Current Therapeutic Options for Antibody Mediated Rejection (Mayo Clinic Experience)
Options thérapeutiques pour le rejet humoral

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Nouméa, Nouvelle Calédonie
Avril 2019

Outline

- Introduction
- Definitions
  - ABMR (acute & chronic)
- Pathophysiology
  - DSA (**D**onor-**S**pecific **A**ntibodies: pre-existing & de novo)
  - C4d
- Discuss the current therapeutic options of ABMR in different clinical scenarios
- Discuss management of recipients with De Novo DSAs and normal kidney function

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Introduction

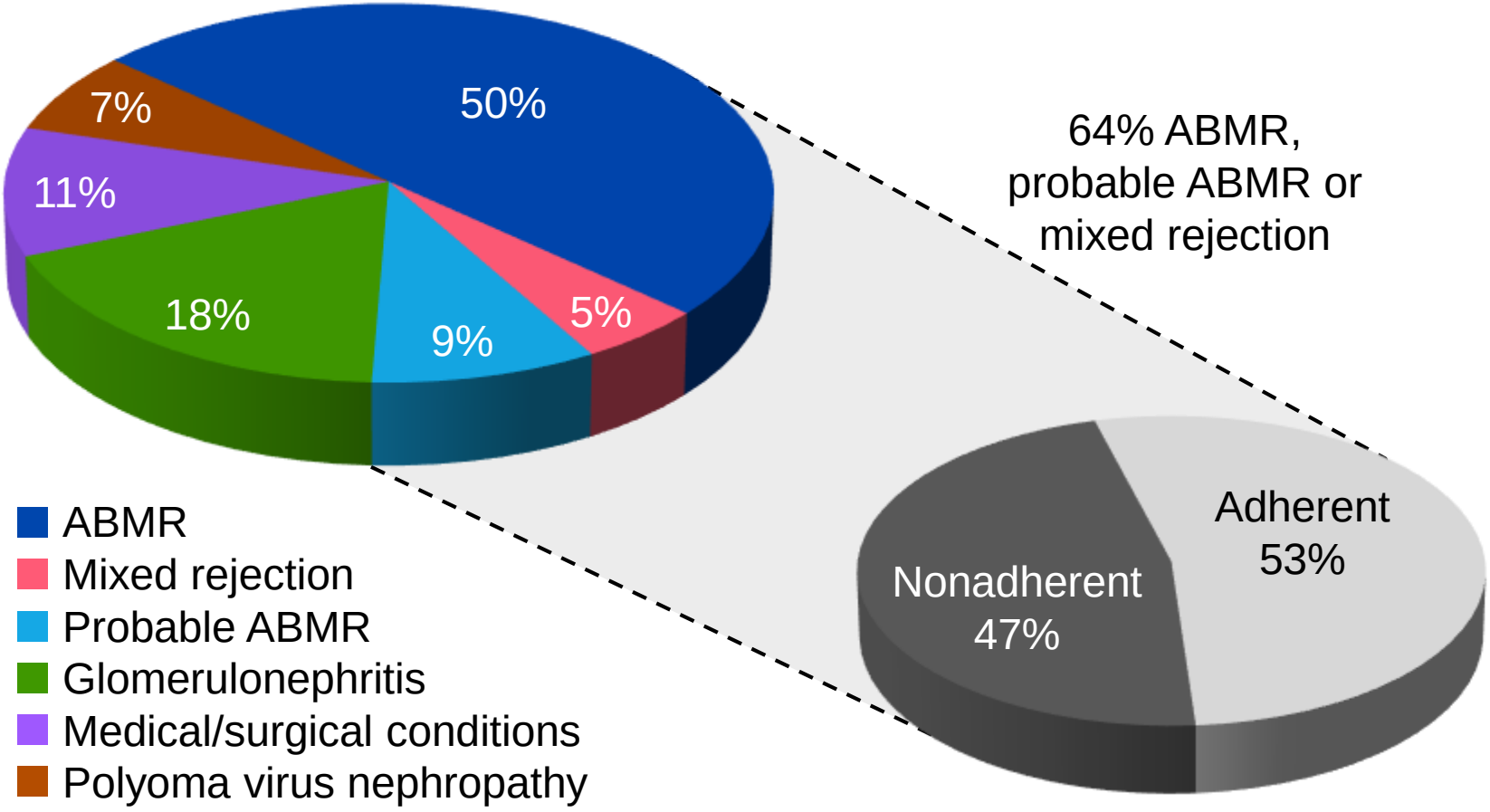
- One-year graft survival after kidney transplantation has substantially improved
  - Multimodal Immunosuppression therapy: Tacro + Mycophenolate
  - Substantially decreased acute cellular rejection rates
- Long-term (10-year) graft survival rates have stagnated over the past decade
- Antibody-mediated rejection (ABMR) is among the most important barriers to improving long-term outcomes

➢ **Le rejet par anticorps (ABMR) est l'un des principaux problèmes pour la survie du greffon rénal à long terme**

Antibody Mediated Rejection (ABMR)

Important Cause of Late Graft Failure

Rejet induit par les anticorps: principale cause d'échec de la greffe rénale



Sellares et al: Understanding the causes of kidney transplant failure: the dominant role of antibody-mediated rejection and nonadherence, AJT 2012

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Definitions: Antibody Mediated Rejection

Types of ABMR:

- **Hyperacute ABMR**

  - Due to ***preformed*** donor specific antibodies (DSA) present in high titers

  - Graft failure within minutes after transplantation

  - **Nearly eliminated** because of the universal adoption of pre-transplantation cross-matching

- **Acute ABMR:**

  - Characterized by graft dysfunction manifesting over days and is a result of **DSA's**, that may either be ***preformed or develop de novo*** after transplantation

- **Chronic ABMR:**

  - Antibodies can mediate chronic allograft injury: transplant glomerulopathy (TG) on kidney transplant biopsies

Defining & Diagnosing ABMR

Acute ABMR:

Past,

1. ***Neutrophils*** in peritubular capillaries (PTC'itis) = *Capillaritis*
2. De Novo anti-donor (HLA) antibodies (+ DSA)
3. C4d +
4. Graft dysfunction: ATN…

ABMR Diagnosis (Banff 2013 Criteria)
Introduced C4d Negative ABMR

- **Evaluation meeting ALL 3 of these features:**
  - **Histologic evidence of acute injury** including one or more of the following:
    - Microvascular inflammation (ptc'itis)
    - Intimal or transmural arteritis
    - Acute thrombotic microagiopathy
    - ATN lacking other causes
  - **Evidence of capillary injury**, including one or more of the following:
    - Linear C4d staining in peritubular capillaries (PTC) or,
    - At least moderate capillaritis (g+PTC scores >2)
  - **Serologic evidence of donor specific antibodies** (HLA or other antigens)

➢ **La positivité de C4d n'est plus nécessaire pour diagnostiquer le rejet provoqué par les anticorps**

and Now, (Banff 2017)

more refined and incorporated gene transcripts / Substitutes for DSA: C4d+ and molecular ABMR correlates

Active ABMR; all **3 criteria** must be met for diagnosis

1. Histologic evidence of acute tissue injury: capillaritis…

2. **Evidence of current/recent antibody interaction with vascular endothelium, *including 1 or more of the following*:**

- Linear C4d staining in peritubular capillaries (C4d or C4d by IF on frozen sections, or C4d > 0 by IHC on paraffin sections)
- At least moderate microvascular inflammation ([g + ptc] ≥2) in the absence of recurrent or de novo glomerulonephritis, although in the presence of acute TCMR, borderline infiltrate, or infection, ptc ≥ 2 alone is not sufficient and g must be ≥1
- Increased expression of gene transcripts/classifiers in the biopsy tissue strongly associated with ABMR, *if thoroughly validated*

3. Serologic evidence of donor-specific antibodies (DSA to HLA or other antigens):

➢ **C4d staining or expression of validated transcripts/classifiers may substitute for DSA**

Chronic Active ABMR: Banff 2017

All 3 CRITERIA must be present for diagnosis:

1. Morphologic evidence of **chronic tissue injury**, including 1 or more of the following:
   - Transplant glomerulopathy (cg >0) if no evidence of chronic TMA or chronic recurrent/de novo glomerulonephritis; includes changes evident by electron microscopy (EM) alone (cg1a)
   - Severe peritubular capillary basement membrane multilayering **(requires EM)**
   - Arterial intimal fibrosis of new onset, excluding other causes; leukocytes within the sclerotic intima favor chronic ABMR if there is no prior history of TCMR, but are not required
2. Identical to criterion 2 for active ABMR, above
3. Identical to criterion 3 for active ABMR, above, including strong recommendation for DSA testing whenever criteria 1 and 2 are met

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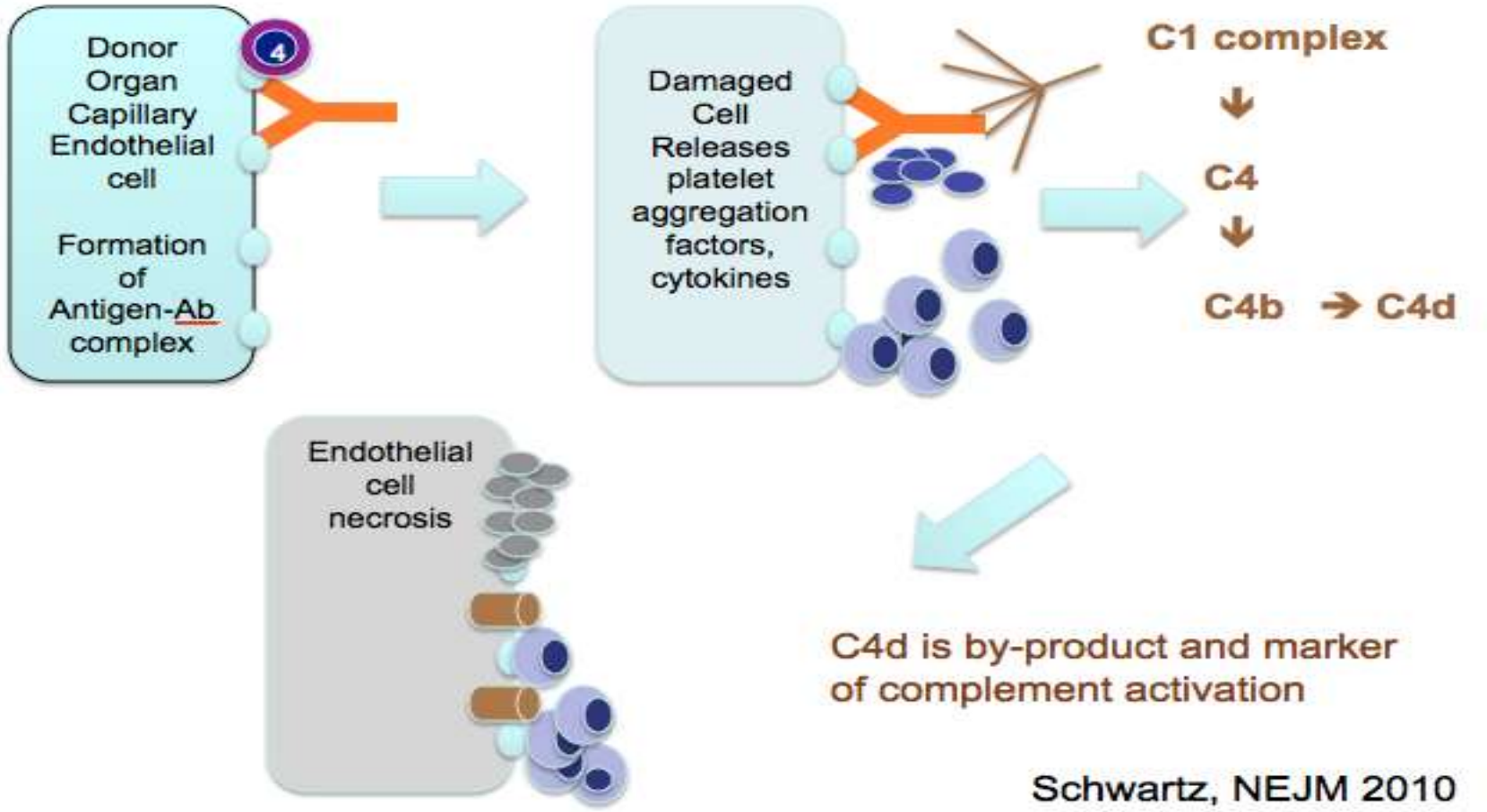
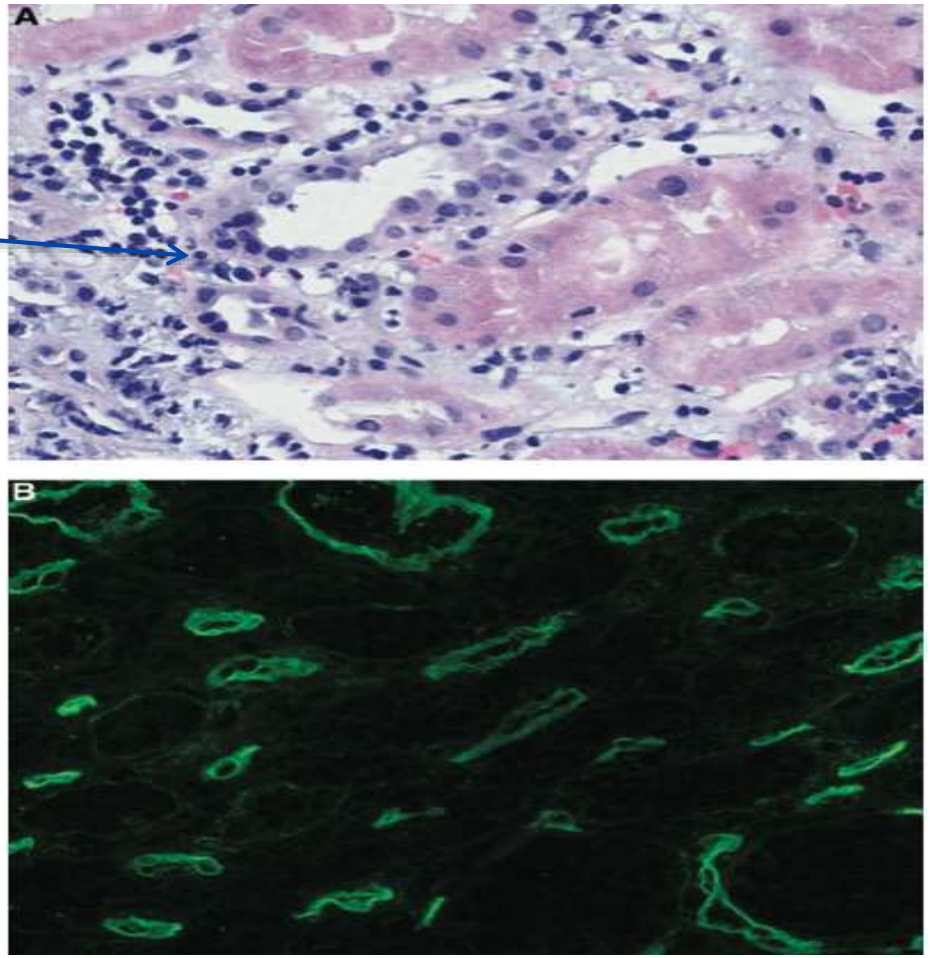
Pathophysiology of ABMR



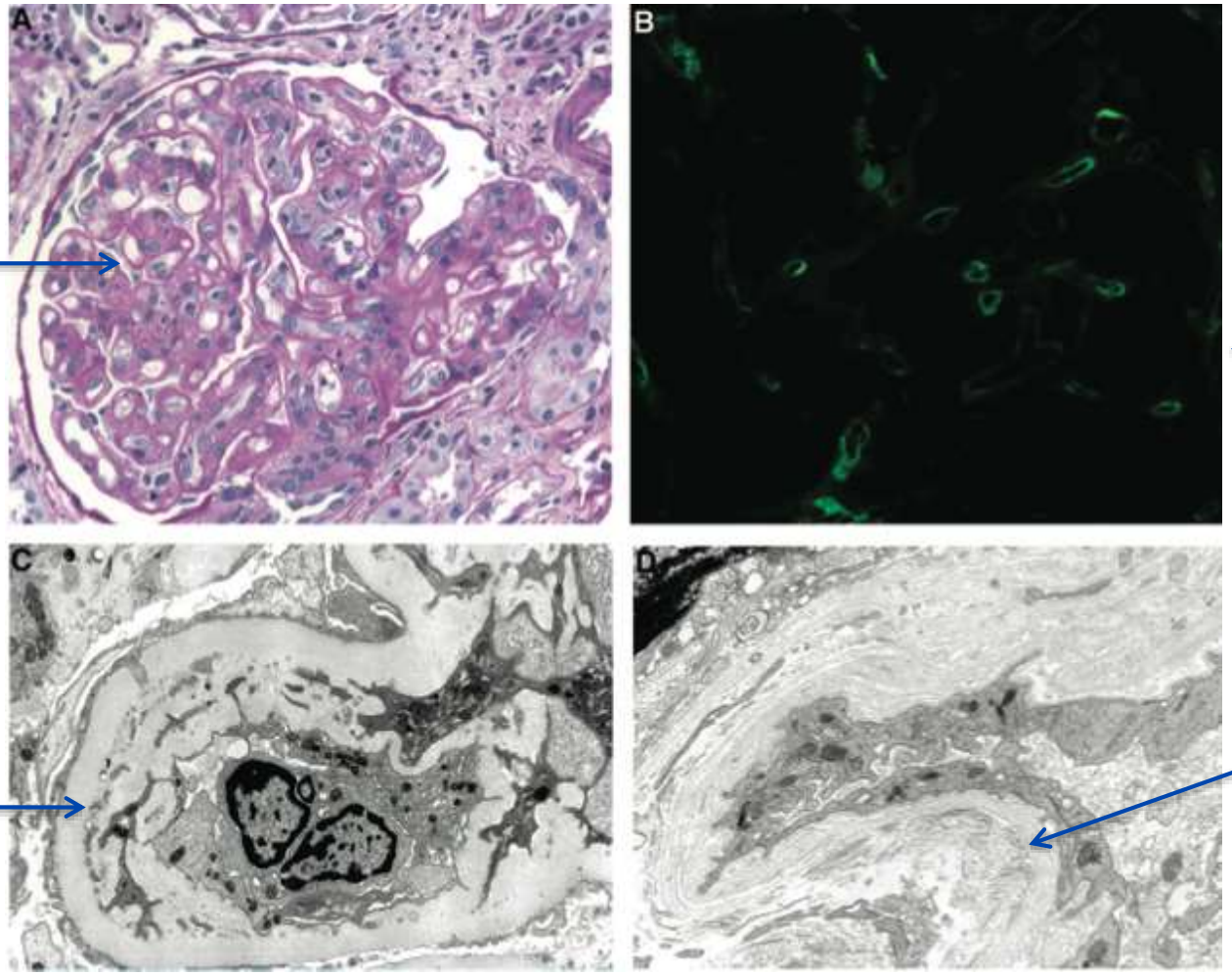
Acute ABMR

Peritubular capillaritis (PTC'itis)



C4d + in Peritubular capillaries

Chronic ABMR



Donor Specific Antibodies: DSA

- DSA may be directed against HLA or other endothelial cell antigens
- DSA presence **was required (before Banff update 2017)** for the diagnosis of acute and chronic active ABMR/ ***now use of correlates for DSA***: C4d+/gene expression if no DSA detected or can be obtained

- **Not all DSA's fix complement** or **cause ABMR**
- Some **patients with DSA maintain normal kidney function for years** and have long-term outcomes similar to non-sensitized patients

Donor Specific Antibodies: DSA

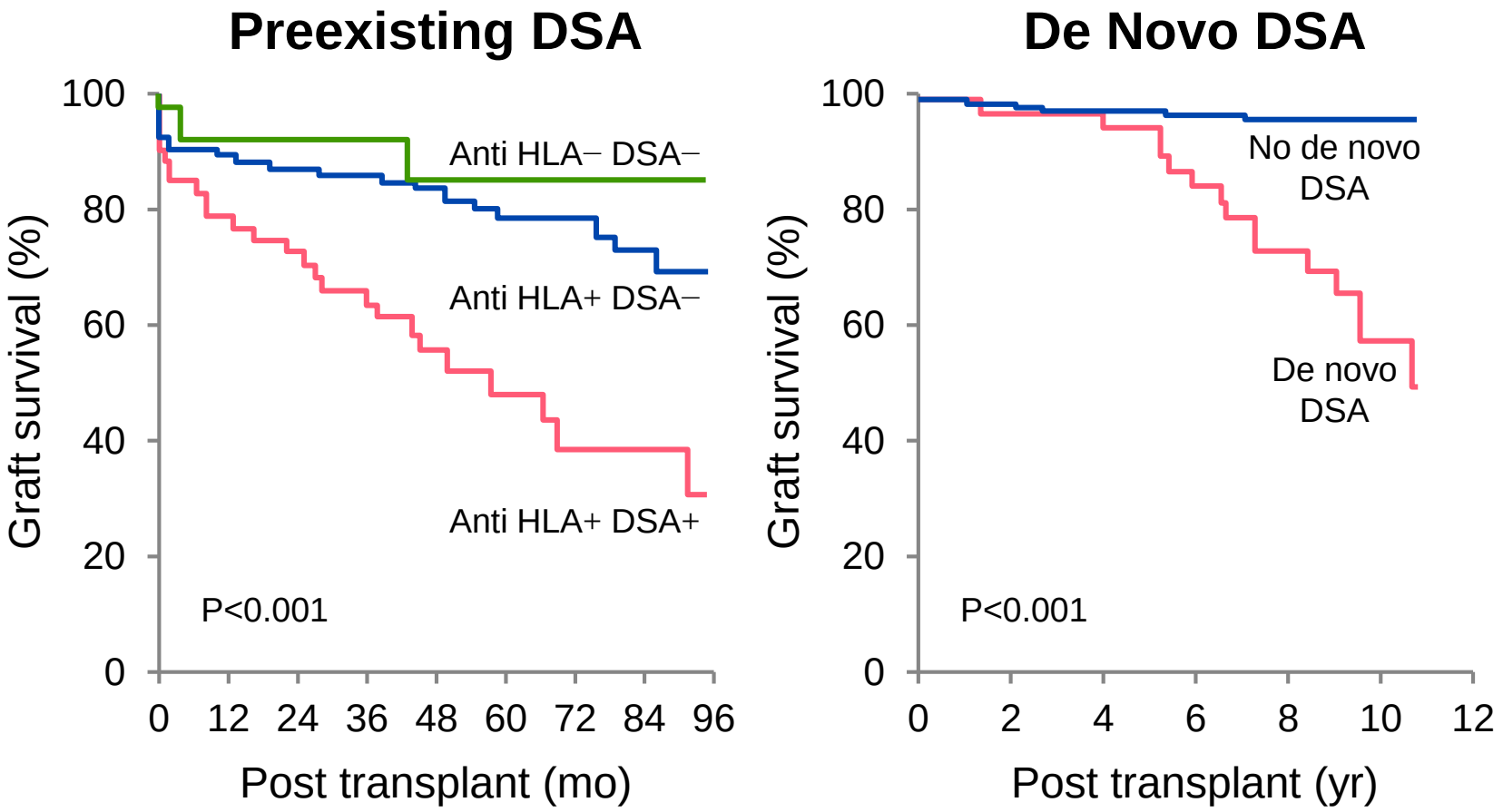
- De Novo: pre-existing or De Novo
- Directed against:
  - **HLA**
  - Endothelial
    - MICA
    - AT_1R
  - Other
    - Vimentin (heart)
    - ICAM-1 (heart)

AT_1R: angiotensin type 1 receptor; MICA: major histocompatibility HLA class I-associated peptide; HLA: human leukocyte antigen; ICAM: intercellular adhesion molecule.

Wiebe C, et al. *Am J Transplant* .2012;12:1157-1167.
Zou Y, et al. *N Engl J Med.* 2007;357:1293-300.
Dragun D,et al. *N Engl J Med*. 2005;352:558-569.
Dragun D, et al. *Transplantation* .2008;86:1019-1025.
Banff '09 Meeting Report. *Am J Transplant* . 2010;10:464-471.

DSA's = Lower Graft Survival

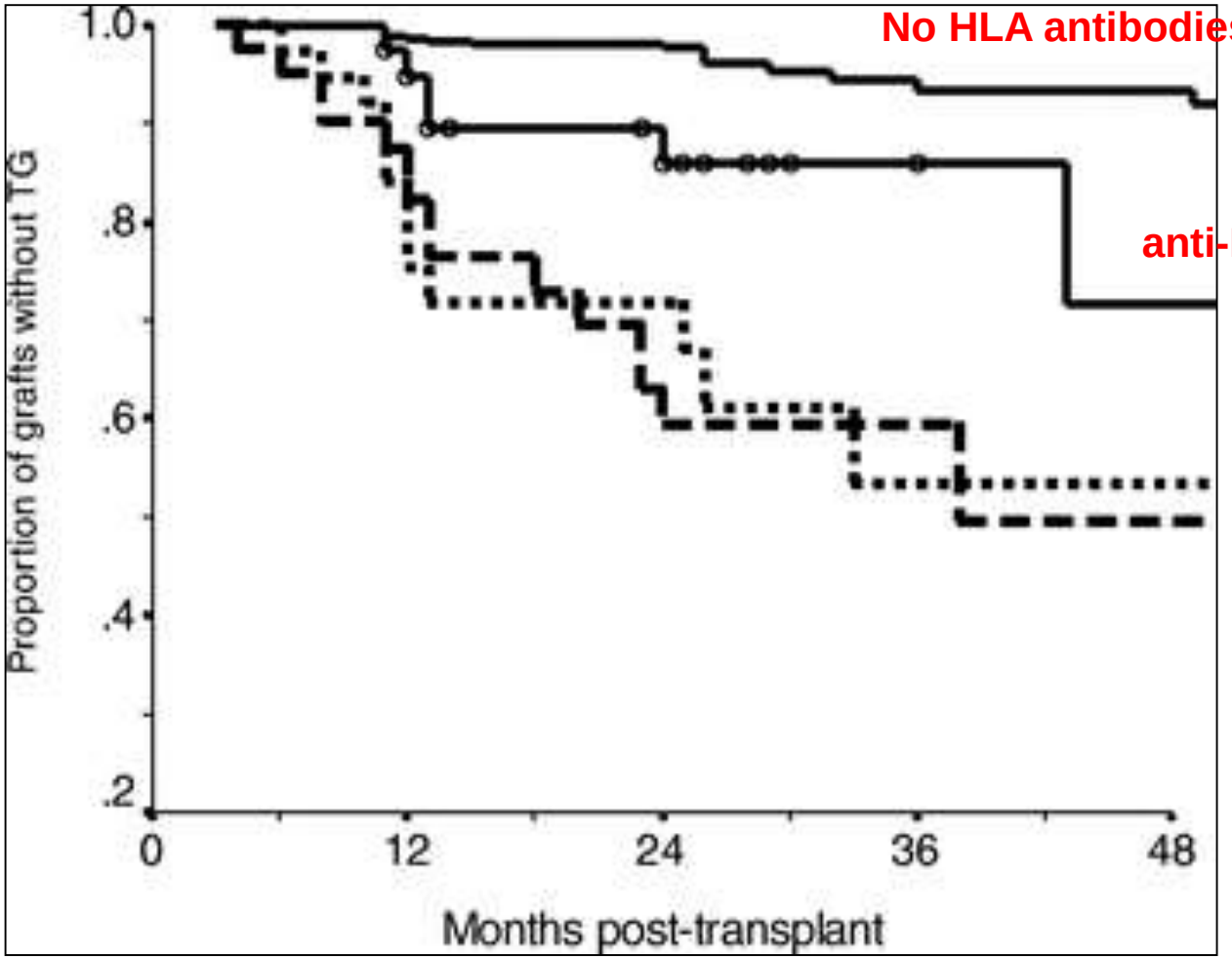
La présence d'anticorps spécifiques du donneur (DSA) (préformés avant la transplantation ou de novo après la transplantation) est associée à une réduction de la survie du greffon rénal



MAYO CLINIC

Lefaucheur et al: J Amer Soc Nephrol 21:1398, 2010
Wiebe et al: Am J Transplant 12:1157, 2012

The “Strength” of the anti-Class II DSA (Higher MFI’s) Correlates with Outcomes

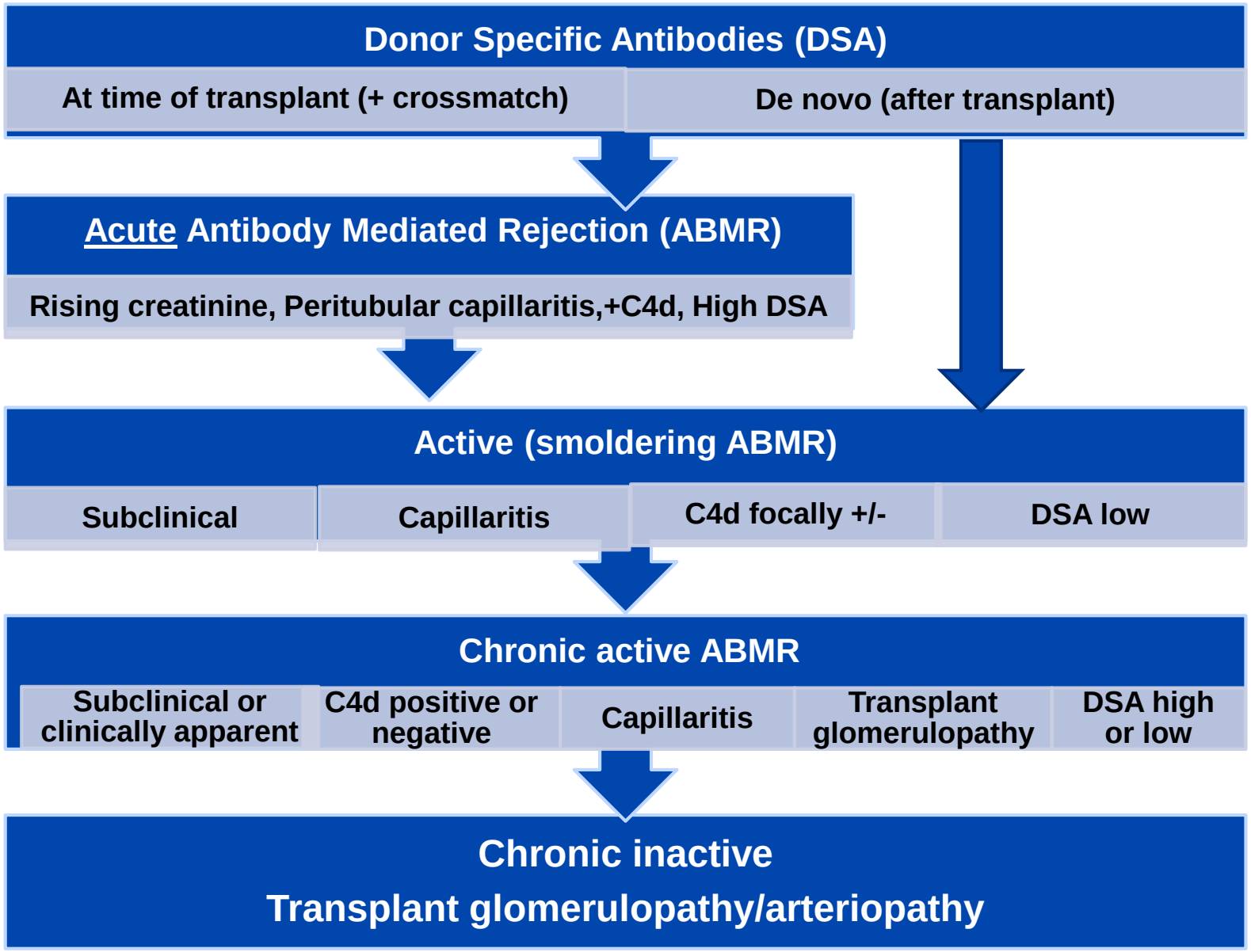


Transplant Glomerulopathy: Risk and Prognosis Related to Anti-Human Leukocyte Antigen Class II Antibody Levels. Issa N et al; Transplantation. 86(5):681-685,Sep 2008

ABMR “Continuum”

Le rejet induit par les anticorps est un spectre continu d'événements résultant de l'interaction dynamique des anticorps avec l'endothélium (pouvant être aigu, subaigu ou chronique (actif ou inactif))

	Acute ABMR	Active (smoldering) ABMR	Chronic Active ABMR		Chronic Inactive ABMR
Clinical Setting	Usually clinically apparent: Acute Kidney injury	Subclinical	Subclinical or clinically apparent: Progressive renal insufficiency, proteinuria		Subclinical or clinically apparent
Histology	ATN, thrombi, microvascular inflammation	Capillaritis only	Capillaritis only	Capillaritis and TG, TA or PTC	TG, TA or PTC
C4d	++	–/minimal	+/–/focal/minimal		–
Serum DSA MFI’s	High	Low	High, mid or low		Low
EM Endothelial Activation	+	+/–	+/–		+/–



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Current Therapeutic Options

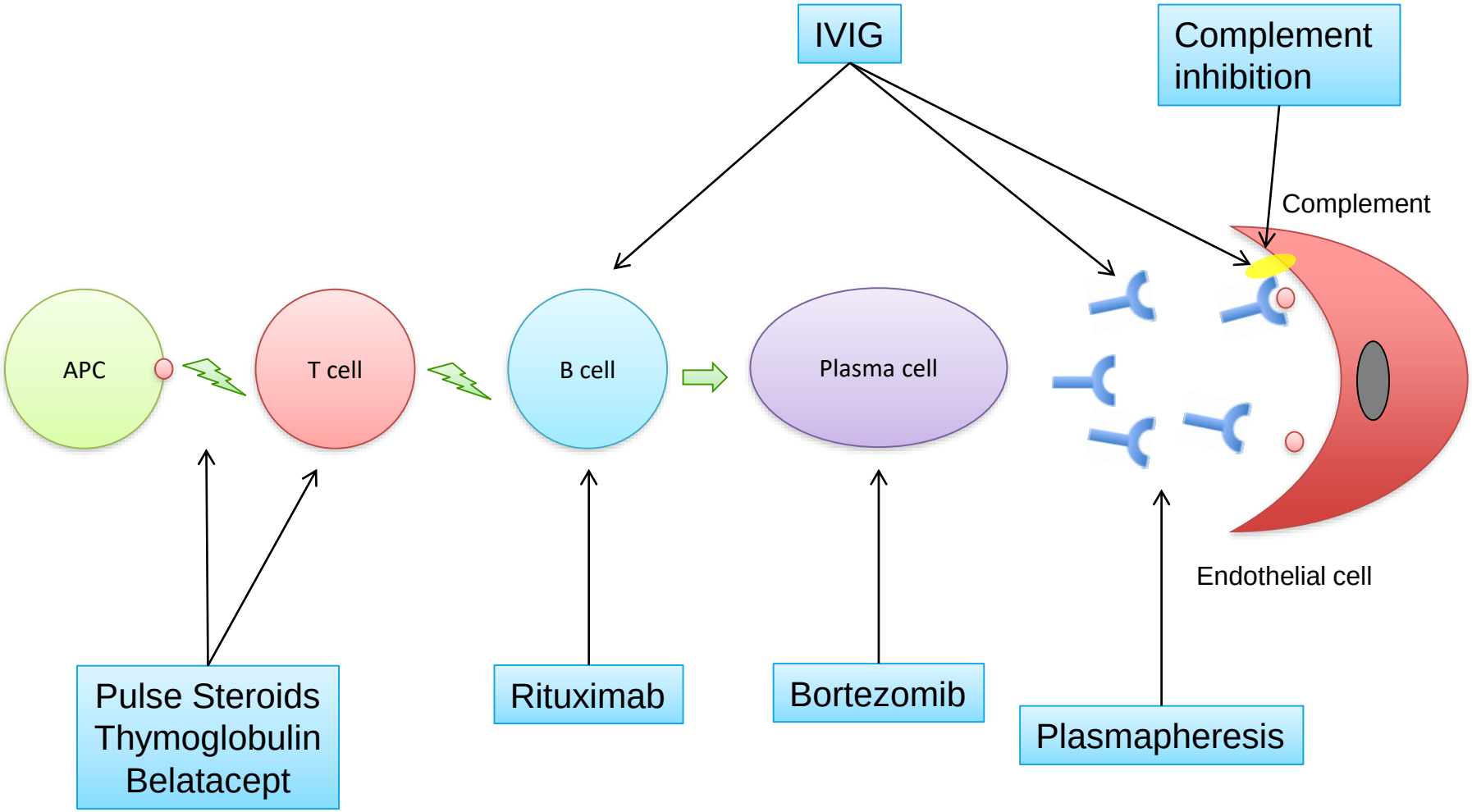
Options Thérapeutiques Actuelles

Goals of ABMR Therapy

- Prolong kidney allograft survival
- Improve kidney allograft function
- Improve kidney allograft histology *(improvement in mean Banff scores of ABMR)*
- Decrease in DSA MFI's

Potential Targets of Therapy

Le traitement est principalement axé sur la production des anticorps



Clinical Scenario #1

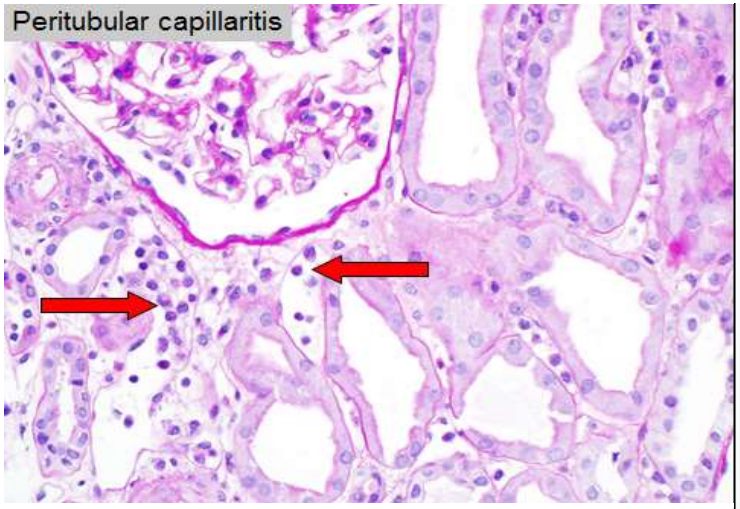
- 54 yo woman with ESRD secondary to ADPKD
- Preemptive living kidney donor transplant from her husband
- cPRA pre-transplant: 95%, One DSA MFI 1,000 (anti-B6); Negative B- and T- Cell Flow Crossmatch
- 5 days post-transplant creatinine 0.9 mg/dL (79 µmol/L)

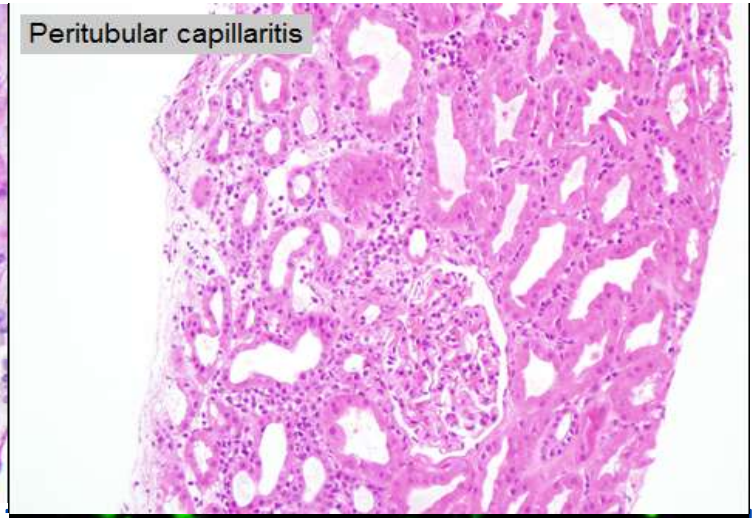
- ***14 days post-transplant:***

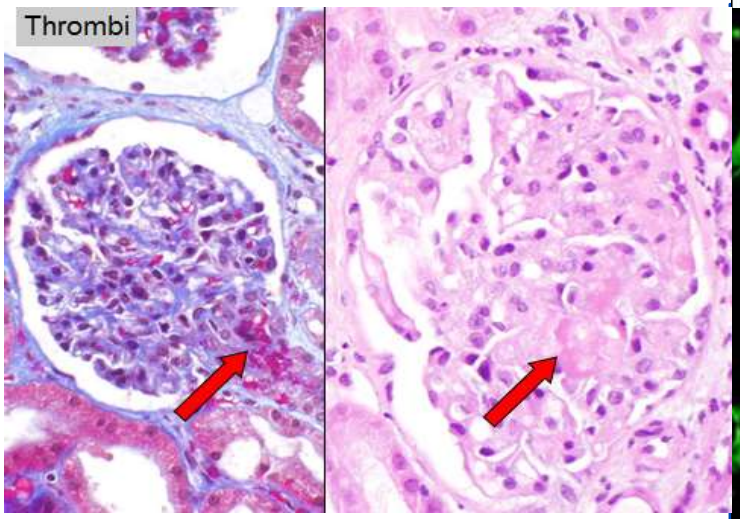
- Acute rise in creatinine to 3.1 mg/dL (274 µmol/L) over 2 days
- Oliguric
- DSA MFI up to 12,000 (anti-B6)

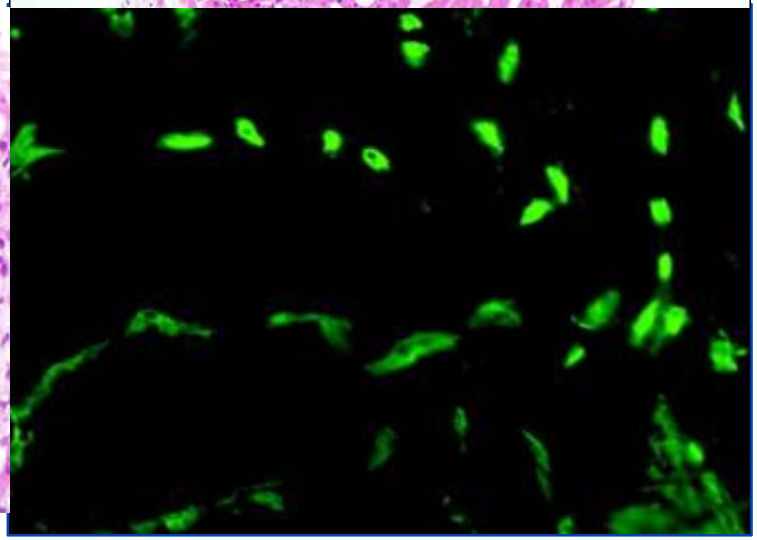
Kidney Transplant Biopsy

Features of acute antibody mediated rejection









Courtesy of Dr. Lynn Cornell

What do we do?

- Plasmapheresis?
- IVIG?
- Complement inhibition?
- Rituximab? (anti-CD20/anti-B Cell)
- Bortezomib? (Proteasome Inhibitor)

Il n'existe aucun protocole de traitement approuvé par la FDA pour le rejet induit par les anticorps. Mais pour le rejet précoce aigu provoqué par des anticorps, nous avons tendance à être très agressif dans le traitement pour réduire la charge en anticorps et réduire l'inflammation dans les capillaires

Management of **Early** Acute Antibody Mediated Rejection – *Mayo Clinic Approach*

- Plasmapheresis ((1-1.5 volume) daily x 4 days then every other day x 7 days) + low dose IVIg of 100mg/kg
- Consider Methylprednisolone 3-5 mg/kg IV once daily for 3 days
- Suggest target **Mycophenolic Acid level: 3-3.5**
- Increase Tacrolimus to maintain trough level of **8-10 ng/dL**

- **High dose of IVIG** (1 g/kg) at ***the end of last plasmapheresis***

Management of **Early** Acute Antibody Mediated Rejection - *Mayo Clinic approach*

- Treatment response parameters:
  - Presence of **2** of the following:
    - Allograft function (drop of serum creatinine to baseline)
    - Follow up allograft biopsy showing improvement of ABMR changes and/or
    - Demonstrable reduction in the quantity of DSA

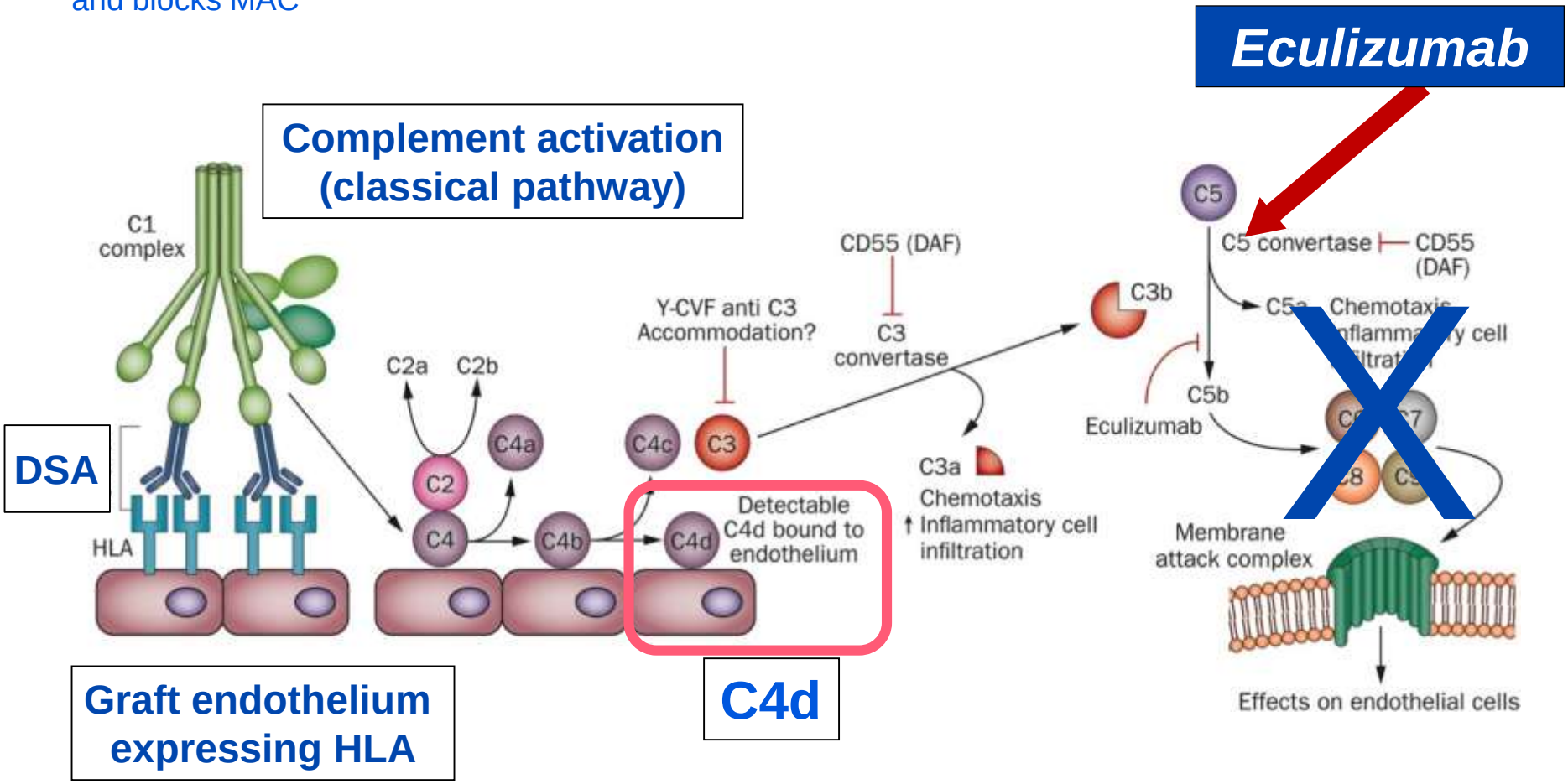
Management of **Early** Acute Antibody Mediated Rejection- *Mayo Clinic Approach*

- Non-responders:
  - In patients who have **no or partial response** after the first treatment cycle, **an additional 5 sessions of TPE** to start after 2 days of completing the 1st cycle, to be followed by 100 mg/kg of IVIg (Consider repeat biopsy before starting treatment)
  - Patients who have response to the 2nd cycle of TPE should receive IVIg 1 gm/kg after the last session of plasma exchange

  - Other options to treat ABMR include:
    - **Eculizumab:** Prior to Eculizumab treatment patient should receive meningococcal vaccination (can be done the day before)
    - **Rituximab once** (**likely ineffective** in lowering antibody levels and also ineffective in the acute treatment of AMR)
    - **Splenectomy**

Why Eculizumab?

Monoclonal antibody against C5: by blocking C5 activation it decreases downstream complement activation and blocks MAC



Stegall at al: AJT 11:2405, 2011

What is the Evidence for Other Therapies?

Rituximab
Bortezomib
C1 inhibitors

Rituximab for Early Acute ABMR?

American Journal of Transplantation 2009; 9: 1099–1107
Wiley Periodicals Inc.

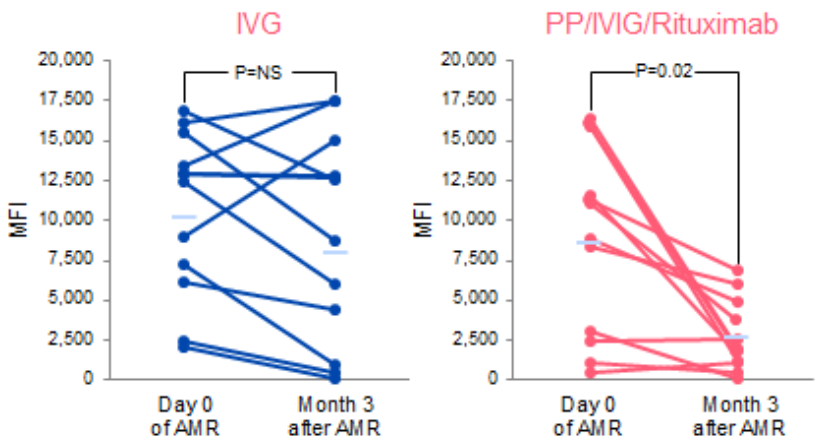
doi: 10.1111/j.1600-6143.2009.02591.x

Comparison of Combination Plasmapheresis/IVIg/ Anti-CD20 Versus High-Dose IVIg in the Treatment of Antibody-Mediated Rejection

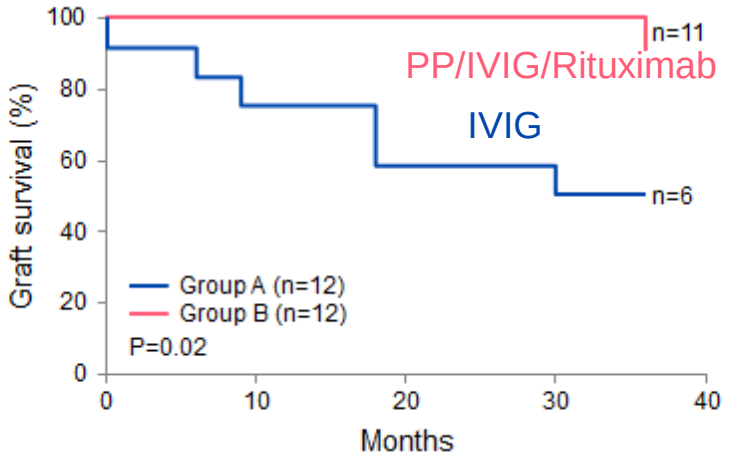
C. Lefaucheur[a,*], D. Nochy[b], J. Andrade[a,c], J. Verine[d], C. Gautreau[c], D. Charron[c,e], G. S. Hill[b], D. Glotz[a,e] and C. Suberbielle-Boissel[c]

Received 24 October 2008, revised 27 January 2009 and accepted for publication 28 January 2009

DSA MFIs Significantly Improved in Recipients Treated With PP/IVG/Rituximab



Graft Survival Significantly Better in Patients Treated With PP/IVIG/Rituximab



Lefaucheur et al: Am J Transplant 9:1099, 2009

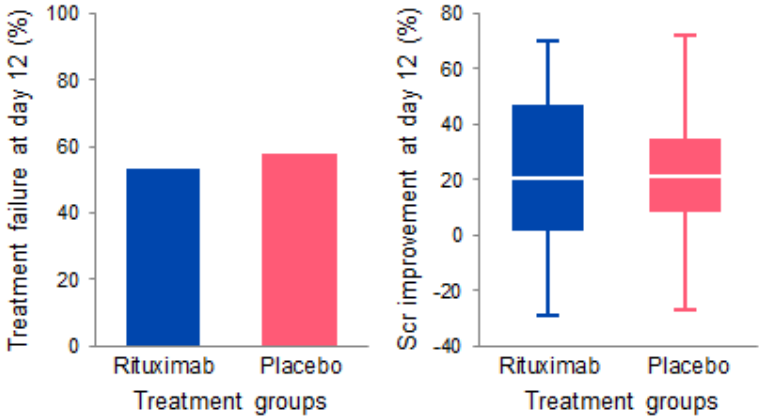
One-year Results of the Effects of Rituximab on Acute Antibody-Mediated Rejection in Renal Transplantation: RITUX ERAH, a Multicenter Double-blind Randomized Placebo-controlled Trial

Bénédicte Sautenet, MD,[1,2] Gilles Blancho, MD, PhD,[3] Mathias Büchler, MD, PhD,[1,2,4] Emmanuel Morelon, MD, PhD,[5] Olivier Toupance, MD,[6] Benoit Barrou, MD, PhD,[7] Didier Ducloux, MD, PhD[8]

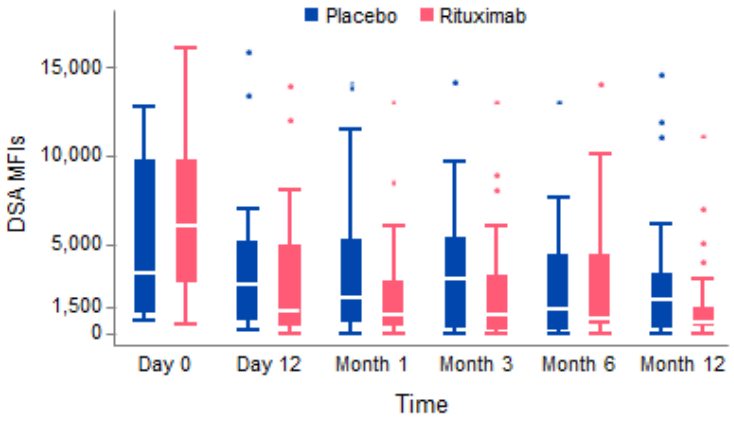
Adding Rituximab was **NOT** superior in terms of graft function and survival (lowered DSA's), at least in the short term follow-up

Treatment protocol: Plasmapheresis/IVIG/steroids ± **Rituximab** **or** **Placebo**

Primary Outcome Was Not Different in Rituximab Group Comparing to Placebo



DSA MFIs Significantly Lower With Treatment but Not Different Between Groups



Sautenet et al: Transplantation 100:391, 2016

Bortezomib for Early Acute ABMR?

Proteasome Inhibitor-Based Primary Therapy for Antibody-Mediated Renal Allograft Rejection

R. Carlin Walsh,[1] Jason J. Everly,[1] Paul Brailey,[2] Adele H. Rike,[1] Lois J. Arend,[3] Gautham Mogilishetty,[4] Amit Govil,[4] Prabir Roy-Chaudhury,[4] Rita R. Alloway,[4] and E. Steve Woodle[1,5]

Background. Rapid and complete elimination of donor-specific anti-human leukocyte antigen antibodies (DSA) during antibody-mediated rejection (AMR) is rarely achieved with traditional antihumoral therapies. Proteasome inhibitor-based therapy has been shown to effectively treat refractory AMR, but its use as a primary therapy for AMR has not been presented. Our initial experience with proteasome inhibition as a first-line therapy for AMR is presented.

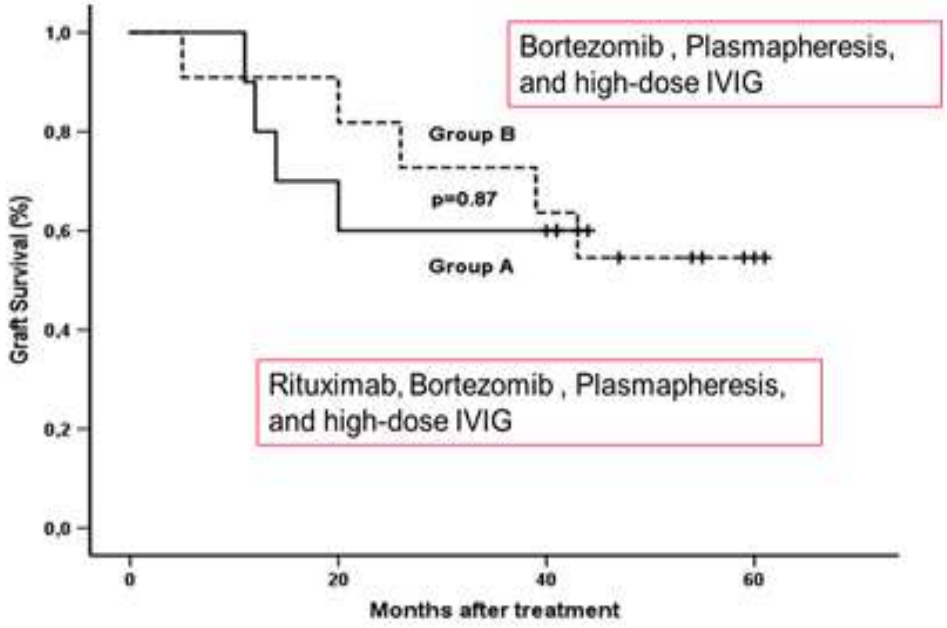
- Bortezomib, in addition to Plasmapheresis and Rituximab, **was effective** in reversal of Acute Antibody Mediated Rejection
- Only 2 patients!

Walsh et al. Transplantation 2010

Rituximab in Combination With Bortezomib, Plasmapheresis, and High-Dose IVIG to Treat Antibody-Mediated Renal Allograft Rejection

Johannes Waiser, MD,[1] Michael Duerr, MD,[1] Constanze Schönemann, PhD,[2] Birgit Rudolph, MD,[3] Kaiyin Wu, MD,[1,3] Fabian Halleck, MD,[1] Klemens Budde, MD,[1] and Nils Lachmann, PhD[2]

- Addition of Rituximab ***not beneficial***
- Increased side effects:
  - Thrombocytopenia
  - Bacterial infections
  - GI side effects



Waiser et al., Transplantation Direct 2016

American Journal of Transplantation 2016; 16: 1596–1603
Wiley Periodicals Inc.

doi: 10.1111/ajt.13663

Brief Communication

C1 Inhibitor in Acute Antibody-Mediated Rejection Nonresponsive to Conventional Therapy in Kidney Transplant Recipients: A Pilot Study

No benefits *of* ***C1 inhibitor*** *in graft function and histology in short-term follow-up*

American Journal of Transplantation 2016; XX: 1–11
Wiley Periodicals Inc.

doi: 10.1111/ajt.13871

Plasma-Derived C1 Esterase Inhibitor for Acute Antibody-Mediated Rejection Following Kidney Transplantation: Results of a Randomized Double-Blind Placebo-Controlled Pilot Study

R. A. Montgomery[1,*], B. J. Orandi[1], L. Racusen[2], A. M. Jackson[3], J. M. Garonzik-Wang[1], T. Shah[4], E. S. Woodle[5], C. Sommerer[6],

patients achieved supraphysiological levels throughout. This new finding suggests that C1 INH replacement may be useful in the treatment of AMR.

Other Therapies?

Rituximab
Bortezomib
C1 inhibitors

Limitations:

- Case reports or small series; no randomized clinical trials
- Only short term outcomes
- NOT MUCH EVIDENCE as first-line therapy
- Complications: infectious risk, peripheral neuropathy with Bortezomib…

Il existe peu de preuves concernant l'utilisation du rituximab ou du bortézomib dans la littérature scientifique. Elles proviennent principalement de séries de cas contenant de petits échantillons et non d'essais cliniques randomisés

Clinical scenario #1

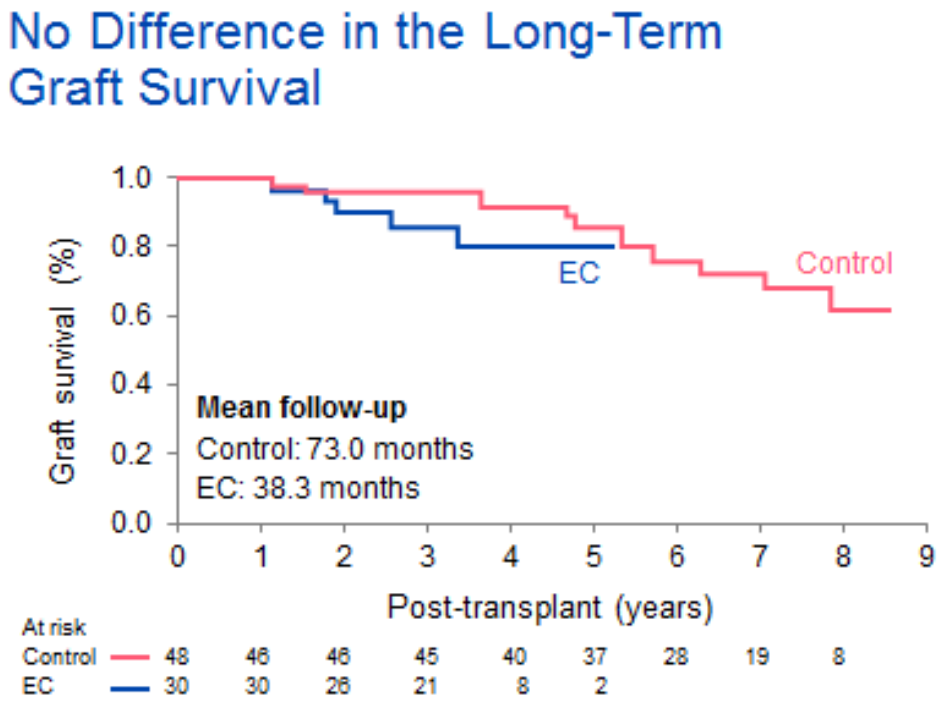
- 54 yo women with acute ABMR
- Treatment: Plasmapheresis/IVIG + Eculizumab
- Responded well to therapy – creatinine returned down to baseline
- DSA MFI decreased to 3,000

- ***Long-term outcomes?***

Acute ABMR **Early** Post Transplant

- Almost exclusively in **sensitized** patients
- **Responsive** to therapy, at least short term
- **No** preferred treatment strategies: *Anything you can do to save the kidney!*
- DSA MFI's usually significantly decrease
- ***Long-term outcomes compromised!***

Treatment with Eculizumab **does NOT** Prolong Graft Survival
(Mayo Clinic Experience)



- **L'utilisation de l'Eculizumab n'a pas été associée à une survie à long terme des greffons rénaux**

Cornell et al: AJT 15:1293, 2015

Clinical scenario #2

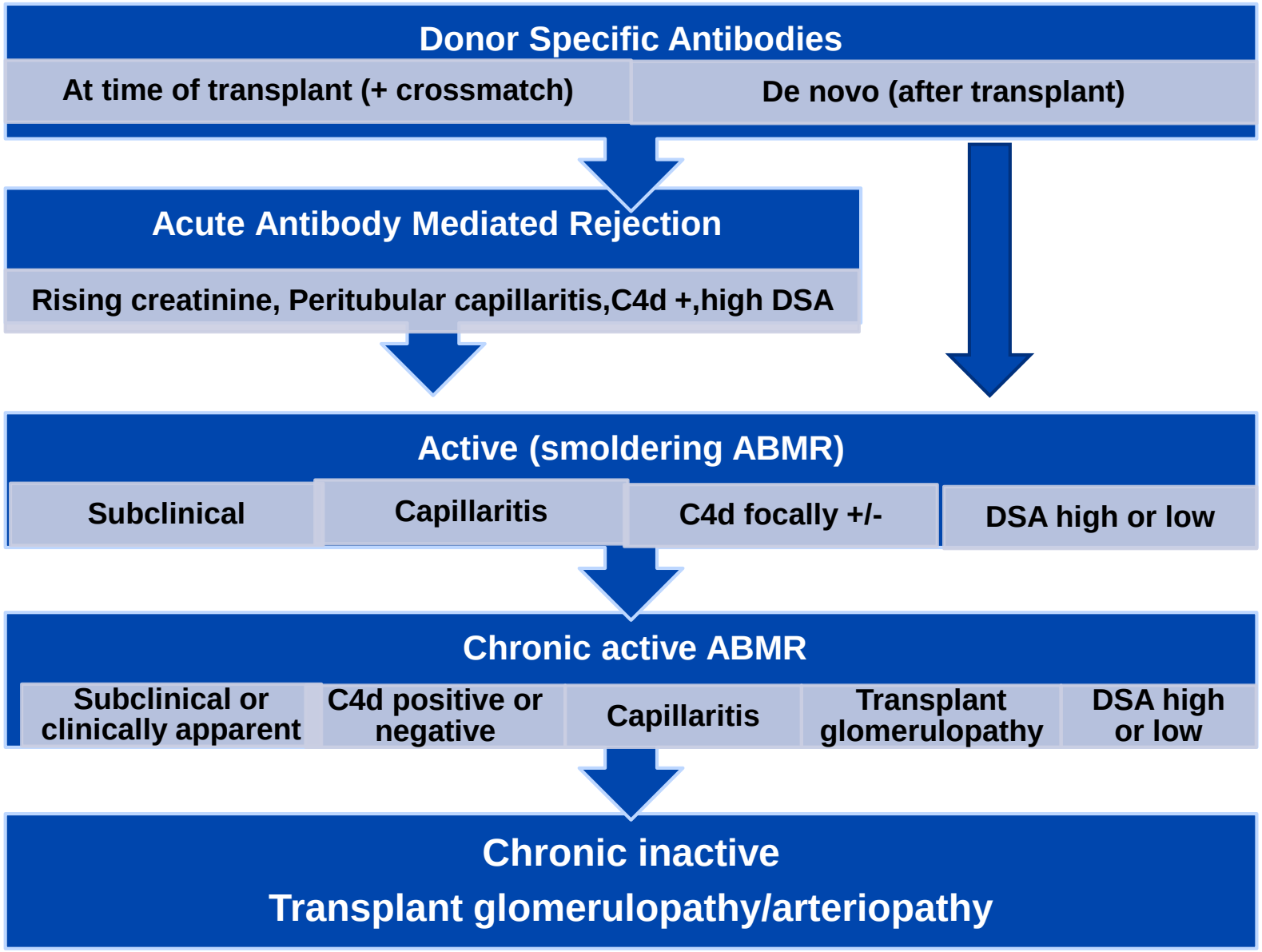
- 35 yo man with ESRD secondary to membranous nephropathy
- cPRA pre-transplant: 10%, **no DSA** pre-transplant
- Baseline creatinine 1.2 mg/dl (106 µmol/L)

- **Clinical presentation at 3 years:**

- Creatinine 1.6 mg/dl (142 µmol/L)
- **Proteinuria 2 grams/24h**
- Tacrolimus and Mycophenolic acid levels **are not done on regular basis**
- ?? Recurrence of disease: membranous nephropathy

- **Kidney transplant BIOPSY:**

- **Peritubular capillaritis PTC 2**; **C4d Negative**, **TG: cg 2**
- **DSA: MFI 3,000 (DR7)**



Management of **Chronic Active** ABMR
Mayo Clinic Protocol

- High dose of IVIG: *mixed success!*
- Augmentation of immunosuppression:

- Target Higher Tacrolimus trough levels: ?? 8-10 ng/L
- Switch to Tacrolimus if on Cyclosporine A *(or Sirolimus)*
- Switch to Mycophenolate Mofetil (CellCept) if on Azathioprine (Imuran)

- **La gestion du rejet actif chronique induit par des anticorps est plus difficile car il n'existe aucun traitement prouvé pour en venir à bout**
- **Nous recommandons d'augmenter l'immunosuppression (augmentation du taux sanguin d'inhibiteurs de la calcineurine)**

High Dose Intravenous Immunoglobulin Therapy for Donor-Specific Antibodies in Kidney Transplant Recipients With Acute and Chronic Graft Dysfunction

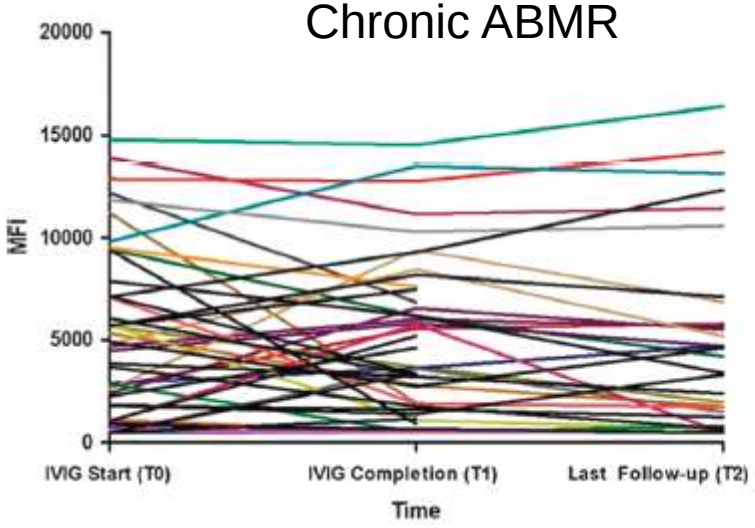
James E. Cooper,[1,4] Jane Gralla,[2] Patrick Klem,[3] Laurence Chan,[1] and Alexander C. Wiseman[1]

High dose IVIg may benefit early Acute ABMR but **no benefit** in **Chronic ABMR**

Time from transplant 44 months (47d to 119m)

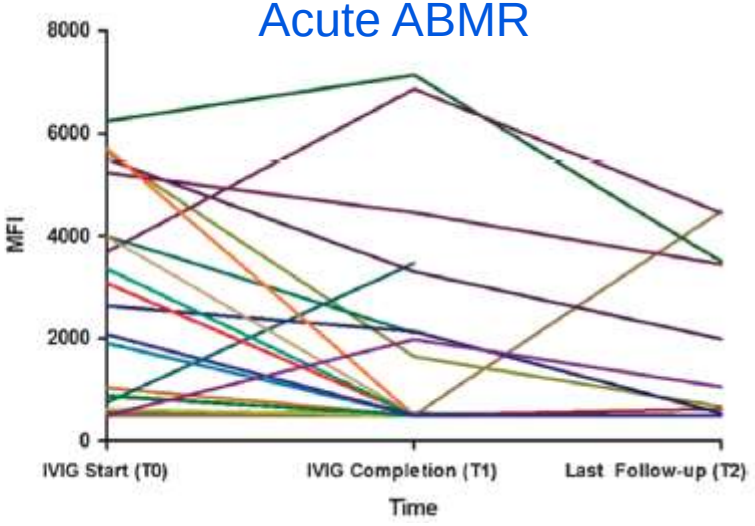
Time from transplant 15 months (23d to 82m)

Chronic ABMR



Graft function declined

Acute ABMR



Graft function stabilized

Cooper at al. Transplantation 2014

Late ABMR is Poorly Responsive to Therapy

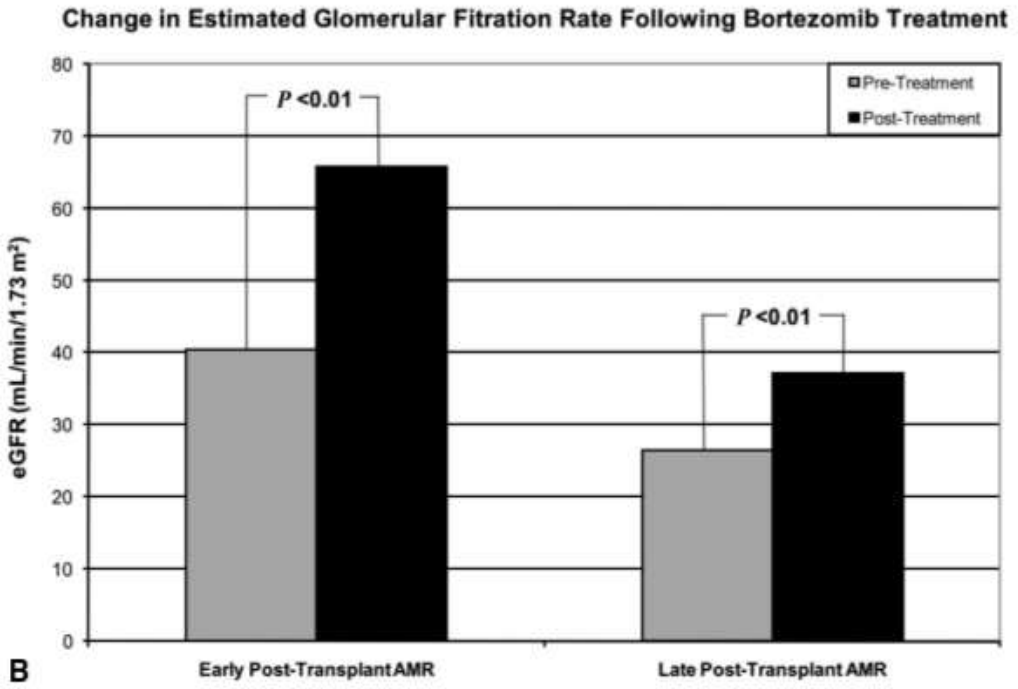
Early ABMR (if treated) Responds Better!

Early and Late Acute Antibody-Mediated Rejection Differ Immunologically and in Response to Proteasome Inhibition

R. Carlin Walsh,[1] Paul Brailey,[2] Alin Girnita,[2] Rita R. Alloway,[3] Adele Rike Shields,[1] Garth E. Wall, Basma H. Sadaka, Michael Cardi,[4] Amit Tevar,[1] Amit Govil,[3] Gautham Mogilishetty,[3] Prabir Roy-Chaudhury,[3] and E. Steve Woodle[1,5]

Early ABMR: < 6 months post-transplant
Late ABMR > 6 months post-transplant

Treatment: Plasmapheresis, IVIG, Rituximab and Bortezomib



Walsh RC et al, Transplantation 2011

Late ABMR

> 6 months post-transplant

- Usually in the context of **noncompliance** or **physician driven decrease in immunosuppression**
- Patients are more likely to have concomitant T cell mediated rejection
- DSA mostly HLA-Class II
- **Poorly responsive** to therapy
- **No preferred agents!**

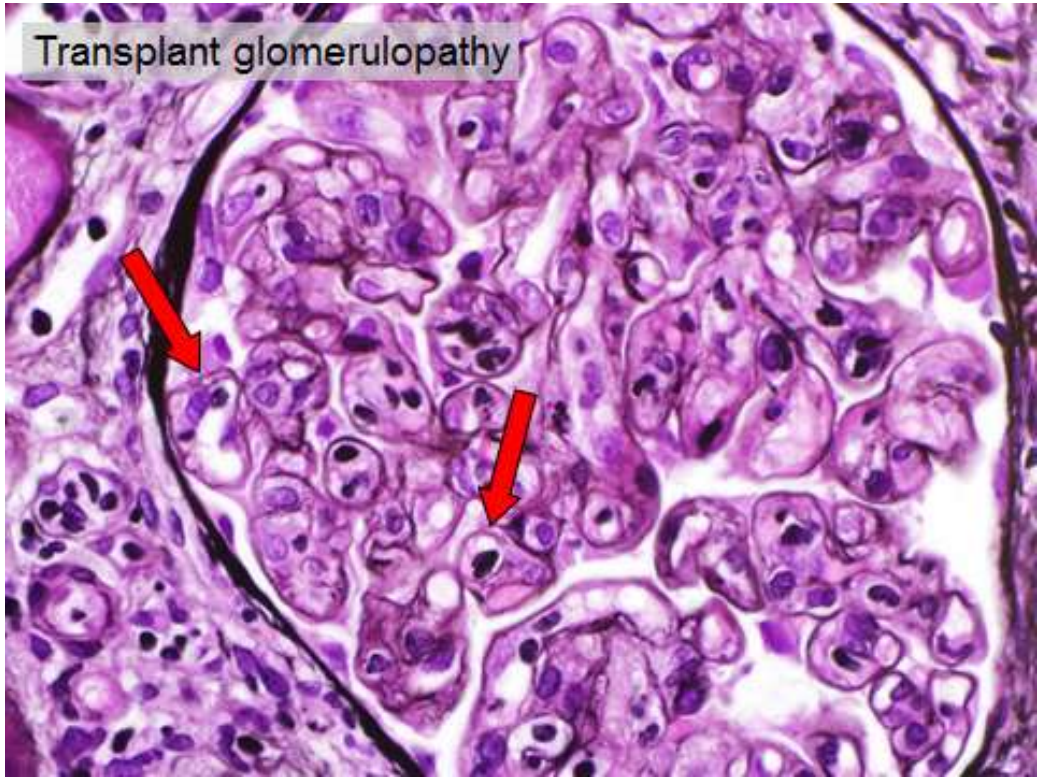
➢ **Le principal facteur de risque d'apparition d'un rejet tardif induit par des anticorps est la diminution volontaire de l'immunosuppression par les greffiers, ainsi que le manque de compliance du patient au traitement immunosuppresseur**

Case #2

- Received IVIG 1 g/kg monthly for 6 months
- Kidney function is gradually declining/more proteinuria
- DSA MFI 3000 – 4000 (DR7)

Clinical Scenario # 2

Transplant Glomerulopathy (glomerolopathie de l'allo-greffe)



No effective therapy!
Pas de traitement efficace!
(ACE-inhibitors/ARB)

Courtesy of Dr. Cornell

Outline

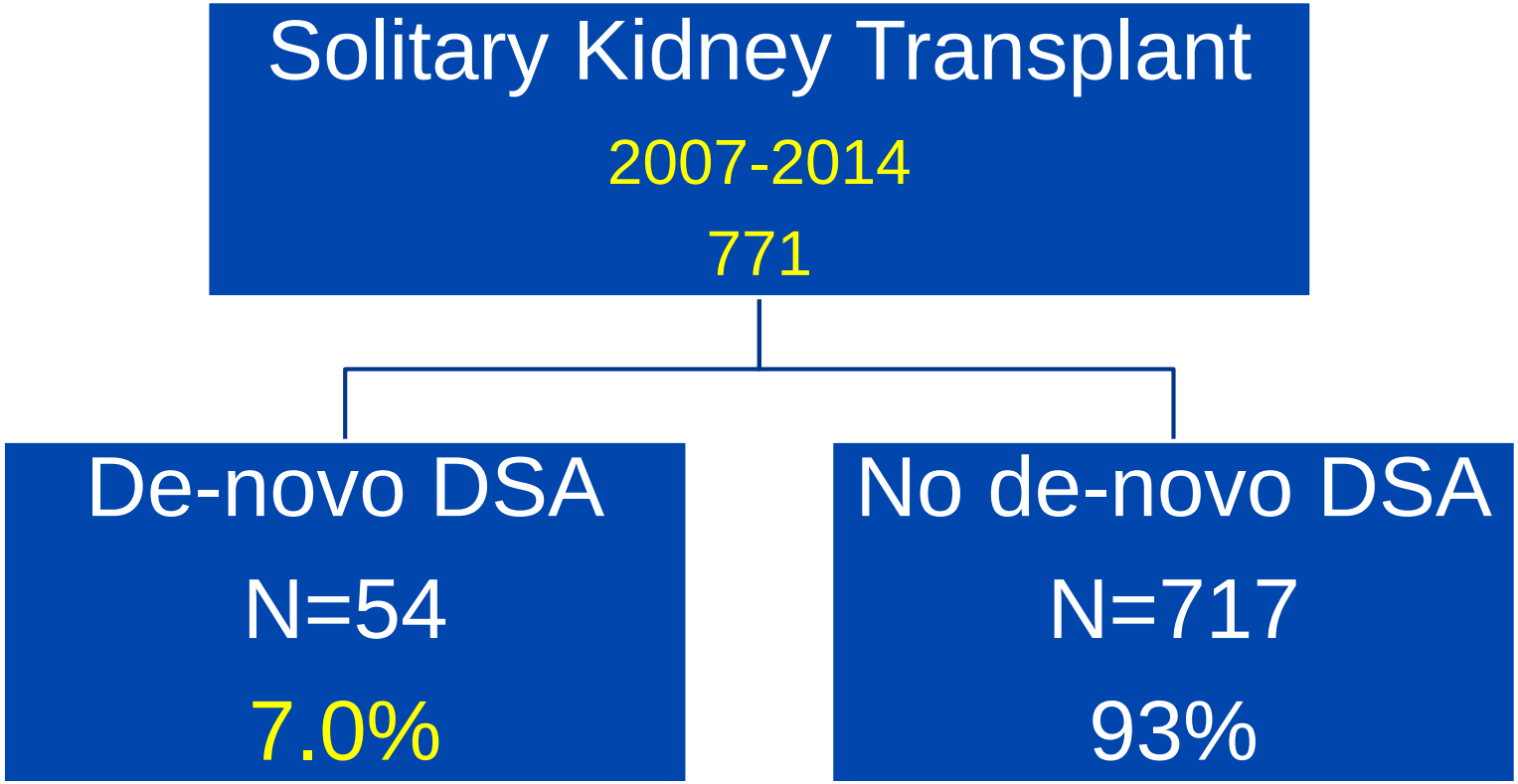
- Introduction
- Definitions
  - ABMR (acute & chronic)
- Pathophysiology
  - DSA (**D**onor-**S**pecific **A**ntibodies: pre-existing & de novo)
  - C4d
- Discuss the current therapeutic options of ABMR in different clinical scenarios
- Discuss management of recipients with **De Novo DSAs** and **normal kidney function**

Management of Recipients with De Novo DSAs *and* Normal Kidney Allograft Function

- Observation only?
- Changes in immunosuppression regimen?
- Kidney transplant biopsy?

Sensitization after Transplant—De Novo DSA

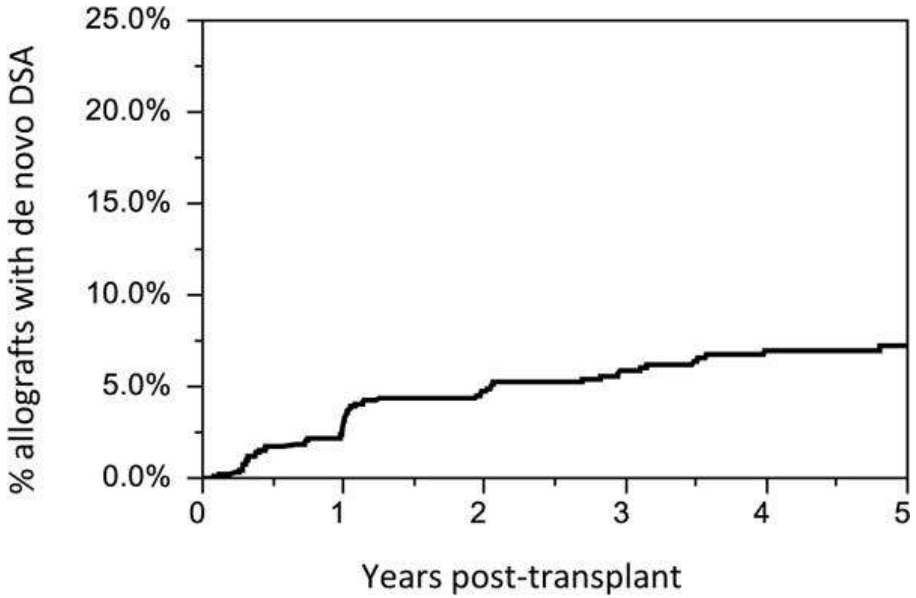
Mayo Clinic Experience



Schinstock CA, Cosio F et al,The Value of Protocol Biopsies to Identify Patients With De Novo Donor-Specific Antibody at High Risk for Allograft Loss. AJT 2017

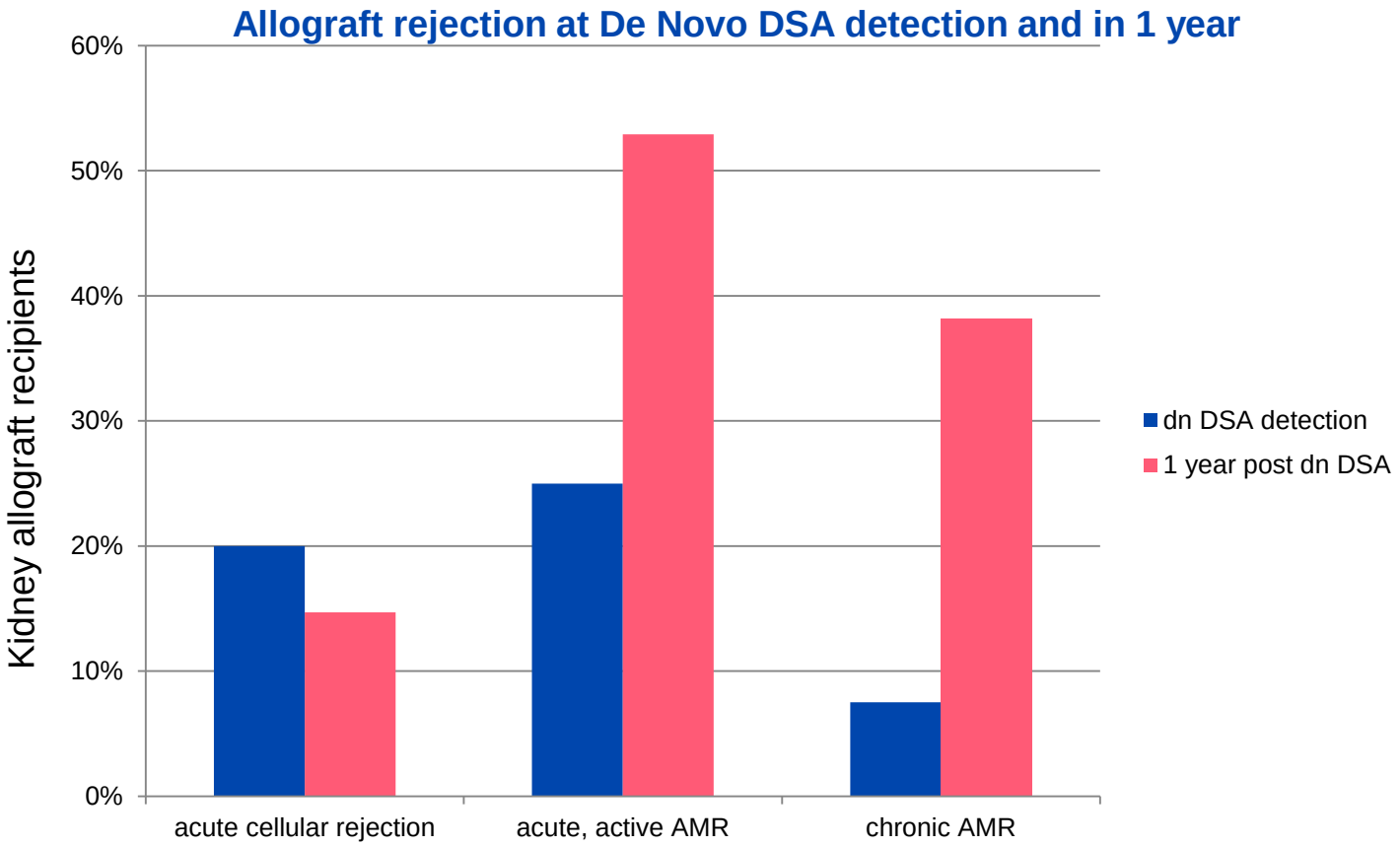
De Novo DSA Course

- Mean time to DSA detection was 1.8 (±1.6) years
- DSA: Class I: 9%, ***Class II: 70%***, class I and II: 20%
- 17% spontaneously resolved
- Follow up period: 4.2±1.9 years



Schinstock CA, Cosio F et al,The Value of Protocol Biopsies to Identify Patients With De Novo Donor-Specific Antibody at High Risk for Allograft Loss. AJT 2017

Detection of De Novo DSAs is Associated with Higher Risk of ABMR



Schinstock CA, Cosio F et al,The Value of Protocol Biopsies to Identify Patients With De Novo Donor-Specific Antibody at High Risk for Allograft Loss. AJT 2017

Outcome	+ De Novo DSA	No De Novo DSA	*P value*
Graft loss + 50% decline in GFR	**27.8%**	9.6%	<0.05
Acute **Active** ABMR	**54.9%**	8.1%	<0.05
cABMR	**37.2%**	6.8%	<0.05
T-Cell mediated Rejection	**20%**	12.5%	<0.05

- ***Le pronostic de la survie de la greffe rénale chez les patients qui développent des anticorps spécifiques de Novo contre le donneur est mauvais***

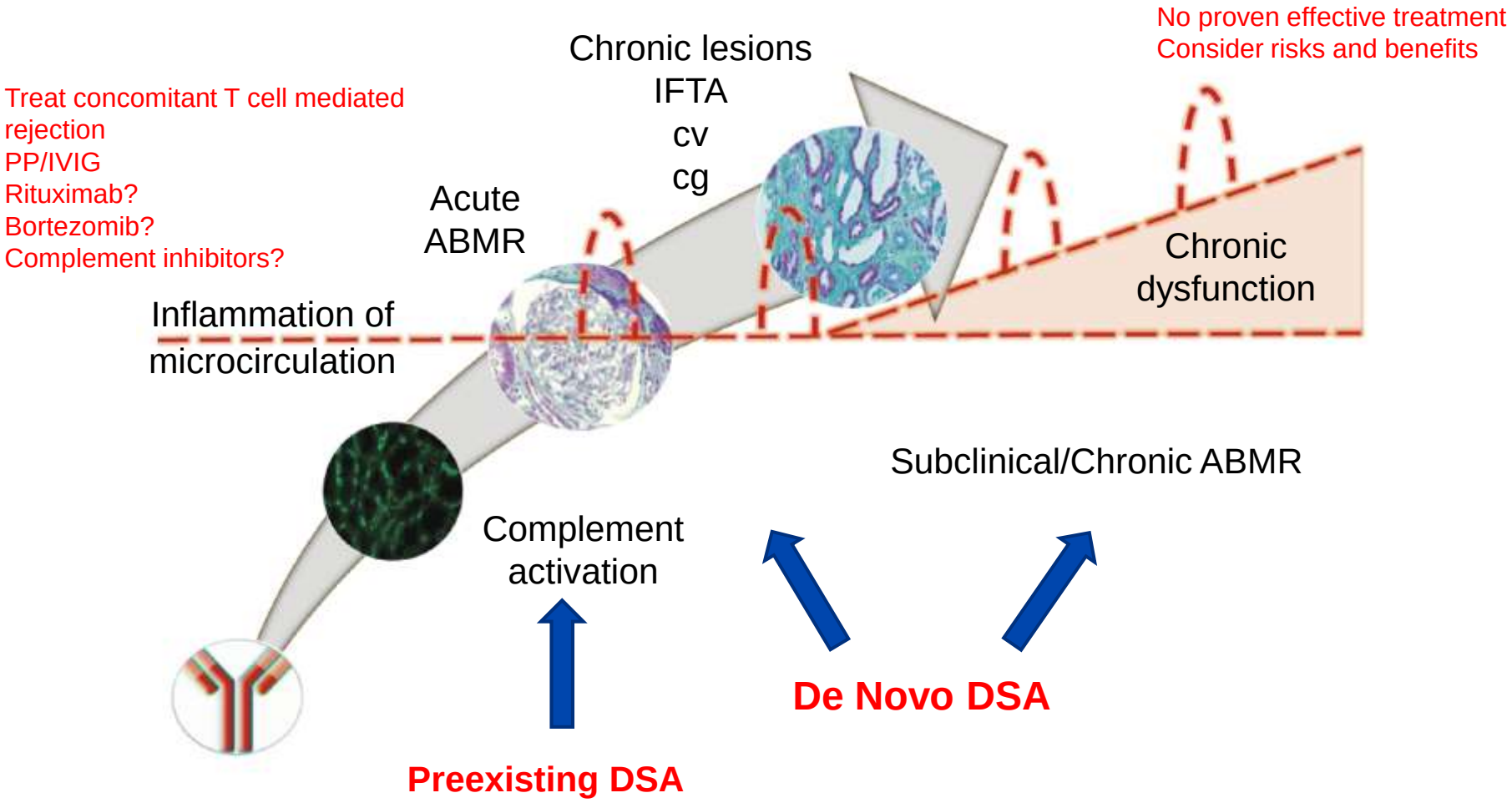
Schinstock CA, Cosio F et al,The Value of Protocol Biopsies to Identify Patients With De Novo Donor-Specific Antibody at High Risk for Allograft Loss. AJT 2017

Management of Kidney Transplants Recipients with **De-Novo DSA**

Mayo Clinic Approach

- Kidney transplant biopsy– *important to identify high risk patients*
- **If no rejection**, **augment** immunosuppression and consider repeating kidney transplant biopsy in 6-12 months
- If subclinical rejection–? consider treatment: ? Try IVIg
- *We need a multicenter randomized controlled trials!*

Antibody Mediated Rejection is a Spectrum!



Gosset at al: Curr Opin Nephrol Hypertens 23:597, 2014

Conclusion

- Treatment of ABMR is challenging- no silver bullet yet!

  (Il n'y a pas de formule magique ou de solution simple!)

- L'ABMR aigu (précoce <6 mois) est principalement causé par un anti-HLA DSA via la voie médiée par le complément et il est plus sensible au traitement que l'ABMR tardif, mais les résultats à long terme sont compromis
- ABMR tardif - (> 6 mois) est principalement le résultat de De Novo DSA et il est peu réactif au traitement: les risques et les avantages d' immunosuppression supplémentaire doivent être pris en compte
- Des essais contrôlés randomisés sont nécessaires

Questions & Discussion