

Delisting strategies with respect to Imlifidase usage for highly sensitized renal patients

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Disclosure

I have no potential conflict of interest to report

Our HLA laboratory LUMC is the reference laboratory for the PAES: Post Approval Efficacy Study



Outline

Introduction

Why delisting?

Approaches

Several policies

A balancing act

- Weighing transplant risk versus allocation probability
- For the regularly sensitized patient:
 - Avoiding any risky antigen generally still leads to an acceptable probability of transplant.

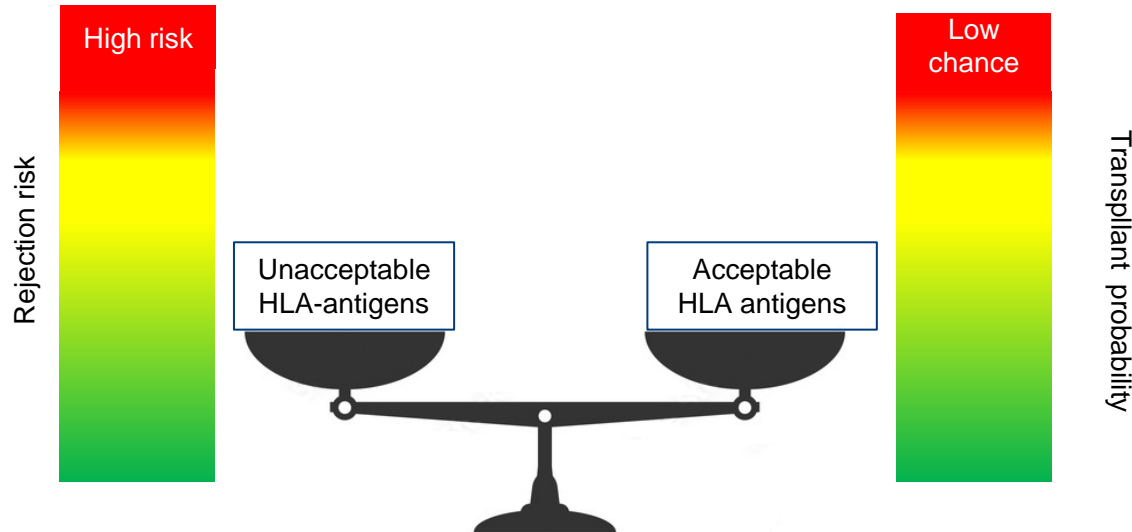


Figure:
D. Van den Broek

A balancing act

In case of highly sensitized patients (vPRA >85%)

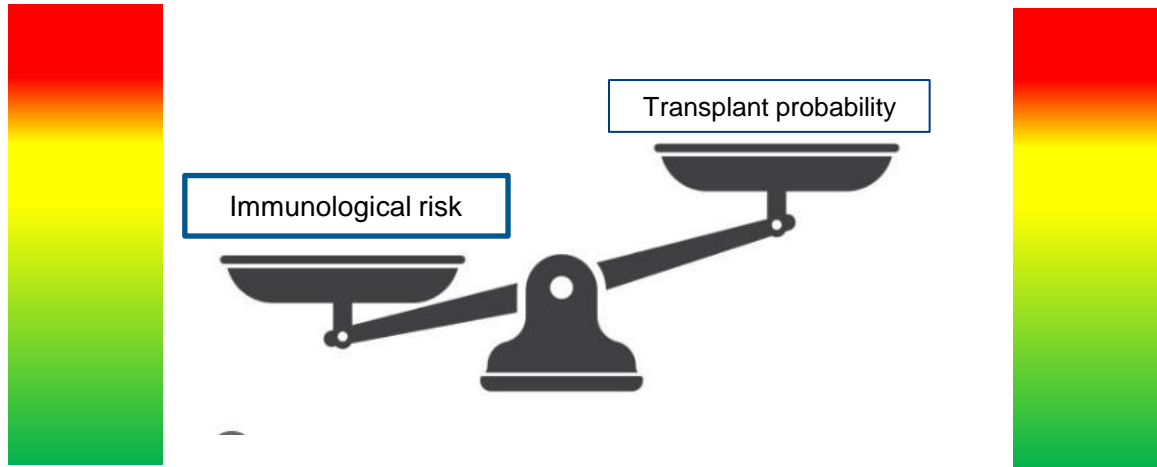


Figure:
D. Van den Broek

Restoring balance

- When the probability of a donor offer has become $<0.1\%$, it is no longer in the patient's interest to avoid all "risky antigens".
- 5-year survival rate of a dialysis patient is 50%. (Orandi, AJT 2014)
- How to limit the immunological risk but still increase transplant probability?
 - Delisting
 - Desensitization
 - Delisting and desensitization

Delisting

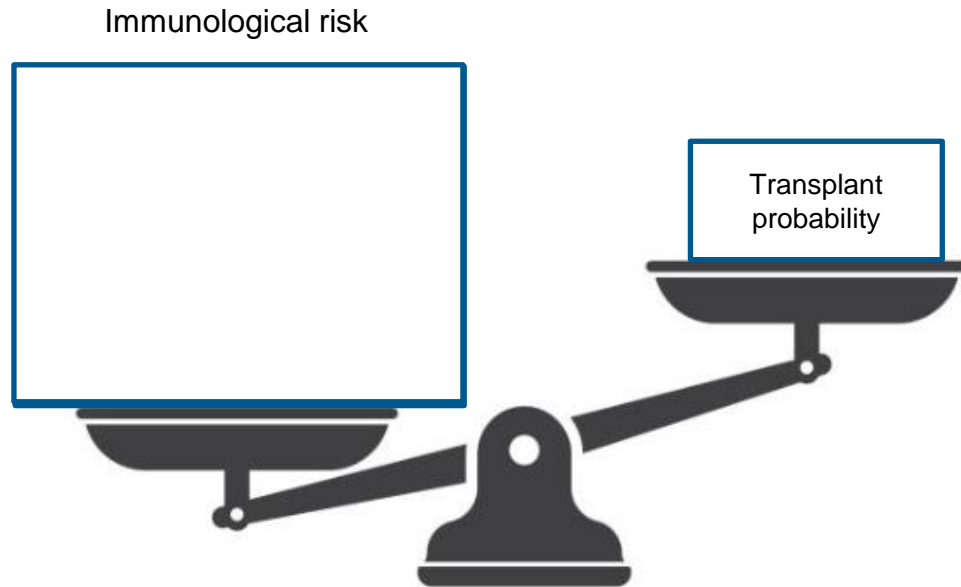


Figure:
D. Van den Broek

Delisting

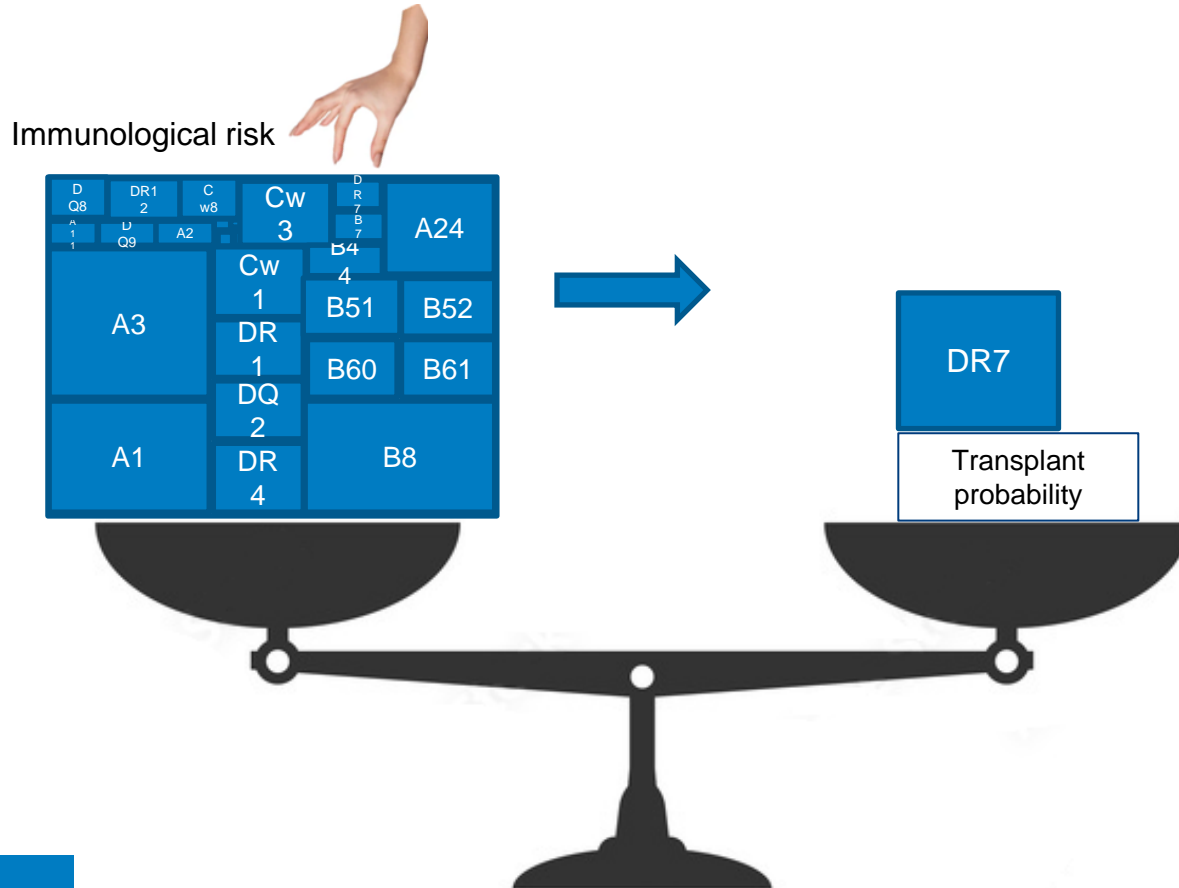
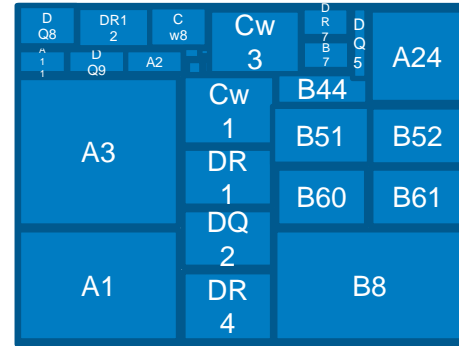


Figure:
D. Van den Broek

Determining block size

How to determine the risk per antigen?

- CDC-assay: Avoid the big blocks
→ 80% hyperacute rejection (Patel, NEJM 1969)
- Flow-cytometry: Avoid the slightly less bigger blocks
→ 25-70% ABMR (Schinstock, AJT 2019)
- Luminex SAB: Avoid all blocks
→ 25% ABMR and 15% graft loss (Caro-Oleas NDT, 2012)
- Repeated HLA mismatches (in case of DSA) (Lucisano AJT 2019)



How to select antibodies which can be delisted as unacceptable??

Various approaches:

New York approach from Massimo Mangiola

Leiden-Rotterdam approach

Barcelona approach

Using antibody titer to stratify patients with vPRA>99.9% for desensitization treatments

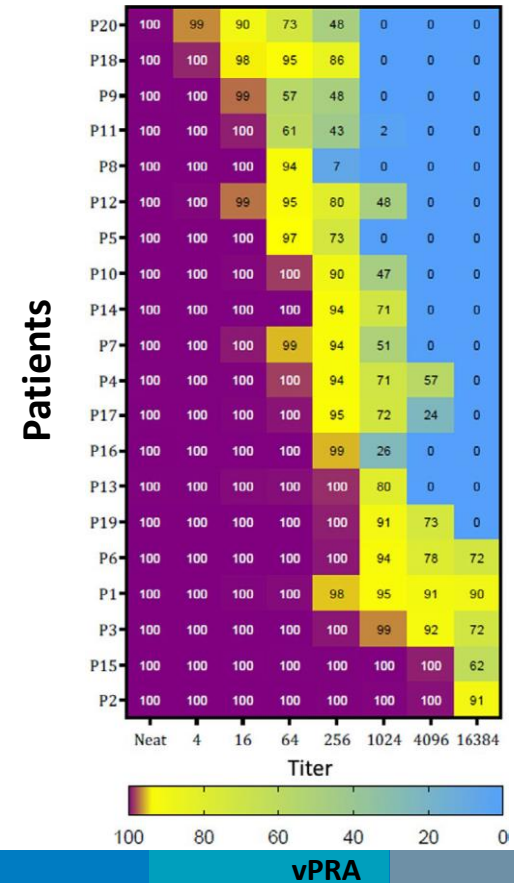
Received: 12 July 2020 | Revised: 30 September 2020 | Accepted: 5 October 2020
 DOI: 10.1111/ajt.16363

BRIEF COMMUNICATION AJT

Estimating alloantibody levels in highly sensitized renal allograft candidates: Using serial dilutions to demonstrate a treatment effect in clinical trials

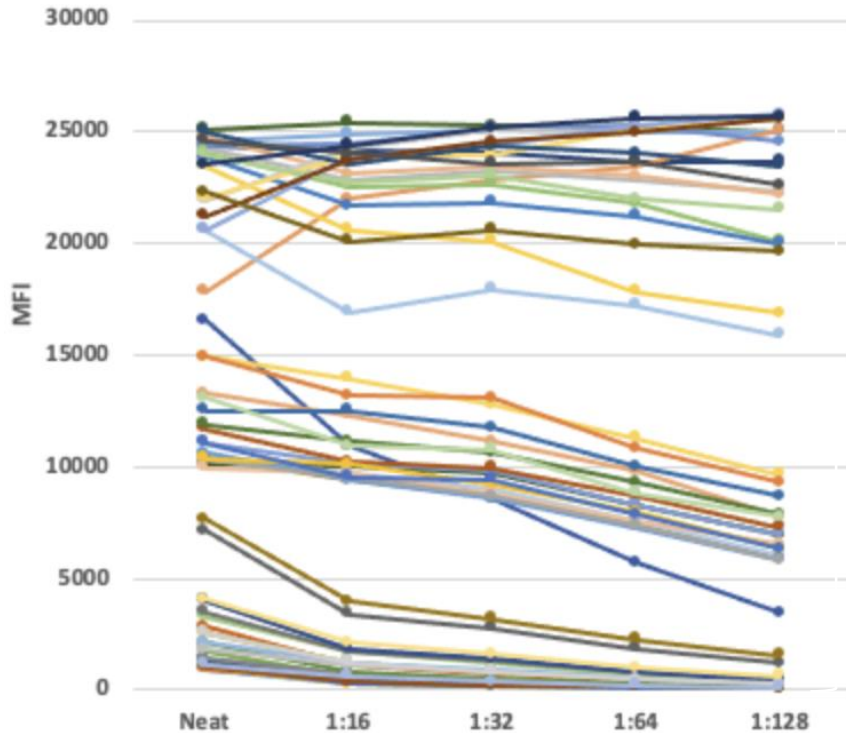
Anat R. Tambur¹ | Carrie Schinstock² | Chelsea Maguire¹ | David Lowe³ | Byron Smith² | Mark Stegall²

- ...Stepwise dilution of the serum will gradually eliminate antibody positivity and thus decrease the vPRA because the corresponding antigens would no longer be considered unacceptable...
-This approach will help stratify patients prior to inclusion in studies and help in discerning partial therapeutic effects..



Case study

PRE-IMLIFIDASE TITER STUDY



GROUP 1

IMMUNODOMINANT ANTIBODY(ies)

Likely to rebound strongly and cause ABMR within weeks post-transplant

GROUP 2

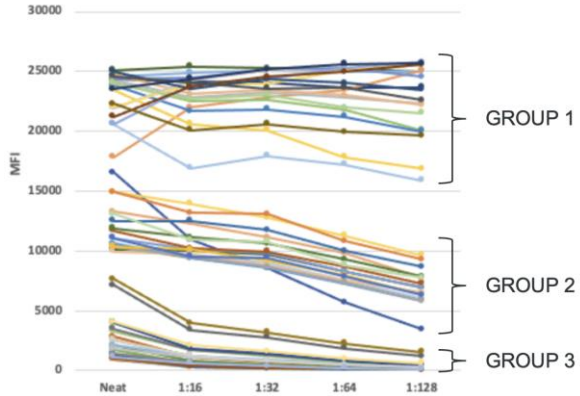
ANTIBODY(ies) WITH LOWER TITER

rebound with lower titer (strength) and not cause ABMR

GROUP 3

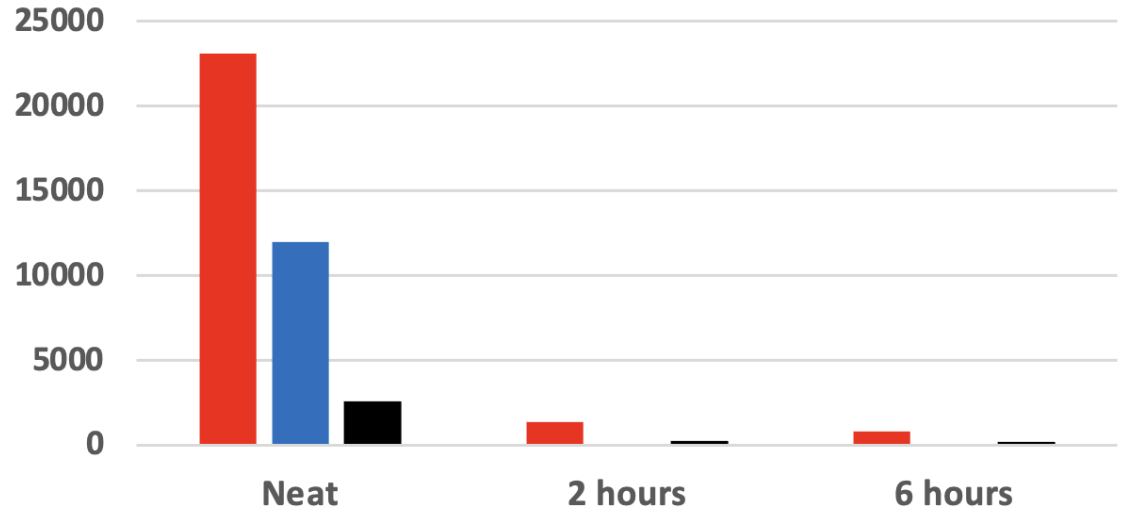
Case study

PRE-IMLIFIDASE TITER STUDY



ANTIBODIES DEPLETION

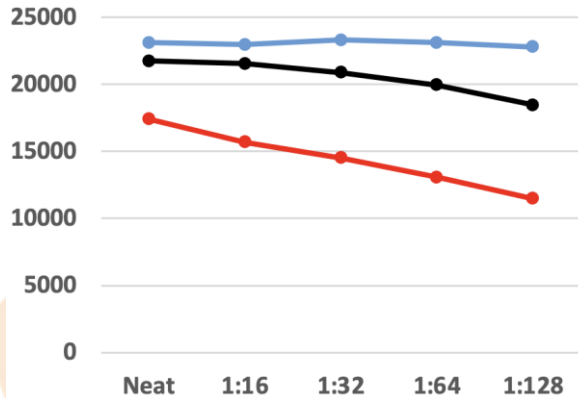
■ Dominant ■ Moderate ■ Weak



Case study

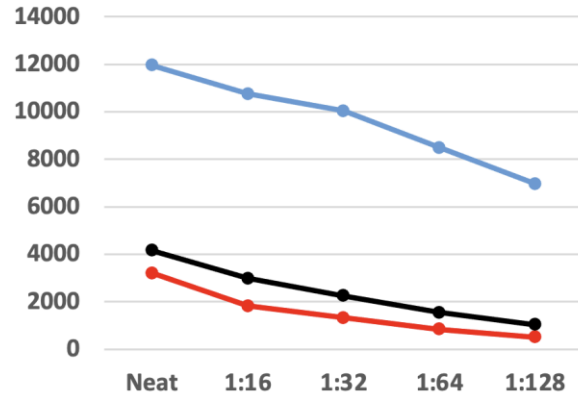
IMMUNODOMINANT GROUP

PRE 6 days 28 days



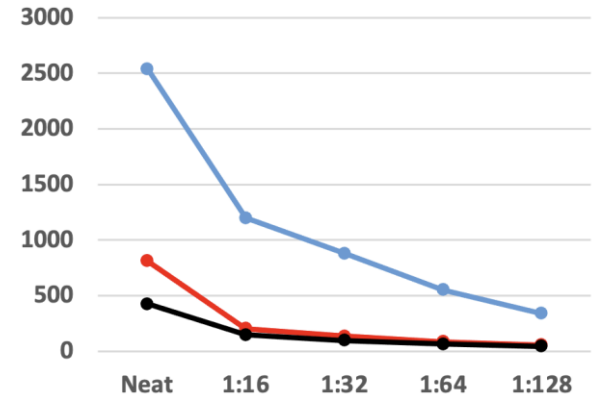
MODERATE TITER GROUP

PRE 6 days 28 days

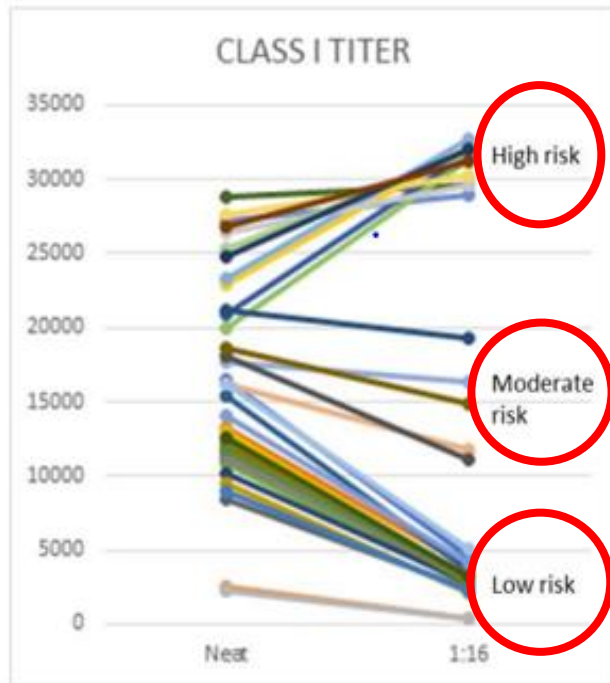


WEAK GROUP

PRE 6 days 28 days



Neat vs dilution 1: 16



Unpublished data kindly provided by Dr Massimo Mangiola, NYU Langone Immunogenetics

Suggested approach

- Depict Single Antigen results in clear way
- Taking into account
 - CDC results,
 - epitopes,
 - earlier transplants,
 - pregnancies
- Check effect on chance of a suitable donor

Effect of delisting Antigens I



Eurotransplant Reference Laboratory
Donor Frequency Calculator ABO identical



[Information](#)

Unacceptable antigens:

A2 A23 A24 A10 A11 A19 A28 A36 A43 B7 B12 B13 B63 B57 B58 B21 B22 B27 B40 B41 B42 B47
B48 B67 B73 Cw2 DR2 DR11 DR12 DR13 DR14 DR7 DR8 DR51 DQ1 DQ4 B81 B82 Cw16 Cw17

vPRA
99,34%

Unacceptable antigens can only be entered divided by a space or a comma.

ABO:

A ▼

Calculate frequency

Clear

Frequency of compatible donors within the Eurotransplant area: 0,320% (32 out of 10000, ETRL HLA database version 3.0)

Effect of delisting Antigens II



Eurotransplant Reference Laboratory
Donor Frequency Calculator ABO identical



Information

Unacceptable antigens:

A2 A23 A10 A11 A19 A28 A36 A43 B7 B12 B13 B63 B57 B58 B21 B22 B27 B40 B41 B42 B47 B48
B67 B73 Cw2 DR2 DR13 DR7 DR51 DQ1 DQ4 B81 B82 Cw16 Cw17

vPRA
98,41%

Unacceptable antigens can only be entered divided by a space or a comma.

ABO:

A ▼

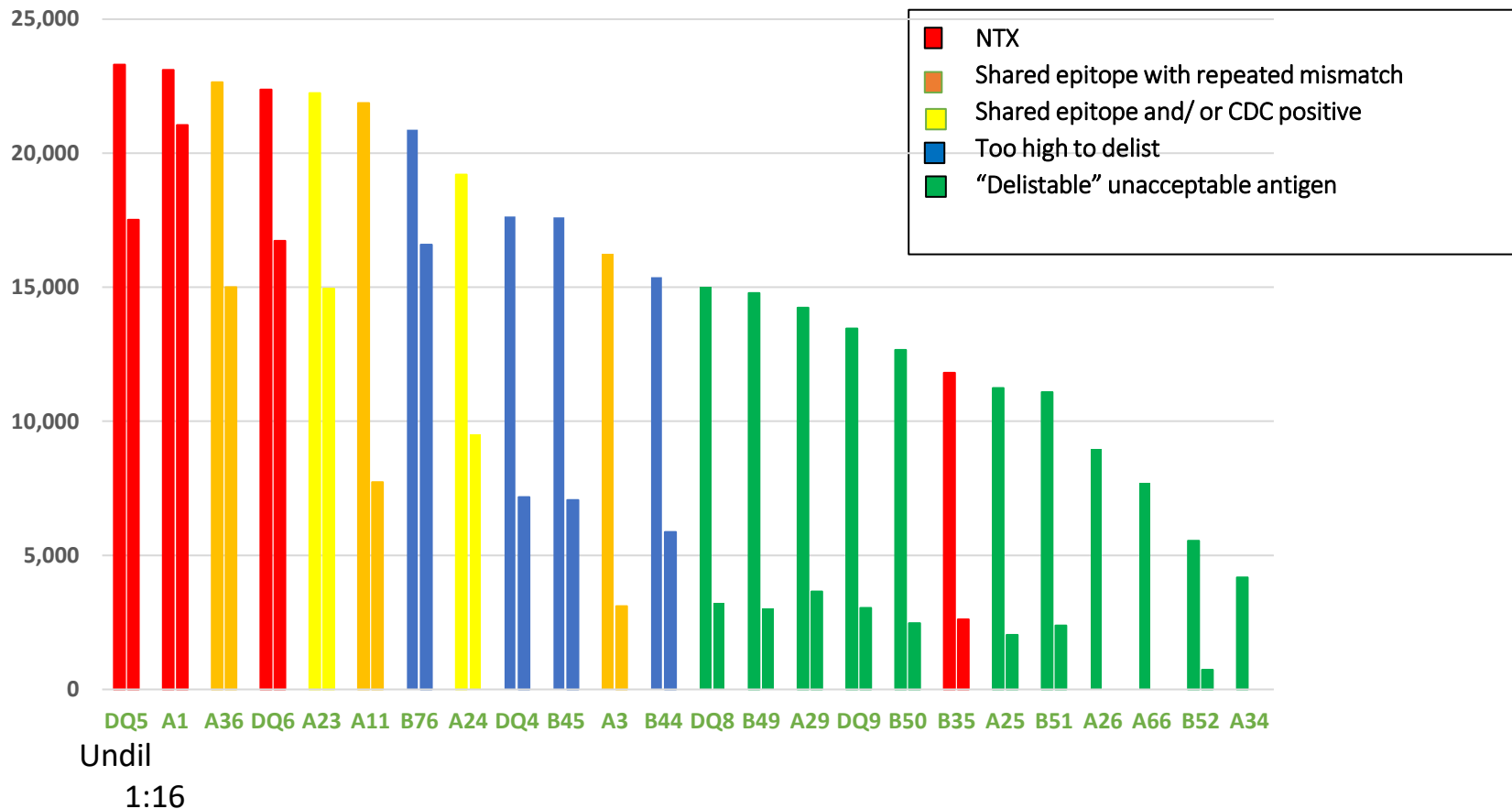
Calculate frequency

Clear

Delisted: HLA-A24, DR11, DR12, DR14, DR8

Frequency of compatible donors within the Eurotransplant area: 0,670% (67 out of 10000, ETRL HLA database version 3.0)

Example from Erasmus MC



Suggested approach: different steps/ layers

- don't delist antibodies that are possible repeated mismatches (present on earlier Tx)
- don't delist antibodies that are positive in current CDC screening
- 3 layers of Antibodies
 - A) antibodies with MFI < 7.000 in last 4 years
 - B) antibodies with MFI < 10.000 in last 4 years
 - C) antibodies with MFI > 10.000 in last 4 years

Use layer 1 first: check chance: wait for 3-4 months or go to next step when chance low

No transplant within 3-4 months: go to next layer.

Bloodgroup AB, male, 1 transplant: RMM A1, B8, B35, DQ5, DQ6

Unacc:

A1 A3 A9 A25 A26 A34 A66 A11 A29 A31 A32 A33 A74 A68 A36 A43 A80 B5 B8 B12
B14 B62 B63 B75 B76 B77 B16 B17 B18 B21 B54 B55 B56 B27 B35 B37 B46 B47 B48
B53 B59 B67 B71 B72 B78 Cw3 DQ1 DQ8 DQ9 DQ4 B82

AM since 26-06-2018

Acc A69 B40 B60 B61 Cw1 Cw2 Cw4 Cw5 Cw7 DR17 DR4 DR12 DR13 DR8 DR9 Cw12
Cw14 Cw16 Cw17 Cw18

Pat G from Erasmus MC

[Information](#)

Unacceptable antigens:

A1 A3 A9 A25 A26 A34 A66 A11 A29 A31 A32 A33 A74 A68 A36 A43 A80 B5 B8 B12 B14 B62 B63
B75 B76 B77 B16 B17 B18 B21 B54 B55 B56 B27 B35 B37 B46 B47 B48 B53 B59 B67 B71 B72 B78
Cw3 DQ1 DQ8 DQ9 DQ4 B82

Unacceptable antigens can only be entered divided by a space or a comma.

ABO:

AB ▼

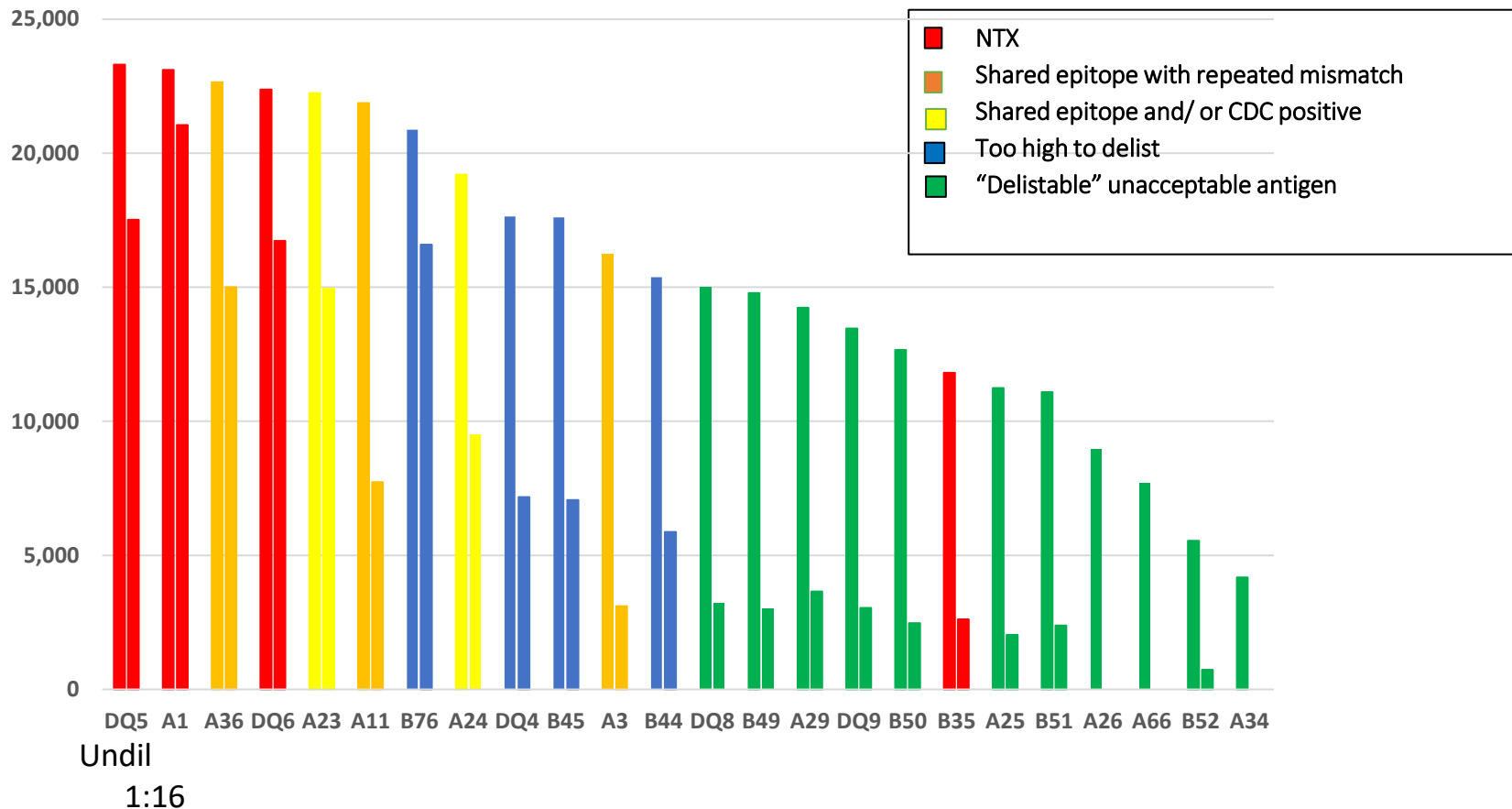
Calculate frequency

Clear

Frequency of compatible donors within the Eurotransplant area: **0,010% (1 out of 10000, ETRL HLA database version 4.0)**

vPRA
99,96%

Example from Erasmus MC



Option 1: delist in case MFI is below 10.000

No CDC, no RMM

| | | |
|----------------------|--|----------|
| Delisted as unaccept | A34, 66, 31, 32, 33,74,68 | Cw9 Cw10 |
| | B52, B64,65,62,63,75,77, 38,39,57,58,54,55,27,37,46,47,48,59,67,72,78 | |



Eurotransplant Reference Laboratory
Donor Frequency Calculator ABO identical



[Information](#)

Unacceptable antigens:

A1 A3 A9 A25 A26 A11 A36 A43 A80 B8 B12 B76 B18 DQ1 DQ4 A29 B51 B49 B50 B56 B53 B71 B82
DQ8 DQ9

Unacceptable antigens can only be entered divided by a space or a comma.

ABO:

Calculate frequency

Clear

Frequency of compatible donors within the Eurotransplant area: **0,050% (5 out of 10000, ETRL HLA database version 4.0)**

vPRA
99,48%

Option 2: delist in case MFI is below 15.000

No CDC, no RMM

| | |
|----------------------------|-------------------------|
| extra delisted as unaccept | A29 |
| | B51, 49,50,56,53,71,82, |
| | DQ8,9 |



Eurotransplant Reference Laboratory
Donor Frequency Calculator ABO identical



vPRA
97,29%

[Information](#)

Unacceptable antigens:

A1 A3 A9 A25 A26 A11 A36 A43 A80 B8 B12 B76 B18 DQ1 DQ4

Unacceptable antigens can only be entered divided by a space or a comma.

ABO:

AB ▾

Calculate frequency

Clear

Frequency of compatible donors within the Eurotransplant area: **0,220% (22 out of 10000, ETRL HLA database version 4.0)**

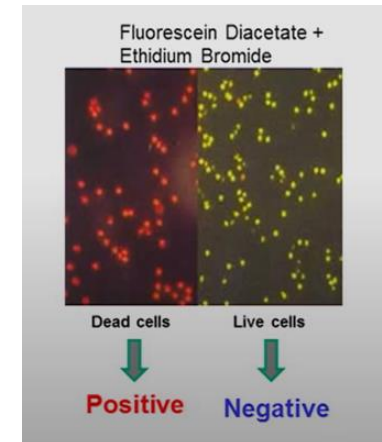
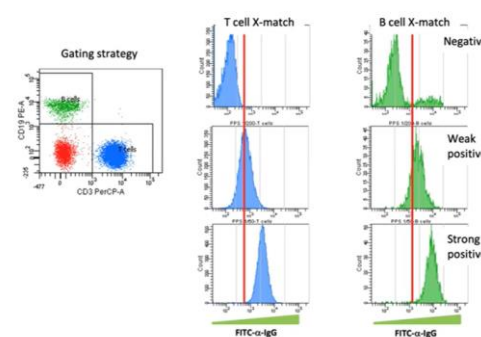
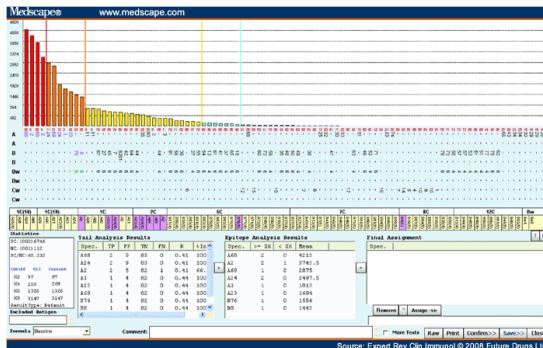
Delisting procedure

- Having stratified the antibody present in each patient based on the dilution data.
- Use your Frequency Calculator to determine the effect of the delisting on the donor frequency.
- Avoid delisting of several antigens with High MFI values (i.e. High Risk Antibody, red color)

| Antibody Titer | Specificity | Tiered Delisting Strategy | | |
|-----------------------|-------------|---------------------------|----------------|----------------|
| | | 1st Round (3m) | 2nd Round (3m) | 3rd Round (3m) |
| Decreasing PRA values | | | | |
| High risk | A1 RMM | | | |
| Moderate risk | A2 | | A2 | |
| | A203 | | | |
| High risk | A3 | | | A3 |
| High risk | A23 | | | |
| High risk | A24 | | | |
| | A2403 | | | |
| High risk | A25 | | | |
| Moderate risk | A26 | | A26 | |
| Moderate risk | A34 | | A34 | |
| Moderate risk | A66 | | A66 | |
| High risk | A11 | | | |
| High risk | A29 | | | A29 |
| Moderate risk | A30 | | A30 | |
| Low risk | A31 | A31 | | |
| High risk | A32 | | | |
| Low risk | A33 | A33 | | |
| | A74 | | | |
| High risk | A68 | | | A68 |
| Low risk | A69 | A69 | | |
| High risk | A36 | | | |
| Moderate risk | A43 | | A43 | |
| High risk | A80 | | | |
| High risk | B51 | | | |
| High risk | B52 | | | |
| | B7 | | | |
| | B703 | | | |
| | B8 | | | |
| Moderate risk | B44 | | B44 | |
| Low risk | B45 | B45 | | |

Delisting procedure

- Focus on HLA-A, HLA-B, HLA-DR and HLA-DQ and pay less attention to HLA-C, HLA-DP, HLA-DR51, HLA-DR52 and HLA-DR53.
- Use a Donor Frequency Calculator (country specific) and check how much the donor frequency has increased by your delisting.
- Make a Crossmatch (VXM/FCXM/CDCXM) plan of action with your PI (which sera will you use, how do you report DSA MFI, titer and MCS, is a follow-up call needed).
Use your standard procedure for deceased donor transplants.



Immunological characteristics

Pre-Tx Selection

Anti-HLA Ab delisting

- Chronology and level anti-HLA Ab (MFI)
 - “Risk layers”: 5,000 → 6-10,000 → >10,000
- **Non-C'-fixing**
- Repeated anti-HLA Ab (B-cell memory)
 - Previous Tx -> Pregnancies (->Transfusions)
- Abs with shared Eplet in previous sensitizing HLA Ag
- Ab clearance in previous desensitization therapies
- Reduction of Ab titers after Serial dilutions

Thank you

Immunology

- Gonca Karahan
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- LUMC HLA lab



LEIDEN UNIVERSITY MEDICAL CENTER

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- Aiko de Vries
- Dennis van den Broek
- Joris Rotmans
- Leiden Transplant Center





LUMC

Universitair Medisch Centrum

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