Comment transplanter un patient hyperimmunisé?
« How to transplant a highly sensitized patient? »

Dominique Bertrand
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Rouen University Hospital
Wednesday 17th May 2023
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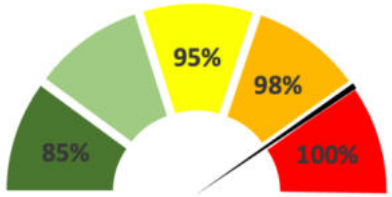
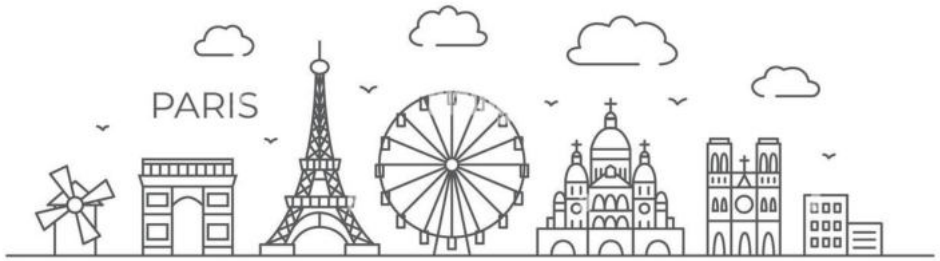
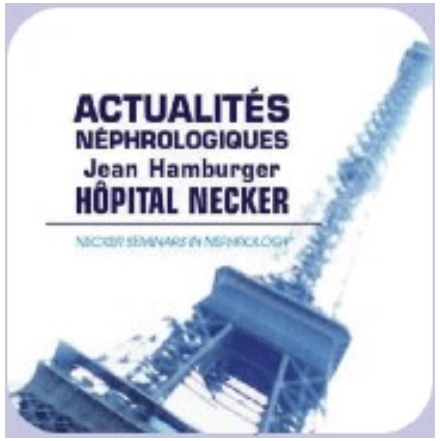




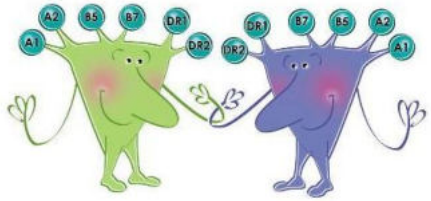
CHU ROUEN NORMANDIE



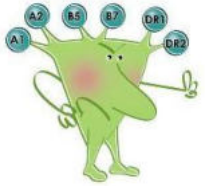
Conflict of interest

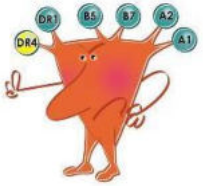
Speaker fees and participating in advisory boards:

- Alexion
- Astellas
- BMS
- Chiesi
- Hansa Biopharma
- Sanofi



Definition of Sensitized patients



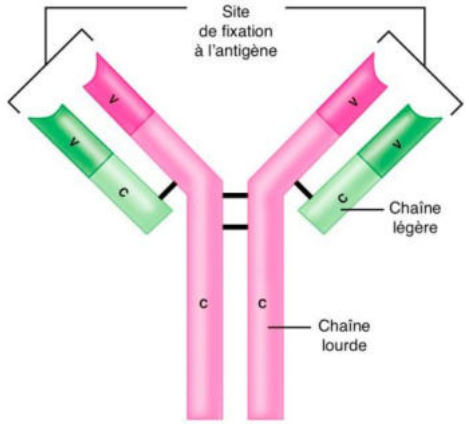


« At least one anti-HLA Antibody »

Transfusion

Pregnancy

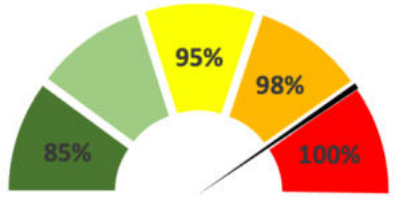
Transplantation



Heidt, Expert revoew of clinical immunology, 2019

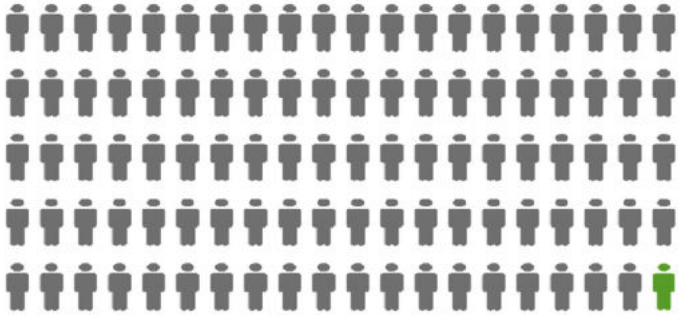
Definition of Highly sensitized (HS) patients?

PRA: Estimate of the proportion of the deceased donor population to which the candiadte has anti HLA antibodies



Eurotransplant

10,000 donors

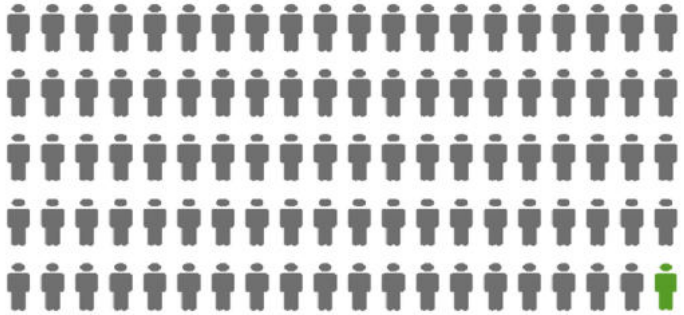


cPRA / vPRA / cRF > 85%

https://www.etrl.org/vPRA.aspx

UNOS
UNITED NETWORK FOR ORGAN SHARING
Saving lives together

12,000 donors

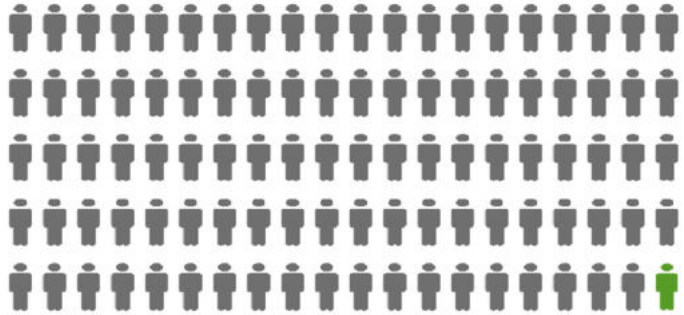


cPRA > 80%

https://optn.transplant.hrsa.gov/data/allocation-calculators/cpra-calculator/

agence de la biomédecine
Agence relevant du ministère de la santé

Donors from the last 5 years calculated every day

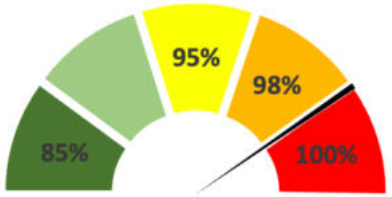


TGI > 85%

Unavailable

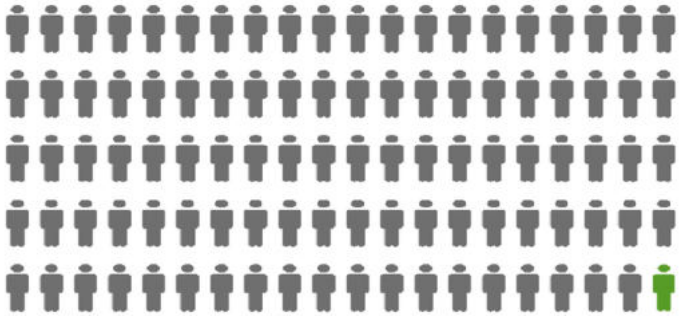
Definition of Highly sensitized (HS) patients?

PRA: Estimate of the proportion of the deceased donor population to which the candiadte has anti HLA antibodies



Eurotransplant

10,000 donors



cPRA / vPRA / cRF > 85%

https://www.etrl.org/vPRA.aspx

UNOS
UNITED NETWORK FOR ORGAN SHARING
Saving lives together

12,000 donors

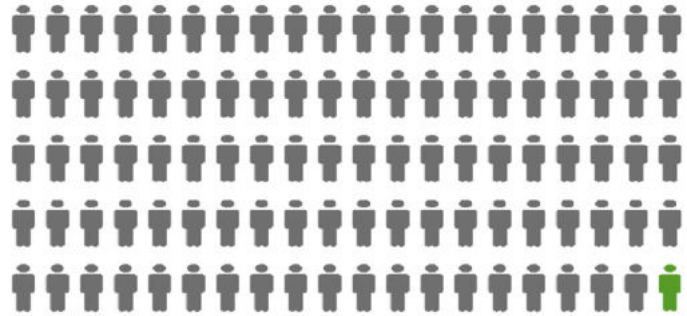
99,9% = 1/1000 donor are HLA « compatible »

cPRA > 80%

https://optn.transplant.hrsa.gov/data/allocation-calculators/cpra-calculator/

agence de la biomédecine
Agence relevant du ministère de la santé

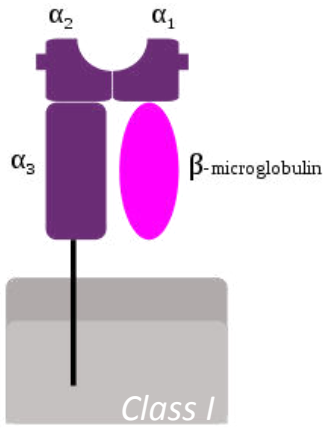
Donors from the last 5 years calculated every day

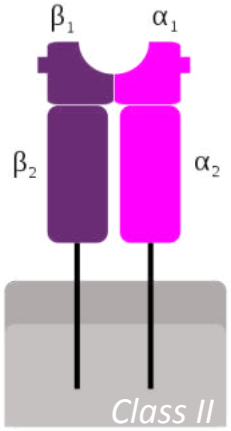


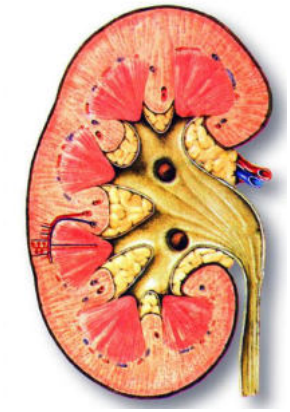
TGI > 85%

Unavailable

Definition of a DSA (Donor Specific Antibody)



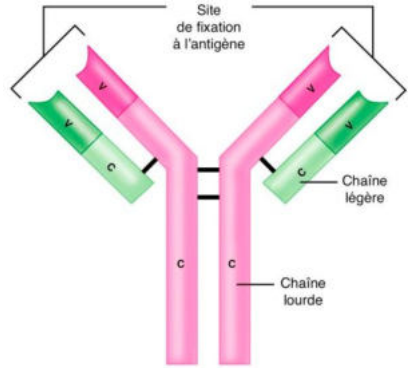




Anti DQ5

Anti B27

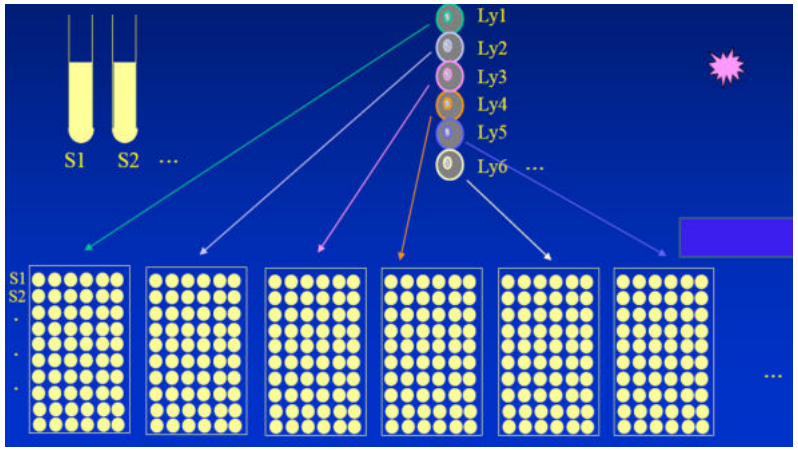
Anti A2



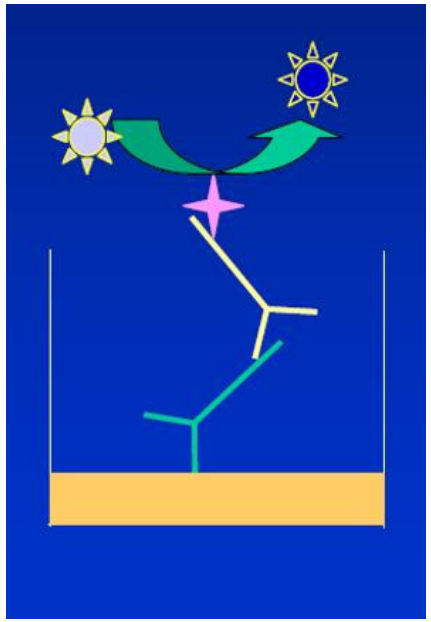
A2 A24 B12 **B27** DR4 DR11 DQ2 **DQ5**

Anti A2 + Anti B27 + Anti DQ5

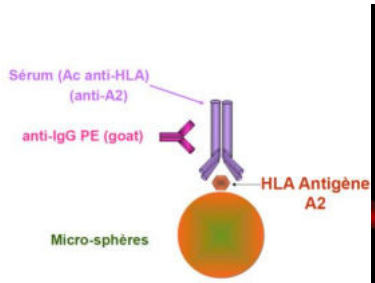
PRA: from LCT to ELISA to Luminex…

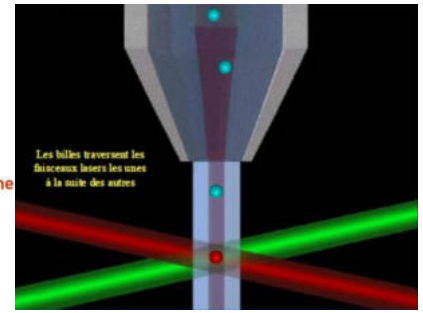


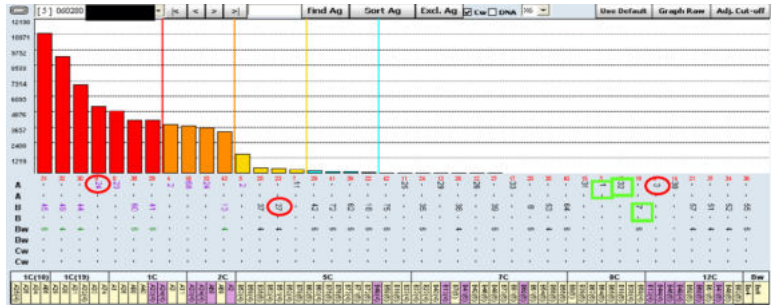
Lymphocytotoxic: PRA



ELISA : PRA







Luminex : MFI

Sensitivity

Specificity

Luminex: caution for interpretation

Cut off for pathogenic HLA Ab?

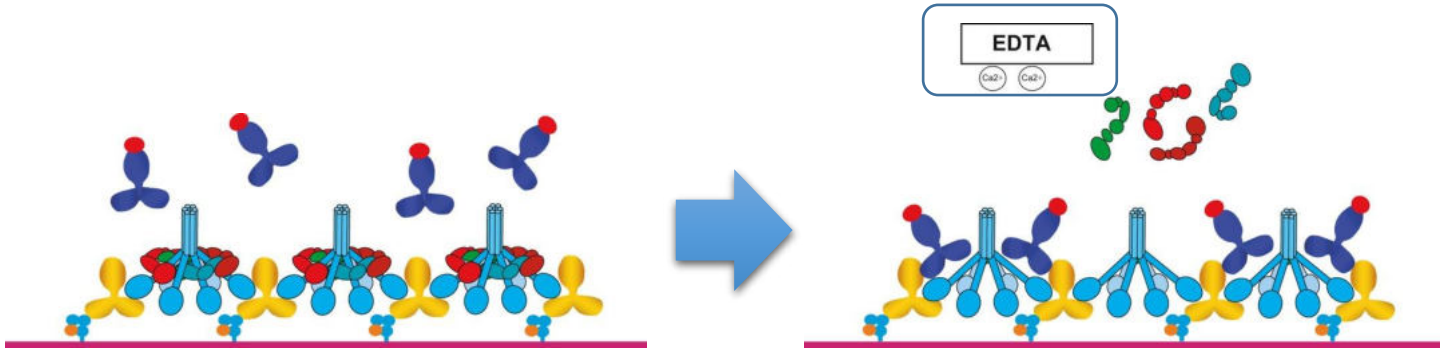
Prozone effect

Denatured antigen

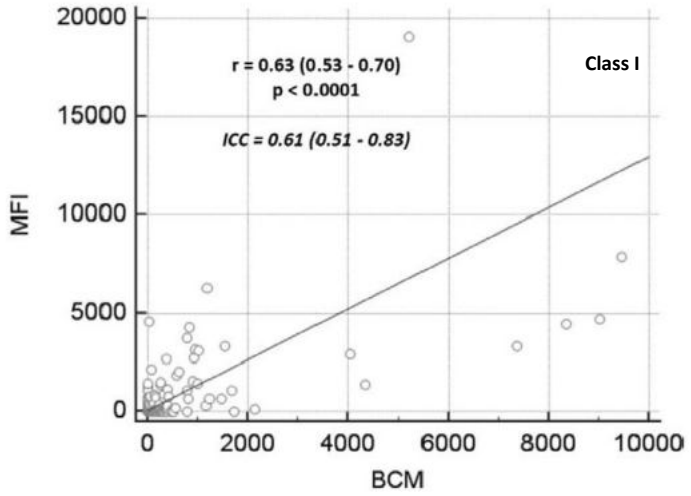
Inter laboratory variability…

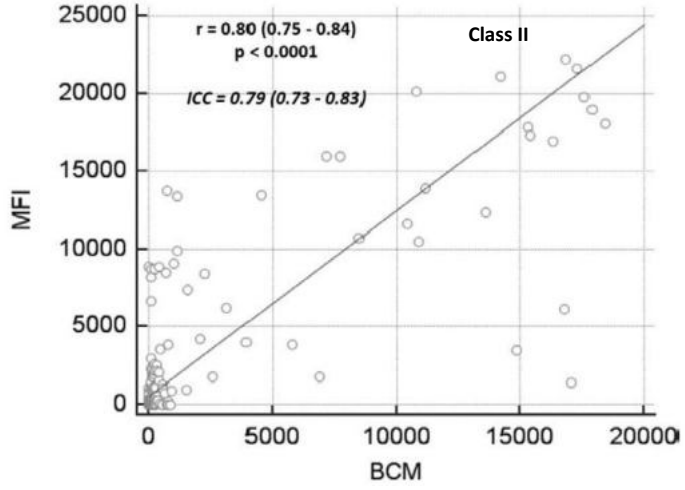
One Lambda vs Immucor?

<u>Need for standardization for the use of Luminex testing</u>



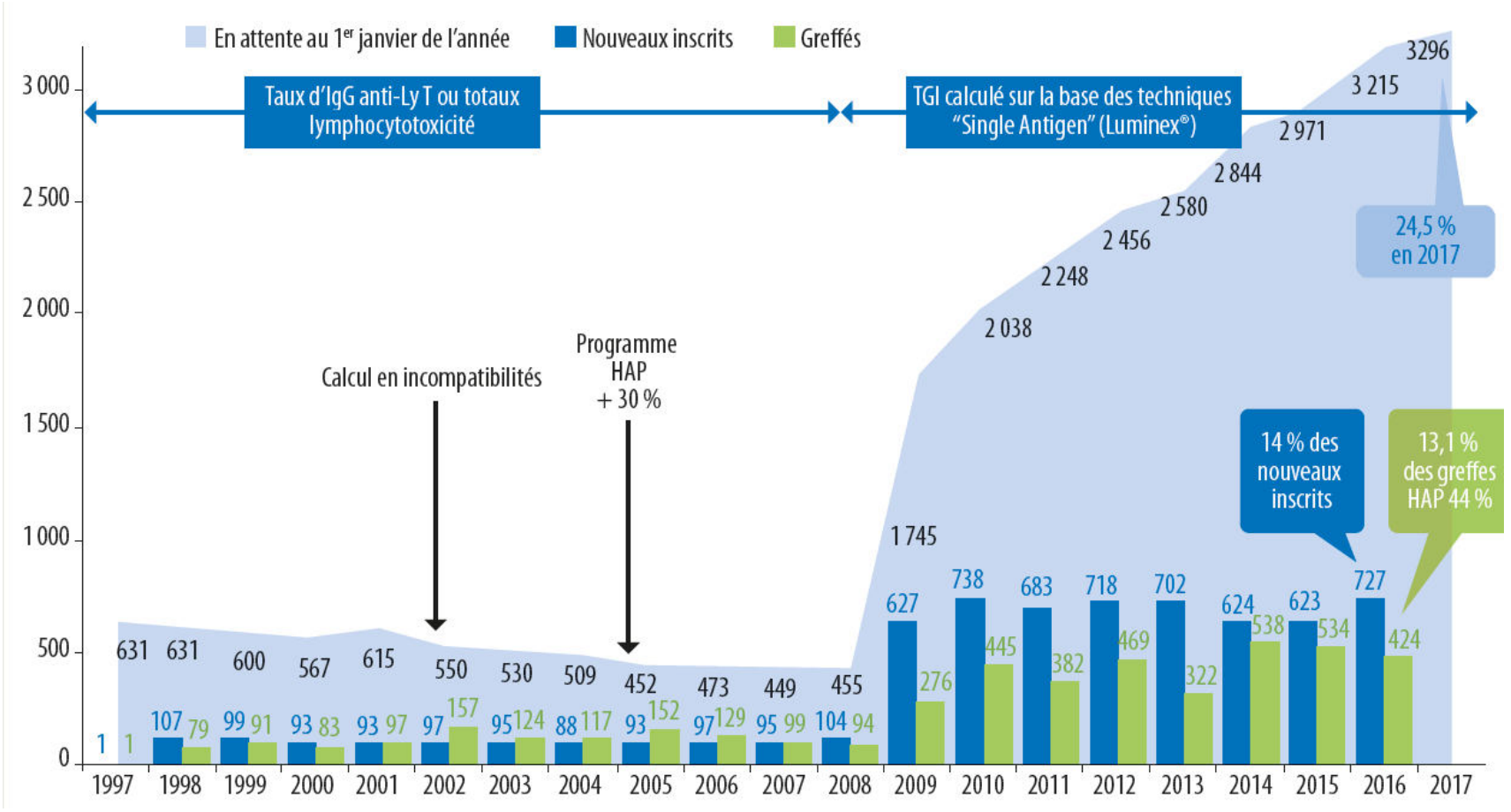
Weinstock, Int J Immunogenet, 2012





Bertrand, Transplantation, 2019

Evolution of HS patients in the waiting-list in France



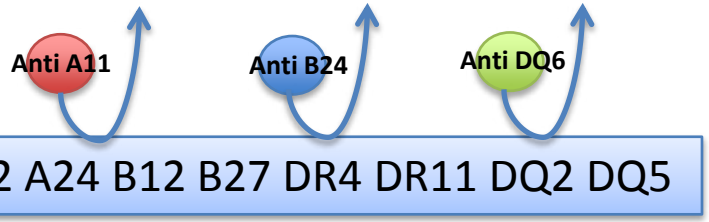
With the advent of Luminex technology, the number of HS patients increase dramatically

Antoine, Néphrologie et Thérapeutique, 2018

HS patients: a stepwise approach

1

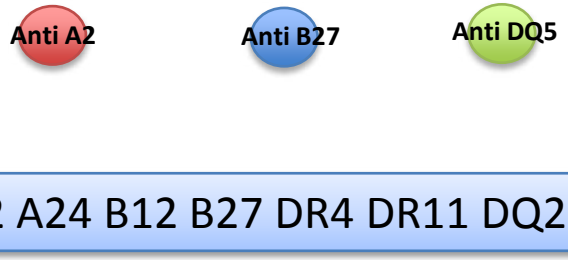
Avoid immunological conflict



HLA MATCHING BETWEEN DONOR AND RECIPIENT
NO DSA
➡ **Negative CROSS MATCH**

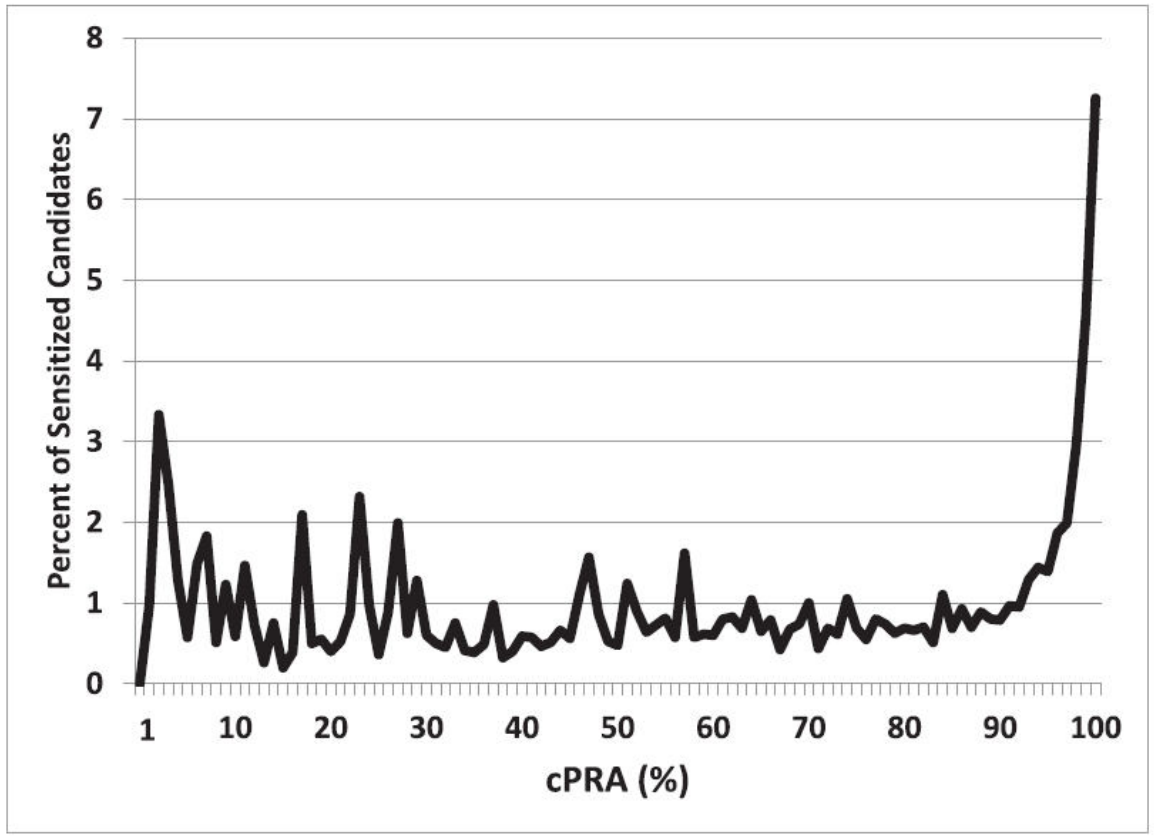
2

Immunological High Risk Transplantation



CONSIDER KTR WITH PREFORMED DSA
Risk of ABMR and inferior graft survival
➡ **Risk of Positive CROSS MATCH**

Give priority for HS patients on the waiting list



Accumulation of very HS patients in the waiting list

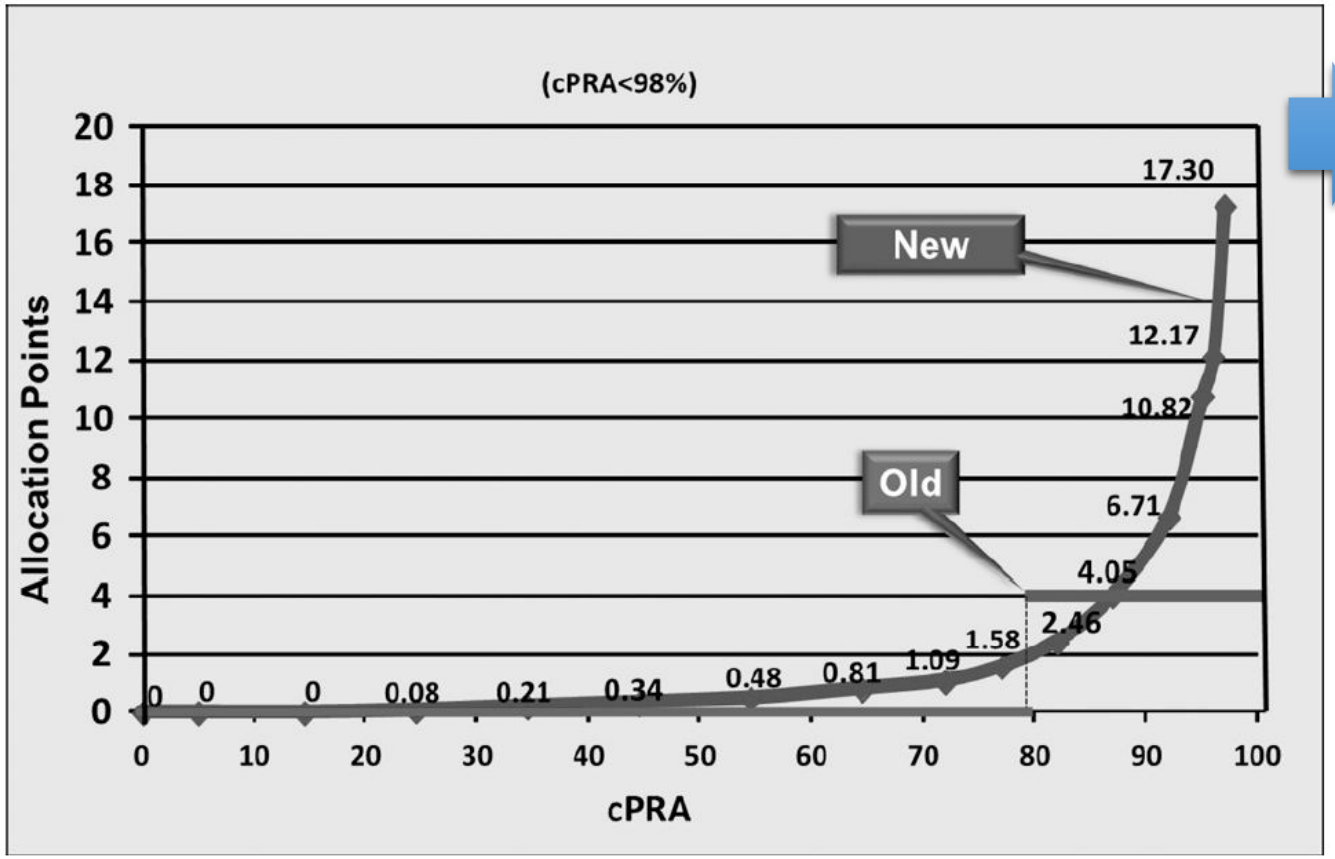
Table 4. Estimated number of match runs needed to have a 95% probability of finding an acceptable donor based on candidate cPRA

cPRA, %	Theoretical number of match runs to have a 95% chance of finding an acceptable donor
10	2
20	2
30	3
40	4
50	5
60	6
70	9
80	14
85	19
90	29
95	59
99	300
99.5	600
99.9	3000
99.99	30,000
99.999	300,000

cPRA, calculated panel-reactive antibody.

Keith, cJASN, 2016

Give priority for HS patients on the waiting list



98%: + 24,4 points
99%: + 50,1 points
100%: +202,1 points

Under the new allocation system, additional points are awarded for sensitization on a sliding scale.

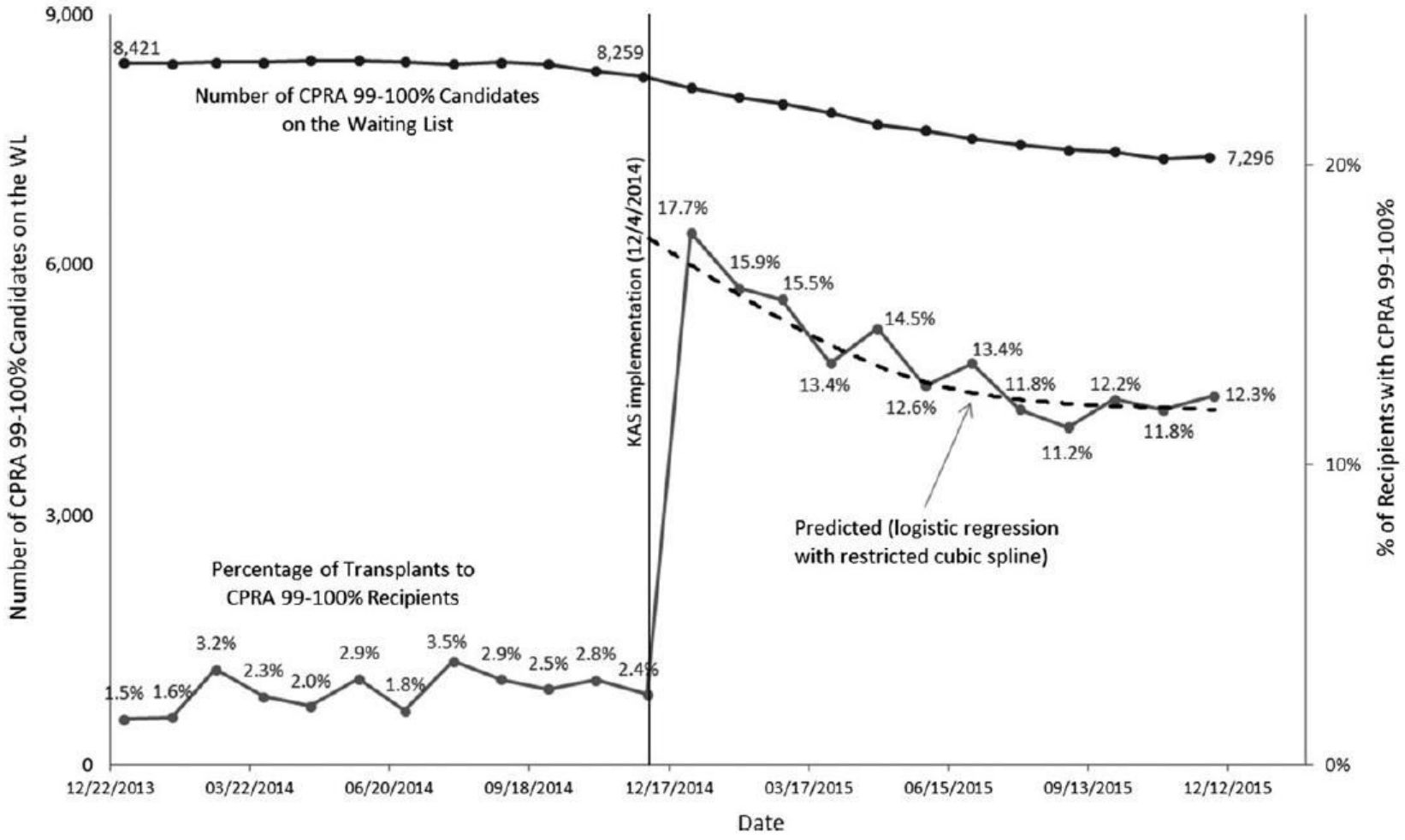
Keith, cJASN, 2016

Give priority for HS patients on the waiting list

Before KAS, 2.4% of transplants went to CPRA 99–100% recipients.

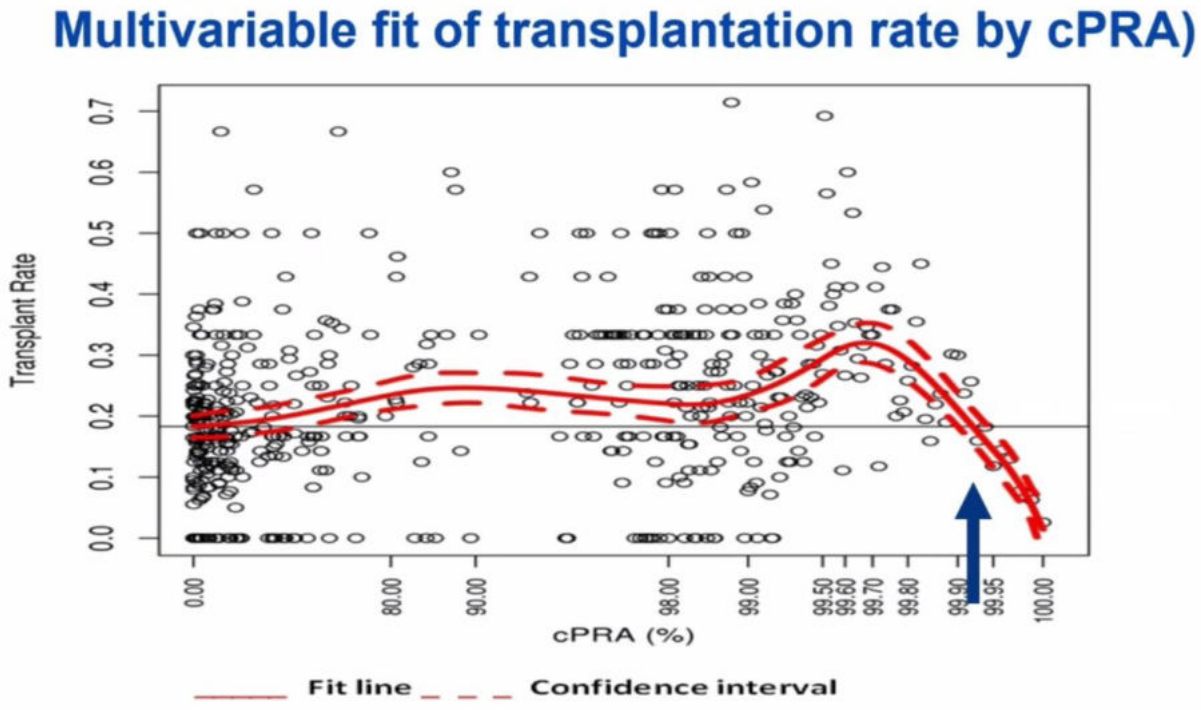
Immediately after KAS, CPRA 99–100% transplants rose to nearly 18%

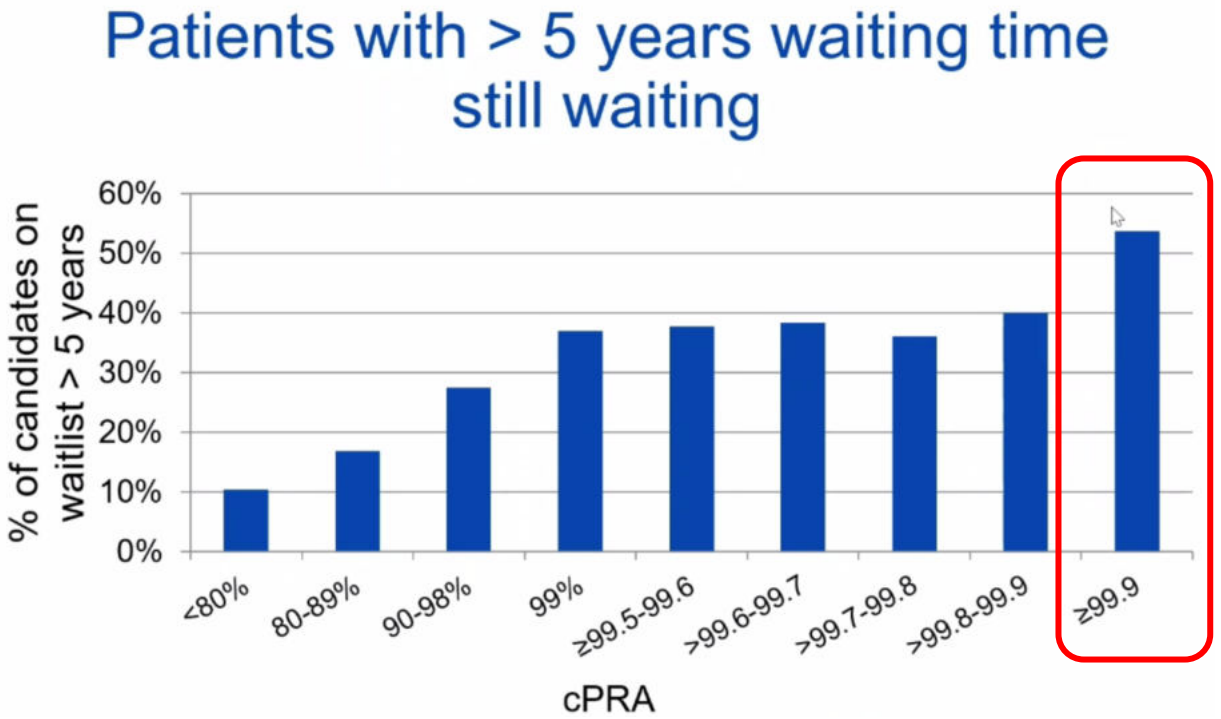
The number of CPRA 99–100% patients remaining on the waiting list has declined.



Stewart, AJT, 2016

Give priority for HS patients on the waiting list

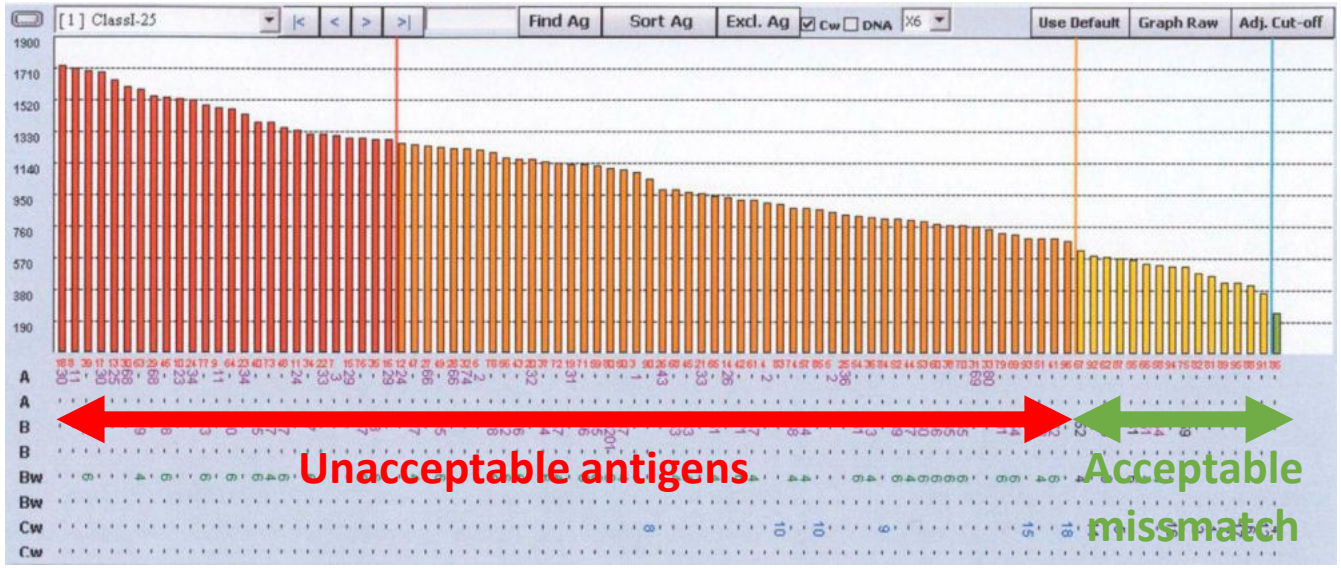




But very HS patients won't benefit from this program…

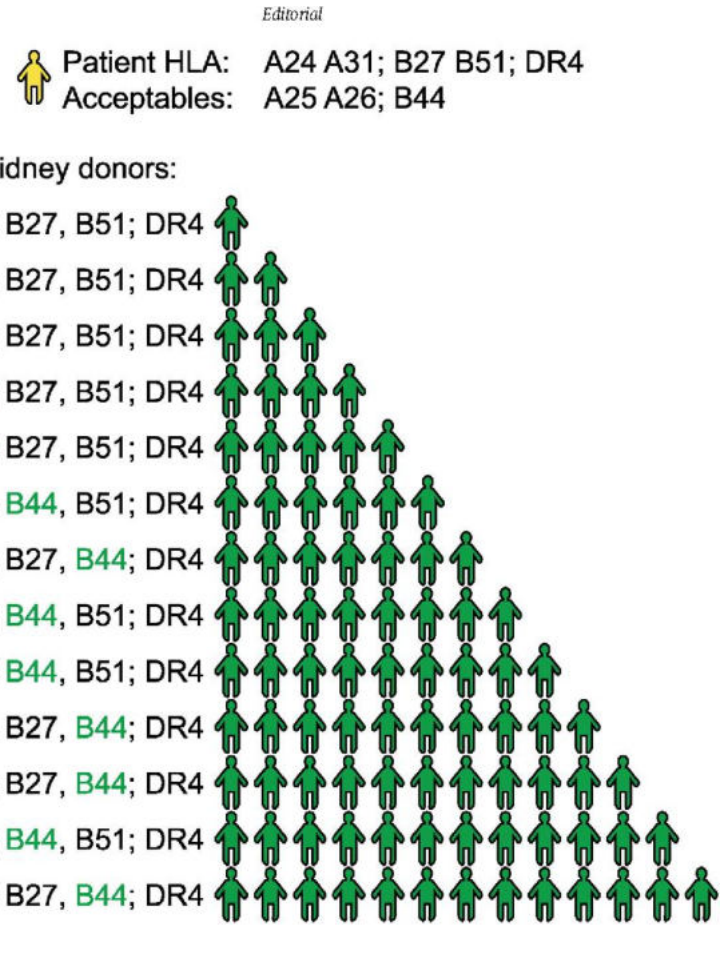
Schinstock, Clin Transplant. 2019

The acceptable mismatch program



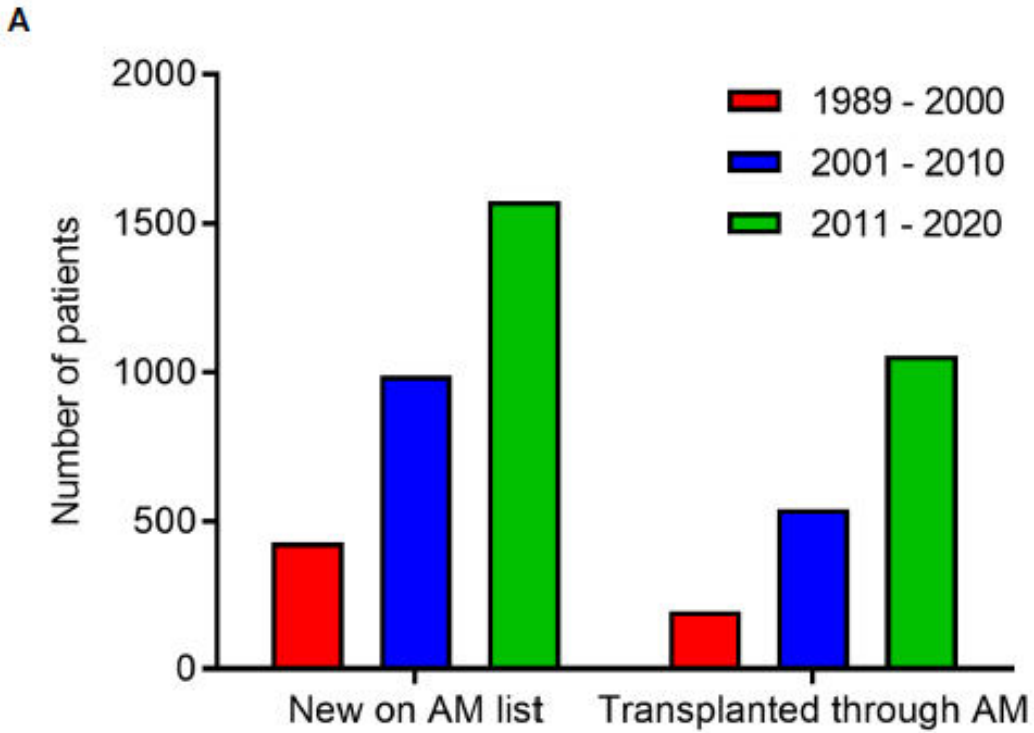
Current and historic sera analysis: allocation through the Eurotransplant Acceptable Mismatch (AM) program is based on extension of the patient's own HLA type with so called acceptable HLA antigens to which strictly no antibodies are formed, as shown by extensive laboratory testing.

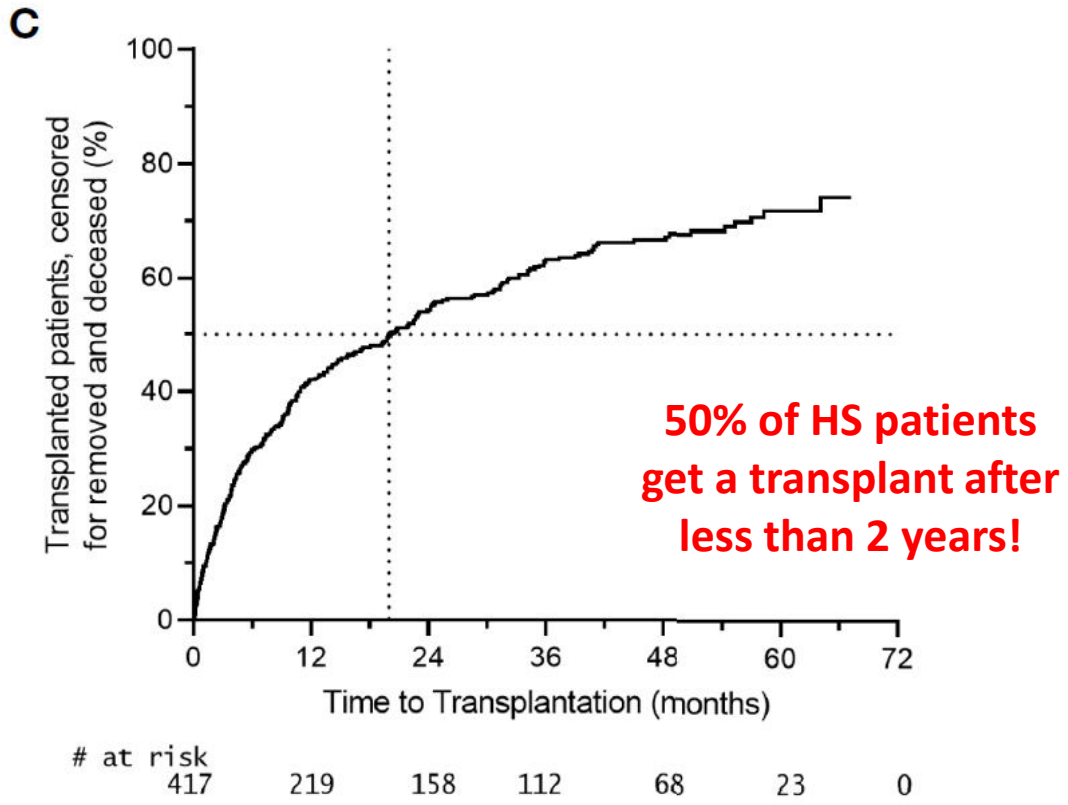
Antibodies to HLA antigens : unacceptable antigens!



Create an « extended HLA phenotype »

Eurotransplant acceptable mismatch

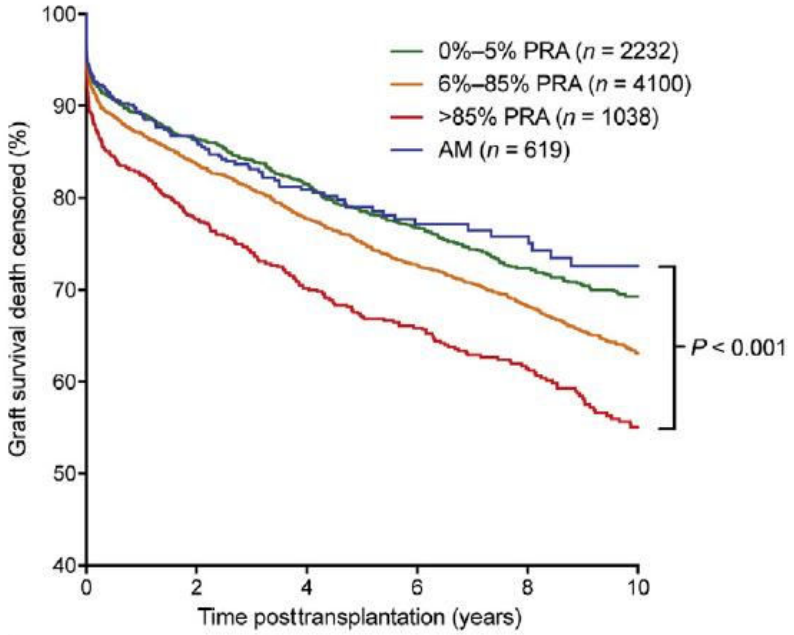




50% of HS patients get a transplant after less than 2 years!

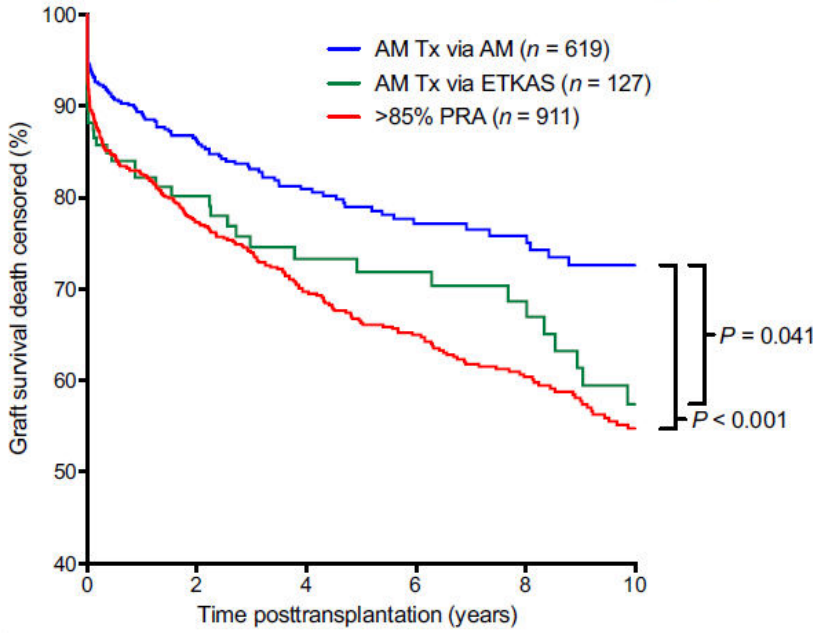
Heidt, Frontiers in Immunology, 2021

Eurotransplant acceptable mismatch



Number of transplants						
0%–5% PRA	2232	1474	1088	845	601	389
6%–85% PRA	4100	2644	1955	1564	1191	834
>85% PRA	1038	581	403	321	243	165
AM	619	349	229	146	97	63

Graft survival in HS patients comparable to low sensitized patients



Number of transplants						
AM Tx AM	619	349	229	146	97	63
AM Tx ETKAS	127	75	55	47	40	27
>85% PRA	911	506	348	274	203	138

Graft survival with theAM program much better compared to the usual allocation

Heidt, KI, 2018

The acceptable mismatch program in France 2021

TGI (cPRA)	Wait-listed (active) patients 01/01/2022	Newly wait-listed patients in 2021	Transplanted in 2021	Death in 2021
0%	3 728 (41,7%)	3 176 (59,1%)	1 711 (52,6%)	303 (47,5%)
1-24%	1 395 (15,6%)	774 (14,4%)	510 (15,7%)	93 (14,6%)
25-49%	886 (9,9%)	470 (8,8%)	339 (10,4%)	67 (10,5%)
50-84%	951 (10,6%)	465 (8,7%)	302 (9,3%)	68 (10,7%)
85-100%	1 990 (22,2%)	486 (9,0%)	390 (12,0%)	107 (16,8%)
Total	8 950 (100%)	5 371 (100%)	3 252 (100%)	638 (100%)

The part of wait-listed HS patients in high Accumulation in the wait-list and newly listed Rate of transplantation is low

Rapport scientifique ABM 2022

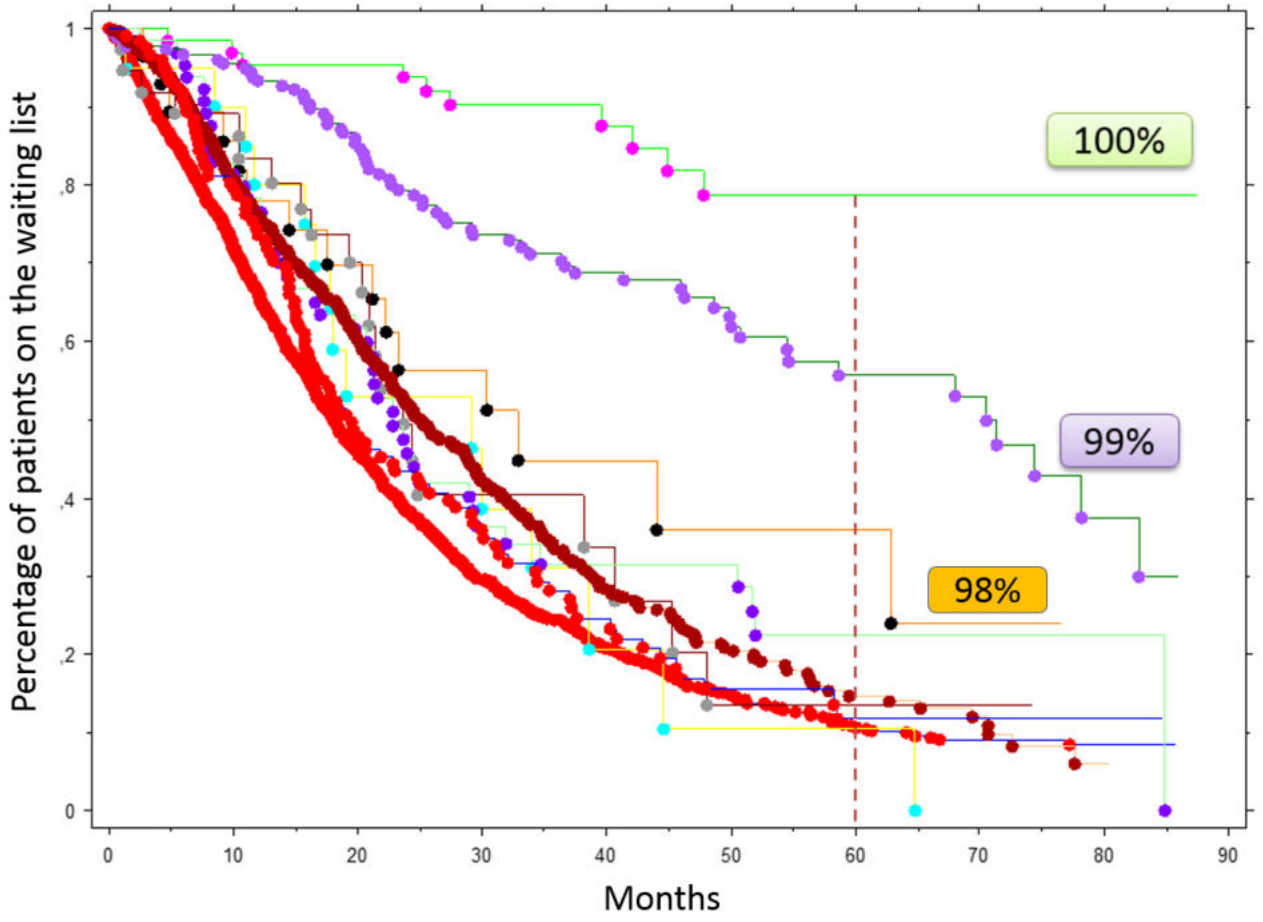
The acceptable mismatch program in France

4 KT centers
(Amiens, Caen, Lille, Rouen)

3096 wait-listed patients between 01/07/2009 and 31/12/2015

Status at the 31/10/2016

KT access according to TGI (cPRA)



Unpublished data. Data from Cristal Database – Agence de la Biomédecine

The acceptable mismatch program in France 2021

		Incidence cumulée des greffes avec prise en compte du risque concurrent de décès en attente ou sorties pour aggravation en % [IC à 95%]					
TGI	effectif	à 3 mois	à 6 mois	à 12 mois	à 24 mois	à 36 mois	Médiane (mois)
98 %	316	4 [2-7]	9 [6-12]	18 [14-23]	39 [33-44]	50 [43-56]	38,0
99 %	881	2 [1-3]	4 [3-6]	9 [7-11]	18 [16-21]	24 [21-28]	NO
100 %	277	0 [0-2]	0 [0-2]	1 [0-3]	3 [2-6]	5 [2-9]	NO

Data from Cristal Database – Agence de la Biomédecine

HS patients: a stepwise approach

1

2

Avoid immunological conflict

Anti A11 Anti B24 Anti DQ6

A2 A24 B12 B27 DR4 DR11 DQ2 DQ5

HLA MATCHING BETWEEN DONOR AND RECIPIENT
NO DSA
➡ Negative CROSS MATCH

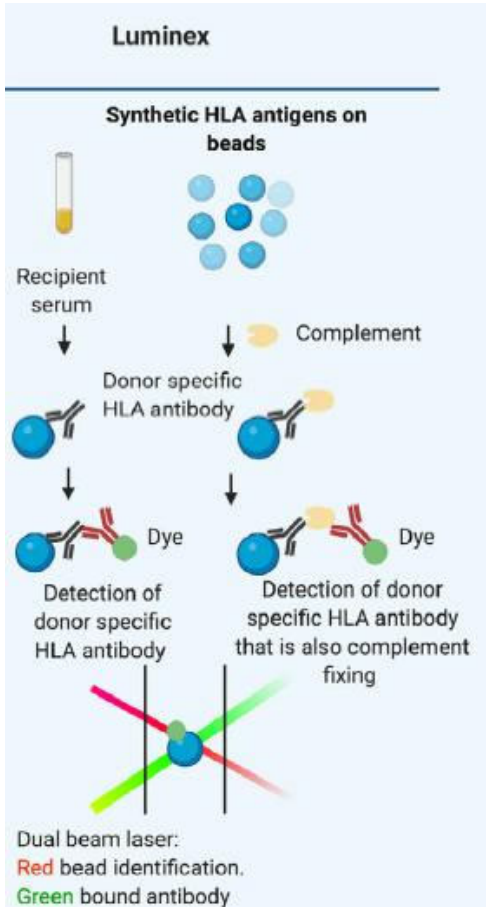
Immunological High Risk Transplantation

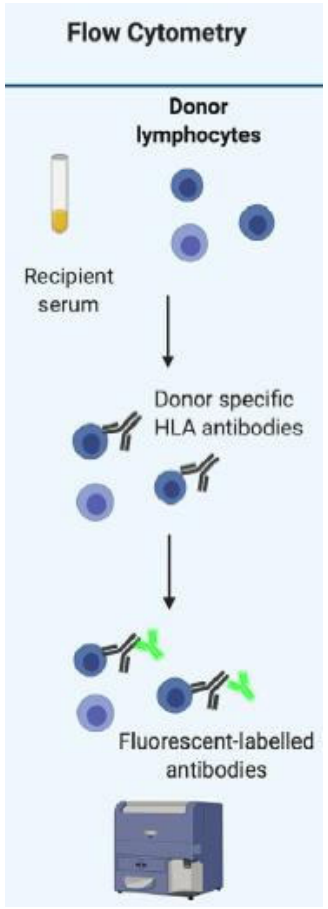
Anti A2 Anti B27 Anti DQ5

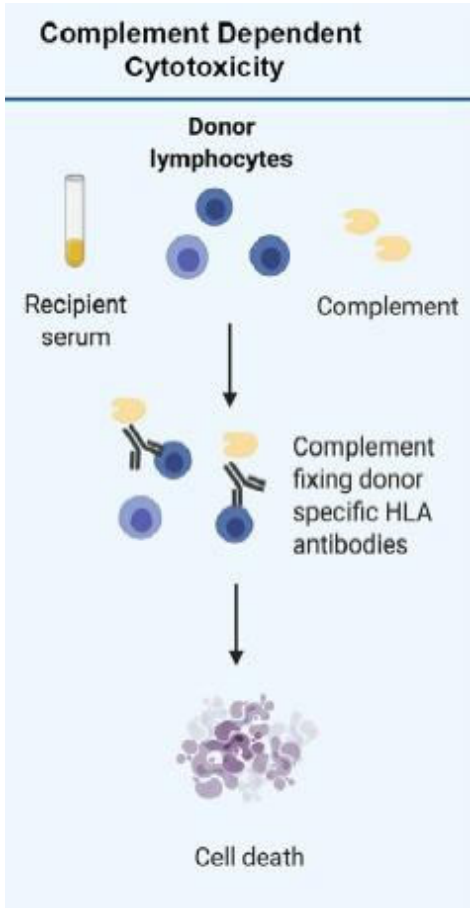
A2 A24 B12 B27 DR4 DR11 DQ2 DQ5

CONSIDER KTR WITH PREFORMED DSA
Risk of ABMR and inferior graft survival
➡ Risk of Positive CROSS MATCH

Desensitization: 3 tools are required!





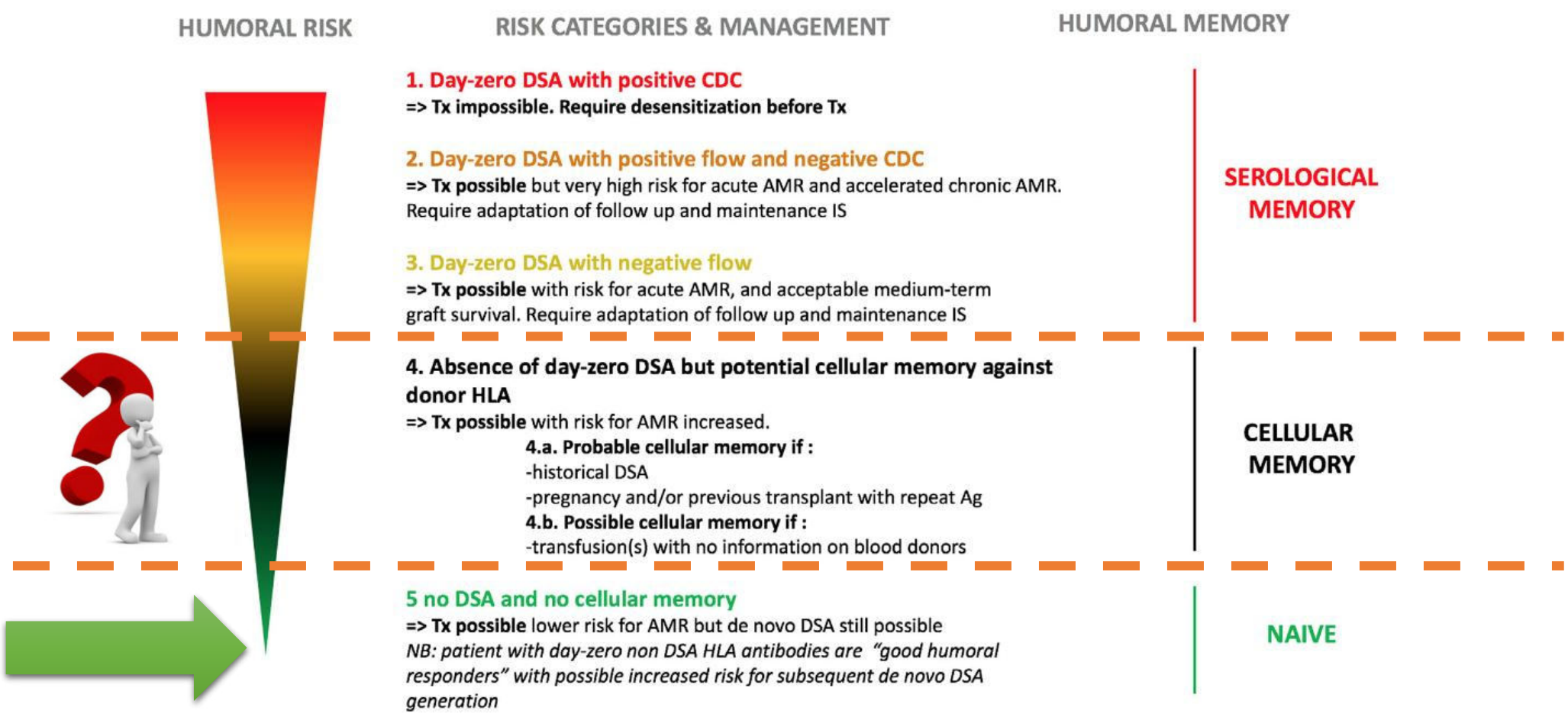


Virtual XM **Flow XM** **CDC XM**

Bestard, Transplant International, 2021

« Natural » desensitization

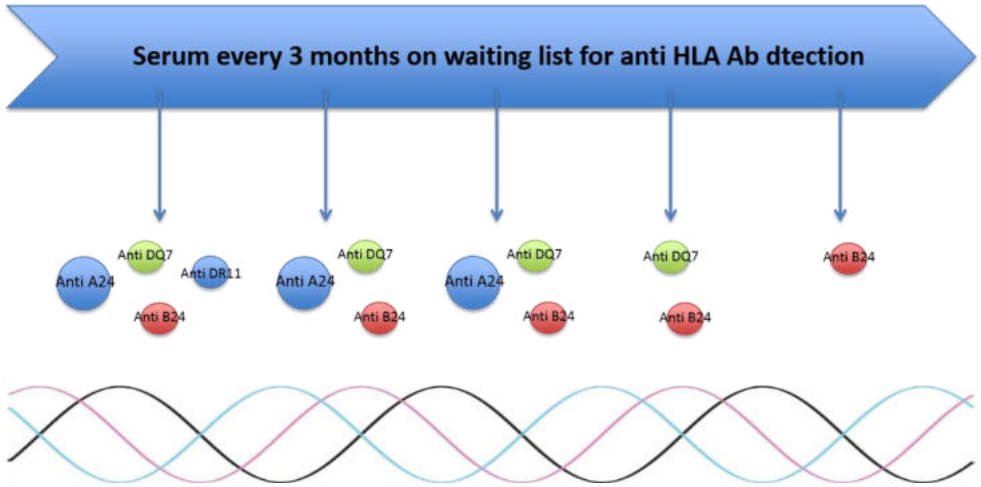
Transplant with historical DSA



Bestard, Transplant International, 2021

Natural desensitization

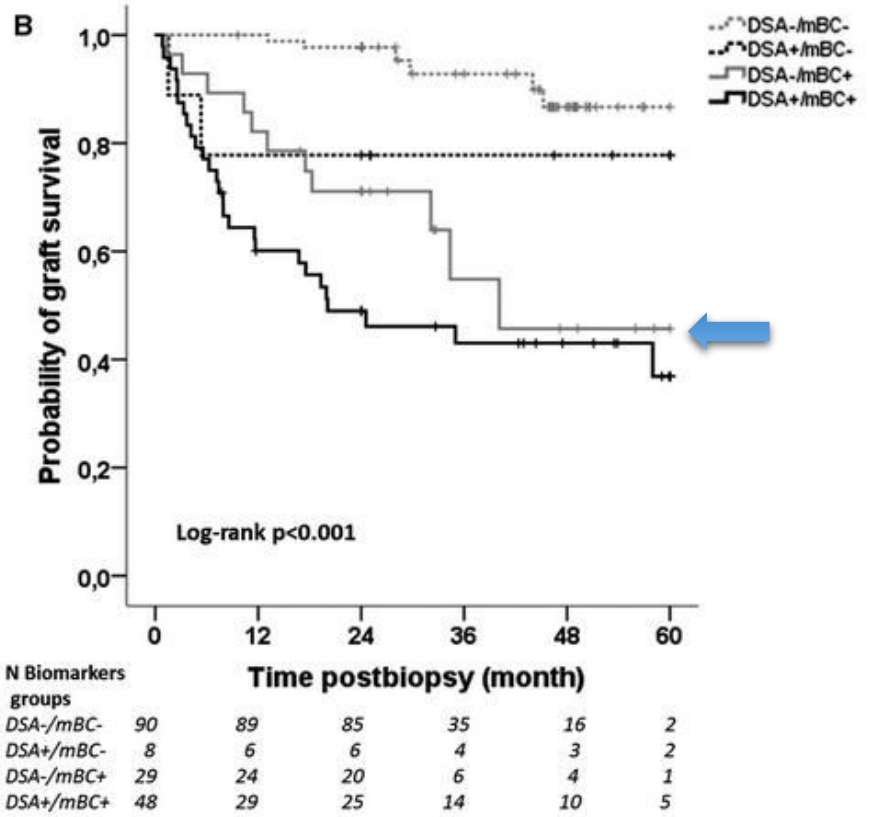
Transplant with historical DSA but cellular memory



In some patients, cPRA decreases over time

These patients could benefit from
a KT with historical but negative Day 0 DSA

Memory B cells

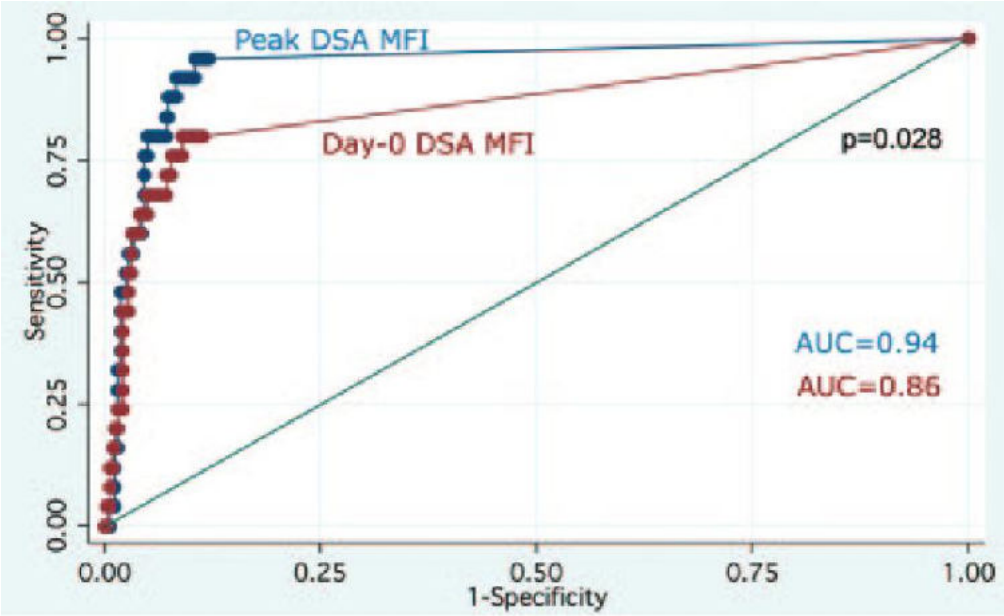


ABMR and Graft failure seem nevertheless higher

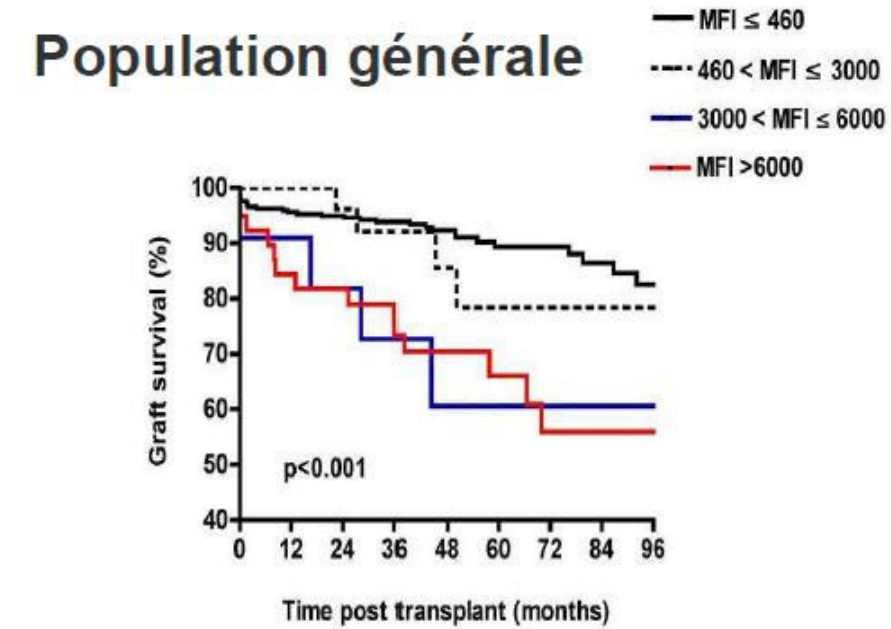
Luque, AJT, 2019

« Natural » desensitization

Transplant with historical DSA



Peak DSA MFI (historical) > Day-0J0
Dans la prédiction de l'ABMR



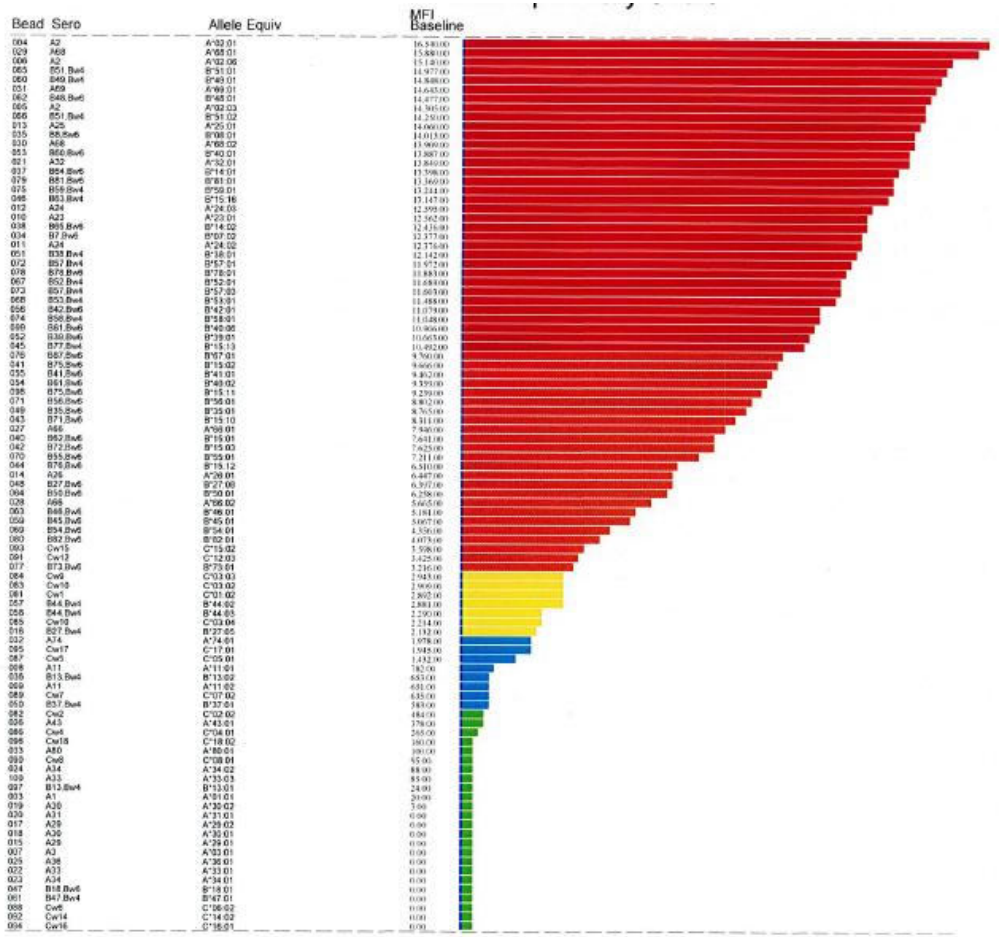
Number at risk

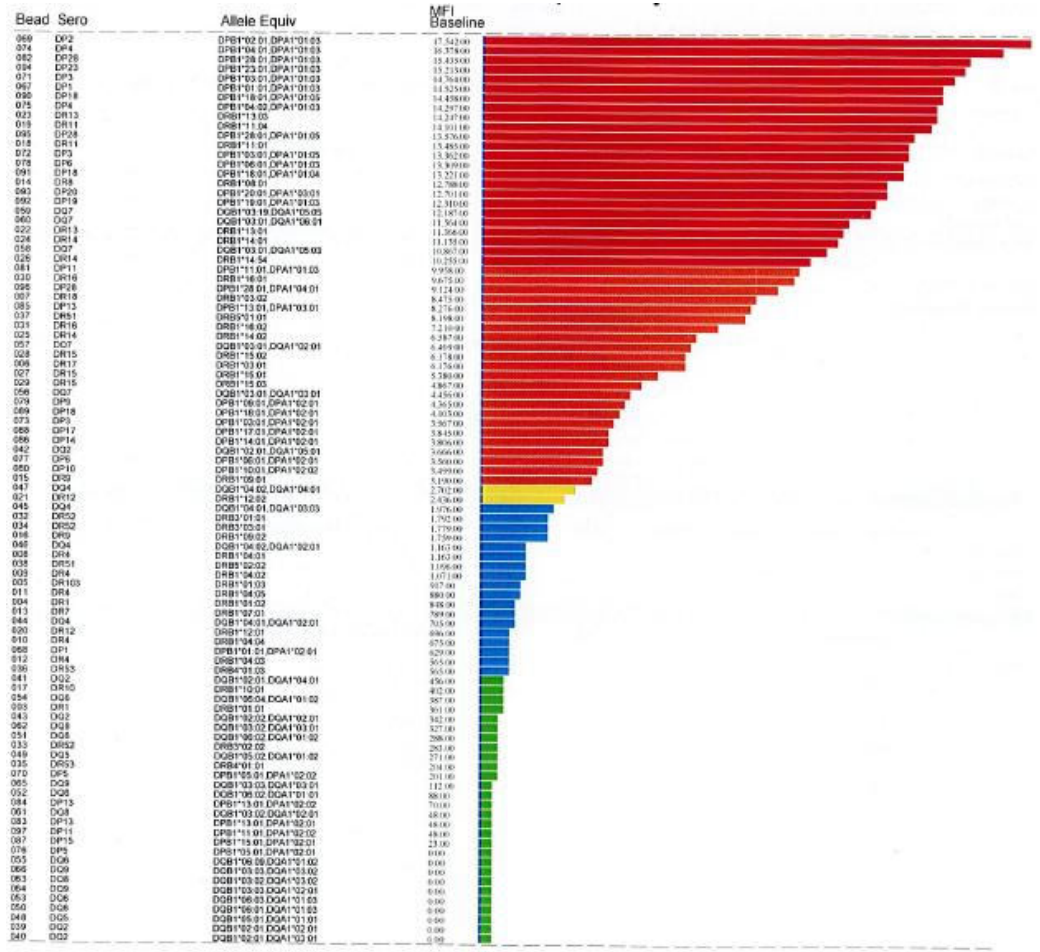
MFI ≤ 460	325	297	285	224	151	103	75	51	33
460 < MFI ≤ 3000	27	27	26	22	13	10	8	7	6
3000 < MFI ≤ 6000	11	11	10	8	4	3	3	2	2
MFI >6000	39	33	30	28	19	16	12	9	5

Lefaucheur, JASN, 2010

Natural desensitization

Sometimes it’s not sufficient…

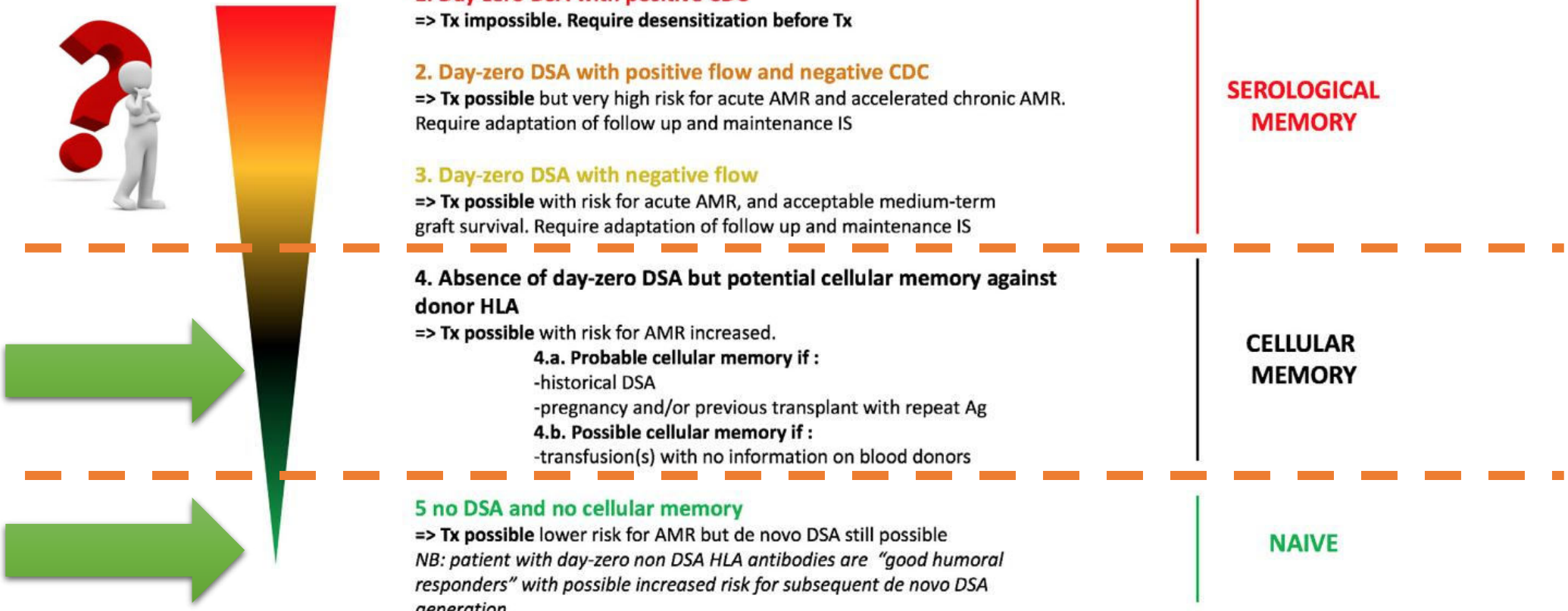




Mme L. , 49 ans

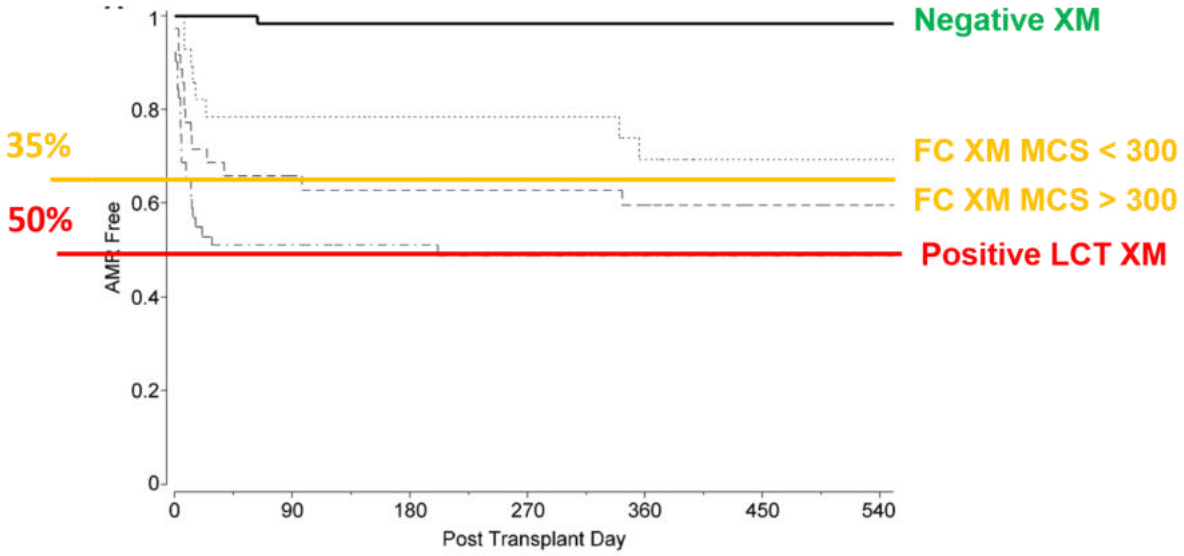
cPRA (TGI) on the last serum: 100% …

« Active » desensitization: Day 0 DSA +
Risk stratification

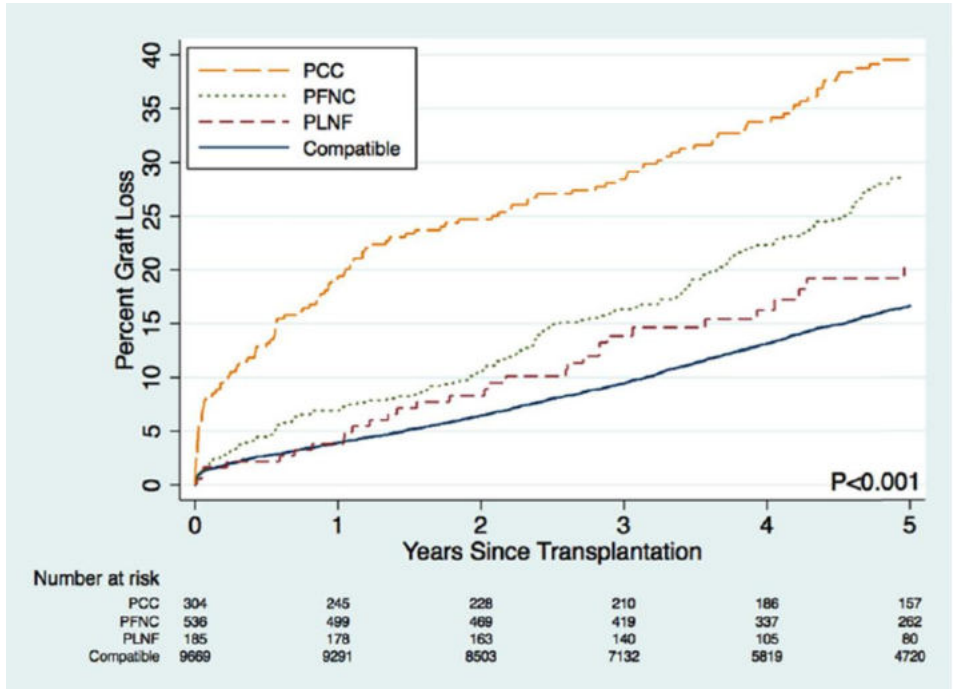


Bestard, Transplant International, 2021

« Active » desensitization: Day 0 DSA +
Risk stratification



Gloor, AJT 2010, 10:582



Positive LCT XM

Positive FC XM

Positive luminex

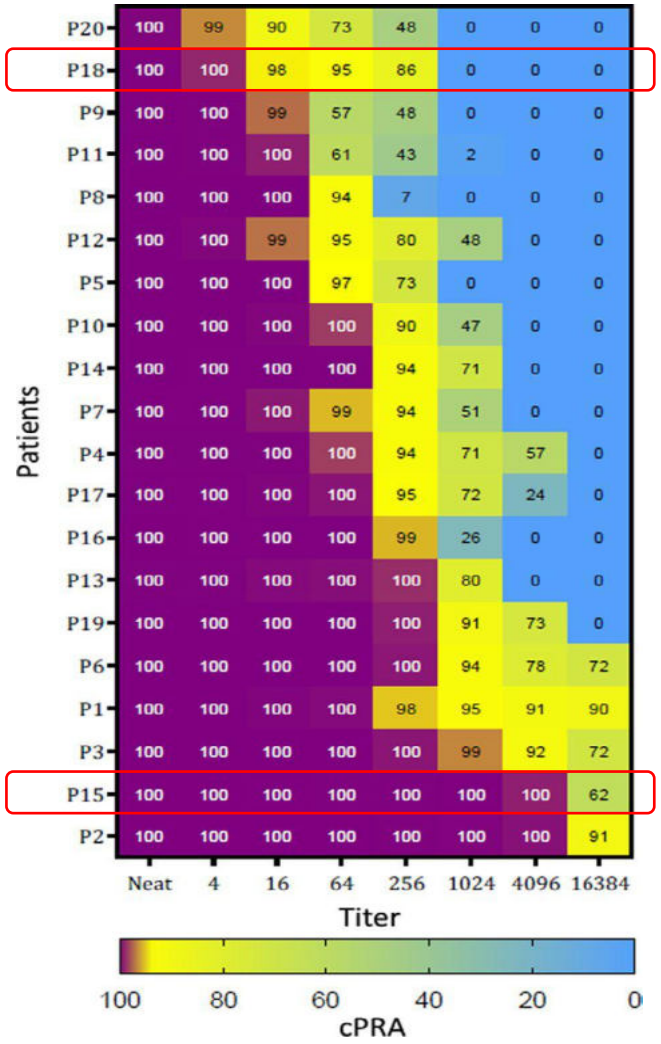
Negative XM

Orandi, AJT, 2014

Dilution of the serum could help!

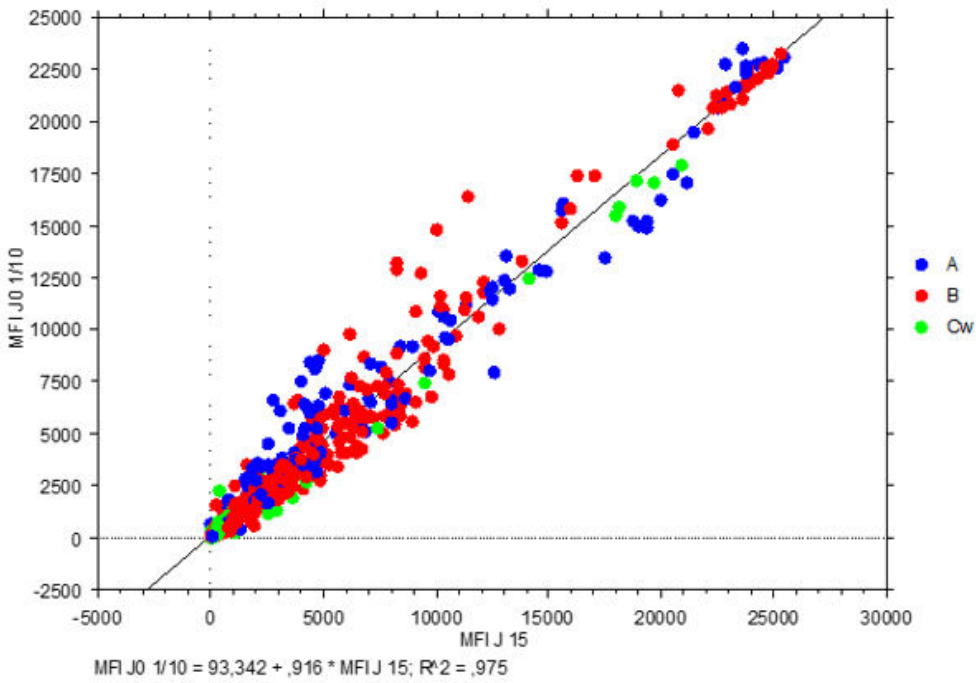
Sera of 20 patients
With cPRA >= 99,9%
HLA Ab + MFI >1000

Patients are not equally immunized despite the same initial 100% cPRA



Tambur, AJT, 2021

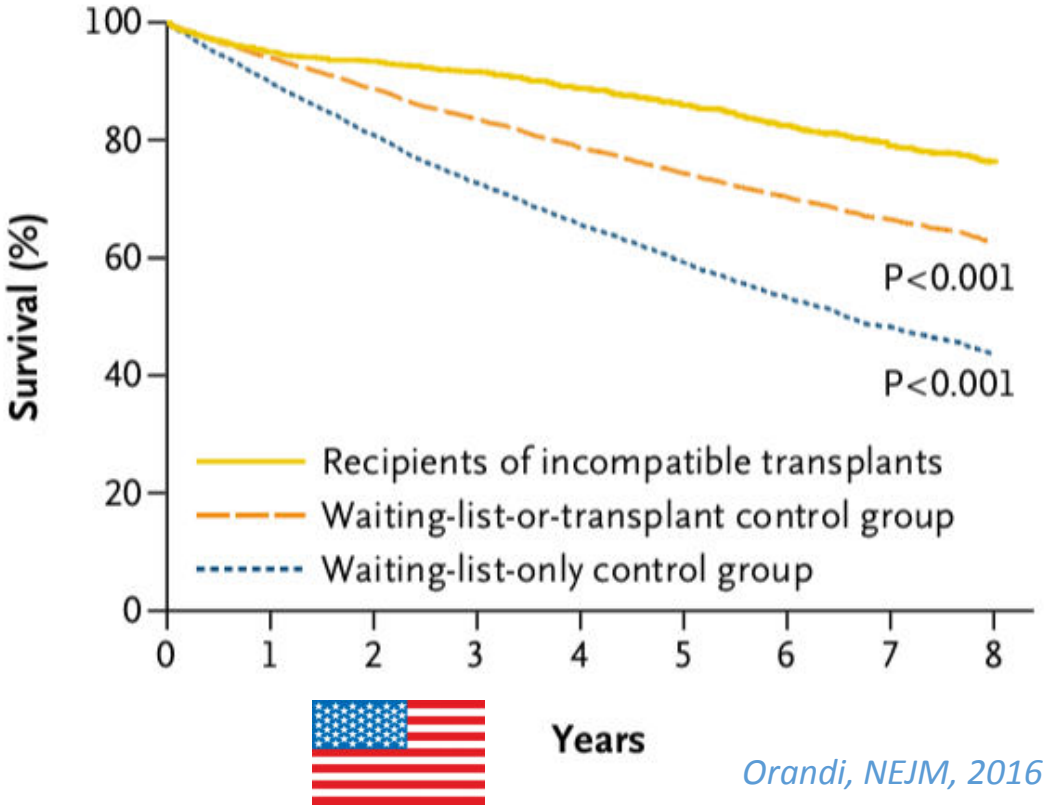
<u>12 patients (TGI > 98%) waiting for KT</u>
Serum before desensitization (pure and 1:10 dilution)
Sérum after 10 sessions of IA (pure)
1067 beads Luminex class 1 et 855 beads Luminex class 2.



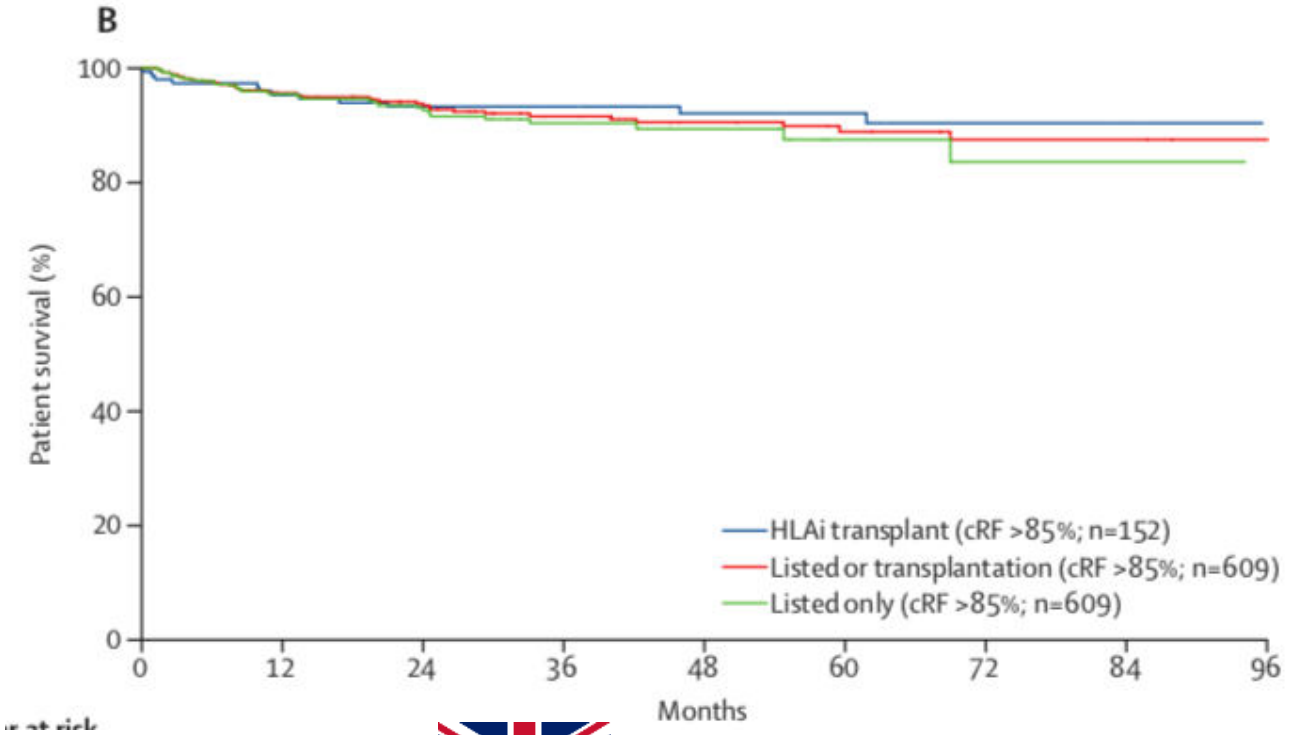
Good prediction of the effectiveness of desensitization by dilution

Bertrand, SFT 2022

Consider desensitization with caution



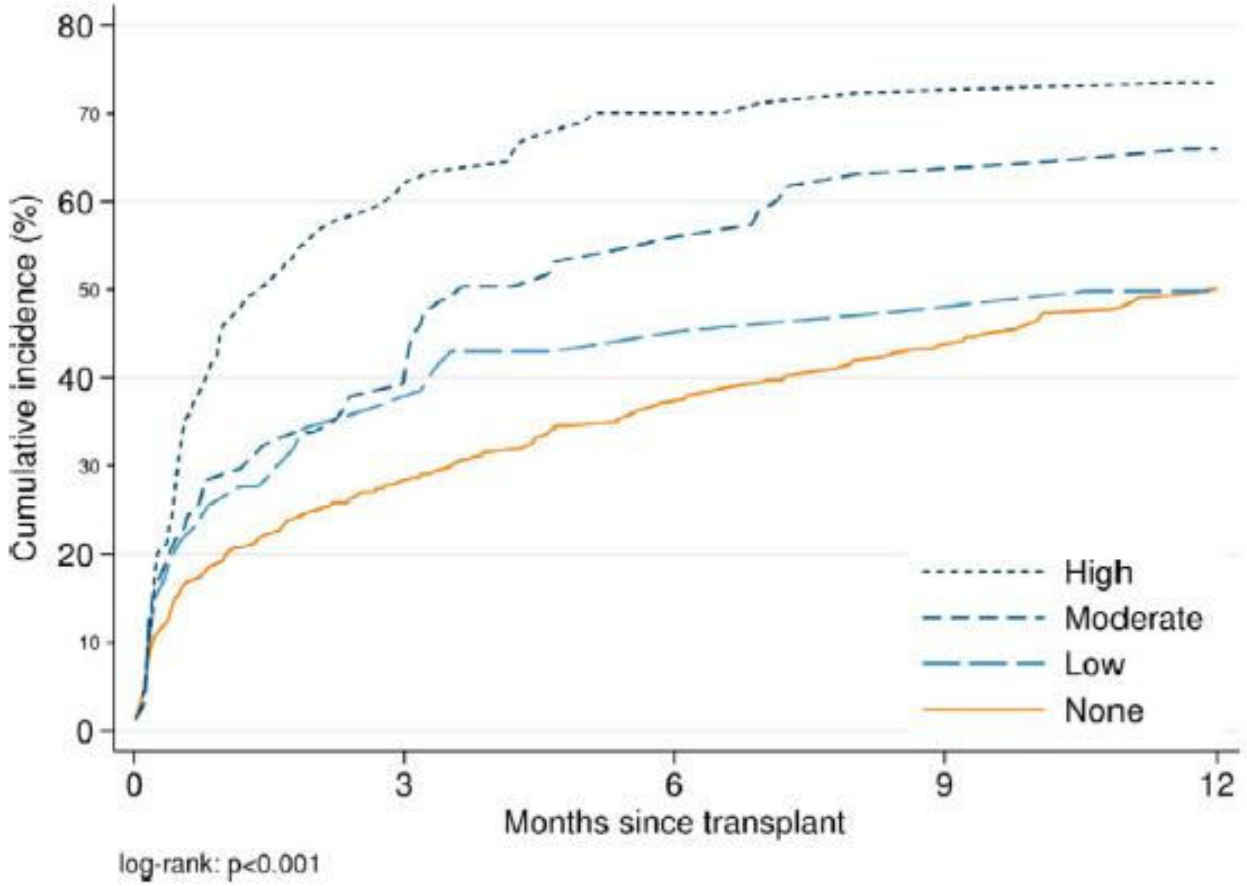
Orandi, NEJM, 2016



Manook, Lancet, 2017

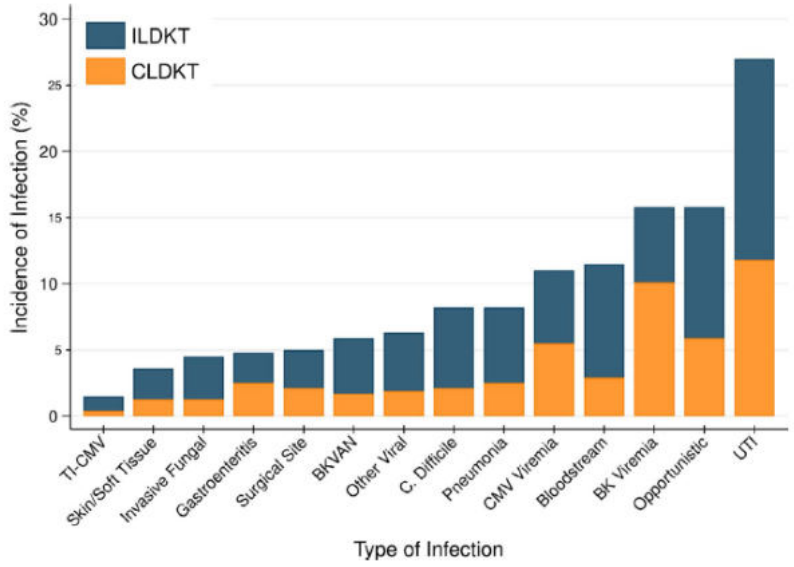
Caution for ABMR risk, infectious risk…. Consider quality of life too

Time to first infection within 1-year postKT, by intensity of desensitization.



Desensitization intensity:

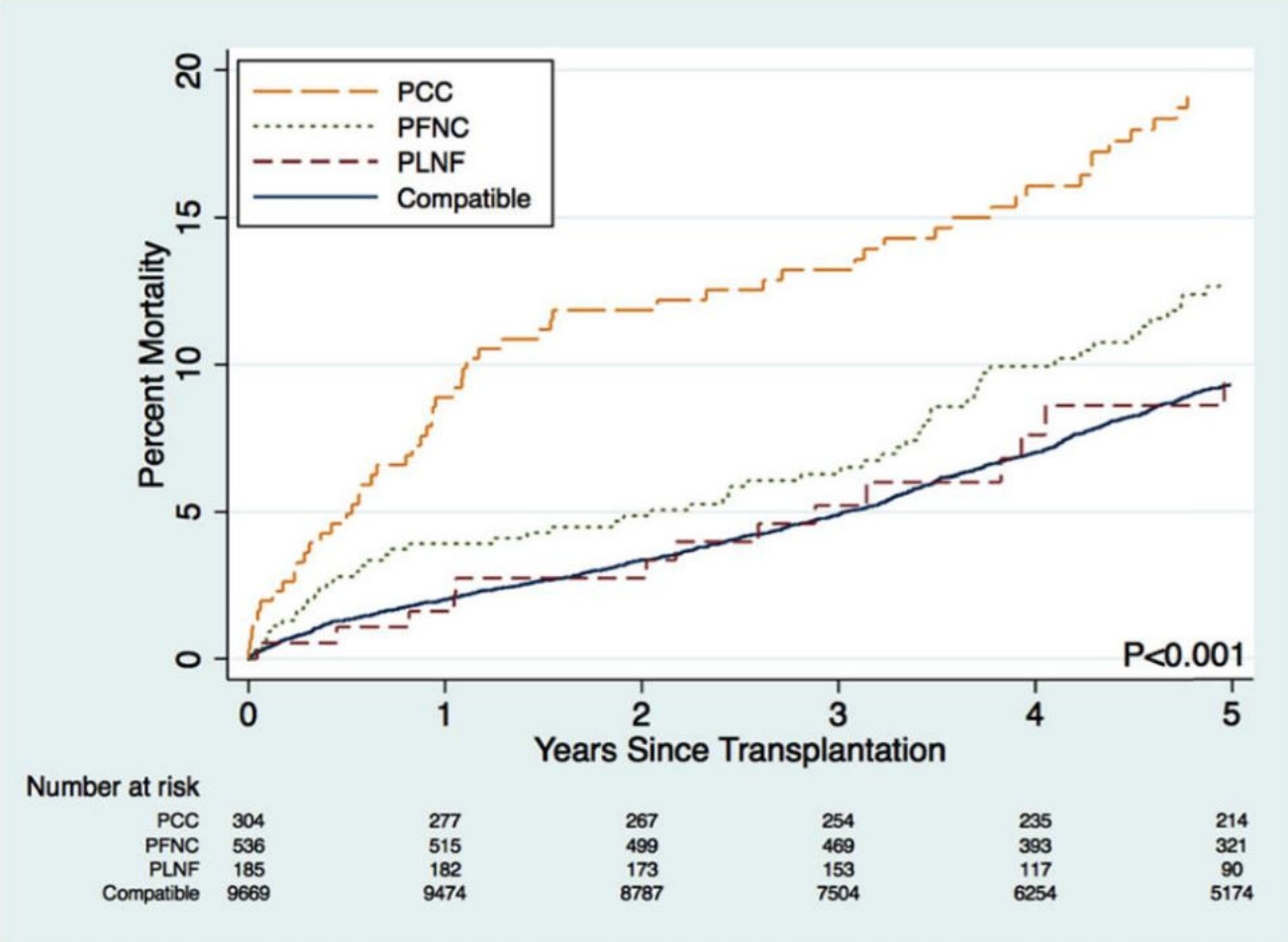
- none/compatible (n = 260),
- low (0-4 plasmaphereses, n = 47),
- moderate (5-9, n = 74),
- high (≥10, n = 94)



Desensitized recipients with ≥4 infections are at higher risk of prolonged hospitalization and death-censored graft loss

Avery, AJT, 2020

Patients undergoing HLA desensitization have a significantly higher risk of death than compatible patients



Positive LCT XM

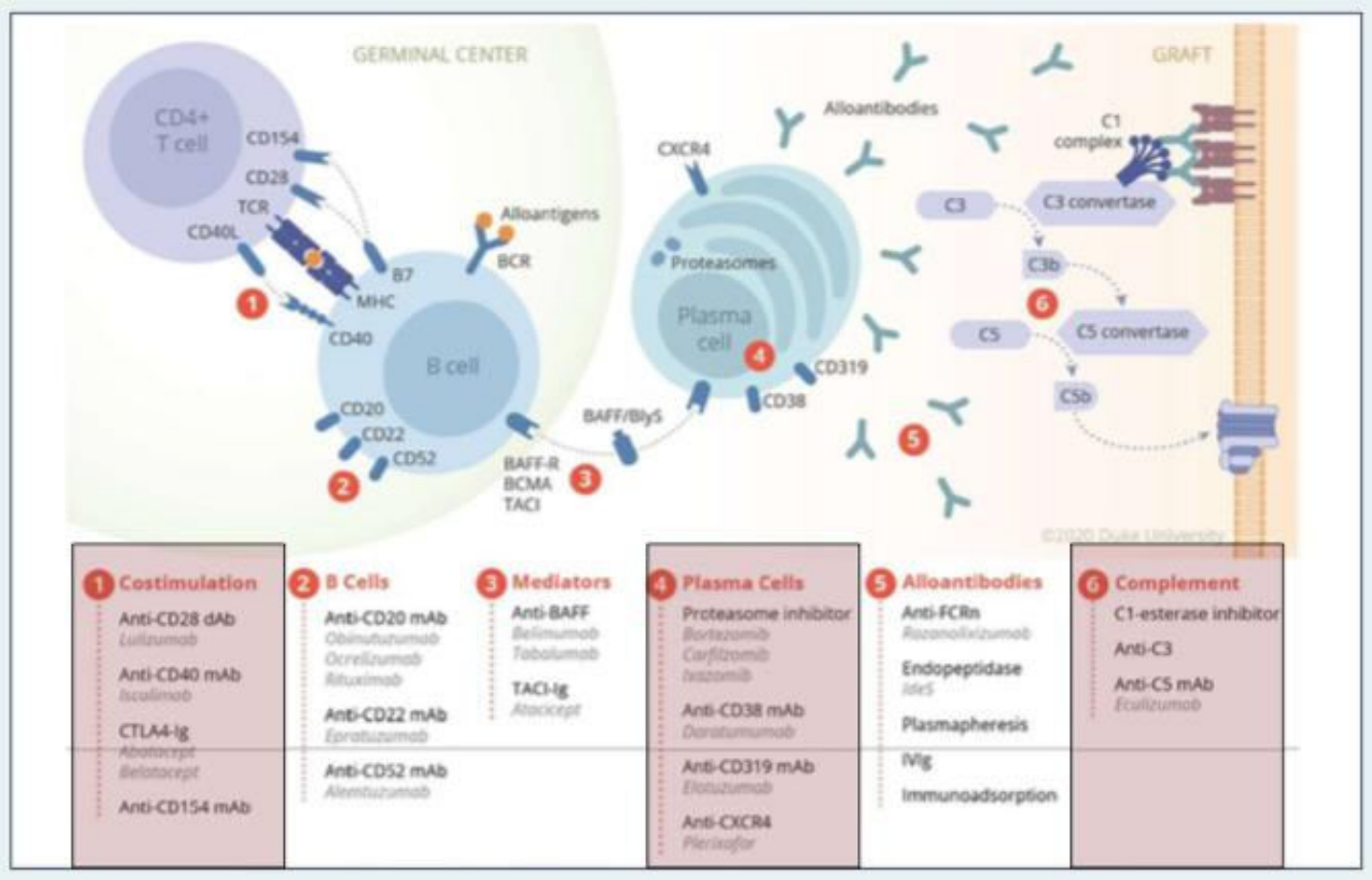
Positive FC XM

Positive luminex

Negative XM

Orandi, AJT, 2014

Desensitization: from Ivlg to imlifidase!



Kwun Am j Transplant 2020

Desensitization: from IvIg to imlifidase!

Avant greffe

IvIg
Glotz, Transplantation, 1993
Jordan, Transplantation 1994

IvIg / Rituximab*
Vo Transplantation 2010

EP/IA + Rituximab*
Noble, KI reports, 2021

Anti IL 6*
Vo Am J Transplant 2022

Daratumumab*
DARDAR *(NCT04204980)* en cours

Belatacept*
ATTAIN *(NCT04827979)*
et ADAPT *(NCT05017545)* en cours

J0 greffe

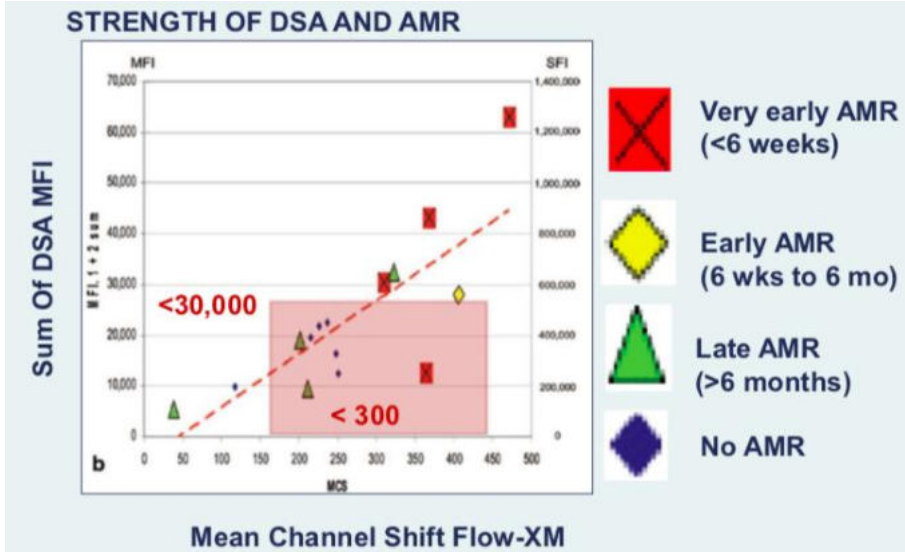
IA
Schwaiger Nephrol Dial Transplant 2016

Imlifidase
Jordan N Engl J Med 2017

Eculizumab*
Glotz Am J Transplant 2019

Post greffe

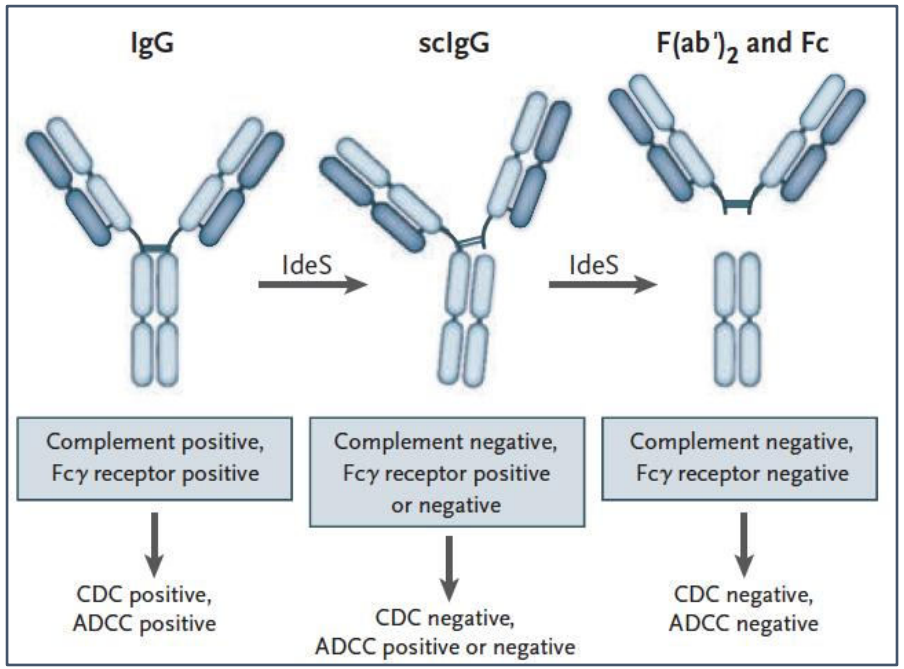
IvIg / Rituximab* / EP
Amrouche Transplantation 2017

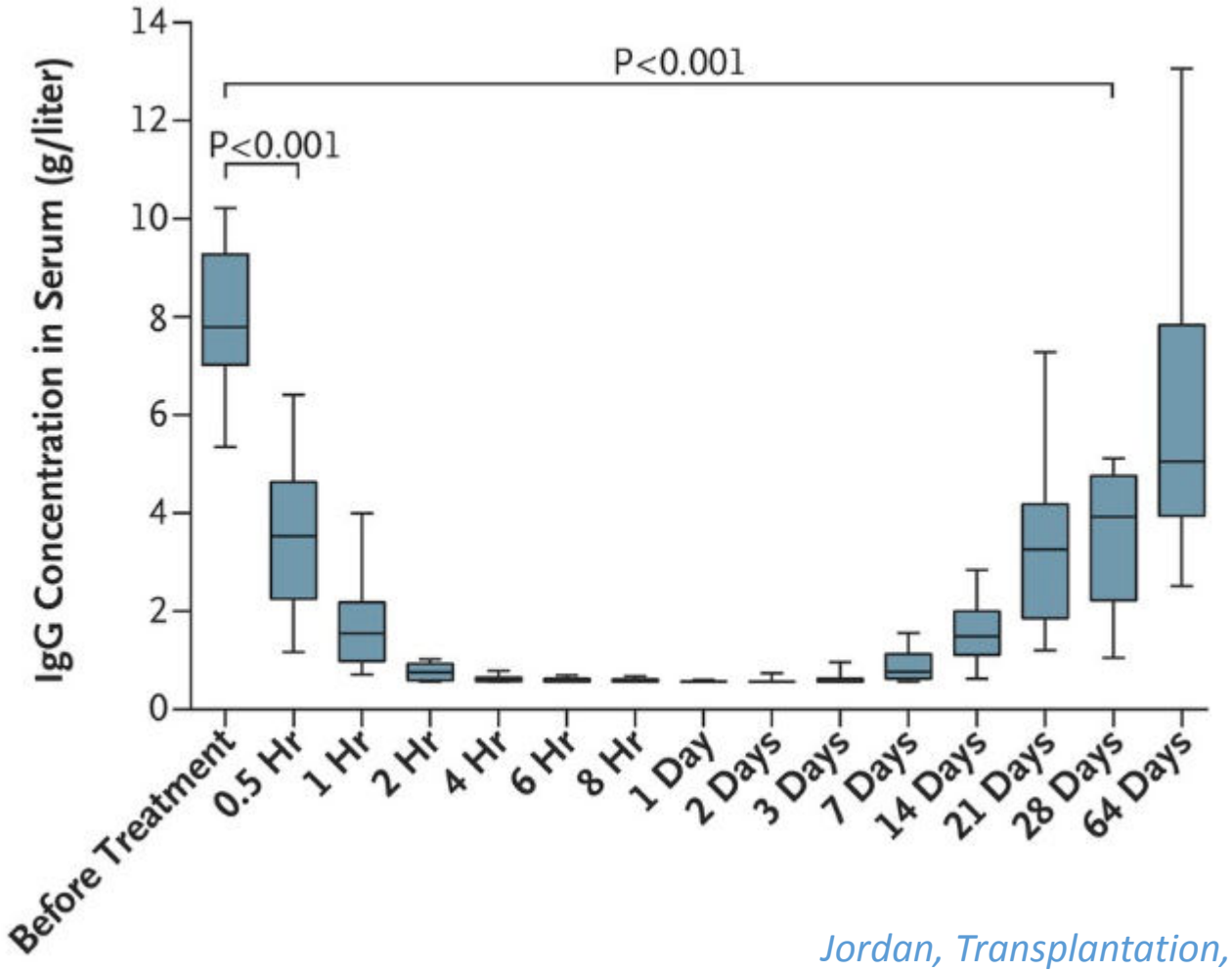


Lai, Transplantation, 2011

**Non approuvées dans cette indication*

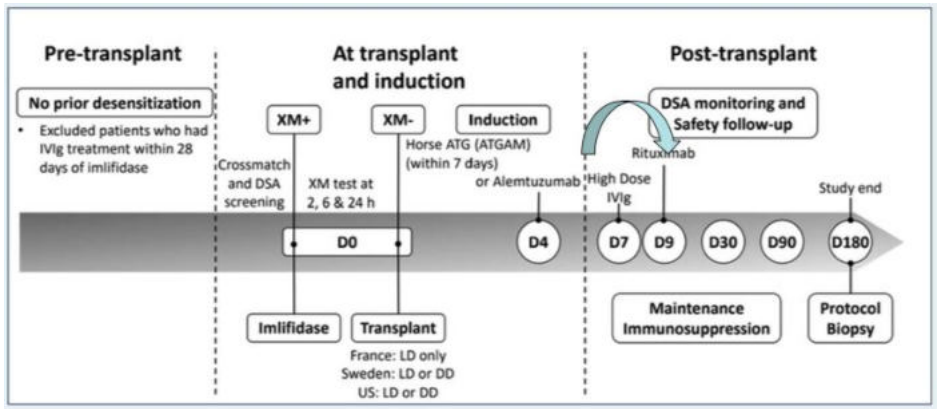
Imlifidase

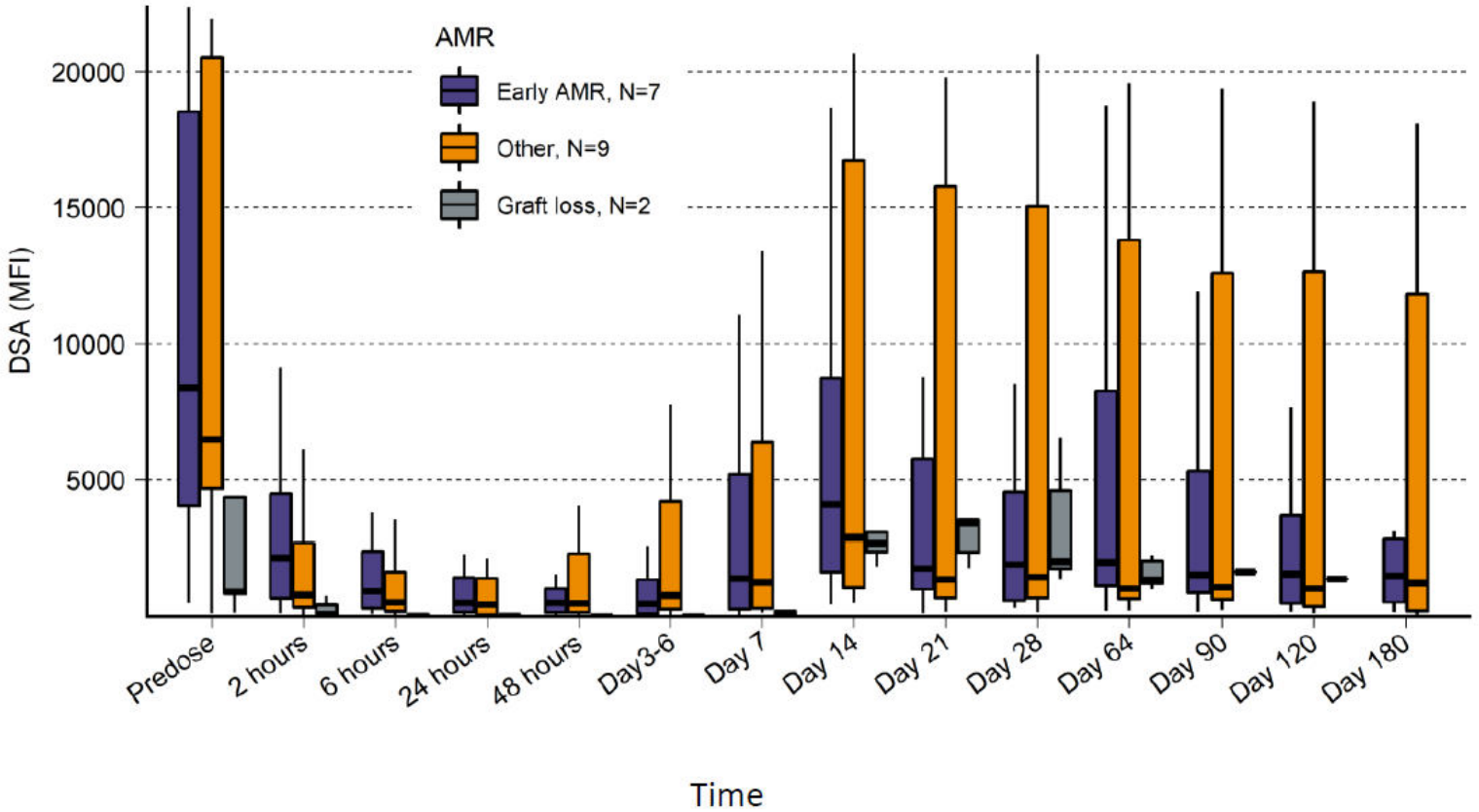




Jordan, Transplantation, 2021
Jordan, NEJM, 2017

Imlifidase

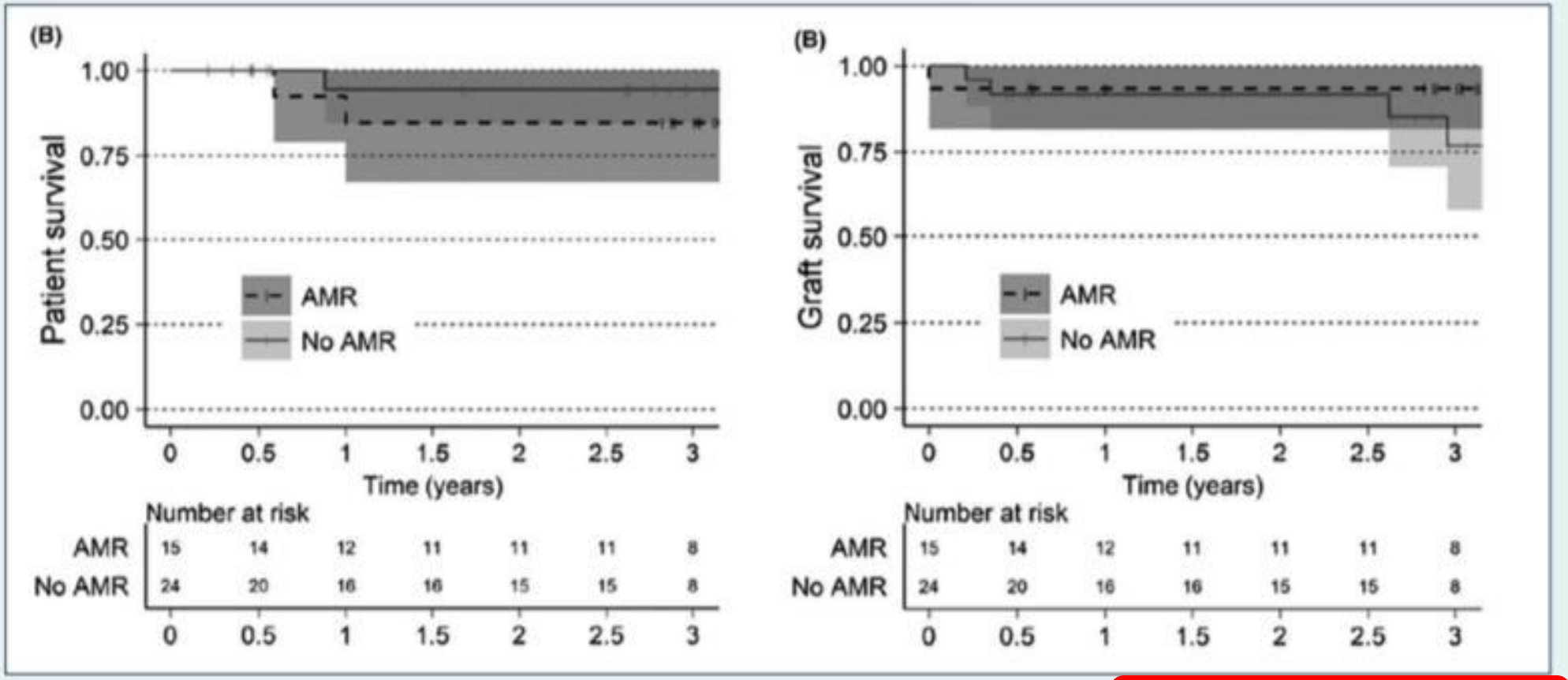




Jordan, Transplantation, 2021
Jordan, NEJM, 2017

Imlifidase

N=39, Median cPRA: 99.62%, Deceased donor 82%



ABMR 38% (15/39)

Study 17-HMedIdeS-14
(Long-term 13-HmedIdeS-02, -S-03 + 14-HMedIdeS-04)

Kjellman, AJT 2021

Requirements for selecting a patient

Patients eligible for this treatment

- cPRA ≥ 98%
- Age ≤ 65 years
- Time on the waiting list ≥ 3 years
- Number of previous kidney transplantation from: 0 to 2 (multidisciplinary consensus required beyond 2 grafts)
- Kidney graft biopsy with a low risk of complication
- Patient information

Transplant unit profile

Access to plasmapheresis 7 days a week

Delisting of HLA antibodies

Allow only HLA antibodies with MFI not exceeding 5000 after 1:10 dilution

Organ offer

Donor profile

Avoid elderly donors

DSA

MFI of immunodominant DSA A, B, DRB1, DQB1 > 6000 except for Cw and DP

Pre-Imlifidase virtual positive crossmatch on recent serum

(No cell crossmatch)

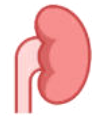
Imlifidase 0.25 mg/kg

4 to 6 hours after Imlifidase infusion

Cell crossmatches

- Post-Imlifidase negative complement-dependent cytotoxicity crossmatch
- Prospective or retrospective flow cytometry crossmatch on recent, and day 0 pre- and post-Imlifidase sera

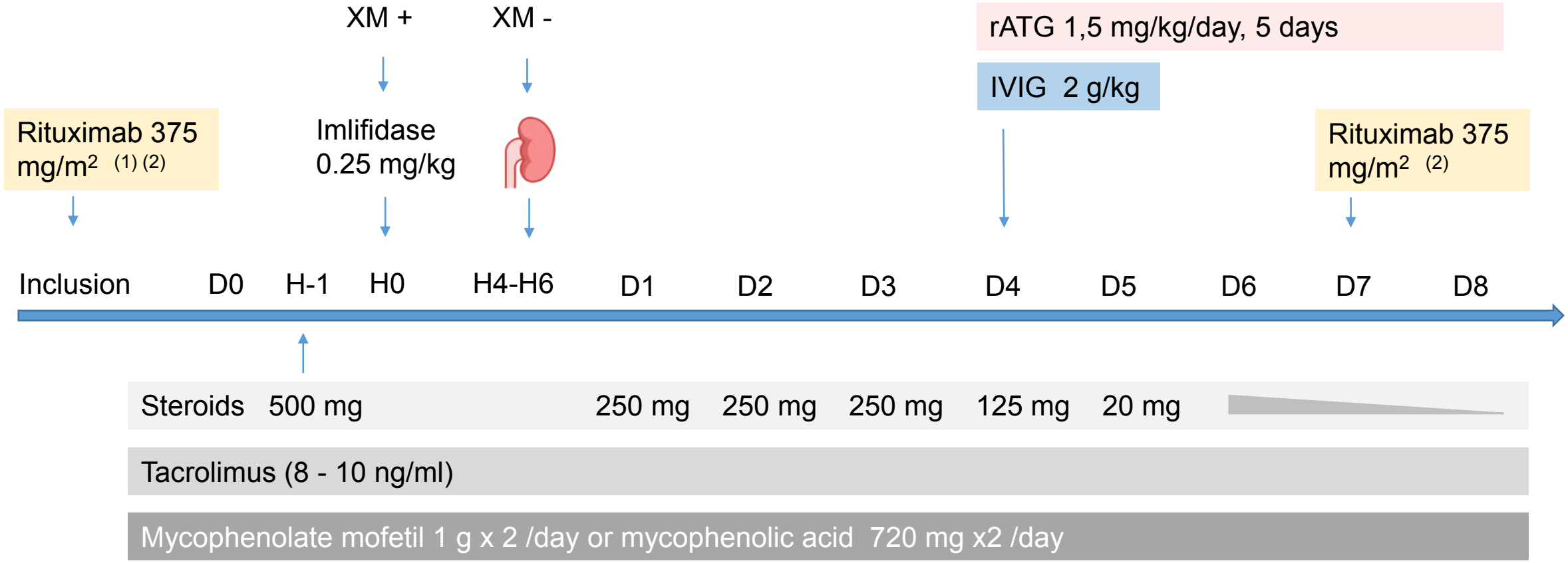
Transplantation



Timeline

Couzi, Transplant international, in press 2023

Figure 3



(1) A pre-transplant injection requires a crossmatch with an anti-rituximab antibody
(2) This is an off-label use of Rituximab

Société Francophone de Transplantation
SFNDT
SFHI Société Francophone d'Histocompatibilité et d'Immunogénétique

cPRA ≥ 98%
Wait listing > 3 ans

Living donor KT?

Current serum analysis
One Lambda* single antigen

Decrease or disappearance of anti HLA antibodies

Persistance of anti HLA antibodies

Decrease of the cPRA

Consider KT with historical DSA

Current serum analysis with dilution
One Lambda* single antigen

Desensitization
(Imlifidase?)

Conclusion

- The number of HS patients is growing on the wait-list, prevention is essential
- A better definition of sensitization is necessary:

eplet/epitope/high resolution of HLA genotyping / pathogenicity of DSA

- Whenever possible consider transplantation without DSA with specific program: avoid immunolgical conflict
- But sometimes, it’s not enough for very HS patients (cPRA=99-100%)
- Consider desensitization but after a stepwise approach!

@dommibertrand