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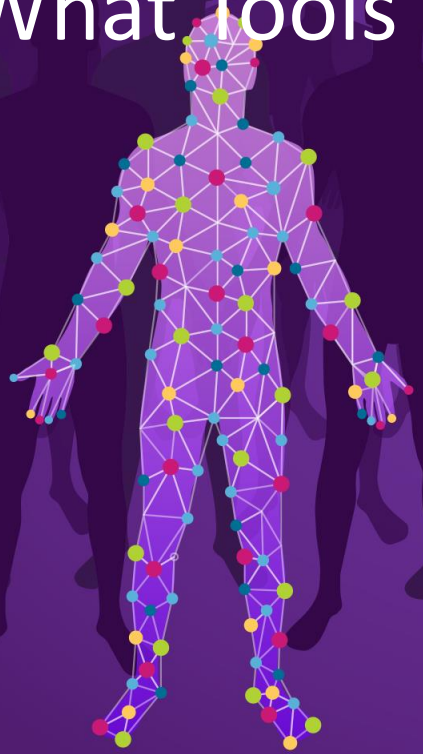
Measuring Immuno-responsiveness: What Tools Do We Have In Our Arsenal?



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CEOT CUTTING EDGE of TRANSPLANTATION

TRANSPLANT SUMMIT 2019

NO SIZE FITS ALL: *Uncovering the Potential of Personalized Transplantation*

FEBRUARY 21–23, 2019 • ARIZONA BILTMORE • PHOENIX, AZ

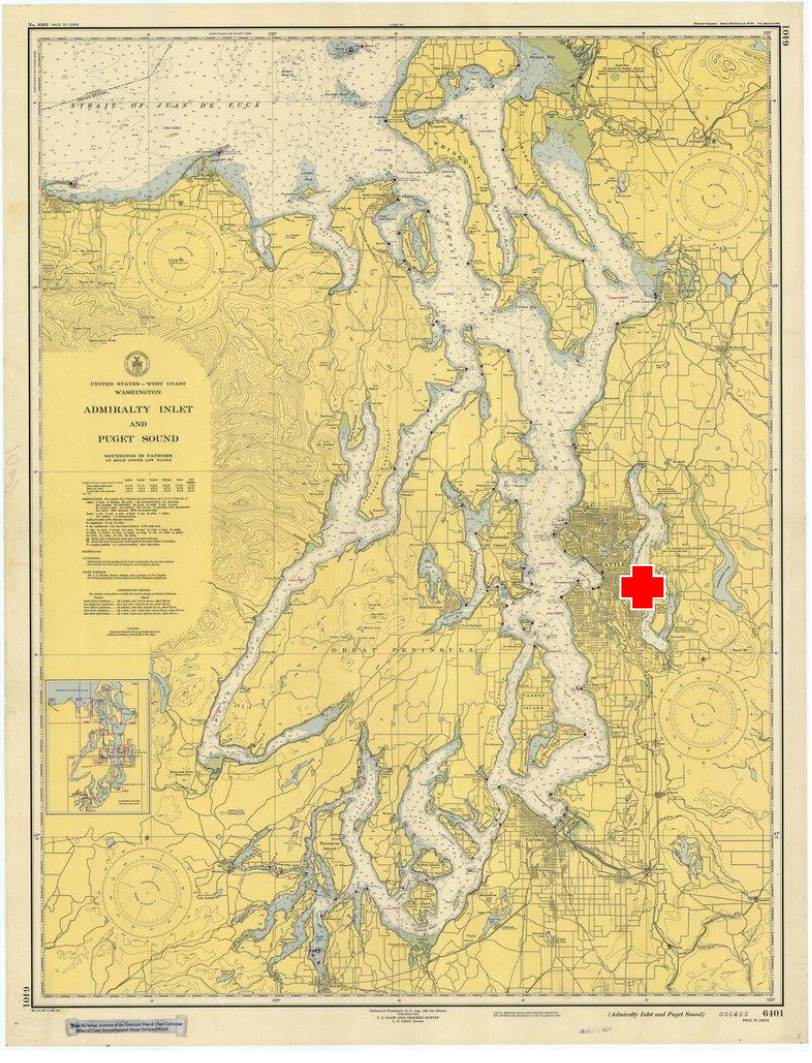
Disclosures

No conflicts of interest

Learning Objectives: Review current available biomarkers reflecting immuno-responsiveness

- Non-specific markers of humoral and cellular immune function
- Viremia and virus-specific responses
- HLA-related responses

Basic Tools of Navigation



Balancing inadequate vs. excessive immunoresponsiveness

GRAFT HEALTH AND FUNCTION

Cellular and Humoral Rejection

INFECTION

DRUG LEVELS AND TOXICITY

MALIGNANCY

Cause of Death	>3 Years - 5 Years (N=3,941)	>5 Years - 10 Years (N=4,992)
OB/BOS	1,176 (29.8%)	1,234 (24.7%)
Acute Rejection	24 (0.6%)	23 (0.5%)
Lymphoma	55 (1.4%)	93 (1.9%)
Malignancy, Non-Lymphoma	478 (12.1%)	761 (15.2%)
CMV	10 (0.3%)	6 (0.1%)
Infection, Non-CMV	694 (17.6%)	835 (16.7%)
Graft Failure	704 (17.9%)	804 (16.1%)
Cardiovascular	184 (4.7%)	293 (5.9%)
Technical	18 (0.5%)	36 (0.7%)
Multiple Organ Failure	158 (4.0%)	233 (4.7%)
Other	440 (11.2%)	674 (13.5%)

Biomarkers
That Reflect or Predict Immune Responses

Non-Specific Pathways

- Humoral immune function
- Cellular immune function
- Drug Metabolism

Allo-Immune Pathways

- HLA Mismatch
- Anti HLA Antibodies
- Cellular rejection

Non-specific immunity: Hypogammaglobulinemia

- IgG < 700
  - 60% overall incidence
- IgG < 400
  - 32% time of transplant.
  - 6-14% 3 months to 1 year
- Hypogammaglobulinemia associated with increased risk for
  - pneumonia
  - BOS

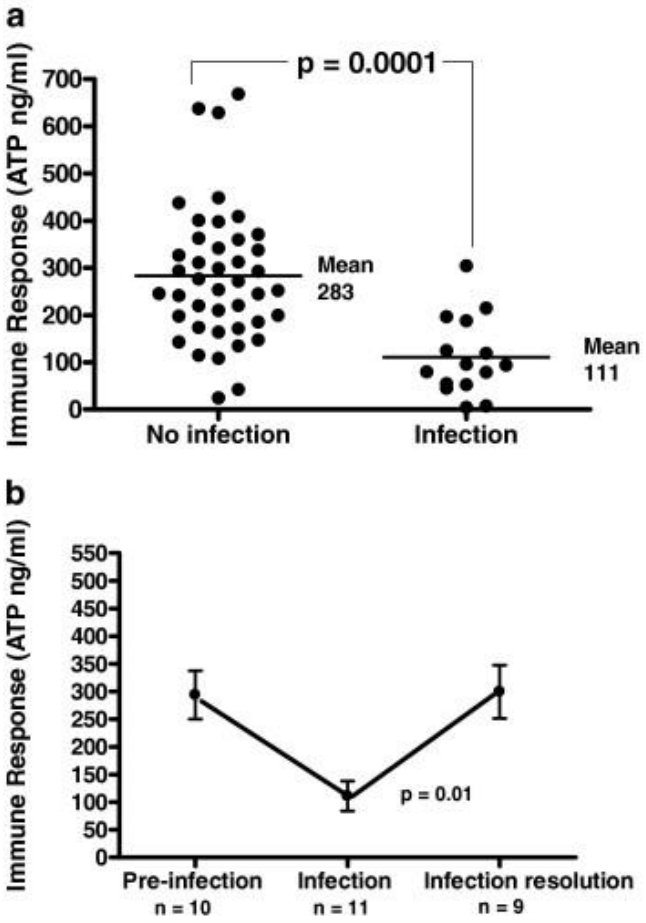
(Kawut et al, Transplantation 2005; Petrov et al, Transplant Direct 2018; Chambers et al, JHLT 2013)

Assessment of T-cell Mitogen Response

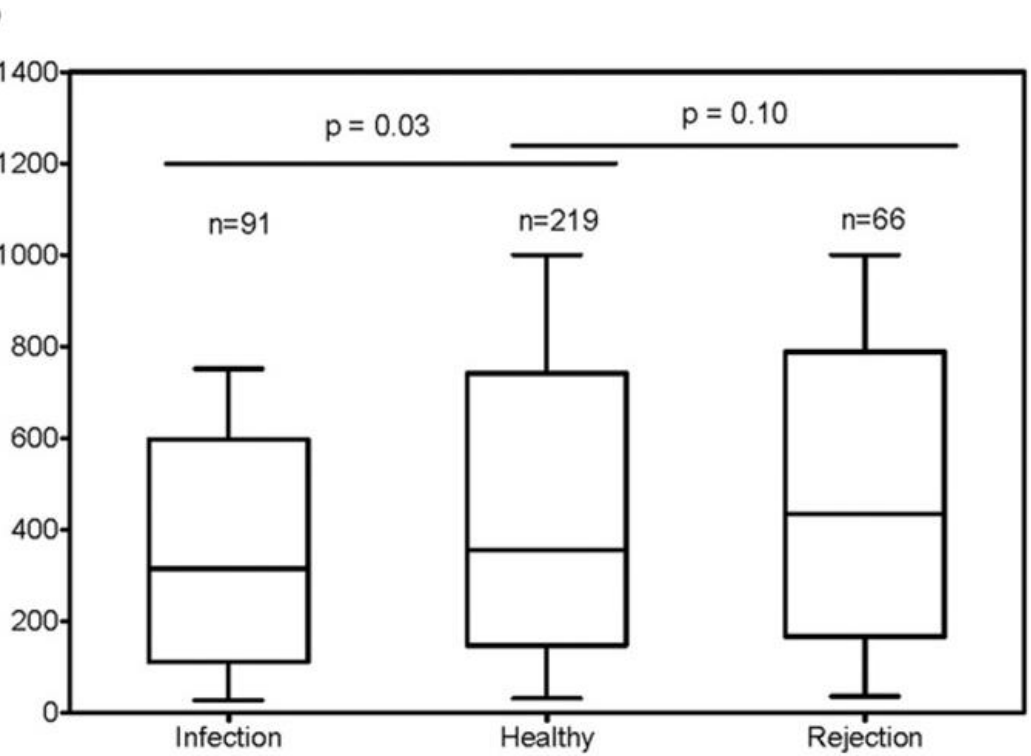
CD4+ T-Cell ATP production in response to the mitogen phytohemagglutinin(PHA)

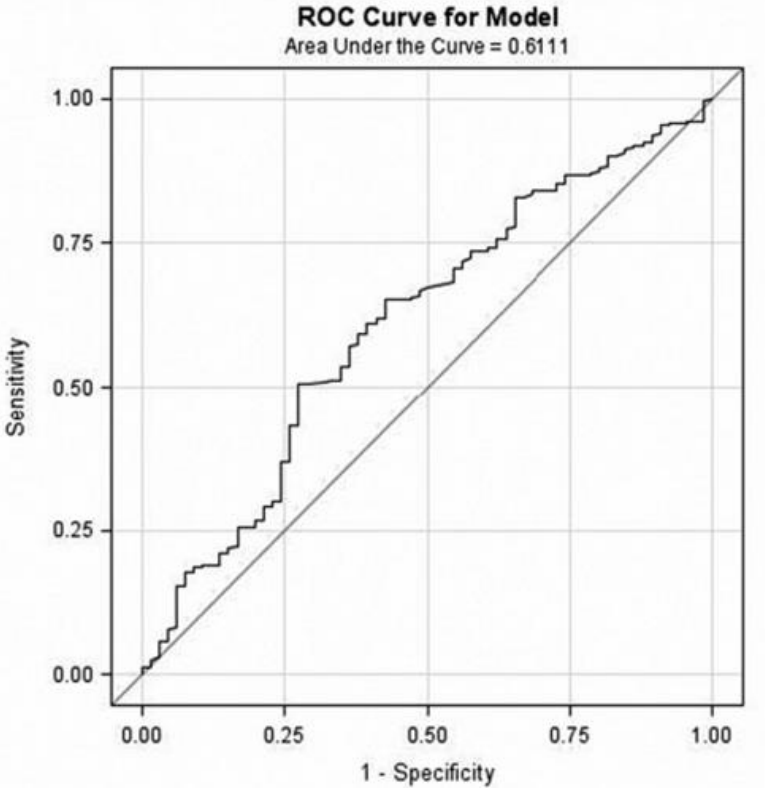
Responses are lower in lung transplant recipients with infection

Bhorade et al, JHLT 2008



Usefulness of immune monitoring in lung transplantation using adenosine triphosphate production in activated lymphocytes:
Shino et al, J Heart Lung Transplant 2012

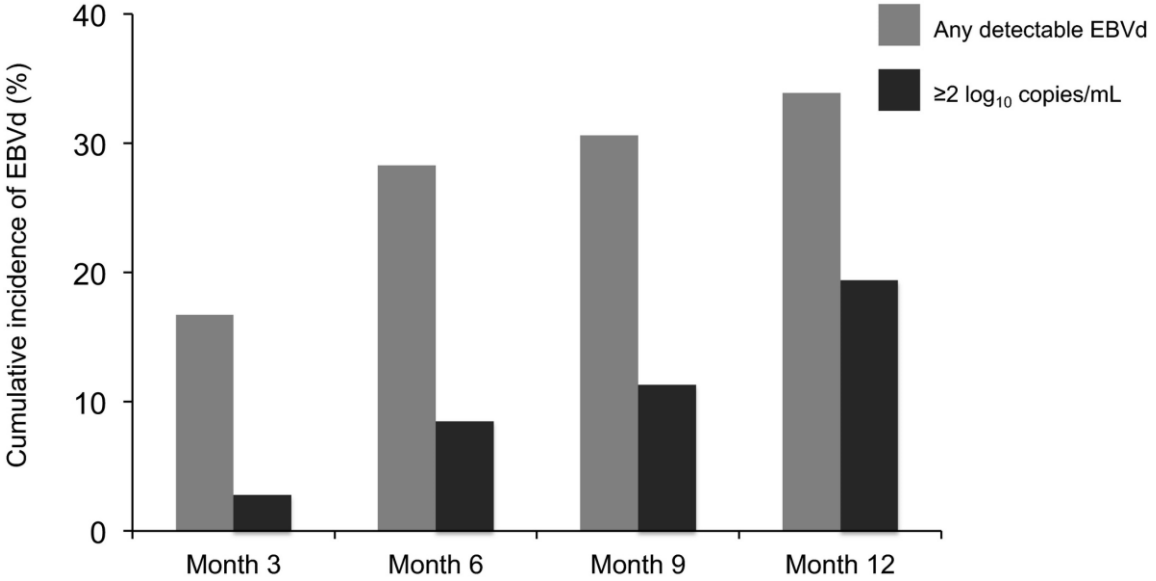




Viremia and Immuno-responsiveness

EBV Viremia

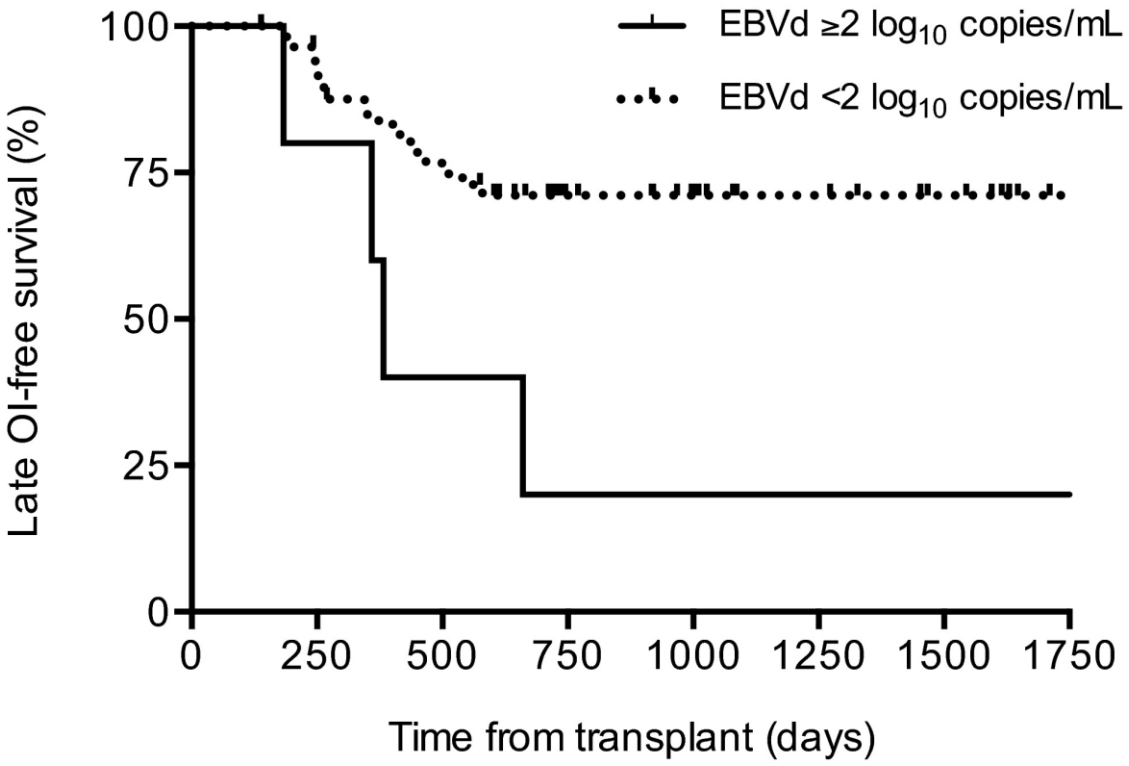
- 1/3 of patients in 1st year
- Tx for AR associated with increased EBV viremia



Silva et al, Transp Inf Dis 2016

EBV Viremia

- Higher levels of EBV viremia within 1st 6 months assoc. with greater long term risk of opportunisitic infection (80% vs. 28%) driven largely by greater incidence of invasive fungal disease
- EBV viremia may be a marker of excessive suppression of the immune response



CMV Immune response

- In-vitro stimulation of CD8+ T-cells with CMV antigen and measurement IFNγ release compared to mitogen response (ELISPOT assay)
- A specific marker of immunoresponsiveness to CMV
- Can can be used to tailor duration of antiviral prophylaxis and reduce the rate of CMV infection

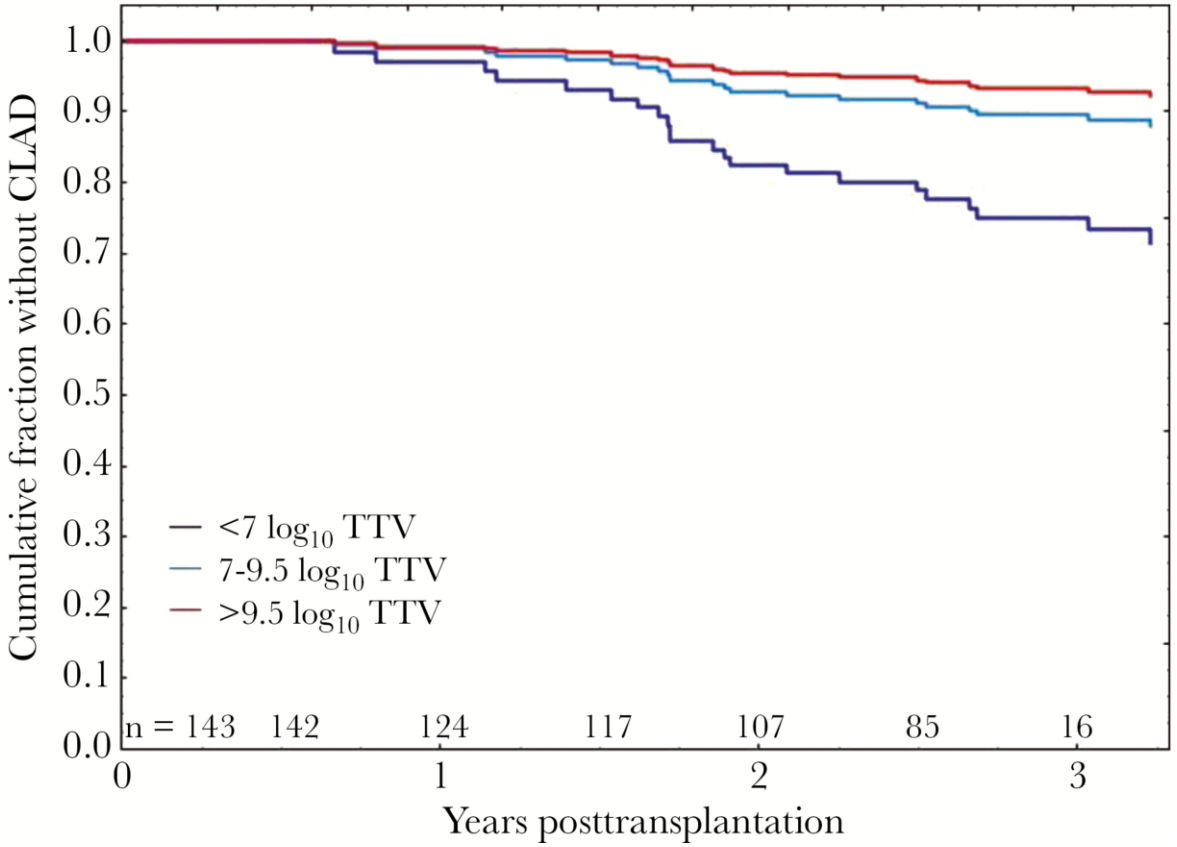
Westall et al, Transplantation 2018
Kumar et al, Am J Transplant 2017

Viral PCR: Torque Teno Virus

- DNA virus present in most humans
- Viremia increases with immune suppression
- Potential negative correlation between viral load and immunoresponsiveness
- A non-specific marker of immunoresponsiveness

Torque Teno Virus as a Novel Biomarker Targeting the Efficacy of Immunosuppression After Lung Transplantation

Lower levels of viremia associated with higher Incidence of CLAD



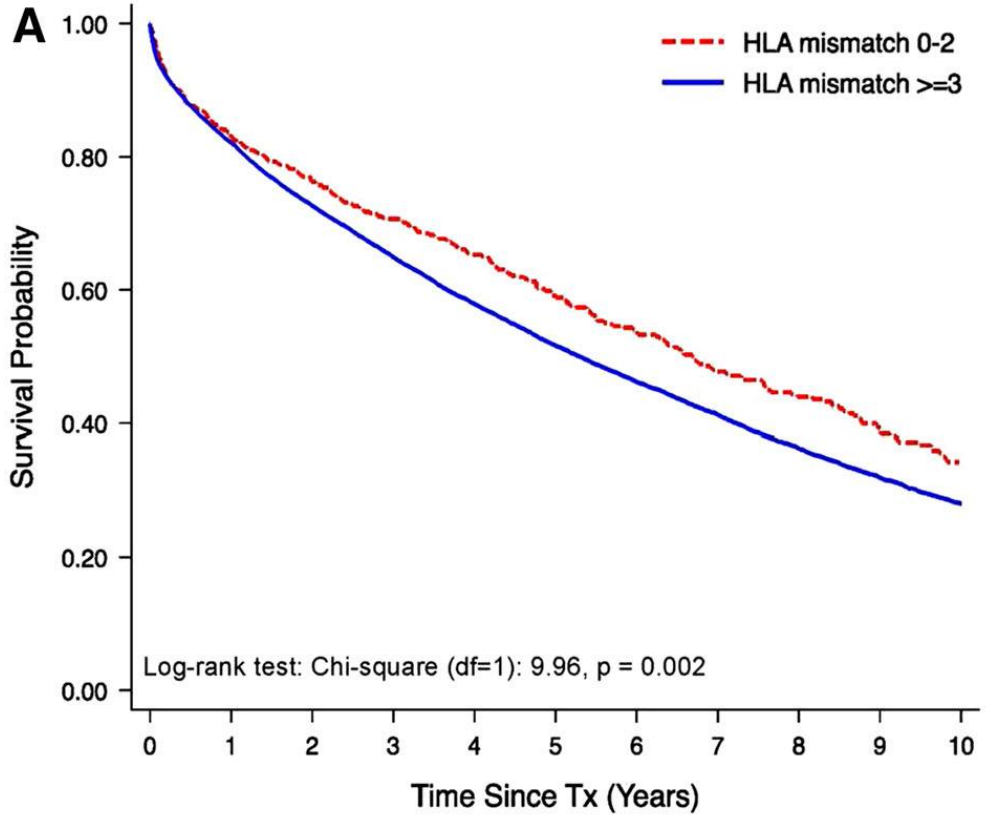
. Jaksch et al, J Infect Dis. 2018

HLA and DSA Assessment

HLA Mismatch & Survival

HLA mismatches ≥ 3
HR of 1.214 for mortality
vs. HLA mismatches 0-2

HLA-A mismatch HR 1.070
HLA-DR mismatch HR 1.054

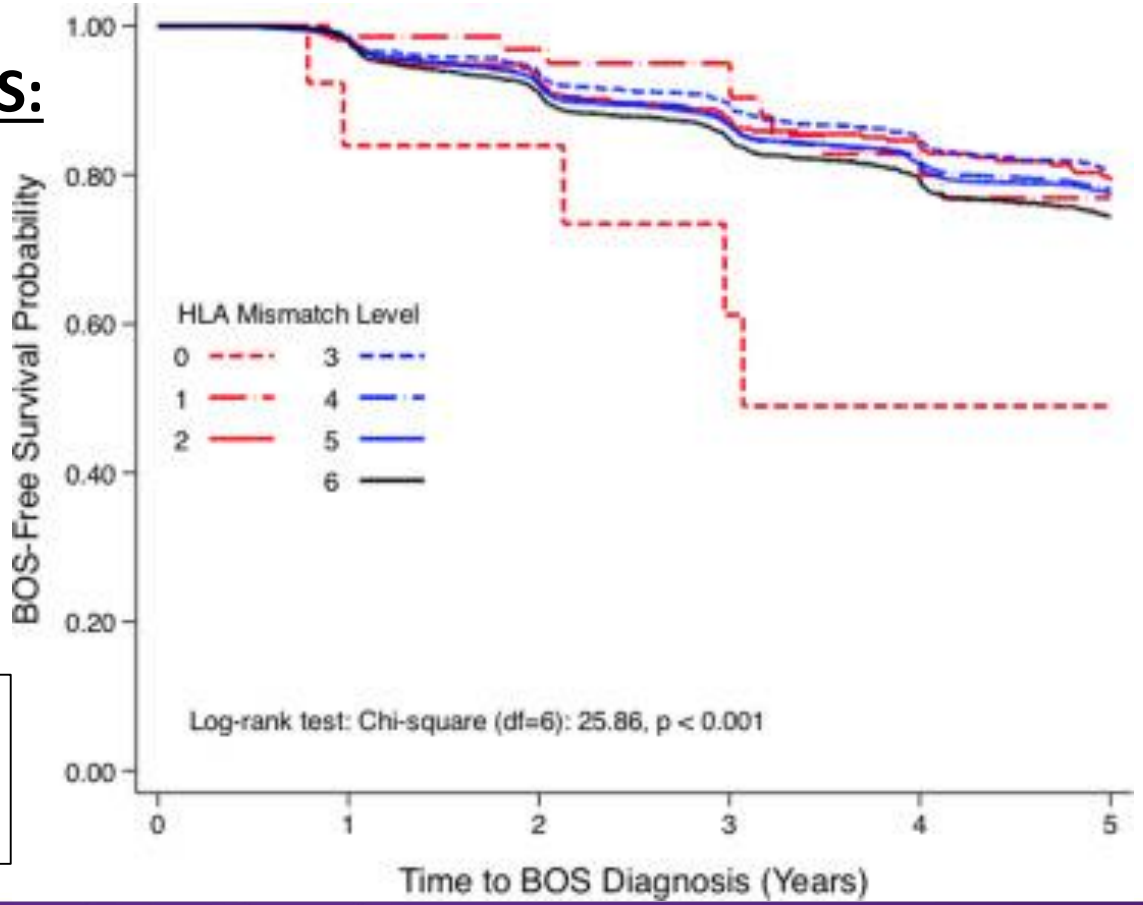


Influence of HLA Mismatching on Survival in Lung Transplantation.
Hayes et al, Lung 2015

HLA Mismatch and BOS:

Number of mismatches associated with BOS risk
HR 1.060 for each 1-unit increase in HLA mismatch

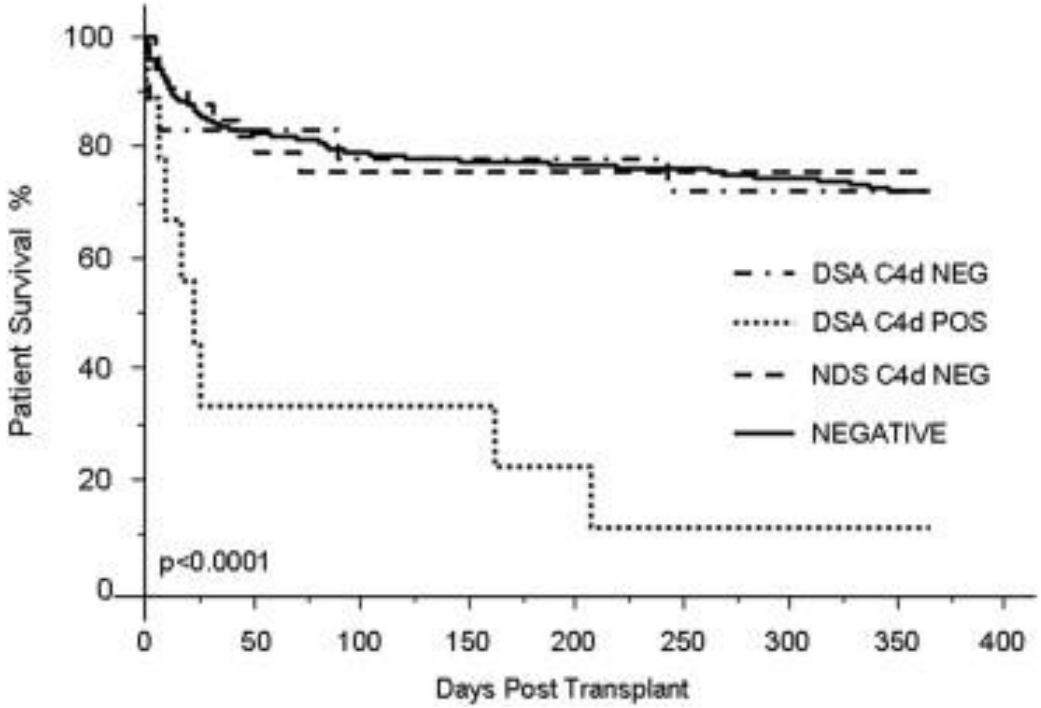
HR for HLA-A mismatch was 1.128



Influence of human leukocyte antigen mismatching on bronchiolitis obliterans syndrome in lung transplantation. Hayes et al, JHLT, 2016

Pre-Transplant Donor-Specific Antibodies

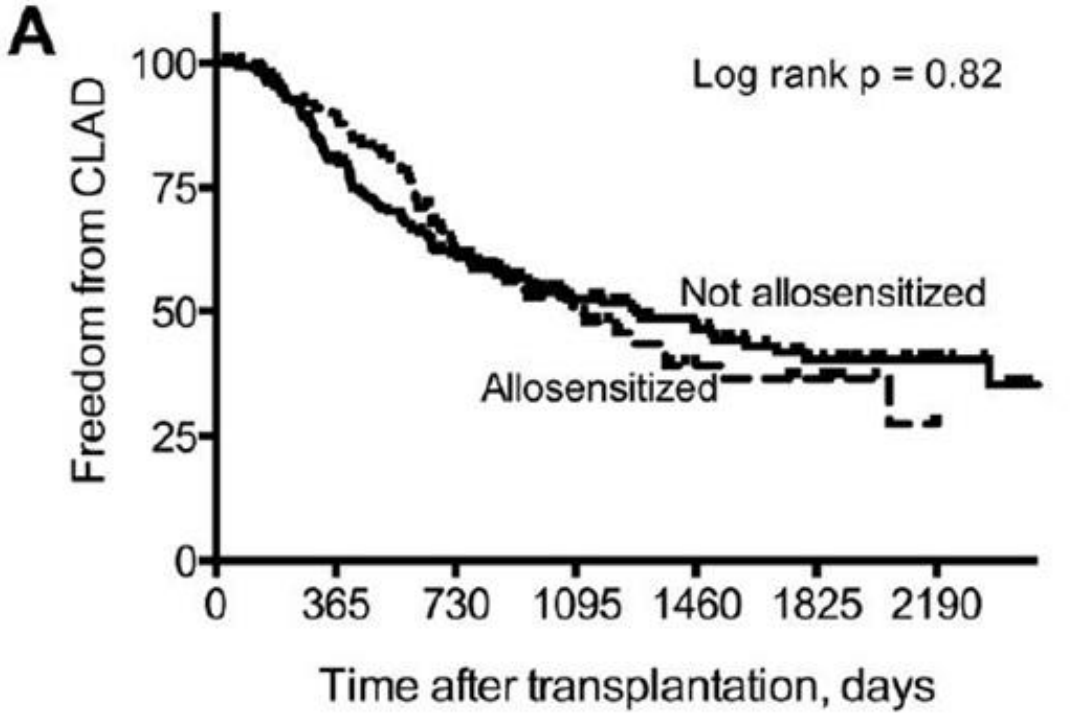
- Retrospective study without virtual x-match:
- DSA is an independent predictor of poor patient survival within 1 year HR 3.569.
- HR for Complement-fixing DSA 11.083 with
- one year survival of 12.5%



Pre-transplant donor HLA-specific antibodies: characteristics causing detrimental effects on survival after lung transplantation
Smith et al, JHLT. 2014

Pre-Transplant Donor-Specific Antibodies

No difference in freedom from CLAD or survival when potentially reactive HLA are avoided by virtual crossmatch

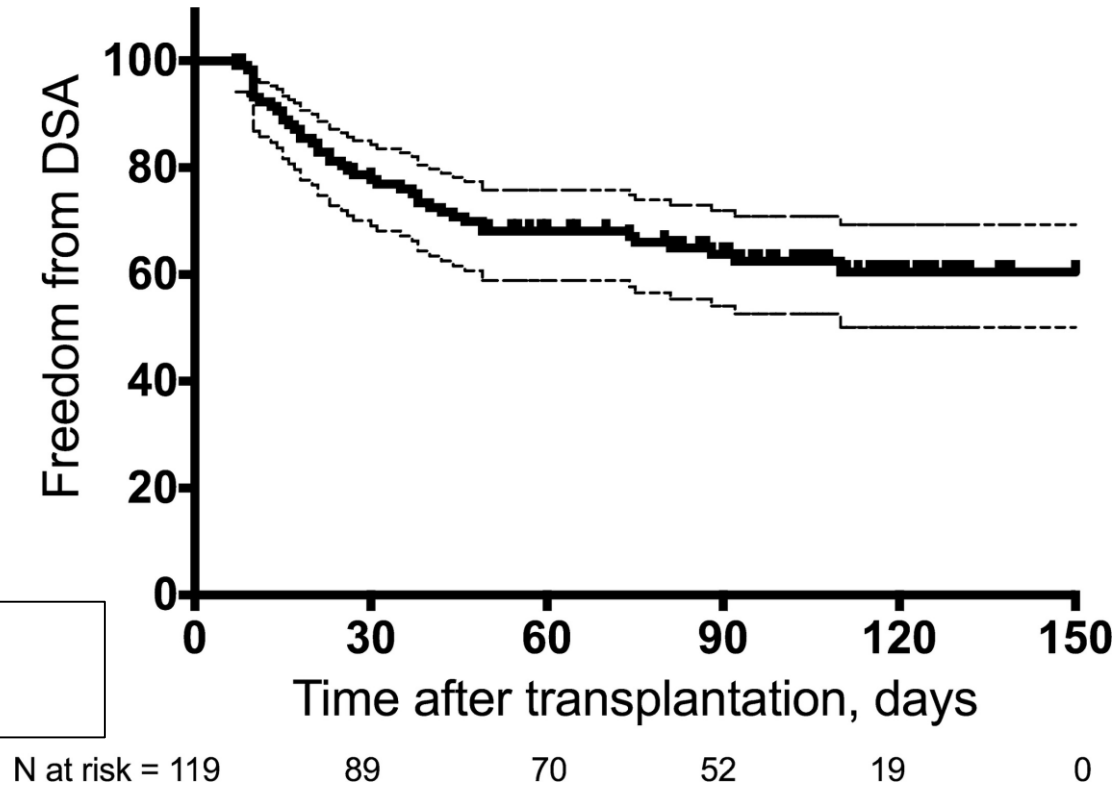


The impact of pre-transplant allosensitization on outcomes after lung transplantation.
Bosanquet et al, JHLT 2015

Post-Transplant DSA

Multicenter prospective study
119 patients.

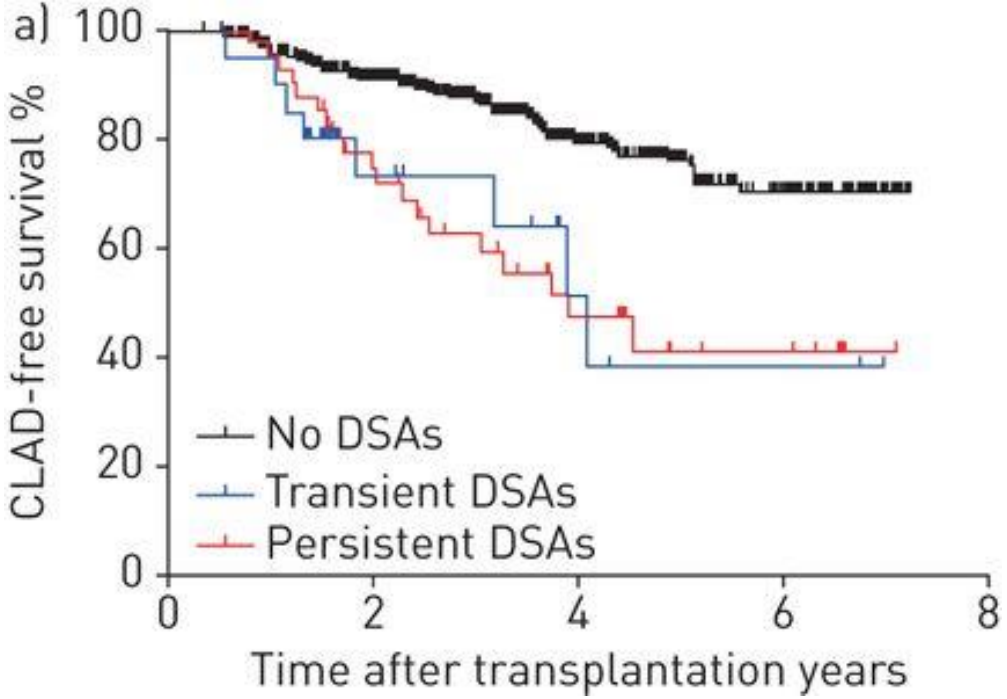
- 36% developed DSA
- DSA with MFI ≥ 3000
- had HR of 2.11 for ACR ≥ A2
- No association between DSA and survival



Human leukocyte antigens antibodies after lung transplantation: Primary results of the HALT study.
Hachem et al, Am J Transplant. 2018 Sep

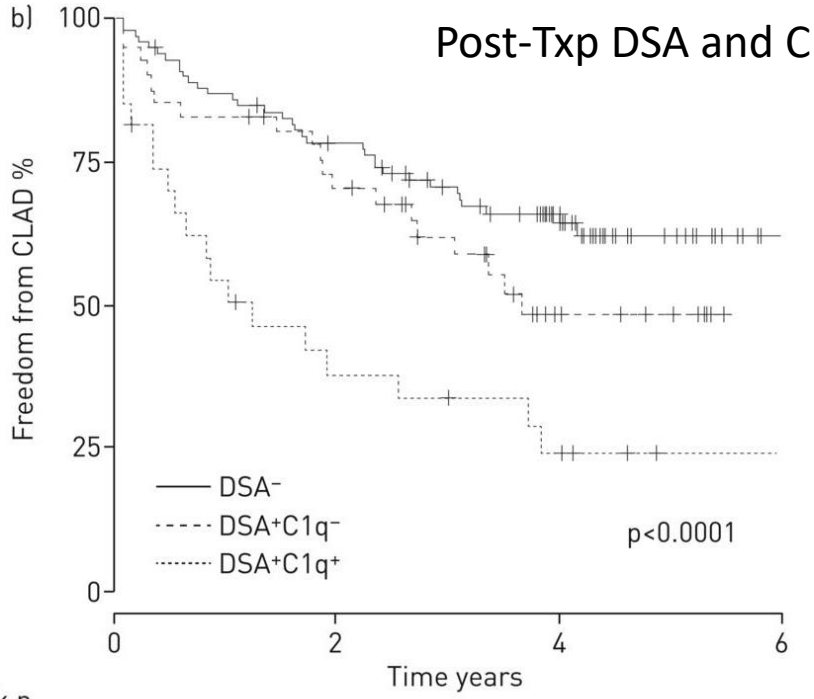
Post-Transplant DSA

362 patients
175 developed DSA
Persistent DSA had HR of
3.39 for CLAD

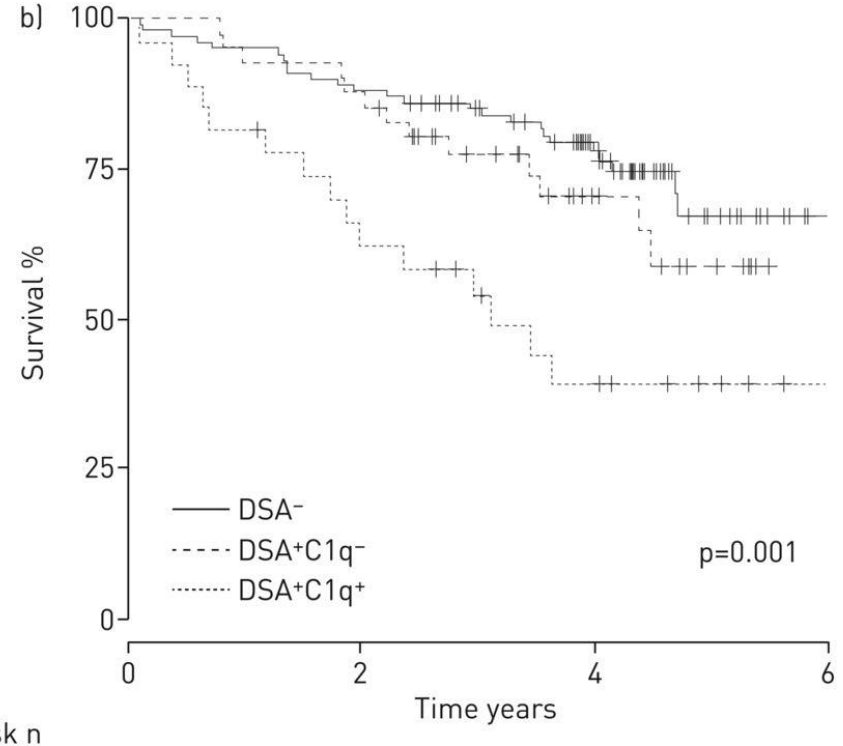


Donor-specific and -nonspecific HLA antibodies and outcome post lung transplantation
Verleden et al, European Respiratory Journal 2017

Post-Txp DSA and C1Q



At risk n			
DSA⁻	99	74	42
DSA⁺C1q⁻	41	29	10
DSA⁺C1q⁺	27	10	6



At risk n			
DSA⁻	100	89	54
DSA⁺C1q⁻	41	37	15
DSA⁺C1q⁺	27	17	9

Brugiere et al, Eur Resp J 2018

Conclusions

1. Non-specific biomarkers of humoral immune function (IgG) may be predictive of infection and BOS
2. Viremia and viral immune responses reflect immuno-responsiveness and may provide avenues for additional study
3. HLA mismatch may identify patients at greater risk for BOS and mortality
4. DSA is a biomarker that is associated with worse outcomes and influences donor selection when present pre-transplant
5. Post-transplant DSA is an accepted biomarker that portends worse outcomes after transplant