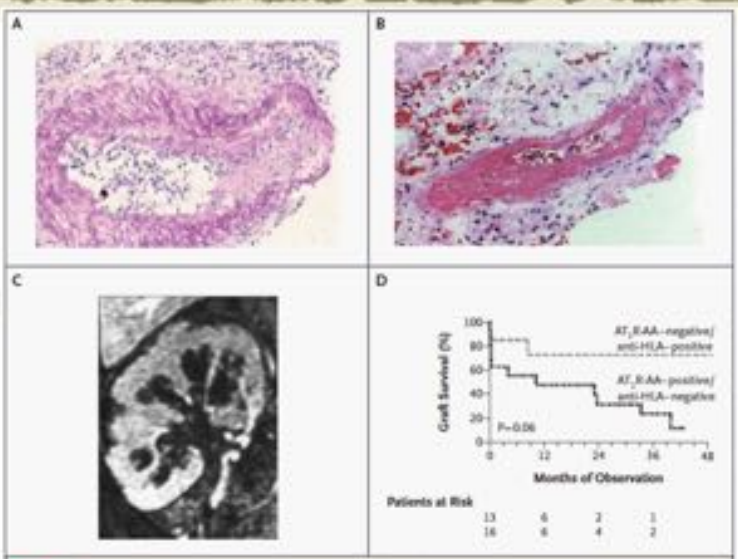


Figure 1. Features of Refractory Rejection in Patients without Donor-Specific Anti-HLA Antibodies.

Biopsy specimens from representative patients (stained with hematoxylin and eosin) show endarteritis (Panel A) and fibrinoid changes and necrosis in the wall of the interlobular artery, with a mural thrombus consistent with acute vascular rejection (Panel B). A magnetic resonance image of the kidney (Panel C) shows multiple perfusion defects consistent with the occurrence of cortical infarctions. The graph in Panel D demonstrates accelerated allograft loss in patients who had refractory vascular rejection with non-HLA antibodies, compared with patients who had vascular rejection and donor-specific anti-HLA antibodies. AT_1R-AA denotes AT_1-receptor antibodies.

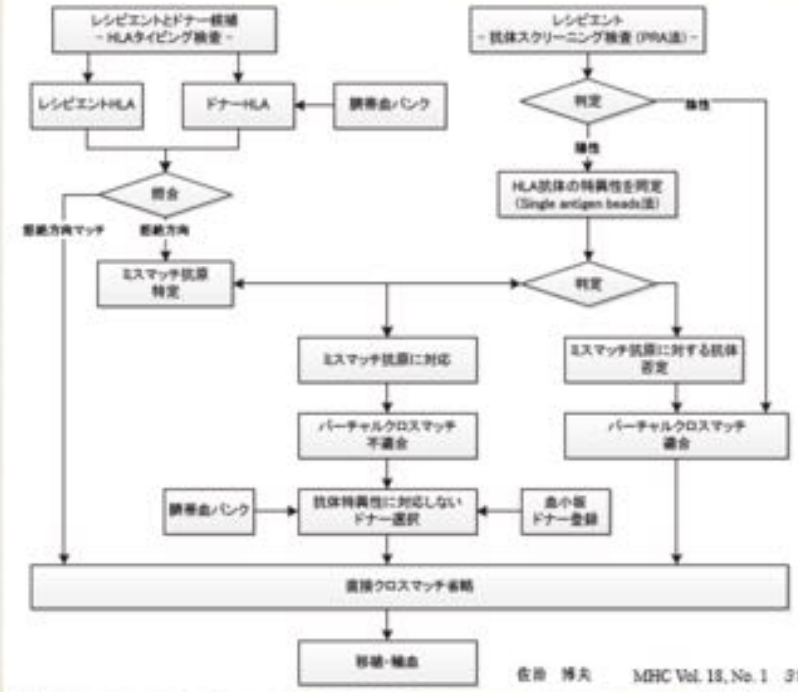
腎移植と抗HLA抗体　最近の話題

Virtual Xm

古典的Xm
→ドナーcell 必要

迅速に大量にできる
方法が望ましい

Solid phase assay
によるXm



腎移植と抗HLA抗体　最近の話題

HLAと連鎖

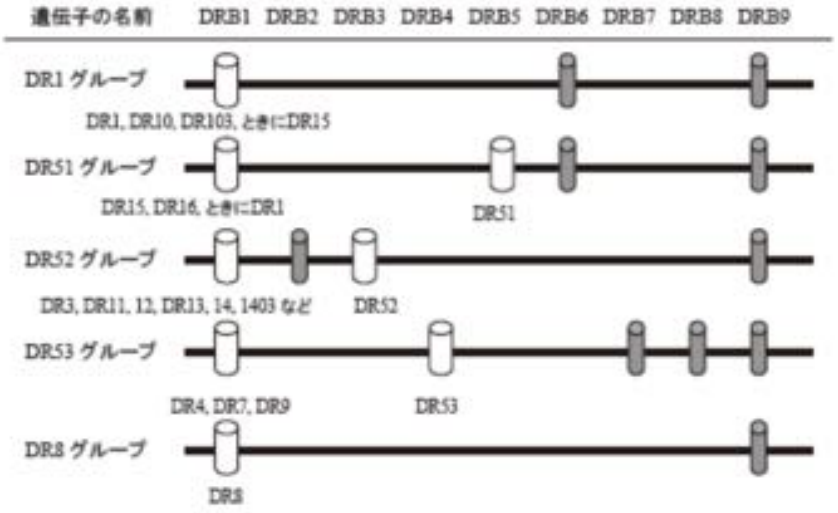
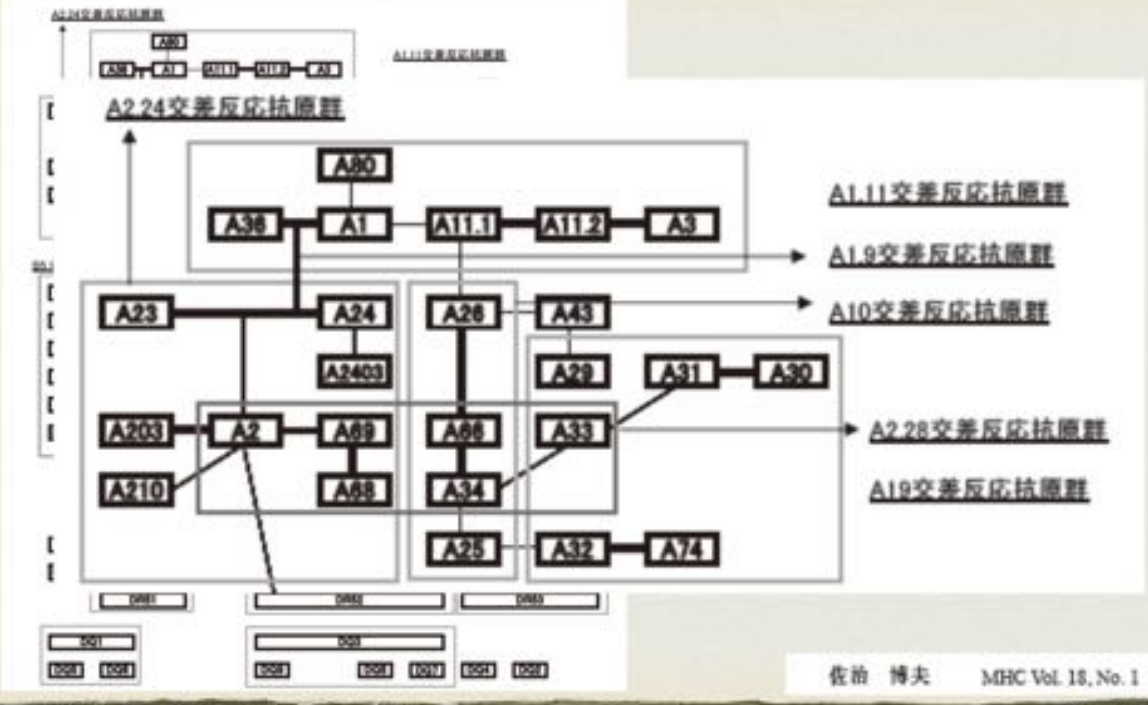


図1　HLA-DRB 領域の構造
DR1 グループや DR8 グループは発現遺伝子として DRB1 のみをもつが，DR51, 52, 53, グループは発現遺伝子として，それぞれ DRB5, DRB3, DRB4 をもっている。偽遺伝子の種類と数もグループによって異なっている。　発現遺伝子　偽遺伝子

佐治　博夫　MHC Vol. 18, No. 1 31

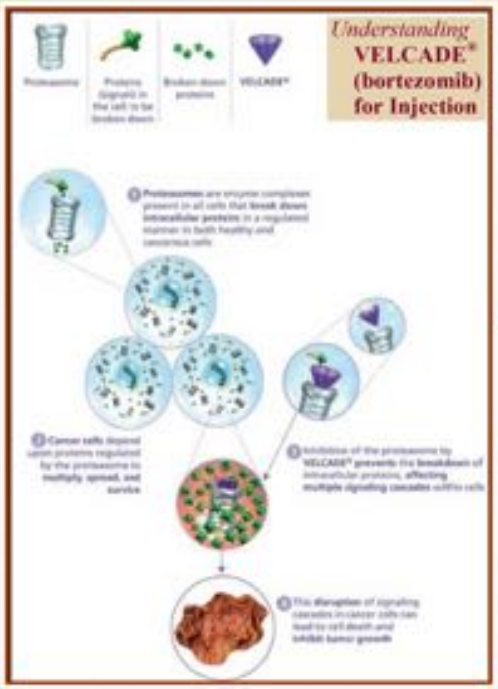
腎移植と抗HLA抗体　最近の問題

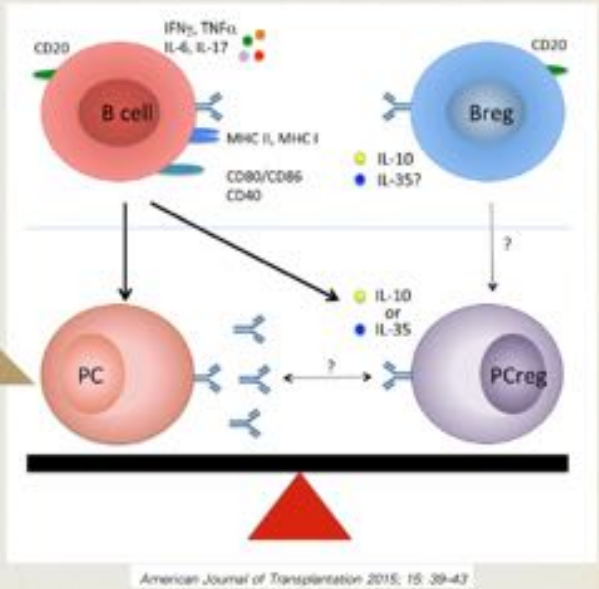
CREG



腎移植と抗HLA抗体　最近の話題

Bortezomib





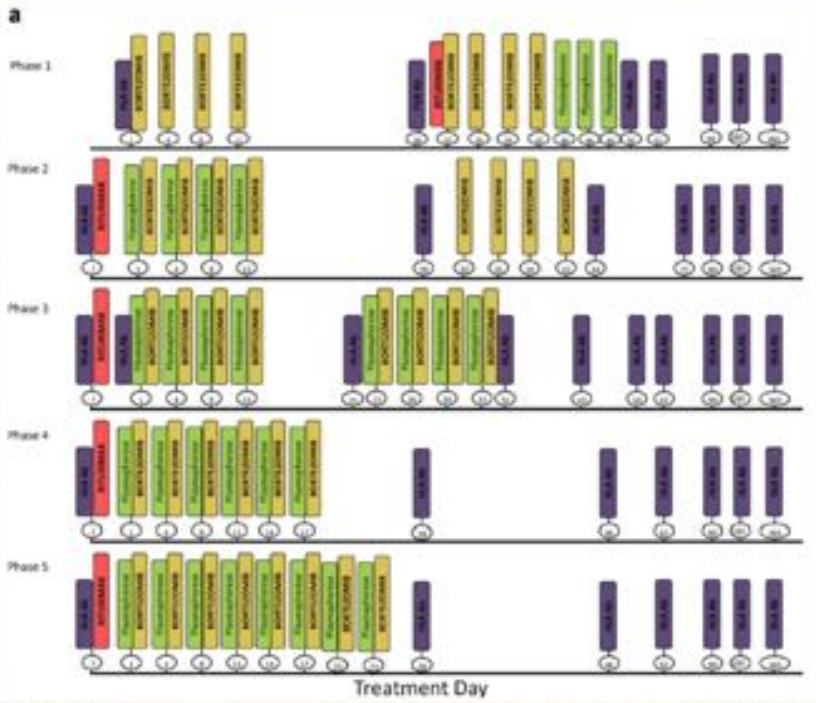
腎移植と抗HLA抗体　最近の話題

Bortezomib

Prospective Iterative Trial of Proteasome Inhibitor-Based Desensitization

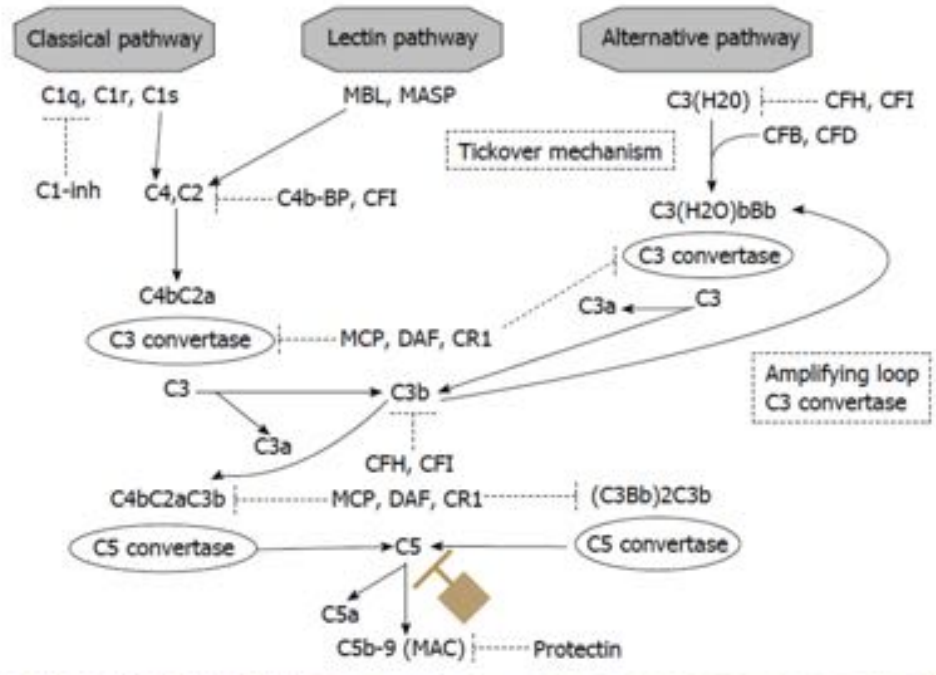
E. S. Woodle[1,*], A. R. Shields[1,†], N. S. Ejaz[1], B. Sadaka[1], A. Girnita[2], R. C. Walsh[1], R. R. Alloway[3], P. Bailey[2], M. A. Cardi[2], S. G. Abu Jawdeh[3], P. Roy-Chaudhury[3], A. Govil[4] and G. Mogilishetty[4]

American Journal of Transplantation 2015; 15: 101–118



腎移植と抗HLA抗体　最近の話題

Eculizumab



腎移植と抗HLA抗体　最近の話題

Eculizumab

Monoclonal antibody	
Type	Whole antibody
Source	Humanized (from mouse)
Target	Complement protein C5

aHUS Adult (≥18 years of age) Dosing Schedule[1]

Pretreatment		Induction Phase				Maintenance Phase					
≥2 weeks before induction	Week	1	2	3	4	5	6	7	8	9+	q14d
Neisseria meningitidis vaccination	Soliris dose	900 mg	900 mg	900 mg	900 mg	1200 mg	—	1200 mg	—	1200 mg	

腎移植と抗HLA抗体　最近の話題

Eculizumab

American Journal of Transplantation 2015; 15: 1293–1302
Wiley Periodicals Inc.

doi: 10.1111/ajt.13168

Positive Crossmatch Kidney Transplant Recipients Treated With Eculizumab: Outcomes Beyond 1 Year

L. D. Cornell[1], C. A. Schinstock[2], M. J. Gandhi[3], W. K. Kremers[2] and M. D. Stegall[2,*]

Introduction

Renal transplant candidates with high levels of antibody

Acute AMRは減少したが、Function, Survival, Chronic changeには差はなし

Limitation

1. 中止後の変化の可能性
2. 最終産物C5b9 MACの阻害ができていない
3. FBXmが一定レベルになるまで加療されていない
4. すべてのDSAが一定の意義を持つわけでない（強度、C-結合度、IgGサブクラス

腎移植と抗HLA抗体　最近の話題

Eculizumab

Report of the Inefficacy of Eculizumab in Two Cases of Severe Antibody-Mediated Rejection of Renal Grafts

Maren Burbach,[1] Caroline Suberbielle,[2] Isabelle Brochériou,[3,4] Christophe Ridel,[1] Laurent Mesnard,[1,4] Karine Dahan,[5] Eric Rondeau,[1,4] and Alexandre Hertig[1,4,6]

Background. Acute antibody-mediated rejection (AMR) is responsible for up to 20% to 30% of acute rejection after kidney transplantation. New therapeutic agents have recently emerged, such as eculizumab, an anticomplement protein-C5 monoclonal antibody. In the setting of renal transplantation, eculizumab has so far proved effective both for preventive and curative treatments of AMR in sensitized patients and patients diagnosed with severe AMR. Unsuccessful eculizumab treatment has only been reported once in the literature by Stegall et al. (*Am J Transplant* 2011; 11: 2405).
Methods and Results. We present two cases of AMR resistant to eculizumab after renal transplantation. One patient received the anti-C5 antibody curatively, and the other patient developed AMR while being treated with eculizumab after a relapse of atypical hemolytic uremic syndrome. The peculiarity of these two cases was the absence of C4d deposition in peritubular capillaries as well as the absence of C1q-binding donor-specific anti–human leukocyte antigen alloantibody, as determined retrospectively, suggesting that a complement-independent mechanism underlies the pathogenesis of these AMR.
Conclusion. The use of eculizumab in C4d-negative or C1q-negative AMR does not seem effective.

Keywords: Antibody-mediated rejection, Eculizumab, Complement, Kidney transplantation.

(*Transplantation* 2014;98: 1056–1059)

腎移植と抗HLA抗体　最近の話題

MVI in Early PBx of CABMR

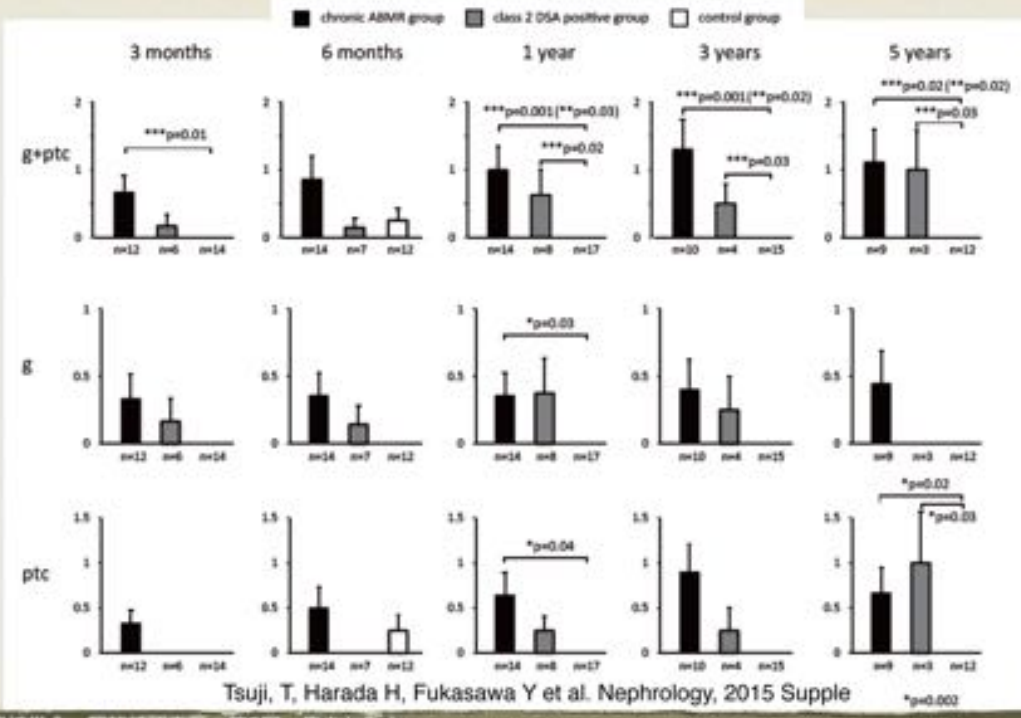
	chronic ABMR group (n = 17)	class 2 DSA positive group (n = 12)	control group (n = 30)	p-value
Recipient age (years, mean±SD)	39.9±14.9	46.8±14.0	40.2±13.8	NS
Recipient sex (male/female)	9/8	6/6	18/12	NS
Donor age (years, mean±SD)	52.7±5.9	56.7±10.3	52.4±11.2	NS
ABO compatible transplantation	17	12	30	NS
Retransplantation	3	1	0	0.047
DSA positive	17†	12	0	<0.001
Anti-class 1 only	1	0	0	NS
Anti-class 2 only	11	8	0	<0.001
Both anti-class 1 and 2	4	4	0	0.002
Preformed/De novo	5/12	6/6		
Histological diagnosis of chronic ABMR	17	0	0	<0.001
Time of histological diagnosis of chronic ABMR (month, mean ± SD (minimum-maximum))	61.2±43.2 (12.0-168.0)			
History of acute ABMR	3	2	0	0.027
Actual time of protocol biopsy (month, mean±SD)				
3 months	3.4±0.5	3.2±0.9	3.2±0.4	NS
6 months	6.7±1.2	6.8±0.9	6.6±0.8	NS
1 year	12.9±1.0	13.3±2.3	12.4±1.6	NS
3 years	37.5±2.2	37.0±1.2	37.4±2.2	NS
5 years	62.6±3.0	61.0±1.6	61.6±2.1	NS
Follow up (month, mean±SD)	96.0±45.6	73.5±57.8	90.0±59.5	NS
Most recent serum creatinine (mg/dL, mean±SD)	1.8±1.4	2.0±1.6	1.2±0.4	0.043
Most recent proteinuria (g/g-Cr, mean±SD)	1.1±1.3	0.9±1.7	0.4±0.6	0.009
Graft loss	2	1‡	0	NS
Patient death	0	2	1	NS

ABMR, antibody mediated rejection; DSA, donor specific antibody
† Including an unknown-DSA positive case
‡ Due to recurrence of focal segmental glomerulosclerosis

Tsuji, T, Harada H, Fukasawa Y et al. Nephrology, 2015 Supple

腎移植と抗HLA抗体　最近の話題

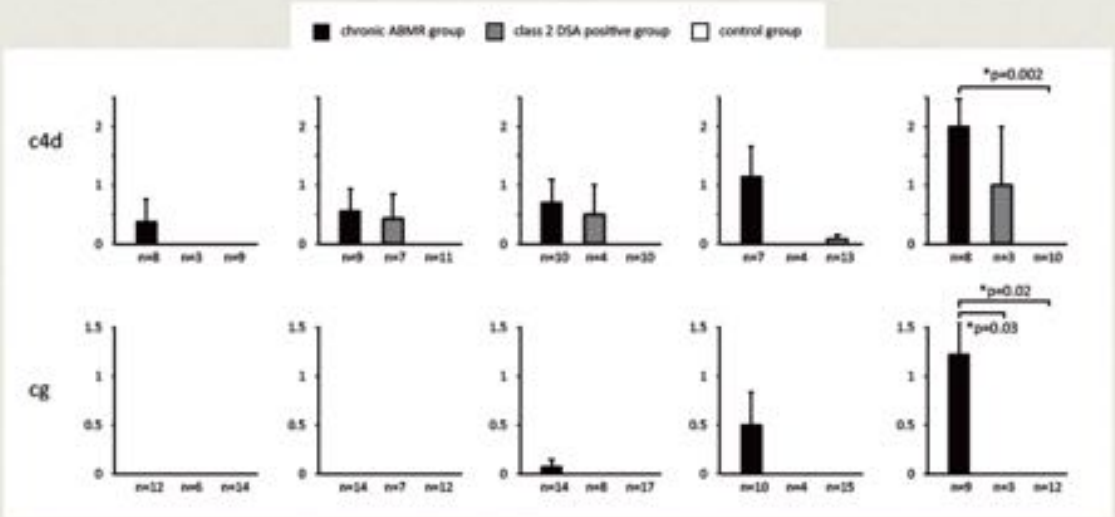
MVI in Early PBx of CABMR



Tsuji, T, Harada H, Fukasawa Y et al. Nephrology, 2015 Supple

腎移植と抗HLA抗体　最近の話題

MVI in Early PBx of CABMR



Tsuji, T, Harada H, Fukasawa Y et al. Nephrology, 2015 Supple

日本臨床腎移植学会　腎移植認定医　第9回　集中セミナー

腎移植と抗HLA抗体　最近の話題

CAABMR, treatments

Rituximab

Bortezomib

Eculizumab

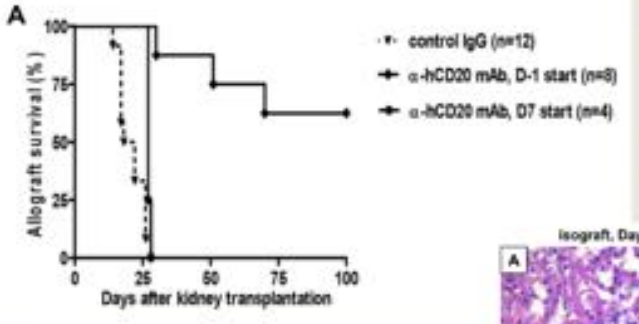
Splenectomy

Deoxyspergualin

PP

腎移植と抗HLA抗体　最近の話題

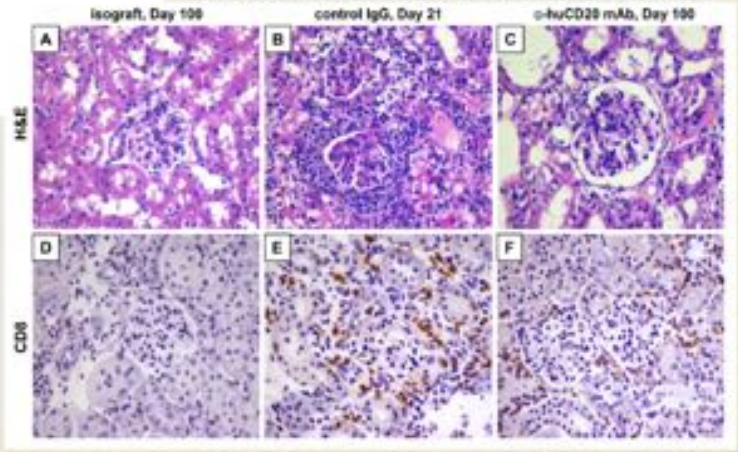
RituximabのBest timingは？



Anti-huCD20 Antibody Therapy for Antibody-Mediated Rejection of Renal Allografts in a Mouse Model

T. Abe[1,2,3,†], D. Ishii[1,2,4,†], V. Gorbacheva[2], N. Kohei[1,2], H. Tsuda[1,2], T. Tanaka[1,2], N. Dvorina[2], N. Nonomura[3], S. Takahara[5], A. Valujskikh[1,2], W. M. Baldwin III[1,2,6] and R. L. Fairchild[1,2,6,*]

American Journal of Transplantation 2015; 15: 1192–1204



腎移植と抗HLA抗体　最近の話題

Table 3: Summary of controlled trials from a systematic review assessing treatment strategies for ABMR[1]

Refs.	ABMR definition	Trial design and intervention (N)	Patients with hemodialysis dependency or graft loss (intervention vs. control
Böhmig et al (123)	Banff 1997	Stratified RCT; 9–14 sessions of immunoadsorption (protein A)	Treatment benefit observed: 0 vs. 4 at 3 weeks ARR = 0.8 (95% CI, 0.2–0.9)
Blake et al (124)	Vascular	Stratified RCT; 5 PP treatments	No treatment benefit: 4 vs. 6 at 6 months; RRR = 0.3 (95% CI, 0.001–0.9) 10 vs. 13 at 5 years; RRR = 0.2 (95% CI, 0.001–0.5)
Bonomini et al (125)	Vascular, MP-resistant	RCT; 3–7 PP treatments	Treatment benefit observed: 7 vs. 17 at 2 weeks; RRR = 0.6 (95% CI, 0.3–0.8)
Krubekaran et al (126)	Vascular	RCT; 8 PP treatments	Trend to harm: 6 vs. 3 at 1 month; RRI = 0.5 (95% CI, 0.001–0.9)
Allen et al (127)	Vascular, MP-resistant	RCT; 6 PP treatments	No treatment benefit (trend to harm at 220 days): 3 vs. 4 at 6 days; RRR = 0.2 (95% CI, 0.001–0.8) 11 vs. 9 at 220 days; RRI = 0.2 (95% CI, 0.001–0.5)
Franco et al (128)	Vascular, MP-resistant	Historical control; 6 PP treatments	Treatment benefit observed: 6 vs. 13 at 3 months; OR = 0.4 (95% CI, 0.1–1.3)
Lefaucheur et al (129)	Banff 1997	Historical control; 4 PP treatments; 2 rituximab doses	Treatment benefit observed: 1 vs. 6 at 3 years; OR = 0.1 (95% CI, 0.008–0.9)
Kapozstas et al (130)	ALG-resistant	Historical control; rituximab	Treatment benefit observed: 2 vs. 8 at 2 years; OR = 0.2 (95% CI, 0.04–1.09)
Vangelista et al (131)	Vascular, anti-HLA	Nonrandomized case-controlled; 4–6 PP treatments	Treatment benefit observed: 1 vs. 3
Macaluso et al (132)	ABMR (no other details)	Nonrandomized, case-controlled; 4 doses of bortezomib, 1 dose of rituximab, 5 PP treatments	Treatment benefit observed: 1 vs. 10 at 3 months; OR = 0.1 (95% CI, 0.01–0.9)
Loupy et al (45)	Vascular with DSA	Nonrandomized, case-controlled; OKT3 vs. IVIG vs. PP and rituximab	Treatment benefit observed for PP and rituximab: HR = 0.19 (vs. OKT3) HR = 0.11 (vs. IVIG)
Lubetsky (133)	With DSA	Nonrandomized, case-controlled; rituximab vs. bortezomib	Treatment benefit observed for bortezomib: 3 vs. 1 at 6 months; OR = 5.3 (95% CI, 0.5–59.3)
Walser et al (134)	With DSA	Historical cohort; 4 bortezomib doses vs. 1 rituximab dose, 6 PP treatments and 30 g IVIG	No treatment benefit: 2 vs. 3 (at 6 months); OR = 0.5 (95% CI, 0.06–4.0)

ABMR, antibody-mediated rejection; ALG, antilymphocyte globulin; ARR, absolute risk reduction; CI, confidence interval; DSA, donor-specific antibodies; HR, hazard ratio; IVIG, intravenous immunoglobulin; MP, methylprednisolone; OR, odds ratio; PP, plasmapheresis; RCT, randomized controlled trial; RRI, relative risk increase; RRR, relative risk reduction; RRI, relative risk increase.

[1]Adapted with permission from Roberts et al (122).

Diagnosis and Management of Antibody-Mediated Rejection: Current Status and Novel Approaches

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American Journal of Transplantation 2014; 14: 255–271

日本臨床腎移植学会　腎移植認定医　第9回　集中セミナー

当科における既存抗体陽性例への対応

腎移植と抗HLA抗体　既存抗体症例への対応

かつての症例(-1995)

Demographics-Past Cases

ID	Age	Sex	TF (Unit)	Imx	Initial (FlowTC Xm ΔMI%)	PreTx	PE	AR	Anti-Rej	Prognosis (Period, sCr)
LD-29	27	M	10	C,M,P	++	ND	ND	D4 (Vas AR)	D	9D, Gx
LD-33	37	F	15	C,M,P,D,L	++	+	3	D11, 36	D	175M, 2.5
LD-35	21	M	9	C,M,P,D	++	-	4	D14 (Acc AR)	MP,L,O,PE	171M, 1.4
LD-39	41	M	4	C,A,P,L	+	+	1	D11	MP,D	62M, HD
LD-54	39	F	5	C,A,P,L	+	ND	ND	D7	MP,D	57M, HD
LD-58	32	M	12	C,A,P,L	+	ND	ND	D7	MP,D	143M, 1.8
LD-59	38	F	>100	C,A,P,L	+	-	3	D50	ATG	141M, 1.8

TF; transfusion, Imx; immunosuppression, C; cyclosporine, M; mizoribine, A; azathioprine, P; prednine, D; deoxy-spergualin, L; anti-lymphocyte globulin, O;OKT3, T; tacrolimus, MF; mycophenolate mofetil, B; basiliximab,Gx; graftectomy, PE; plasma exchange, AR; acute rejection, Gx; graftectomy, HD; hemodialysis

腎移植と抗HLA抗体　既存抗体症例への対応

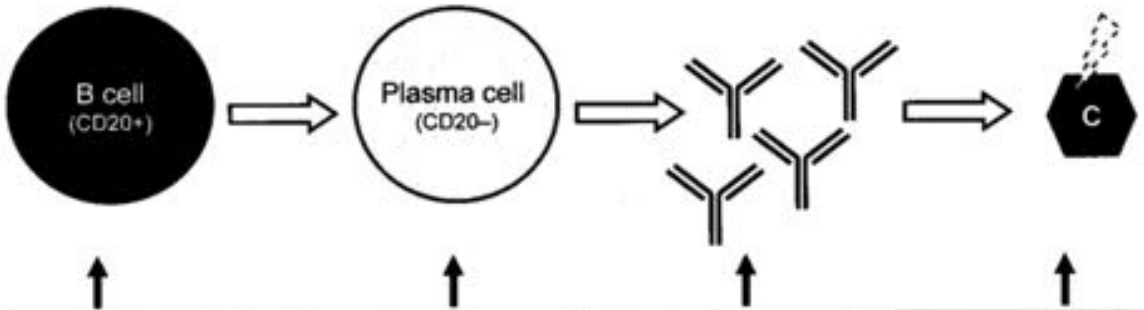
ABMRの制御

B cells
- Plasma cell precursor
- Antigen presentation

Plasma cells
- Antibody formation

Antibodies
- Complement activation
- Immune complexes

Complement
- Target tissue destruction
- Chemotaxis



B cell depletion	Plasma cell depletion	Antibody removal	Complement inhibition
•Rituximab (anti-CD20)	•Bortezomib	•Immunoadsorption •Plasmapheresis*	•Anti-C5 (eculizumab) •Anti-C1

Pleiotropic effects　Intravenous immunoglobulins

Fehr T, Gaspert A: Antibody-mediated kidney allograft rejection: therapeutic options and their experimental rationale. Transplant Int 623, 2012

腎移植と抗HLA抗体　既存抗体症例への対応

ABMRの制御

Table 1. Step-wise treatment approach to the patient with acute AMR.

STEP 1	**Acute allograft dysfunction**	
	Allograft biopsy: acute AMR ± TMR	
	Treatment of AMR component	Treatment of TMR component
	Steroid pulses	Steroid pulses
	Antibody removal (plasma exchange or immunoadsorption)	Switch to tacrolimus/mycophenolate mofetil
	IVIG	
STEP 2	**Persistent allograft dysfunction**	
	Allograft biopsy: persistent/progressive acute AMR ± TMR	
	Treatment of AMR component	Treatment of TMR component
	Bortezomib	ATG
	Rituximab	
STEP 3	**Persistent allograft dysfunction**	
	Allograft biopsy: persistent/progressive acute AMR ± TMR	
	Treatment of AMR component	Treatment of TMR component
	Eculizumab	Anti-CD3 monoclonal antibody (OKT3)
	Rescue splenectomy	

AMR, antibody-mediated rejection; TMR, T cell-mediated rejection; ATG, anti-thymocyte globulin.

Fehr T, Gaspert A: Antibody-mediated kidney allograft rejection: therapeutic options and their experimental rationale. Transplant Int 623, 2012

腎移植と抗HLA抗体　既存抗体症例への対応

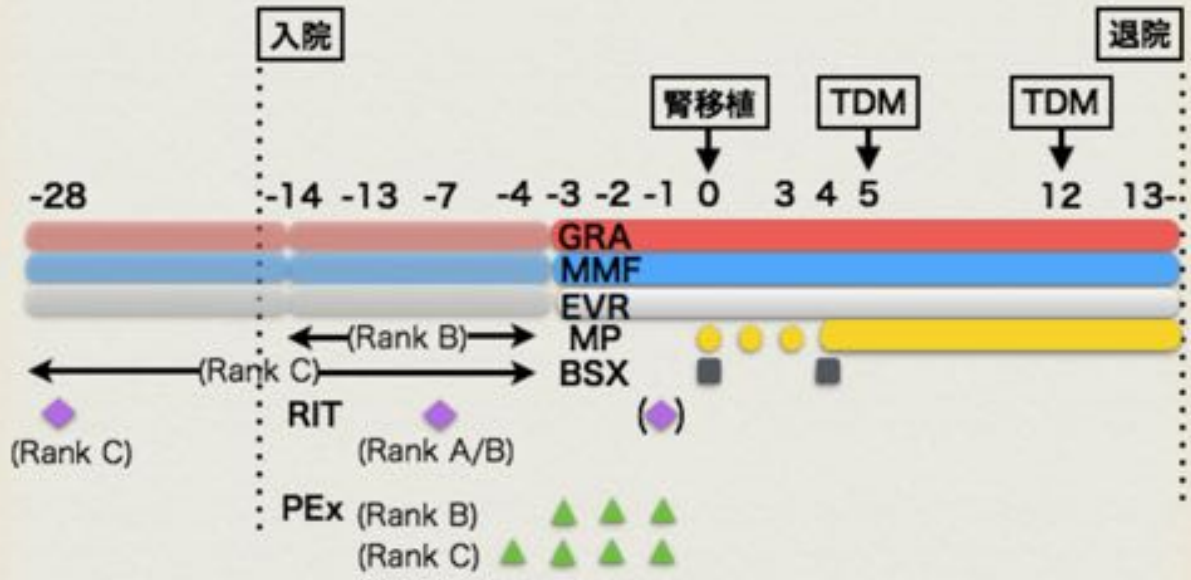
DSA強度と脱感作強度

ランク	FTXM/FlowPRA			IS経口	PP	rituximab
	FTXM	FlowPRA		GRA 0.1mg/kg MMF 25mg/kg EVR 1.5mg/body	-4: DFPP -3: PEX -2: DFPP -1: PEX	初回200mg ＊追加100mg (＊CD19が0.2%以上)
		screening	single			
A	-	-	+	-3	0	-7, (-1)
B	-	+	+	-14	3	-7, (-1)
C	+	+	+	-28	4	-28, (-1)

- MP: day0~パルス3日間、その後40mgから漸減
- basiliximab: 20mg/body (day0, 4)
- 入院時のFlowPRAのstatus変化でプロトコール見直し

腎移植と抗HLA抗体　既存抗体症例への対応

DSA陽性移植Protocol



日本臨床腎移植学会　腎移植認定医　第9回　集中セミナー

腎移植と抗HLA抗体　既存抗体症例への対応

既存DSA陽性腎移植の検討

当科における

既存抗ドナー抗体HLA抗体陽性腎移植

既存DSA-KTx

の短期成績、予後につき検討

腎移植と抗HLA抗体　既存抗体症例への対応

既存DSA陽性腎移植の検討

既存DSA-KTx: 25（生体20、献腎5）

Inclusion	Exclusion
・2003年以降に腎移植 ・1年の経過観察が可能	・ CDC positive

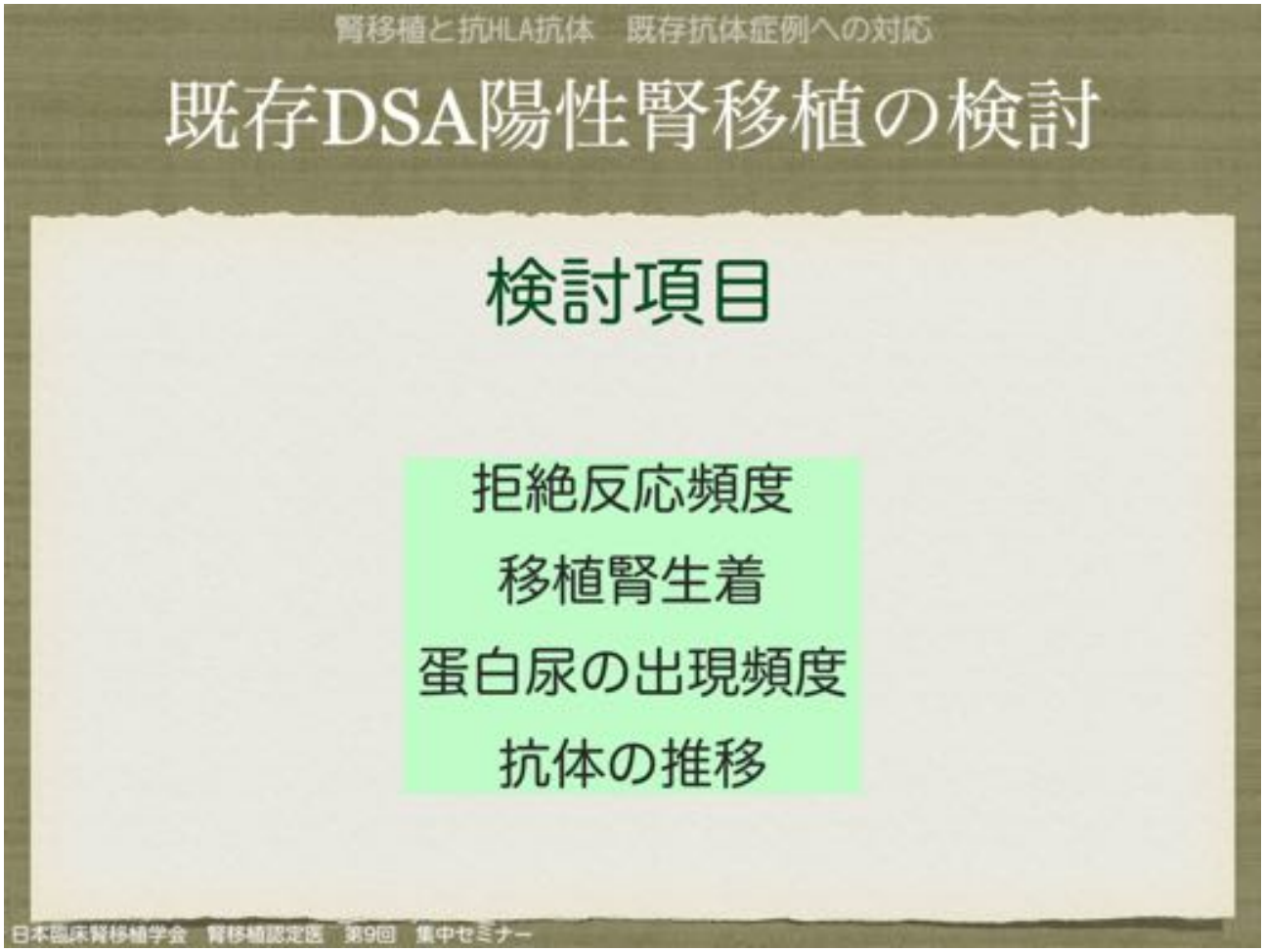
腎移植と抗HLA抗体　既存抗体症例への対応

既存DSA陽性腎移植の検討

DSAの検出

既存DSAの検出

CDCXm, FTXm, FlowPRA-SCT, FlowPRA-SBA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拒絶反応頻度
移植腎生着
蛋白尿の出現頻度
抗体の推移
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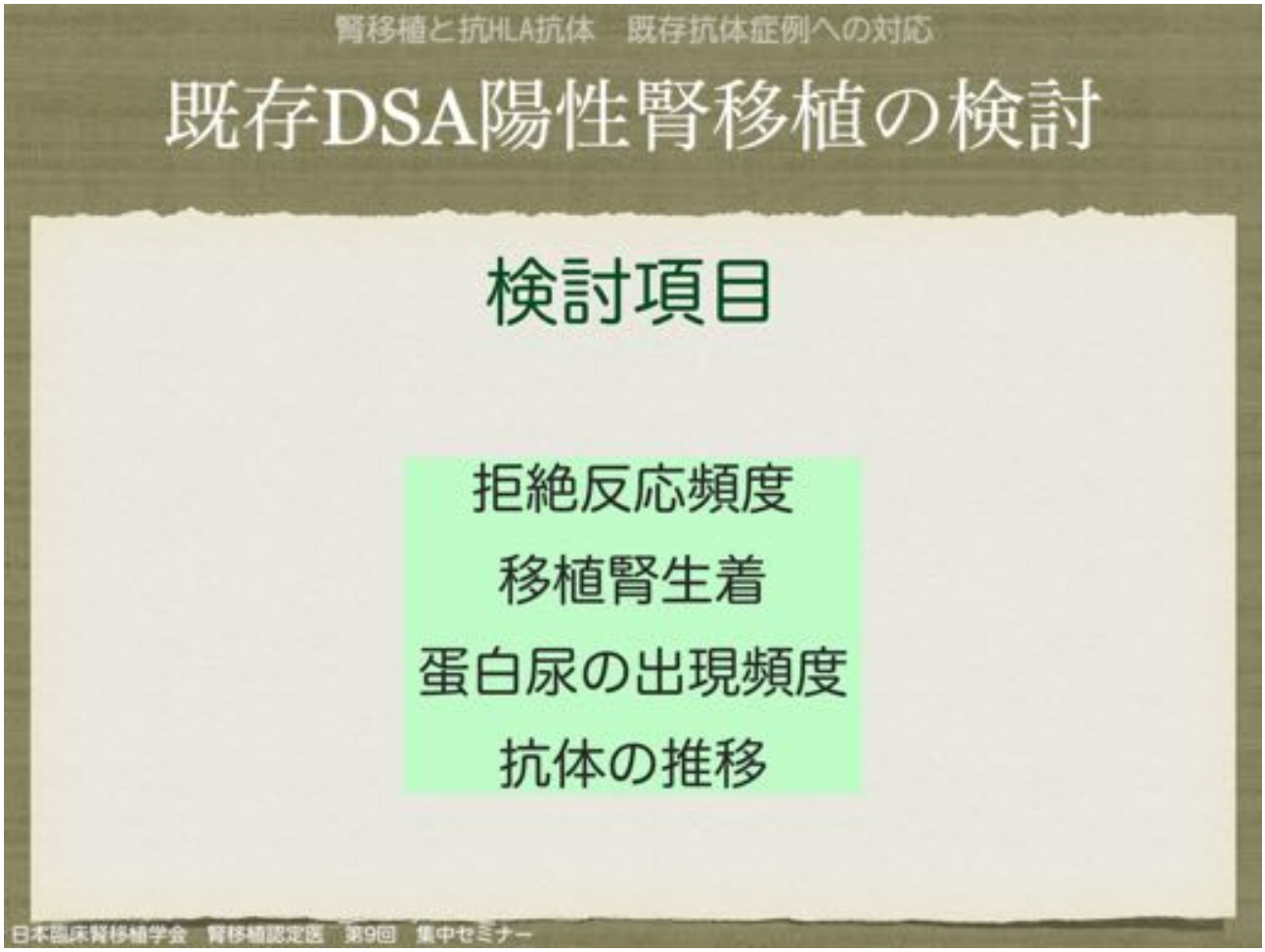
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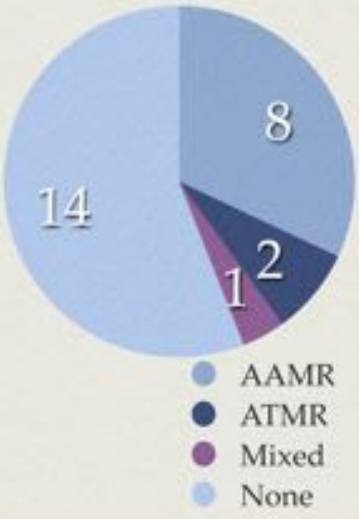
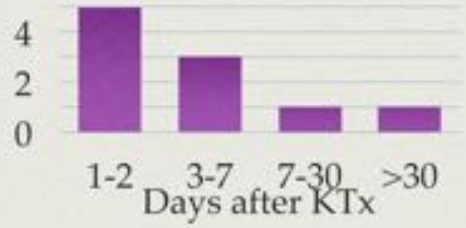
既存DSA陽性腎移植の検討

結果-ARタイプと時期

type of AR



onset of AR



Relationship b/w AR/Ab strength

Strength	Incidence	Rate
Weak	1/3	33.3%
Medium	6/9	66.7%
Strong	4/12	33.3%

NS

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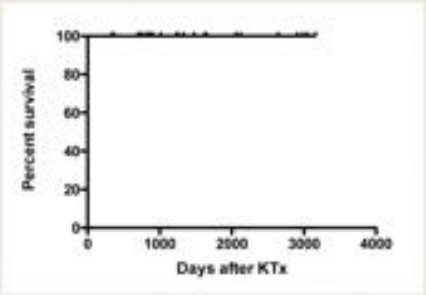
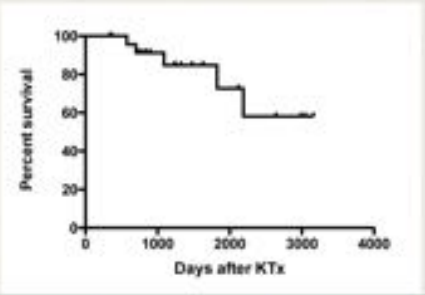
結果-Survival

graft survival



CAMR free graft survival



Relationship b/w CAMR/Ab strength

Strength	Incidence	Rate
Weak	0/3	0%
Medium	2/9	22.2%
Strong	3/12	25%

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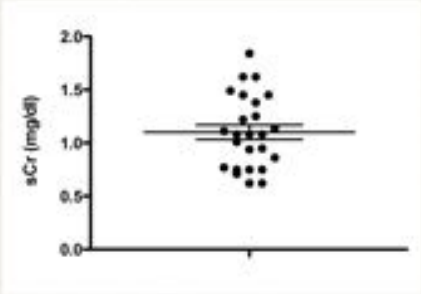
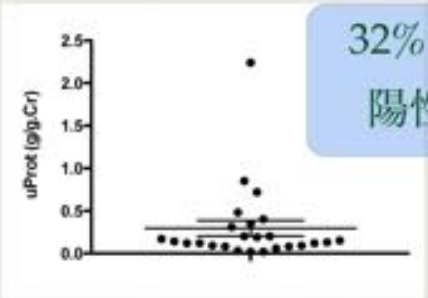
結果-ARタイプと時期

current sCr



current uProt



32%で陽性

Relationship b/w uProt/Ab strength

Strength	Incidence	Rate
Weak	1/3	33.3%
Medium	3/9	33.3%
Strong	4/12	33.3%

NS

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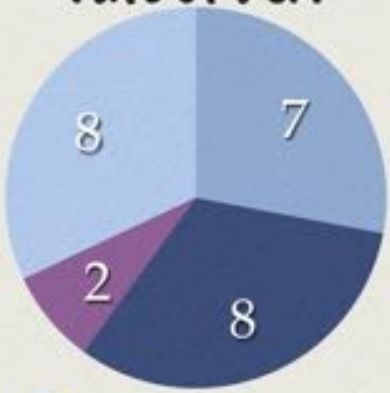
腎移植と抗HLA抗体　既存抗体症例への対応

既存DSA陽性腎移植の検討

結果-DSAのその後

Fate of DSA



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既存DSA陽性腎移植の検討

まとめ

1．CDC陽性以外の短期予後は比較的良好

2．術直後に拒絶反応が好発し、約2割がCAMRを発症

3．有害事象は抗体強度には依らない

4．41%で抗体消失、59%で依然陽性

症例提示（復習を兼ねて）

腎移植と抗HLA抗体　症例提示

CASE 1

*POD*２に*AAMR*併発するも、
その後全く慢性変化を認めていない
*FTX*m陽性の２次生体腎移植症例

腎移植と抗HLA抗体　症例提示

CASE 2

*Preformed DSA*陽性であり
*AABMR*を呈し、無尿となり
血漿交換を*12*回行うこととなった
生体腎移植症例

腎移植と抗HLA抗体　症例提示

CASE 3

*FTX*m, *Preformed DSA (HLA)* 陰性であったが
*Acute Vascular Rejection*から
腎血流喪失→腎皮質壊死となり
*POD3*に*Graftectomy*を行った
献腎（心臓死ドナー）移植症例

腎移植と抗HLA抗体　まとめ

腎移植と抗体関連拒絶

- 感作歴を良く調査
- しつこい位の*Xm*、*HLA*抗体をチェック
- *DSA*の強度判定
- プロトコールに応じた脱感作
- 無理をしない-延期、中止もあり得る
- 移植初期に経過が変-*AMR*を疑う
- 長期の*F/U*も重要-定期*Bx*、*DSA*チェックが鍵
- 適正な免疫抑制薬管理

ご静聴ありがとうございました

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