RELEVANT ENDPOINTS IN Lung AMR treatment

Dr Antoine Roux (MD, PhD)
Pneumologie, Hôpital FOCH

BANFF Barcelona
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Foch Lung Transplant Group

Conflict of interest

BANFF conflict of interest:

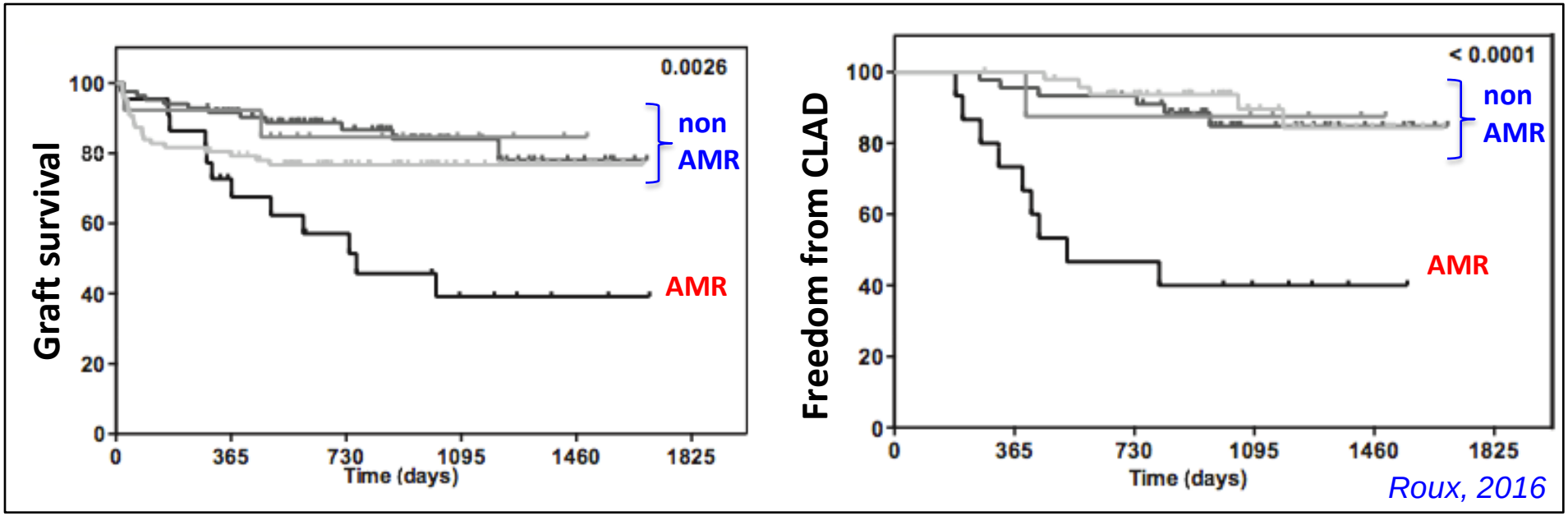
NO conflict of interest for this presentation

General conflict of interest:

Scientific adviser for Novartis (2014, CMV)

Scientific adviser for Biotest (2017, CMV)

Antibody mediated rejection (AMR): THE BIG THREAT



MAJOR IMPACT of AMR in Solid Organ Transplantation

➔ Graft function (chronic dysfunction)

➔ Graft & patient survivals

Antibody mediated rejection (AMR): THE BIG THREAT

The New England
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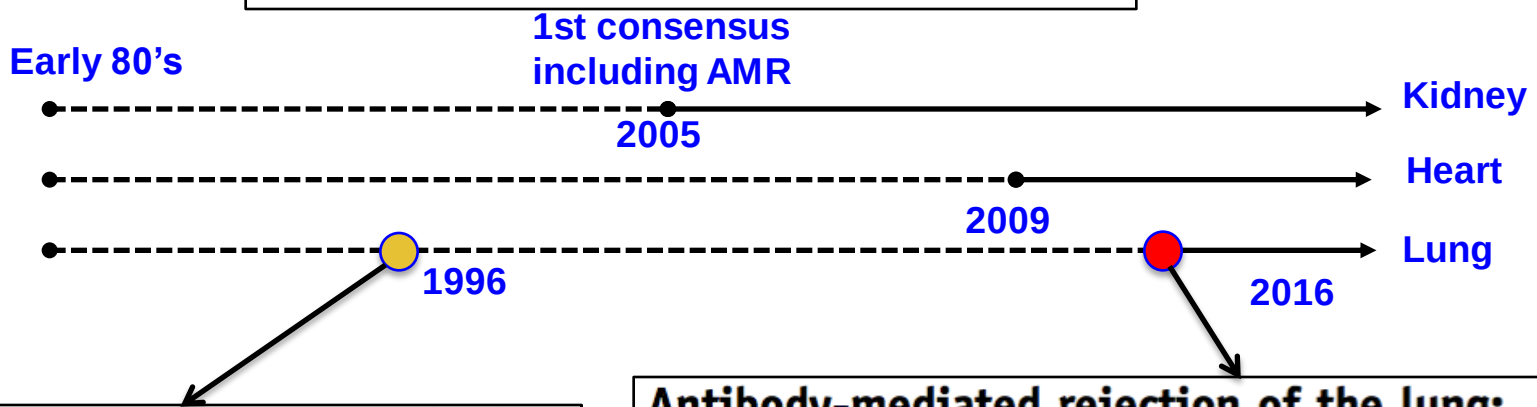
SIGNIFICANCE OF THE POSITIVE CROSSMATCH TEST IN KIDNEY TRANSPLANTATION*

RAMON PATEL, M.R.C.P., AND PAUL I. TERASAKI, PH.D.

Abstract Crossmatch tests of the prospective kidney-transplant donor's lymphocytes with the serum of the prospective recipient in 225 transplants showed that eight of 195 with negative crossmatch failed to function immediately, in contrast to 24 of 30 with positive crossmatch (p less than 0.001). Immediate failure occurred in significantly higher numbers among patients with a higher risk of having antibodies, such as multiparous females and patients receiving secondary transplants. The effect was not a nonspecific one, for more immediate failures occurred among transplants from unrelated than among those from related donors. The corresponding frequency of positive crossmatch was also lower among related donors. The presence of preformed cytotoxic antibodies against the donor appears to be a strong contraindication for transplantation.



Hyperacute Rejection Following Lung Transplantation*

Adaani E. Frost, MD; Cory T. Jammal; and Philip T. Cagle, MD

Antibody-mediated rejection of the lung: A consensus report of the International Society for Heart and Lung Transplantation

Deborah J. Levine, MD,[a] Allan R. Glanville, MBBS, MD,[b] Christina Aboyoun, BA, MBA,[b] John Belperio, MD,[c] Christian Benden, MD, FCCP,[d] Gerald J. Berry, MD,[e] Ramsey Hachem, MD,[f] Don Hayes Jr., MD, MS,[g] Desley Neil, MBBS, PhD,[h] Nancy L. Reinsmoen, PhD, D(ABHI),[i] Laurie D. Snyder, MD,[j] Stuart Sweet, MD, PhD,[f] Dolly Tyan, PhD,[e] Geert Verleden, MD, PhD,[k] Glen Westall, MBBS, PhD,[l] Roger D. Yusen, MD, MPH,[f] Martin Zamora, MD,[m] and Adriana Zeevi, PhD[n]

Clinical AMR

Antibody-mediated rejection of the lung: A consensus report of the International Society for Heart and Lung Transplantation

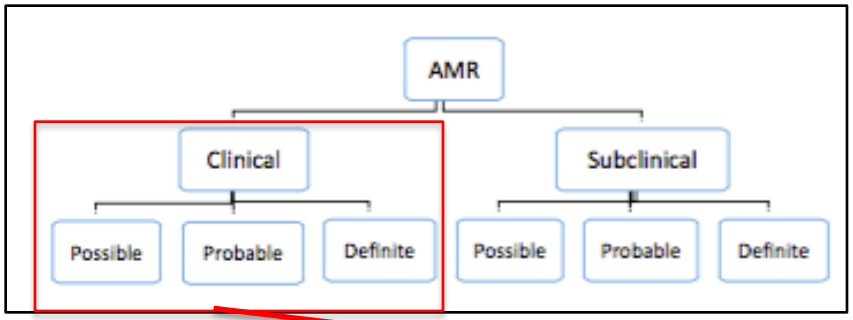


Table 1 Definition and Diagnostic Certainty of Clinical Pulmonary Antibody-mediated Rejection

	Allograft dysfunction	Other causes excluded	Lung histology	Lung biopsy C4d	DSA
Definite	+	+	+	+	+
Probable[a]	+	+	+	–	+
Probable	+	+	+	+	–
Probable	+	+	–	+	+
Probable	+	–	+	+	+
Possible	+	+	+	–	–
Possible	+	+	–	–	+
Possible	+	+	–	+	–
Possible	+	–	+	+	–
Possible	+	–	+	–	+
Possible	+	–	–	+	+

DSA, donor-specific antibodies; +, item present; –, item absent or missing.
[a]There is building evidence that antibody-mediated rejection can be diagnosed confidently in the absence of positive C4d staining, hence this group is recognized separately.

Proactive TBB documentation

Subclinical AMR

Antibody-mediated rejection of the lung:
A consensus report of the International Society for Heart and Lung Transplantation

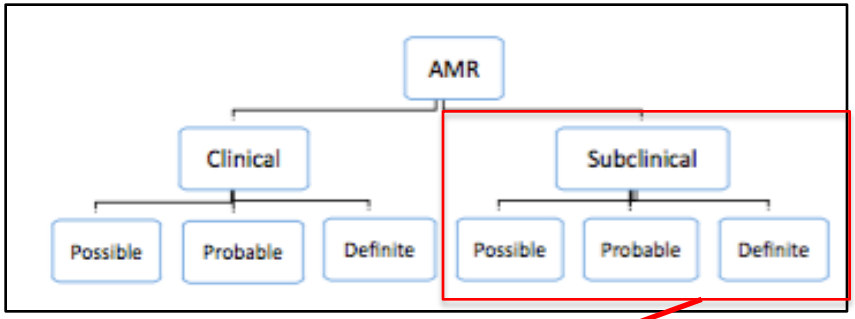


Table 2 Definition and Diagnostic Certainty of Sub-clinical Pulmonary Antibody-mediated Rejection

	Lung histology	Lung biopsy C4d	DSA
Definite	+	+	+
Probable	+	–	+
Probable	–	+	+
Probable	+	+	–
Possible	+	–	–
Possible	–	+	–
Possible	–	–	+

DSA, donor-specific antibodies; +, item present; –, item absent or missing.

Proactive TBB documentation besides graft failure

- **Protocolized TBB**
- **DSA positivity**

Antibody-mediated rejection of the lung: A consensus report of the International Society for Heart and Lung Transplantation

Allograft dysfunction

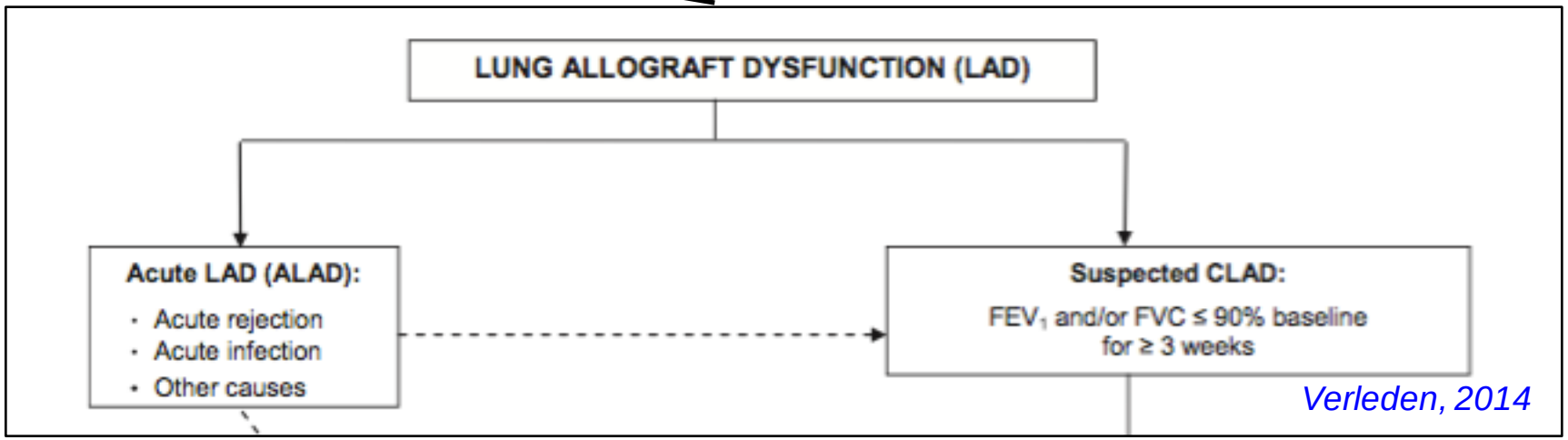
Lung histology

Lung biopsy C4d

DSA

Allograft dysfunction

« decline (…) of FEV1 of > 10% from baseline »



	Definition	Expectations
Acute dysfunction	FEV1 decrease	FEV1 recovery (to baseline)
Early dysfunction	« Insufficient » FEV1 progression	« Better progression …»
Severe dysfunction	Need for O2/ventilation, Infiltrate on CT	Recovery (weaninig O2/ventilation/CT normalisation)
Chronical dysfunction	FEV1 decrease	FEV1 stabilisation
Sub clinical	No graft dysfunction	steady function

Lung Histology

Pathology of pulmonary antibody-mediated rejection: 2012 update from the Pathology Council of the ISHLT

Berry, 2013

Table 2 Histopathologic Indications for Immunopathologic Evaluation

1. Neutrophilic capillaritis
2. Neutrophilic septal margination
3. High-grade acute cellular rejection (≥A3)
4. Persistent/recurrent acute cellular rejection (any A Grade)
5. Acute lung injury pattern/diffuse alveolar damage
6. High-grade lymphocytic bronchiolitis (Grade B2R)
7. Persistent low-grade lymphocytic bronchiolitis (Grade B1R)
8. Obliterative bronchiolitis (Grade C1)
9. Arteritis in the absence of infection or cellular rejection
10. Graft dysfunction without morphologic explanation
11. Any histologic findings in setting of de novo DSA positivity

DSA, donor-specific antibodies.

Poor reproducibility

Table 5. Inter-Observer Reliability

Variable	Median of Kappa	Range of Kappa
Biopsy Adequacy	0.28	(-0.03, 0.42)
ACR	0.40	(0.24, 0.62)
Airway Inflammation	0.23	(0.11, 0.56)
Obliterative Bronchiolitis	0.18	(0.04, 0.58)
Acute Lung Injury DAD	0.20	(0.03, 0.63)
Endotheliitis	0.22	(-0.04, 0.47)
Alveolar Hemosiderosis	0.40	(0.19, 0.62)
Capillary Inflammation	0.17	(0.03, 0.31)
Suspicion for Aspiration	0.14	(-0.02, 0.66)
C4d	0.40	(0.24, 0.78)

Wallace, 2015

NEED IMPROVEMENT for publication AND real life

Standardisation

➔ « common analysis grid »

➔ 6 french centers

Sharing experience/ external validation

➔ Padova experience

lungtransplant.dctv.unipd.it/

UNIVERSITY OF PADOVA

C4d staining

Positivity: capillary staining

Intensity: 0➔+++

Distribution: Diffuse>50%, Focal= 50-10%, Minime <10%

POSITIVITY=?

Positive staining with C4d Ab of non C4d structures (elastic fibre, hyalin membrane)
Internal staining control?

Positive staining with C4d Ab of C4d deposition unrelated to DSA

➔ Ischemia- reperfusion/GERD/infection/CMV

Table 5. Inter-Observer Reliability

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BETTER INTEROBSERVER RELIABILITY

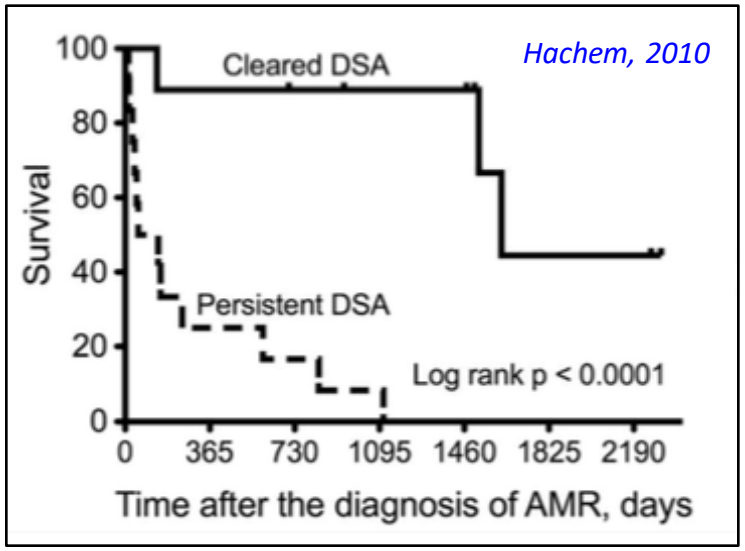
Donor specific antibody

DSA negativation

➔ Drop down below 500 MFI

➔ Associated with better outcomes

(Hachem, 2010) (Witt, 2013)

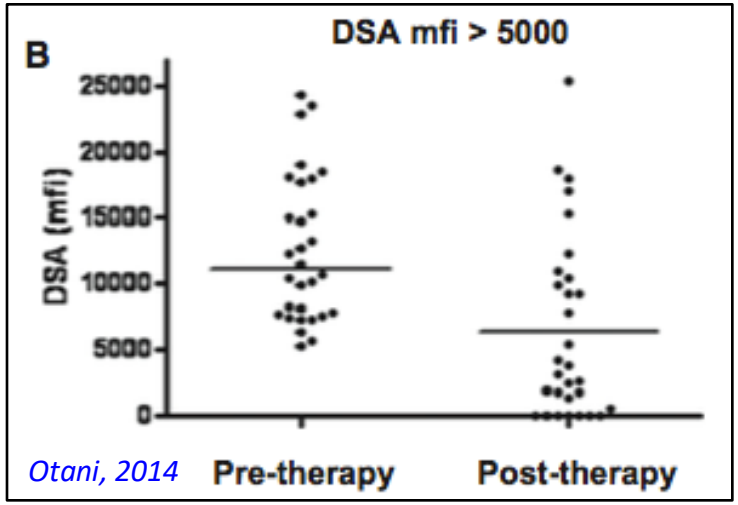


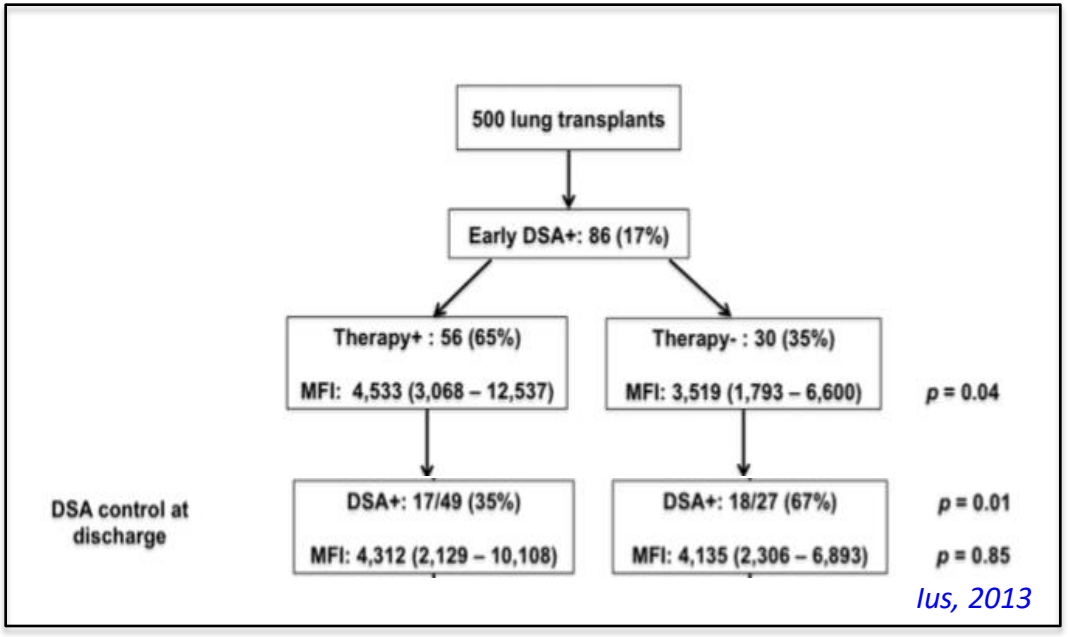
DSA decrease

➔ Only few negativation among treated patient

(Otani, 2014) (Ius, 2015)

➔ What decrease is clinically relevant?





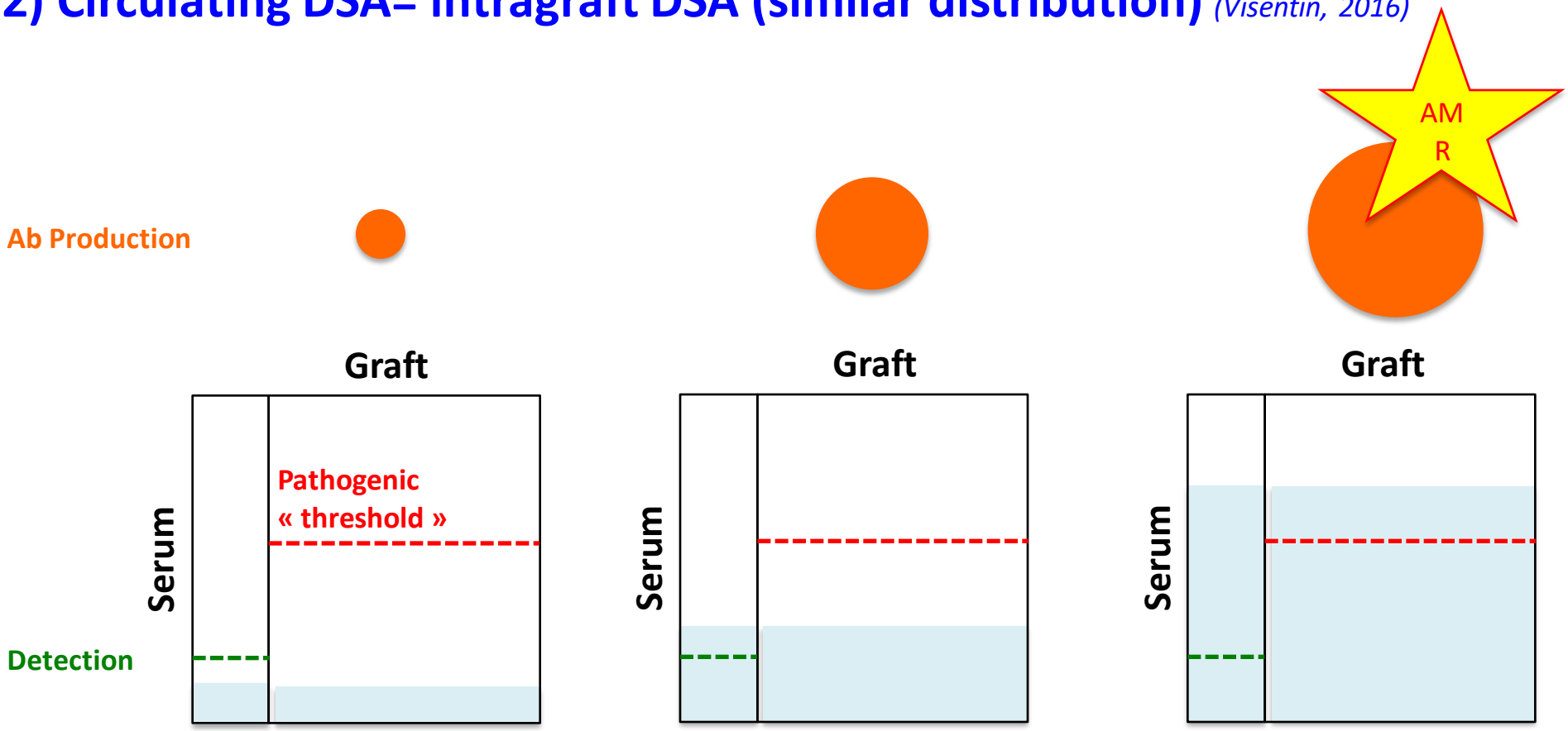
Assumptions for DSA MFI interpretation

1) We can detect DSA if they are present BUT

➔no large screening tools for non HLA DSA

➔ depends on single Ag kit repertoire/Antigen on beads quality

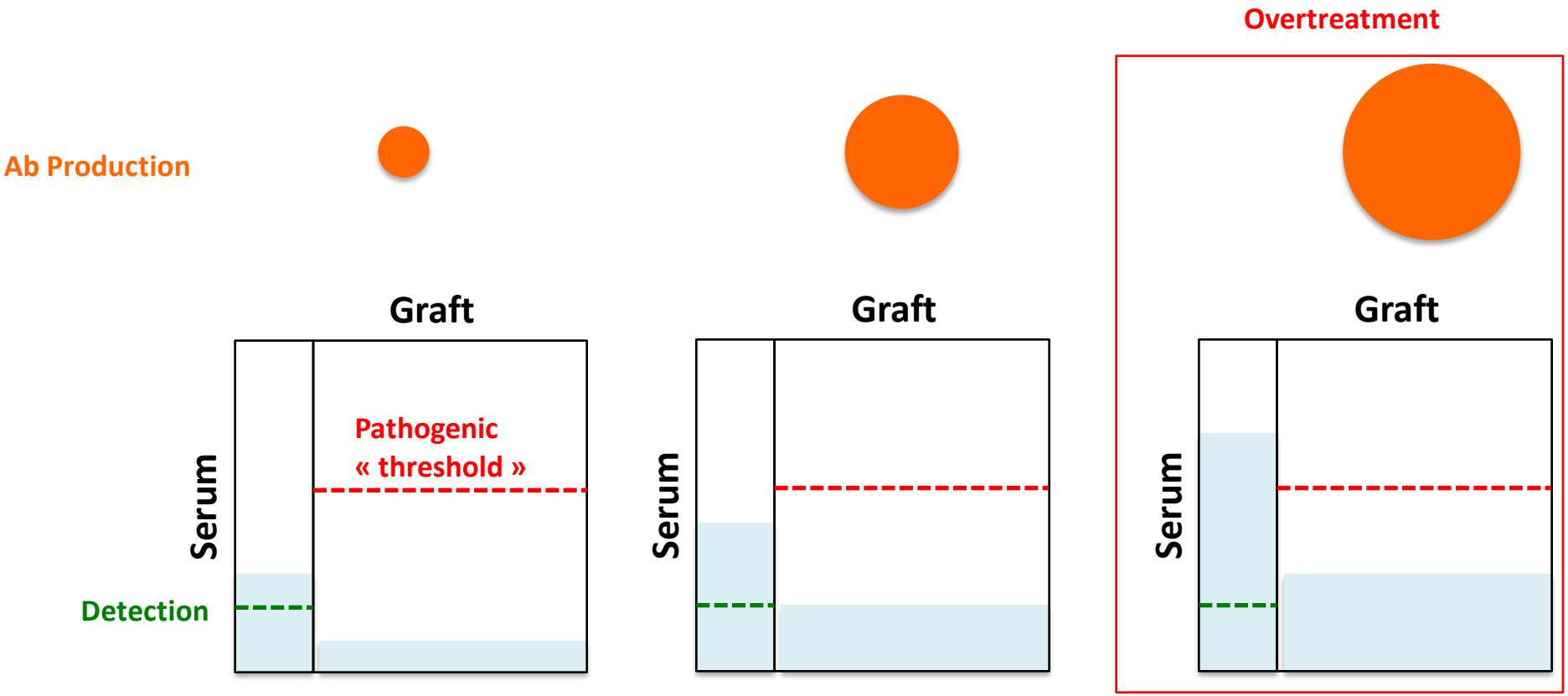
2) Circulating DSA= intragraft DSA (similar distribution) *(Visentin, 2016)*



Assumptions for DSA MFI interpretation

Serum DSA > graft DSA

Low affinity DSA



Assumptions for DSA MFI interpretation

Graft DSA >> Serum DSA

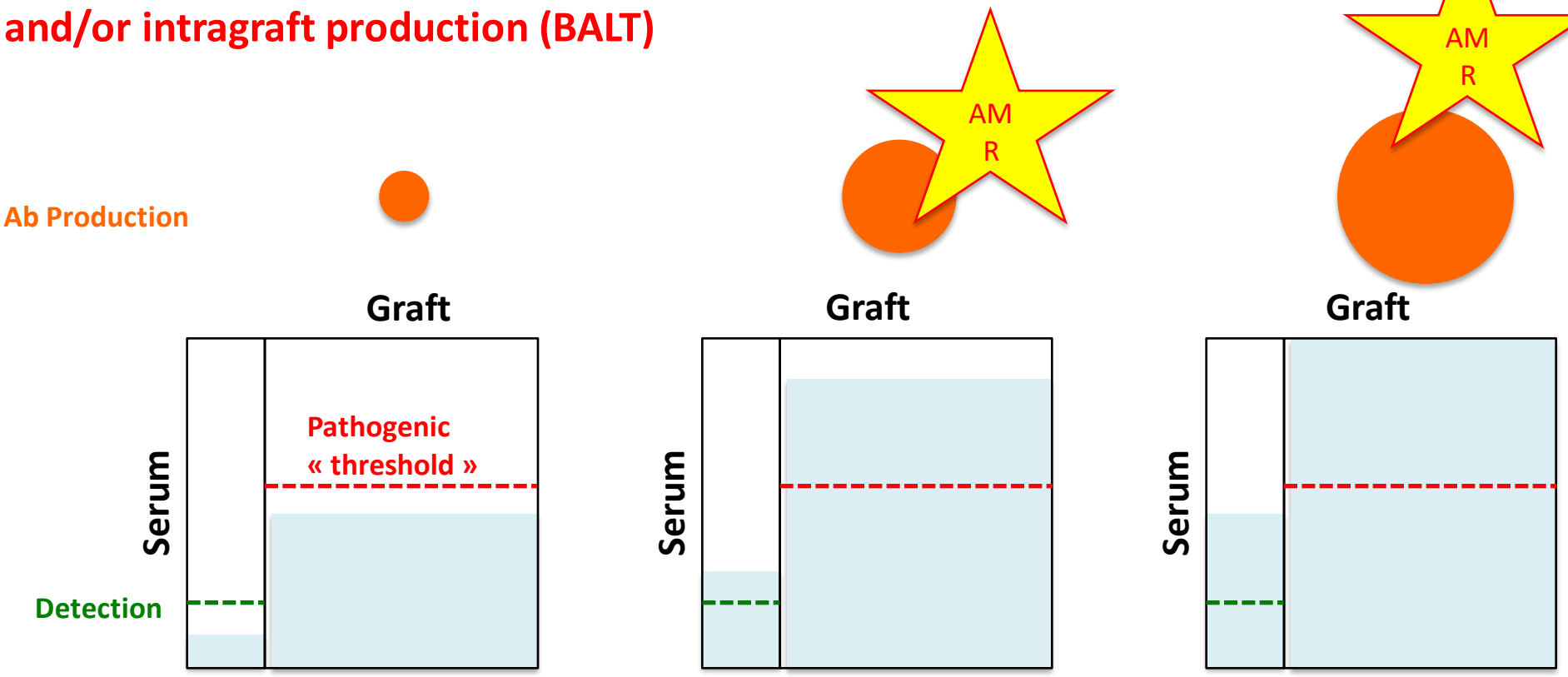
High affinity DSA

Sponge effect+++

➔capillary surface= lung (100m2) >> kidney (10m2)

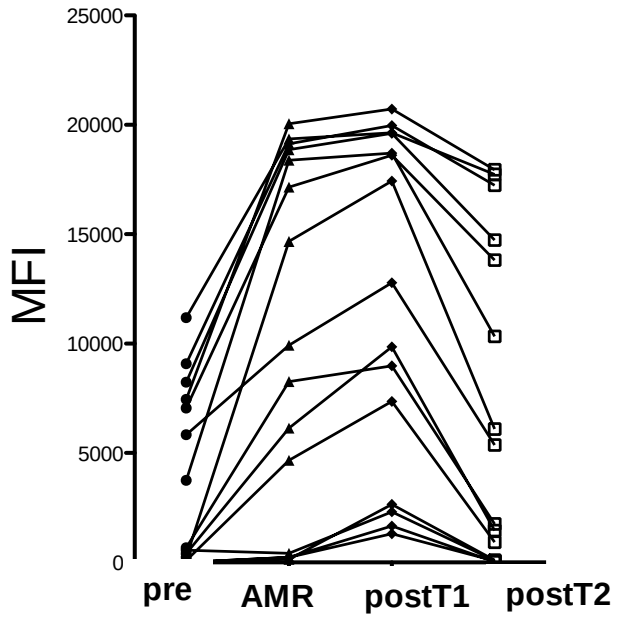
➔ « 1 DSA was in a biopsy specimen only (s–/gþ DSA) » among 11 gDSA+ patients *(Visentin, 2016)*

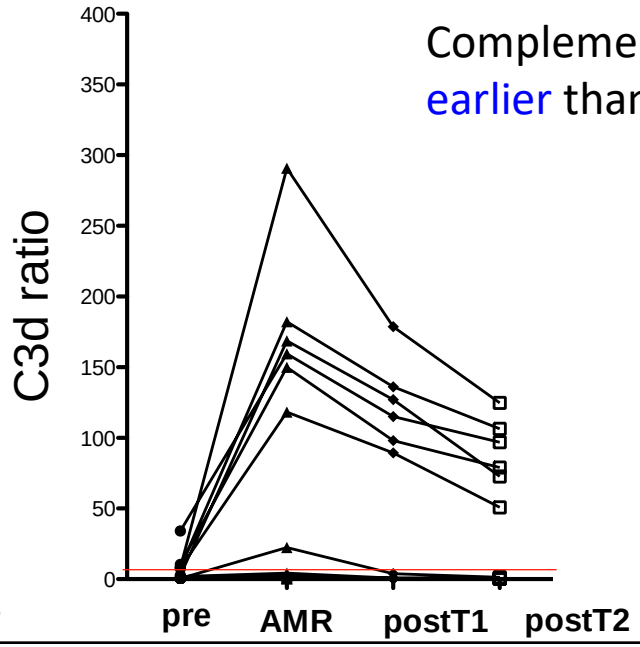
and/or intragraft production (BALT)



DSA: dimensions besides MFI

Complement binding ability

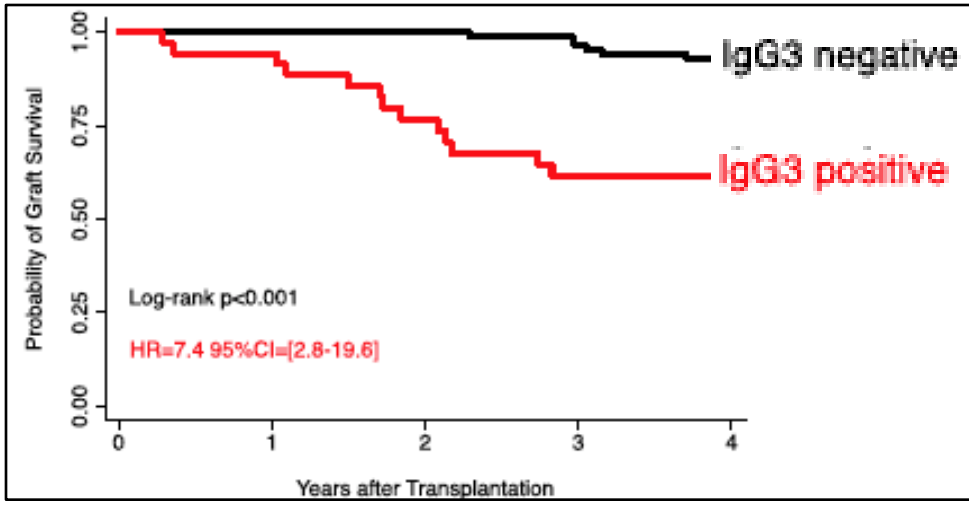




Complement binding decrease earlier than MFI under Treatment

Roux, submitted

IgG subclasses



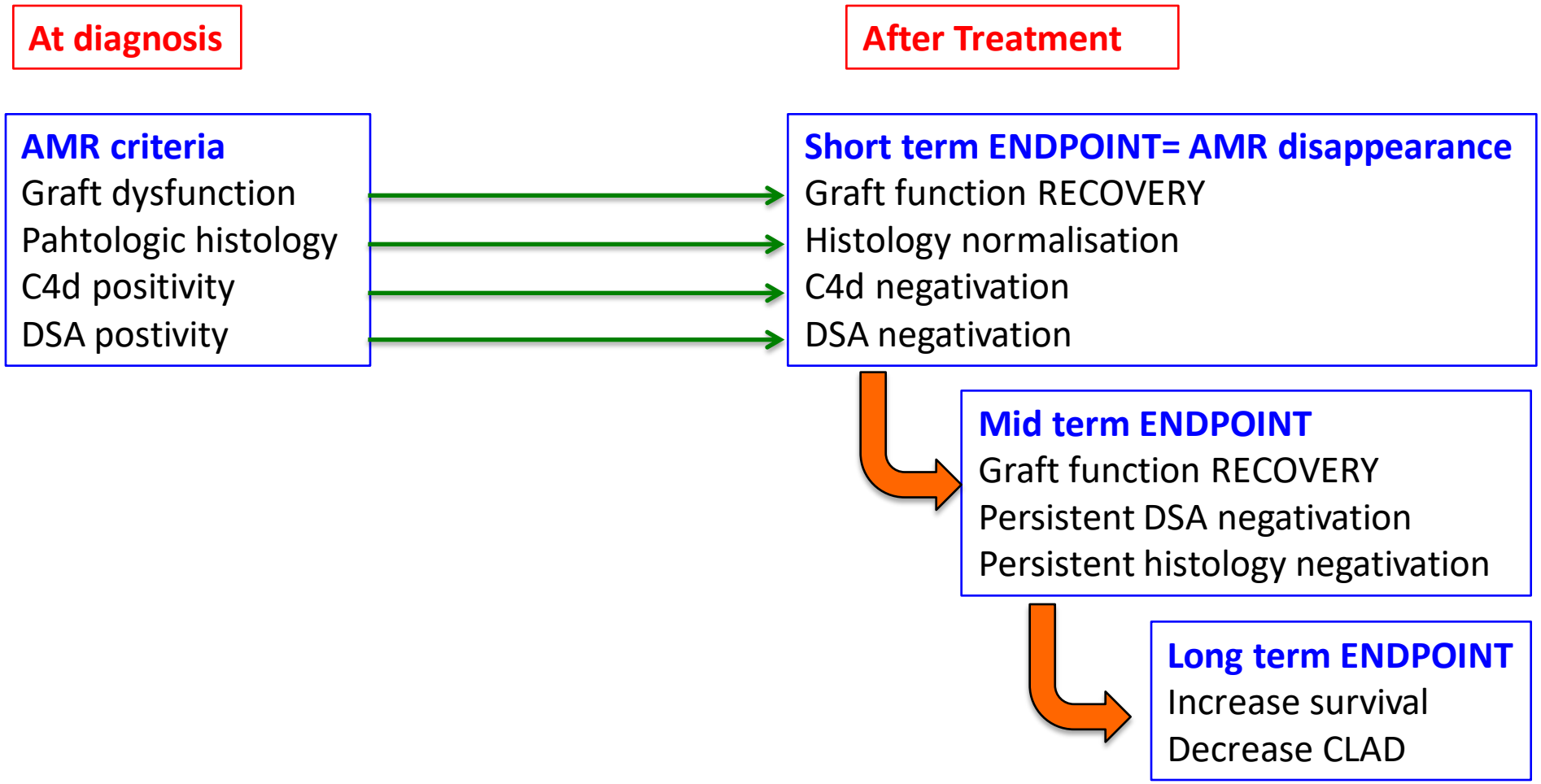
IgG3 ➔ acute AMR

IgG4➔ subclinical AMR

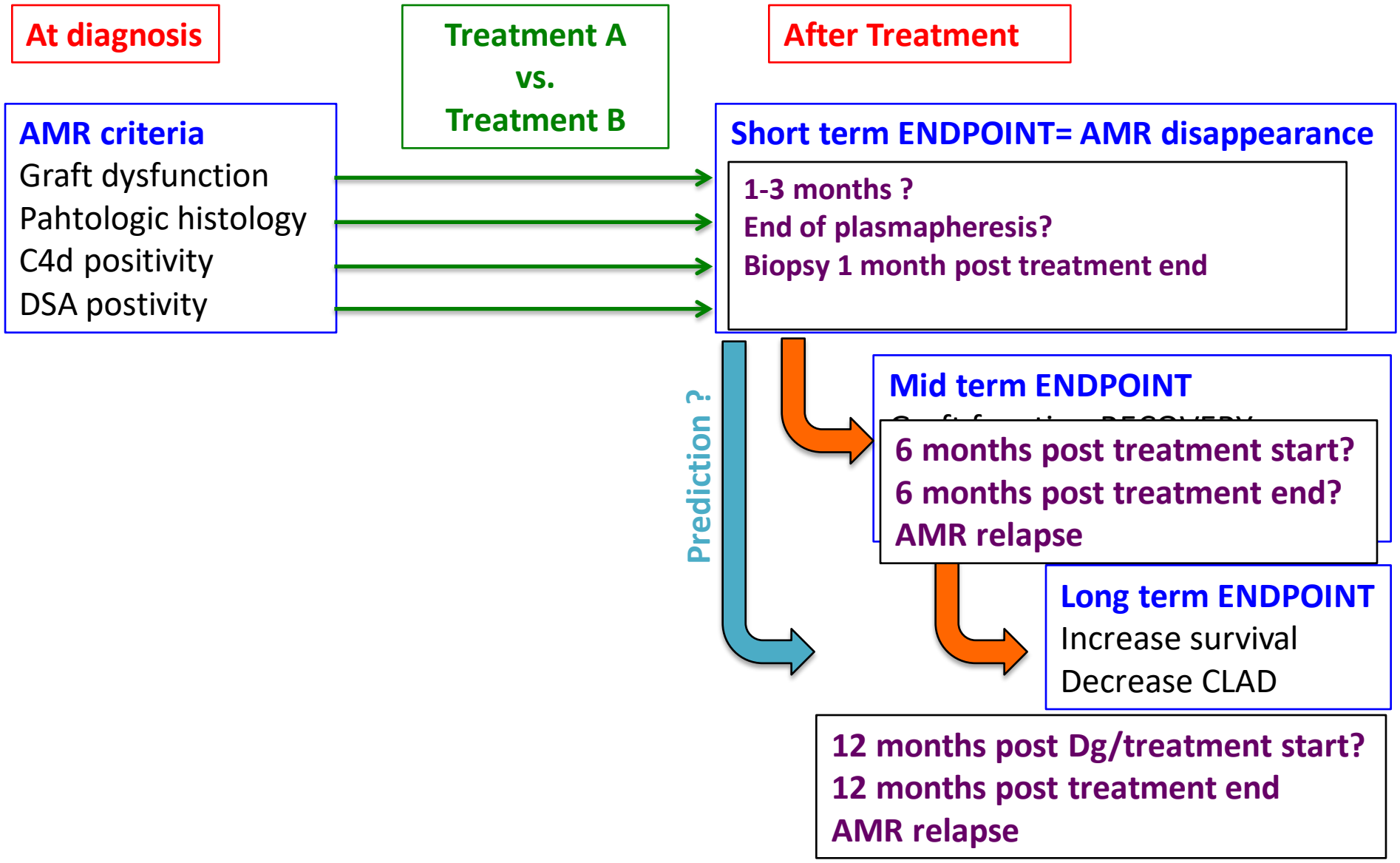
Class switch after treatment?

Lefaucheur, 2016

Relevant Endpoints of AMR treatment



The right timing for evaluation?



Different expectations depending of the combination used

Antibody depletion
PP / Immunoadsorption

→ **DSA decrease/negativation**
➔ *Few days/ last for few weeks*

Antibody production inhibition
***RITUXIMAB** / Bortezomib / **IVIG** / T cell therapy*

→ **B cell depletion**
➔ *Few days/ last for few months*
DSA decrease/production inhibition
➔ *Few months/ several months*

Antibody toxicity inhibition
*Steroid / **IVIG** / Complement Inhibition*

→ **C1q/C3d**
➔ *immediate complement inhibition C1q-C3d binding (few days)*
(Machimoto, Transplant International, 2010)
➔ *C4d staining (few weeks)*

Real Life based proposition

Clinical assessment → **Portative FEV1:** daily
Functional Respiratory test: +3-4 weeks
CT scan: 1st evaluation 3-4 weeks (unless worsening)
chronical dysfunction: +3 months

DSA assessment → **Single Antigen**
After 5 PP; Monthly before IVIG ; /3-6 months after treatment end
No access to C1q/C3d/Subclasses for clinical practice

TBB and C4d staining → **3-4 weeks after treatment of AMR**
Afterwards: DSA increase/graft failure

Conclusion

Pathology of pulmonary antibody-mediated rejection: 2012 update from the Pathology Council of the ISHLT

Antibody-mediated rejection of the lung: A consensus report of the International Society for Heart and Lung Transplantation

- Multicentric evaluation of TREATMENT
- Clinical phenotype
- Improve DSA characterisation
- Improve PATHOLOGY
- New Diagnosis Tools ?
  ➔ Molecular microscopy…

Thank you for your attention