Foundational Concepts of HLA and Compatibility in Living Donation

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Objectives

- Review components of compatibility testing
- Identify the basic principles related to histocompatibility that apply to living donor transplantation
- Discuss strategies to expand access to transplantation for incompatible pairs

No conflict of interest to declare

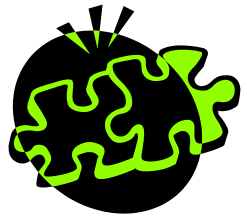
The Three Components of Compatibility Testing

- Blood group
- Tissue typing (HLA match)
- Crossmatch

Blood Group Compatibility

Recipient Blood Group		Donor Blood Group
O	⟵	O
A	⟵	A or O
B	⟵	B or O
AB	⟵	A, B, AB or O

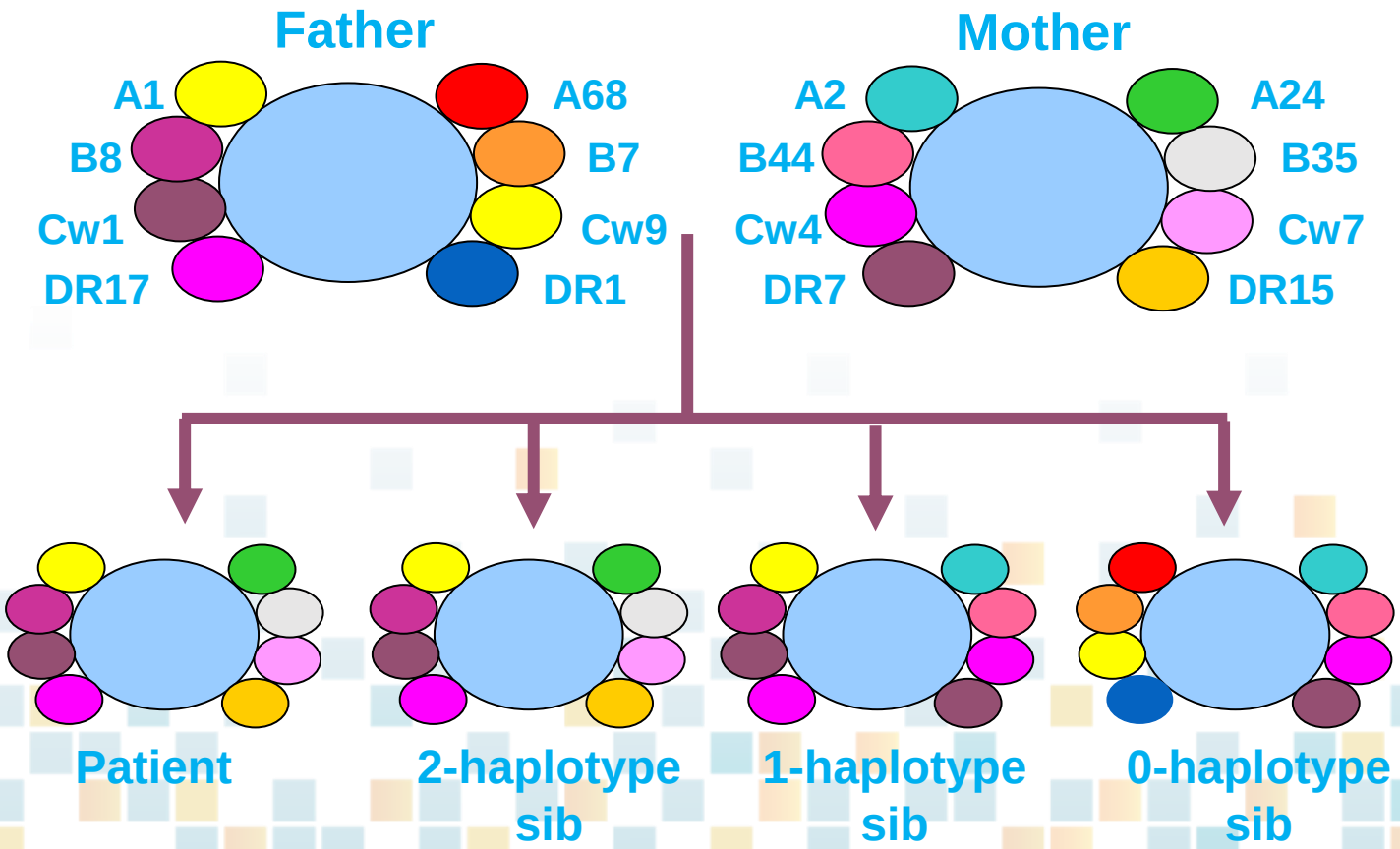
Tissue Typing



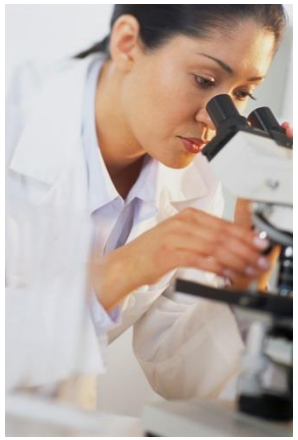
- HLA – Human Leukocyte Antigens
  - Cells express proteins which identify us as “self”
  - Stimulate immune response to foreign “non-self” organisms
  - Antibodies are produced
  - Newly produced antibodies attack foreign organisms
    - Virus
    - Bacteria
    - Fungus
    - Transfused blood, transplanted organ or tissue (“non-self” HLA)
- Shared antigens:
  - Parent/child share 50% HLA
  - Siblings share 0, 50, or 100% HLA
  - Identical twins carry same **DNA** = perfect match *
- *Tissue Typing (HLA) match can impact the life span of the transplanted kidney, but not crucial for success of most*

** Perfect match organ may last a lifetime without immunosuppression*

Inheritance of HLA



Crossmatch



Primary predictor of early rejection risk

- Recipient blood stored, tested for circulating HLA antibodies, caused by sensitizing events
- Single antigen class I/II interval testing monitors to create HLA antibody profile and activity
- Virtual Crossmatch: donor HLA is typed, compared with antibody profile
- Donor Specific Antibody determines virtual compatibility, confirmed with physical crossmatch before donation/transplant
- Physical (final) crossmatch: donor blood specimen mixed with recipient's, analyzed
- Positive reaction may be considered incompatible
  - Antibody to Donor HLA detected
  - High rejection risk
- Negative reaction is likely compatible
  - No/weak antibody to Donor HLA detected
  - Low rejection risk

Sensitizing events

- What causes a recipient to be sensitized?
  - Pregnancies
  - Blood transfusions
  - Prior transplants

Positive Crossmatch between husband and wife; history of multiple pregnancies

IMMUNOGENETICS CENTER REPORT

Virtual Crossmatch Report

HLA Typing Results

Name/ID	Relation	A	B	Bw	C	DR	DRB345	DQB	DQA1	DP	DPA1	Sample Date
[redacted]		24	39	6	7	4	53	2	02	402	01	10/1/20
	Patient	24	51	4	16	7		8	03	401	01	
[redacted]		24	35	6	9	14	52	7	03	402	01	11/15/20
	Spouse	24	52	4	4	14		8	05	14	02	
	Mismatches:	0	2 Ag		2 Ag	1 Ag		1 Ag		1 Ag		

HLA typing was performed by one or more of the following molecular methods: SSOP, SBT, SSP, NGS.

Comments:

Donor is mismatched with the patient for 7/12 HLA-A, B, C, DR, DQ, DP antigens.

Single antigen bead-based antibody testing on the current serum dated 10/01/2020 indicates that the patient carries donor-specific antibodies against HLA-DR14 (MFI:2151) and DR52 (MFI: 1780), which indicates risk of antibody-mediated rejection.

Virtual crossmatch acceptable - same recipient, matched with KPD donor, avoiding HLA antibodies

IMMUNOGENETICS CENTER REPORT

Virtual Crossmatch Report

HLA Typing Results

Name/ID	Relation	A	B	Bw	C	DR	DRB345	DQB	DQA1	DP	DPA1	Sample Date
[redacted]		24	39	6	7	4	53	8	02	402	01	10/1/20
	Patient	24	51	4	16	7		2	03	401	01	
[redacted]		2	62		2	4	53	8		401	01:03:01C	
	Donor Exch	29	27		10	4		8		401	01:03:01C	
	Mismatches:	2 Ag	2 Ag		2 Ag	0		0		0		

HLA typing was performed by one or more of the following molecular methods: SSOP, SBT, SSP, NGS.

Comments:

Donor is mismatched with the patient for 6/12 HLA-A, B, C, DR, DQ, DP antigens.

Single antigen bead-based antibody testing on the current serum dated 02/18/2021 shows that the patient does not display HLA donor-specific antibodies to this potential donor.

No historic donor-specific antibodies were identified.

Based on these results, the T- and B-cell flow crossmatch are predicted to be negative.

Back to compatibility…

- 30% of pairs will be either ABO or HLA incompatible…
- The easiest solution -- is there another donor who might be compatible?

Patient Pathways

- Direct Donation from compatible donor
- No compatible donors?
  - Incompatible donor wishes to proceed
- Transplant options for (in)compatible pairs
  - Desensitization
  - Blood Type (ABO) incompatible
  - Paired Exchange
- Which pathway is right?

HLA – does “the Match” Matter?

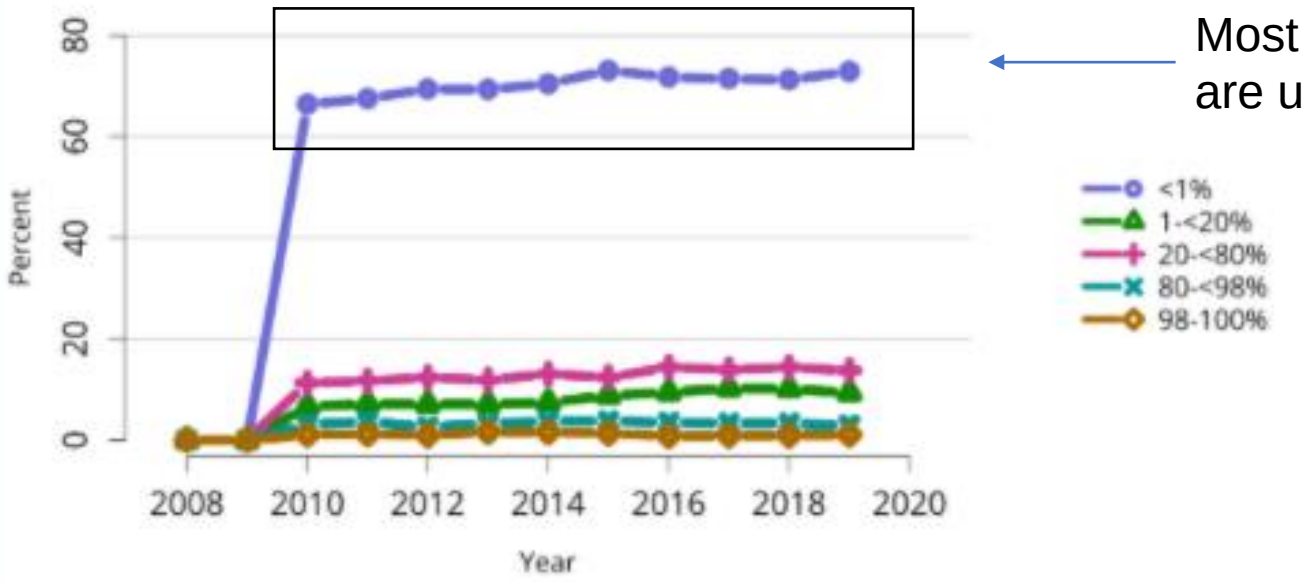
Is donor and recipient HLA mismatch considered significant?

- Maybe…but not always
- Better match means fewer mismatched “targets” for potential rejection
- Pediatric/first transplant with close match means fewer antibodies are formed if subsequent graft is needed later in life
- For older recipients, goal is lifelong function with first kidney, less worry about antibody formation

Can an organ last if there is no HLA match?

- YES!
- Adherence to medication regimen is key (for all recipients)
- Outcome may be impacted by cause of ESRD
- May develop more de novo (new) HLA antibodies when not a close HLA match
- Some mismatched antigens are more immunogenic than others (more likely to cause antibody formation)
- Why some people form antibody and others don’t is still unknown

Figure 84. Peak C/PRA at time of kidney transplant in adult living donor recipients

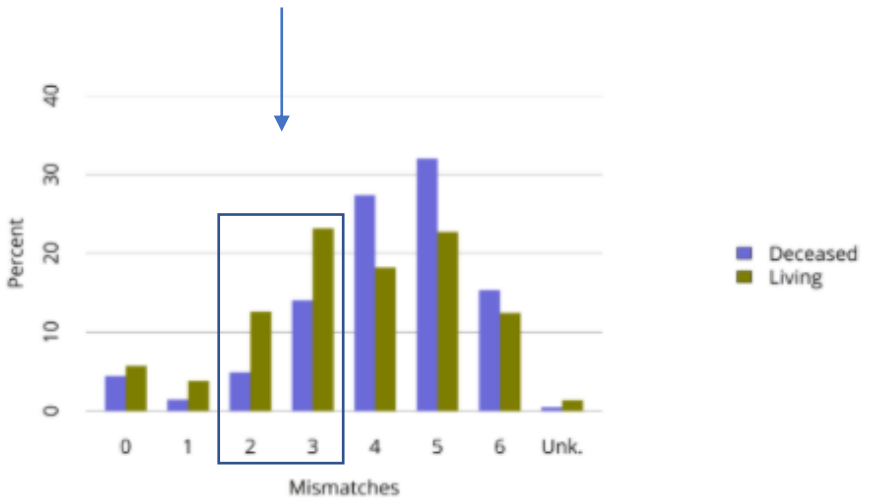


Most first-transplant patients are unsensitized

OPTN/SRTR 2019 Annual Data Report

HLA match weighted more heavily for Pediatric vs Adult recipients

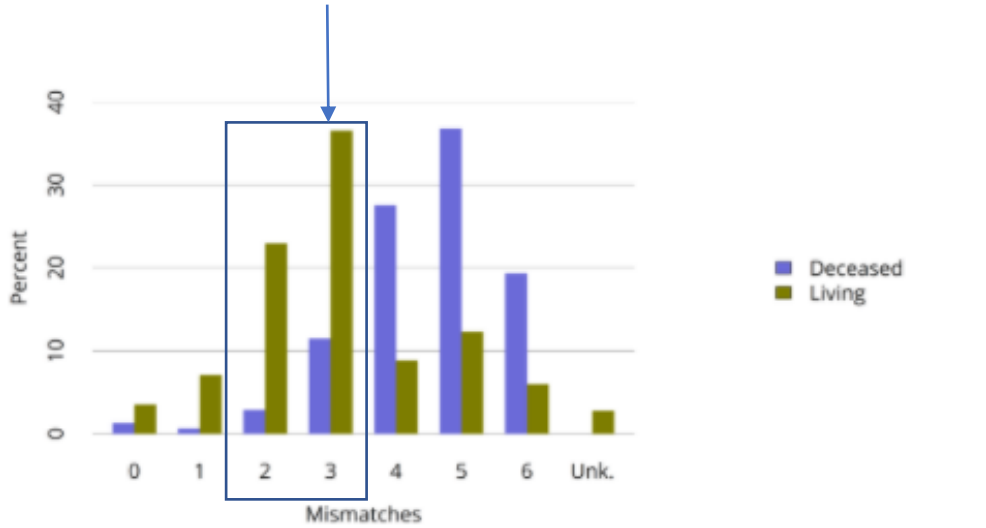
Figure 85. Total HLA A, B, and DR mismatches among adult kidney transplant recipients, 2015-2019



OPTN/SRTR 2019 Annual Data Report

Figure KI 85. Total HLA A, B, and DR mismatches among adult kidney transplant recipients, 2015-2019
Donor and recipient antigen matching is based on OPTN antigen values and split equivalences policy as of 2018.

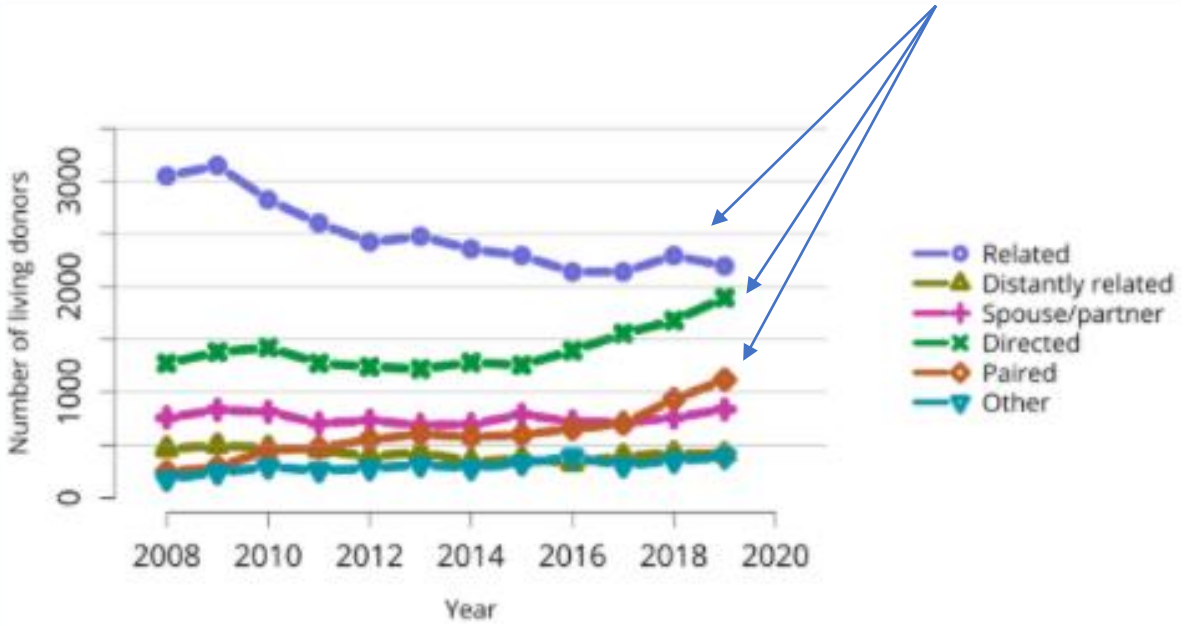
Figure 149. Total HLA A, B, and DR mismatches among pediatric kidney transplant recipients, 2015-2019



OPTN/SRTR 2019 Annual Data Report

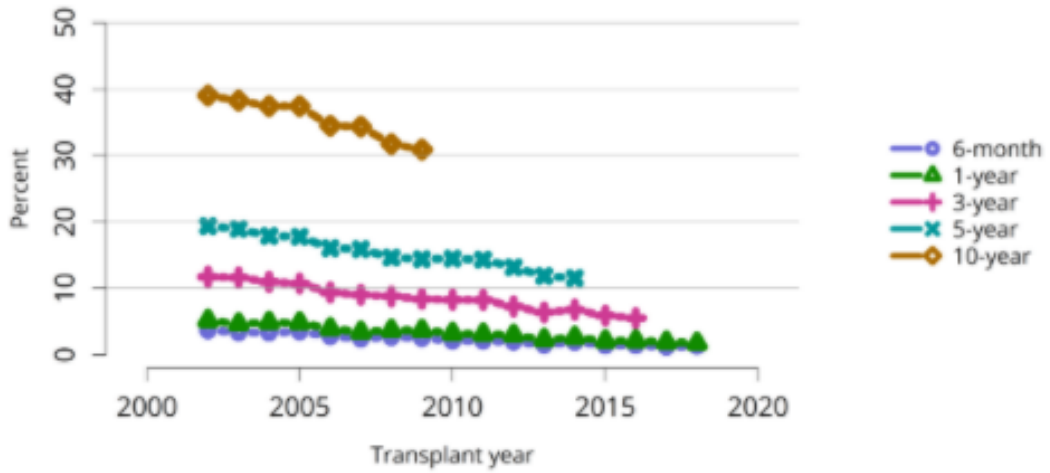
Figure KI 149. Total HLA A, B, and DR mismatches among pediatric kidney transplant recipients, 2015-2019
Donor and recipient antigen matching is based on OPTN antigen values and split equivalences policy as of 2016.

Figure 65. Number of living kidney transplants by donor relation



OPTN/SRTR 2019 Annual Data Report

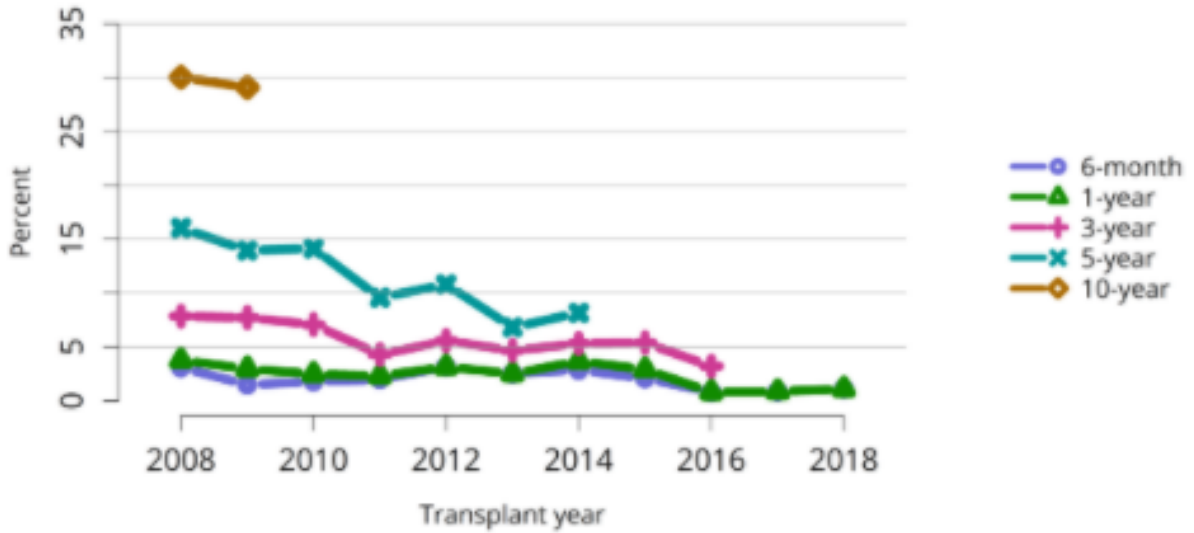
Figure 91. Graft failure among adult living donor kidney transplant recipients



OPTN/SRTR 2019 Annual Data Report

Figure KI 91. Graft failure among adult living donor kidney transplant recipients
Estimates are unadjusted, computed using Kaplan-Meier competing risk methods. Recipients are f
retransplant; return to dialysis; death; or 6 months, 1, 3, 5, or 10 years posttransplant. All-cause gra
months, 1, 3, 5, or 10 years, respectively.

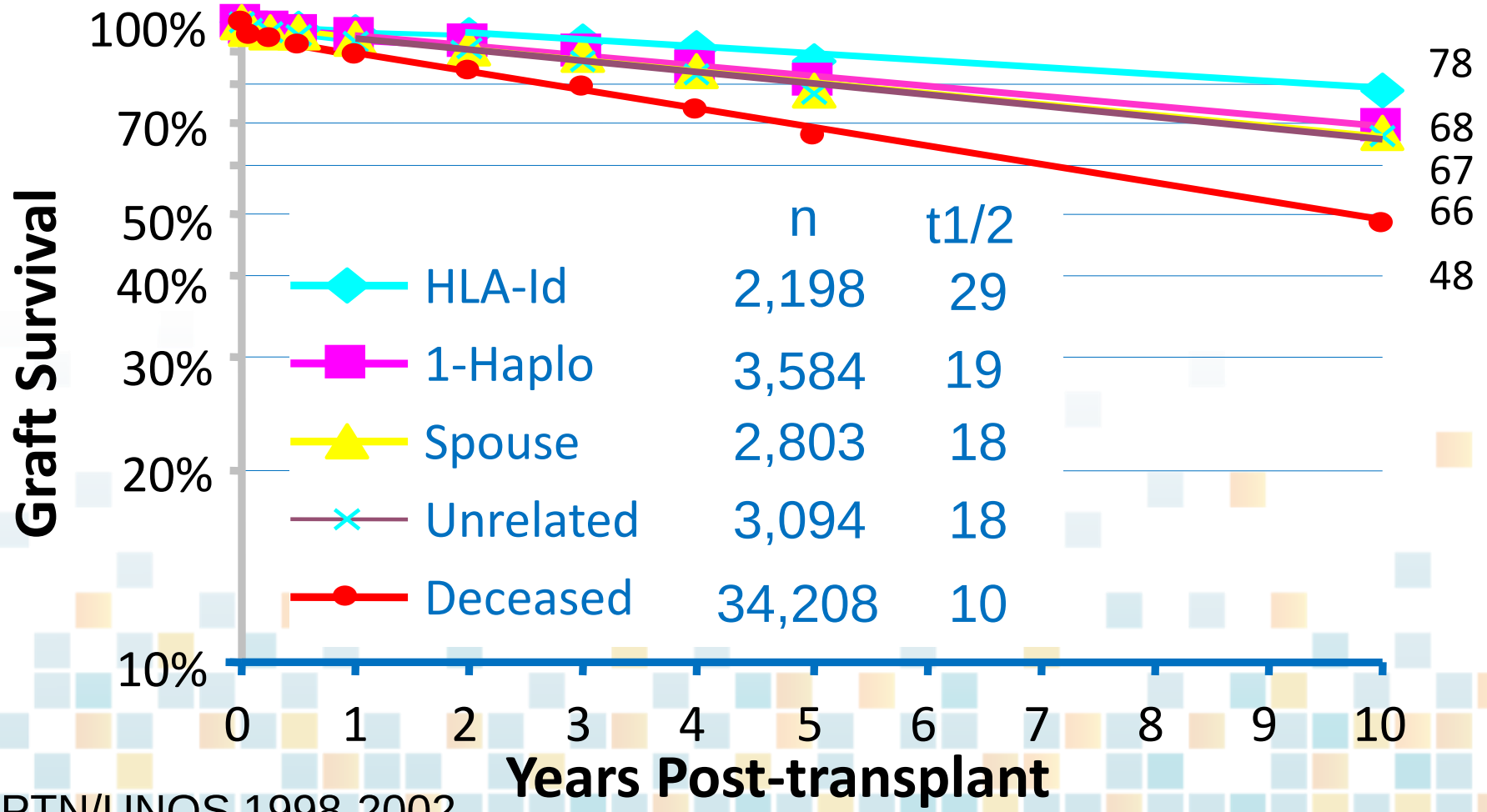
Figure 159. Graft failure among pediatric living donor kidney transplant recipients



OPTN/SRTR 2019 Annual Data Report

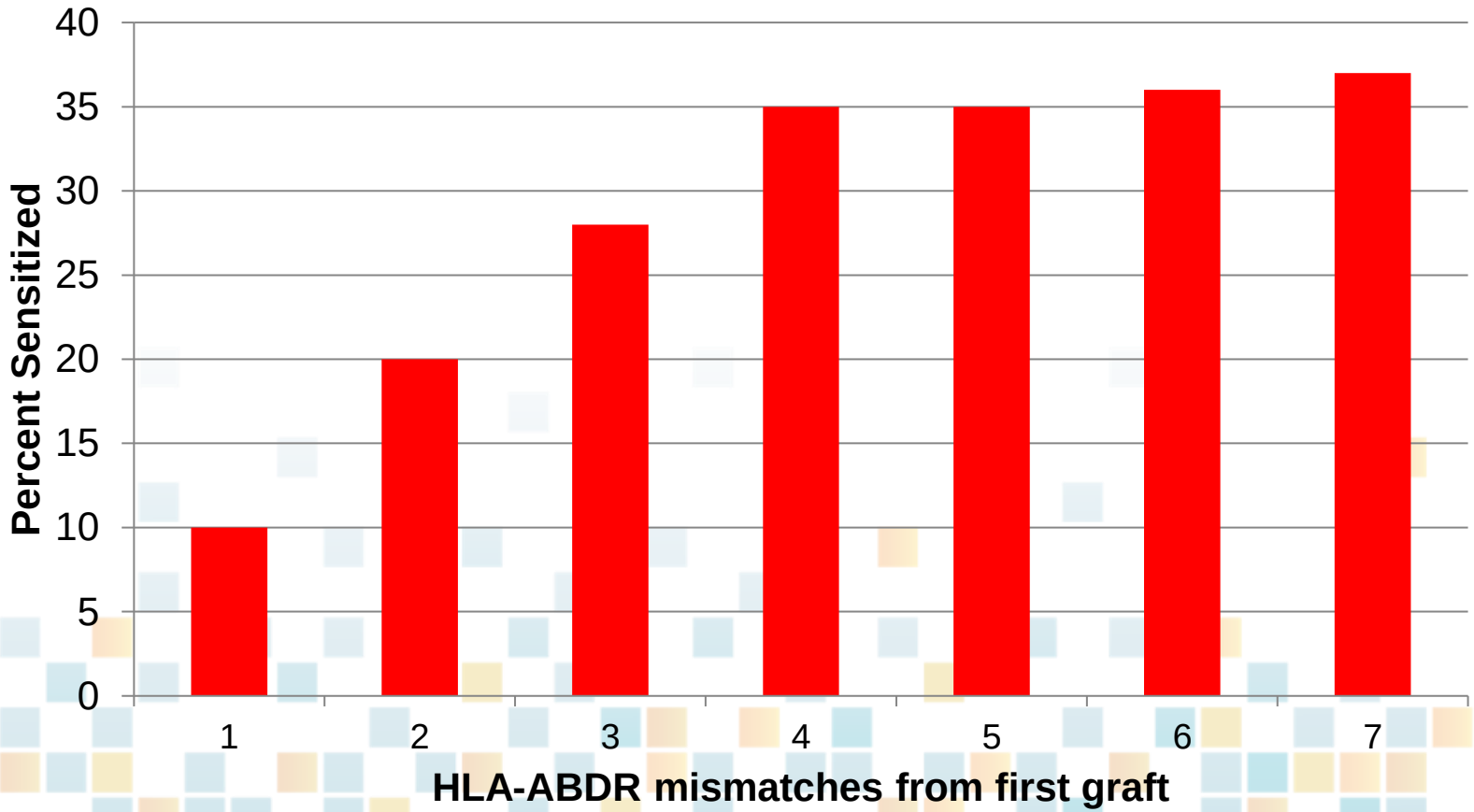
Figure KI 159. Graft failure among pediatric living donor kidney transplant recipients

HLA matching effects– LRD vs LURD vs deceased donor transplants



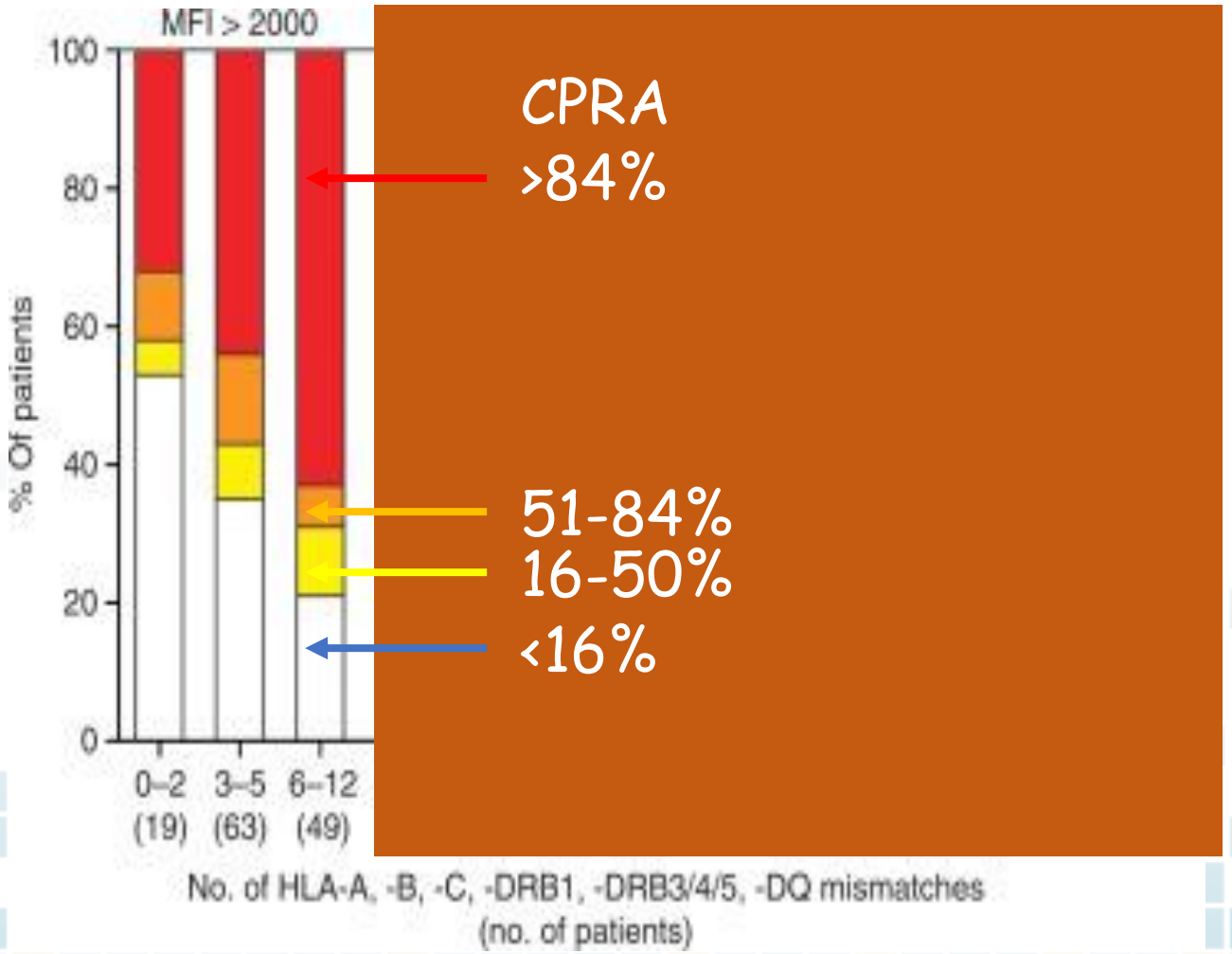
OPTN/UNOS 1998-2002

Sensitization among patients relisted after graft loss increases with HLA mismatches



Meier-Kriesche, et al. Transplantation 2009; 88(1):23-9.

Impact of donor HLA mismatches on the development of HLA-specific antibodies.



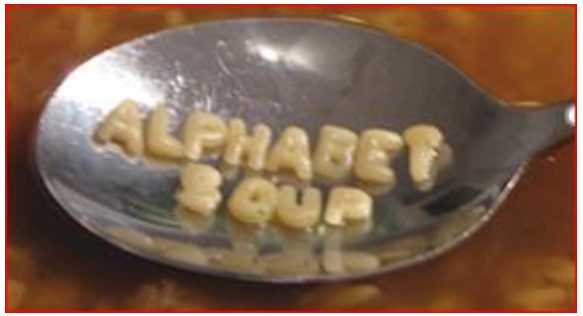
The more HLA antigens mismatched between the donor and recipient the more sensitized the patient becomes if the transplant is rejected.

From: Kosmoliaptsis V, et al. Kidney International 2014, 86:1039

Epitopes and Eplets – to match or mismatch?

- HLA epitopes - antibodies recognize and bind to them
- Eplets - Smaller clusters of amino acids
- Each HLA antigen contains a unique set of epitopes (private epitopes) as well as epitopes that are present in other HLA antigens (shared or public epitopes). There can be cross-reactivity with more than one mismatched HLA antigen.
- Think of the identical twin sib. The identical twin sib shares DNA, so all antigens, epitopes, and eplets are identical – they are all shared, no antibody will form

Alphabet soup



- What is the difference between PRA and cPRA?
  - Panel Reactive Antibody profile (0-100% of panel cells or HLA antigen beads that test positive) reflects recipient sensitization
  - cPRA is the calculated percentage of potential donors who express one or more HLA antigens to which the patient has an antibody.
    - cPRA of up to 99.50% is transplantable (1/200 donors)
    - 99.99% much harder to find a match (<1/10,000 donors)

- Donor Specific Antibody (DSA)
  - Specific antibody to donor's HLA antigen
  - May cause early and/or chronic AMR
  - Some DSAs more problematic than others

- Mean Fluorescence Intensity (MFI)
  - Strength of antibody binding to antigen bead testing : <2000 weak, >8000 strong, >12,000 fully saturated, harder to suppress
  - MFI may be falsely elevated, donor antigen expression may differ

DSA MFIs facilitate virtual crossmatch suitability

Is MCS crossmatch result a deal breaker in compatibility?

- Median Channel Shift -measures antibody binding to donor lymphocytes (i.e., T flow >50MCS positive, B flow >100MCS positive)
- MCS interpretation varies: positive/negative, acceptable/unacceptable
- Usually reflects presence/strength of DSAs, risk of early rejection

Non-HLA Antibodies

Testing for non-HLA antibodies is not widely performed if HLA antibodies are present.

May test for such antibodies in select patients with evidence of antibody-mediated rejection (AMR) without the presence of circulating DSA:

- MICA
- Endothelial cell antibody
- AT1R
- PLA2R

So what do you do with all this information?

Desensitize the recipient to existing DSA of the donor?

Enroll the pair in Kidney Paired Donation Registry to avoid antibody?

Cross blood type incompatibility for close HLA match?

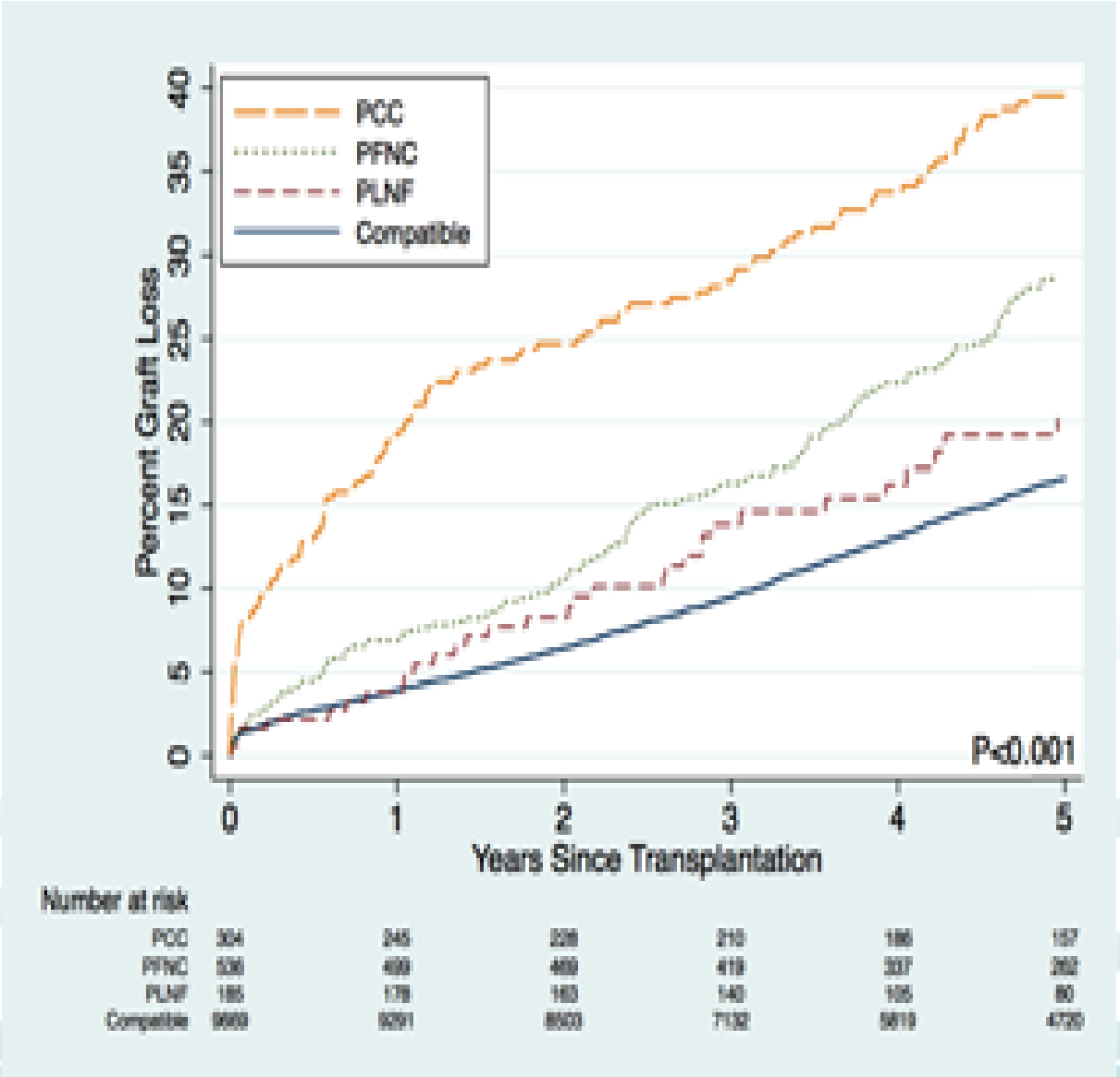
Some combination of the above?

Or just wait for a deceased donor match?

Desensitization

- When does desensitization for a DSA+ match make sense?
  - May be close HLA match
  - Recipient highly sensitized, difficult to match
- When is it best not to desensitize?
  - Patient declines
  - Crossmatch results unacceptable – rejection risk is too high
    - Repeat mismatch DSA (from previous transplant)
    - Antibody strength (MFI) unacceptable
  - Patient health status, treatment tolerance, resources/support
  - If there is another donor available to which recipient has no DSA

Quantifying the Risk of Incompatible Kidney Transplantation: A Multicenter Study



Orandi, et al; AJT 2014; 14(7):1573-1580

Sensitization and Liver Transplantation

- Liver graft is more resilient to the immune system
  - Large organ
  - Regenerative capacity unlike most other organs
  - HLA antigens are shed, can flood/block immune cells, consume antibodies
- Prospective crossmatching/HLA matching not significant in liver donor selection
  - Donor HLA and crossmatch prior to transplant helpful in DSA identification post-transplant, especially if rejection is suspected

UNOS requires a prospective cross match for any combined Liver-Kidney, Heart-Liver or Lung-Liver transplant

99.98% cPRA; 4-year wait, 3rd transplant

Name/ID	Relation	A	B	Bw	C	DR	DRB345	DQB	DQA1	DP	DPA1
[redacted]		2	8	6	7	17	52	2	05:01	401	01:03
	Patient	3	18	6	5	17		2	05	10	02:01
[redacted]		2	8		7	17	52	2	05:01	401	01:03
	Unrelated	68	8		7	17		2	05:01	3	01:03
	Mismatches:	1 Ag	0		0	0		0		1 Ag	

HLA typing was performed by one or more of the following molecular methods: SSOP, SBT, SSP, NGS.

Comments:

Donor is mismatched with the patient for 2/12 HLA-A, B, C, DR, DQ, DP antigens.

Single antigen bead-based antibody testing on the current serum dated 02/19/2021 indicates that the patient carries donor-specific antibodies against HLA-A68 (MFI:9828), which indicates risk of antibody-mediated rejection.

No additional historic DSA to the donor.

Based on these results, the T- and B-cell flow crossmatch are predicted to be positive.

Sometimes taking the risk makes sense

CDC

Serum Date	Treatment	Cell	Method	Result	Comments
02/19/2021	NONE	T	CDC	Neg	
02/19/2021	DTT	T	CDC	Neg	
02/19/2021	NONE	B	CDC	Neg	
02/19/2021	DTT	B	CDC	Neg	

FLOW

Serum Date	Treatment	Cell	Method	MCS*	Result**	Comments
02/19/2021	Pronase	T	FLOW	66	Pos	
02/19/2021	Pronase	B	FLOW	55	Neg	

*Median Channel Shift
**Crossmatch Interpretation

T Cell	
Kidney Transplant (Deceased Donor or Living Donor)	Greater than 50 MCS = Positive
Heart, Liver or Lung Transplant	Greater than 50 MCS = Positive
B Cell	
Kidney Transplant (Deceased Donor)	Greater than 120 MCS = Positive
Kidney Transplant (Living Donor)	Greater than 100 MCS = Positive
Heart, Liver, or Lung Transplant	Greater than 120 MCS = Positive
Endothelial Cell	
Heart Transplant	Greater than 50 MCS = Positive

Comments

The DONOR PAIRED EXCHANGE cytotoxic T- and B-cell crossmatches were negative with this donor. The pronase T-cell crossmatches performed by flow were positive but the B-cell crossmatches were negative. Single antigen bead-based antibody testing on this serum dated 02/19/2021 indicates that the patient carries donor-specific antibodies against HLA-A*68:01 (MFI= 2466), which indicates risk of antibody-mediated rejection.

When does it make sense NOT to cross DSA?

- If and when a more suitable match can be found!
- Pt: 5 yo Filipino M, prenatally dx hydroureteronephrosis 2/2 PUV, PD at 4mos
  - L kidney+ PD cath removed 2015, 2nd to recurrent infections
  - Bladder augmentation 9/16, Mitrofanoff, suprapubic cath; Marginal kidney fx returned, I/O caths daily, off dialysis
- Donor: Mom, 26 y/o, 1-haplo match, IXM (-), O to A
- Blood transfusion January 2017
- LRD tx sched 3/17: repeated XM in Feb 2017, XM (-)
  - New DSA to DR53 (MFI 2900) detected; tx cancelled

- Enrolled in KPD, tight parameters for HLA match, no DSA
- Match identified in 1 wk: 44 yo cauc F, mismatched only at A3
- Transplanted April 2017, current creat 0.74, no DSA noted at age 9!

ABO Incompatible Transplant

- When does ABOI transplant make sense?
  - Close HLA match
  - Anti-ABO titer is low, within program protocol parameters
  - Recipient highly sensitized, difficult to match

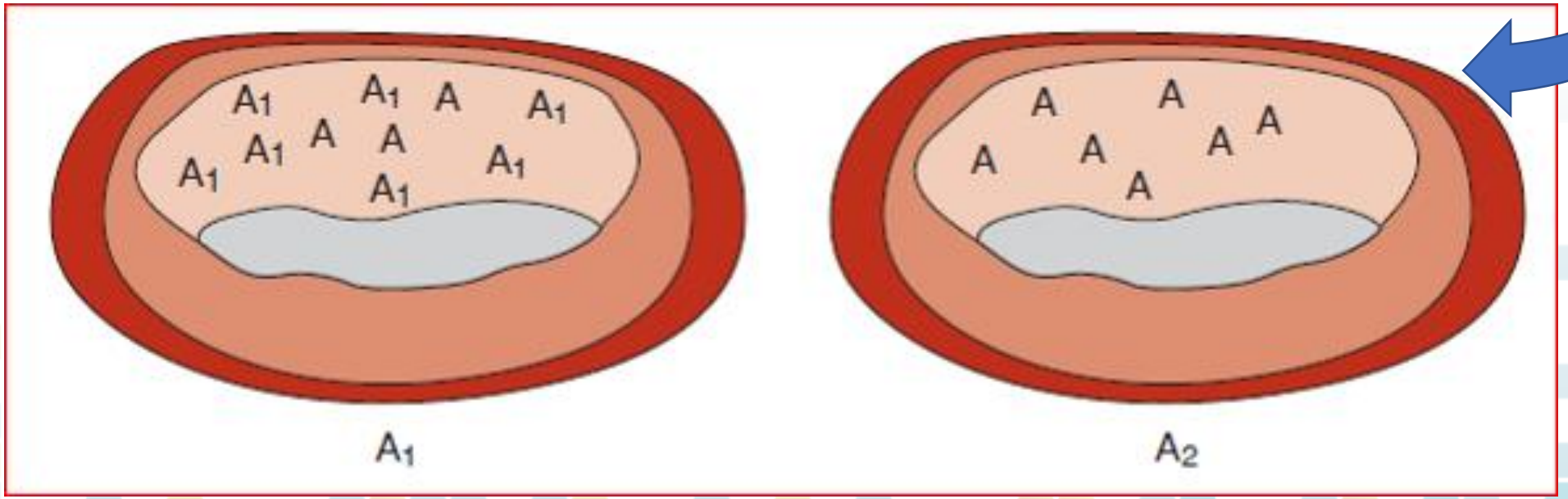
- When is ABO incompatible match not the best option?
  - Anti-ABO titer too high
  - Patient(s) highly anxious, fragile, limited resources/support
  - Poor compliance
  - Minimally sensitized, potential for “clean match” through paired exchange or another direct donor

- DSA + ABOi elevates risk of one antibody stimulating the other

A2/non-A1 blood group donors can be considered for B or O recipients

A1 subtype cells are more antigenic than A2/non-A1 subtype (risk of antibody response is higher)

B and O blood groups typically express more antibody to A1 antigen than A2 antigen and may be able to receive an organ from A2 donor



ABO Incompatible Transplant

- Long-term ABOI outcomes are comparable to compatible outcomes at centers of excellence, but vary nationally

- Points to remember:
  - Risk of early rejection is slightly elevated; close surveillance for rise in anti-ABO titer
  - Risk of early post-transplant complications, infection, bleeding elevated over ABOc transplant
  - Recipient appreciation of risks of non-compliance
  - Weigh options for possible higher risk transplant vs remaining on dialysis
- May be best option but…

  Philosophies and opinions differ

Kidney Paired Donation/Exchange Transplant (KPD)

- Recipient matched with compatible donor
- Intended donor matched with compatible recipient
- Compatibility of all pairs confirmed by crossmatch
- Donor records/images exchanged, surgeries scheduled
- Logistical challenges – Janet's KPD talk is next!

A few thoughts

- Explore all options for living donation
- If your center doesn't offer alternative pathways, consider referring pts for multi-listing at a center that does
- Big picture - weigh the risks of all options and pursue least risky/best pathway for your pair
- Donor awareness of options is as important as recipient's understanding
- Regardless of the HLA match (or lack thereof), for most ESRD patients, receiving a living donor transplant usually means a longer, healthier life than waiting years for a deceased donor transplant

Using all the tools – KPD, ABOI and Desensitization to achieve pediatric transplant!

Transplanted at age 12, in May 2012, A1 to O w/weak DSA. Creatinine 1.26 in 2021, now age 21!

Acknowledgements

Specific thanks and appreciation:

to Gabriel Danovitch, for many years of teaching by example.

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To the UCLA recipient TCs – your dedication to seeing our recipients through their transplant journeys results in more happier and healthier lives than you'd ever be able to count. Know you make a real difference in their lives, and the lives of their families

And to the UCLA living donor team; my work family and colleagues: Jennifer, Rhonda, Sheila, Myrlin, Mara, Lorena, Grace, Jen, Lidia, Carmen, and Dr. A – for your continued dedication and compassion for our donors. You make UCLA, and me, so very proud.

Resources and Citations

- https://srtr.transplant.hrsa.gov/annual_reports/2019/Kidney.aspx#KI_tx_adult_ld_outcomes_DCGF_b64
- Transplantation. 2016 Apr 18. doi:10.1038/nrneph.2016.55. **Survival benefits of incompatible living donor kidney transplants.** Cecka, J.M.
- Am J Transplant 2016 May;16(5):1343-4. doi: 10.1111/ajt.13638. Epub 2016 Jan 22. **ABO-Incompatible Kidney Transplants: Twice as Expensive, Half as Good.** Held PJ[1], McCormick F[2].
- Am J Transplant. 2015 Feb;99(2):400-4. doi: 10.1097/TP.0000000000000312. **Three-year outcomes following 1420 ABO-incompatible living-donor kidney transplants performed after ABO antibody reduction: results from 101 centers.** Opelz G[1], Morath C, Süsal C, Tran TH, Zeier M, Döhler B.
- Transplantation. 2014 Jul 15;98(1):54-65. doi: 10.1097/TP.0000000000000029. **Early clinical complications after ABO-incompatible live-donor kidney transplantation: a national study of Medicare-insured recipients.** Lentine KL[1], Axelrod D, Klein C, Simpkins C, Xiao H, Schnitzler MA, Tuttle-Newhall JE, Dharnidharka VR, Brennan DC, Segev DL.
- Am J Transplant. 2014(7), 1573-1580. doi:10.1111/ajt.12786 **Quantifying the Risk of Incompatible Kidney Transplantation: A Multicenter Study.** Orandi, B. J., Garonzik-Wang, J. M., Massie, A. B., Zachary, A. A., Montgomery, J. R., Van Arendonk, K. J., & ... Shapiro, R.
- Kidney International. 84, 1009–1016; doi:10.1038/ki.2013.206; published online 29 May 2013. **Kidney paired donation in the presence of donor-specific antibodies.** Blumberg, JM, Gritsch, HA, Reed, EF, Cecka, JM, Lipshutz, GS, Danovitch, GM, McGuire, SM, Gjertson, DW, Veale, JL.
- Am J Transplant. 2013: 2075-2082. Doi: 10.1111/ajt. 12332. **Influence of test Technique on Sensitization Status of Patients on the Kidney Transplant Waiting List**. Gombos, P., Opelz, G., Scherer, S., Morath, C., Zeier, M., Schemmer, P., Susal, C.
- Am J Transplant. 2014; 14(7):1573-1580 **Quantifying the Risk of Incompatible Kidney Transplantation: A Multicenter Study.** B. J. Orandi, J. M. Garonzik-Wang, A. B. Massie, A. A. Zachary, J. R. Montgomery, K. J. Van Arendonk, M. D. Stegall, S. C. Jordan, J. Oberholzer, T. B. Dunn, L. E. Ratner, S. Kapur, R. P. Pelletier, J. P. Roberts, M. L. Melcher, P. Singh, D. L. Sudan, M. P. Posner, J. M. El-Amm, R. Shapiro, M. Cooper, G. S. Lipkowitz, M. A. Rees, C. L. Marsh, B. R. Sankari, D. A. Gerber, P. W. Nelson, J. Wellen, A. Bozorgzadeh, A. O. Gaber, R. A. Montgomery and D. L. Segev
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- Zhang Q, Rajalingam R, et al, ABO, Tissue Typing and Crossmatch Incompatibility in RW Busuttil and G.B. Klintmalm (Eds), Transplantation of the Liver, Third Edition, (pp 1245-1256), Philadelphia, PA. Elsevier Saunders
- Kosmoliaptsis V, Gjorgjimajkoska O, Sharples LD, Chaudhry AN, Chatzizacharias N, Peacock S, Torpey N, Bolton EM, Taylor CJ, Bradley JA. Impact of donor mismatches at individual HLA-A, -B, -C, -DR, and -DQ loci on the development of HLA-specific antibodies in patients listed for repeat renal transplantation. Kidney Int. 2014 Nov;86(5):1039-48. doi: 10.1038/ki.2014.106. Epub 2014 Apr 9. PMID: 24717292.
- Mustian MN, Cannon RM, MacLennan PA, et al. Landscape of ABO-Incompatible Live Donor Kidney Transplantation in the US. *J Am Coll Surg*. 2018;226(4):615-621. doi:10.1016/j.jamcollsurg.2017.12.026
- Harmening, D. (2005). *Modern blood banking and transfusion practices*. Philadelphia: F.A. Davis.

Questions?