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14th PAN ARAB TRANSFUSION MEDICINE CONFERENCE QATAR 2024

Inspiring Transfusion Excellence Across Arab Nations

30 November to 2 December 2024

Sheraton Grand Doha Resort & Convention Hotel,
Doha, Qatar

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HLA-Typed Cellular Products as a Desensitization Strategy in Hematopoietic Stem Cell Transplantation

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2024-11-30

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Disclosure Statement

I make the following declaration in relation to this CPD Activity :

- This complies with the Ministry of Public Health in Qatar Department of Healthcare Professions MoPH-DHP accreditation standards.
- There is NO Conflict of Interest.
- There is no plagiarism or copyright infringement.
- The content is balanced and free of bias, either commercial or non-commercial.

Learning Objectives

1. Discuss the impact of donor-specific HLA antibodies (DSAs) in the setting of hematopoietic progenitor cell transplantation (HPCT).
2. Describe and critique the salient features of the evidence thus far on the use of HLA-typed cellular products as a desensitization strategy for HPCT patients.
3. Assess the potential advantages and current limitations HLA-typed cellular transfusions as a desensitization strategy.

Note: The terms BMT (bone marrow transplant), HSCT (hematopoietic stem cell transplant), and HPCT (hematopoietic progenitor cell transplant) are used interchangeably in this presentation.

The primary strategy in HPCT donor selection is Human Leukocyte Antigen (HLA) Matching

Antigen	A	B	C	DR	DQ	DP
Gene/Locus	*A*	*B*	*C*	*DRB1*	*DQB1*	*DPB1*
6/6 Match	A	B		DR		
8/8 Match	A	B	C	DR		
10/10 Match	A	B	C	DR	DQ	
12/12 Match	A	B	C	DR	DQ	DP

- The table above indicates the **order of importance** of which loci to match:

A, B, C, DR > DQ, DP

HLA Mismatches (MMs) pose an increased risk for **Graft versus Host Disease (GVHD)**

HLA Class I - on all Nucleated Cells (A, B, C) & Platelets (A, B)

Antigen	A	B	C	DR	DQ	DP
Gene/Locus	***A***	***B***	***C***	***DRB1***	***DQB1***	***DPB1***
6/6 Match	A	B		DR		
8/8 Match	A	B	C	DR		
10/10 Match	A	B	C	DR	DQ	
12/12 Match	A	B	C	DR	DQ	DP

- The table above indicates the **order of importance** of which loci to match:

A, B, C, DR > DQ, DP

HLA Mismatches (MMs) pose an increased risk for **Graft versus Host Disease (GVHD)**

HLA Class II (DR, DQ, DP) - On Antigen Presenting Cells (Monocytes/Macrophages, B cells, Dentritic Cells)

Antigen	A	B	C	DR	DQ	DP
Gene/Locus	*A*	*B*	*C*	*DRB1*	*DQB1*	*DPB1*
6/6 Match	A	B		DR		
8/8 Match	A	B	C	DR		
10/10 Match	A	B	C	DR	DQ	
12/12 Match	A	B	C	DR	DQ	DP

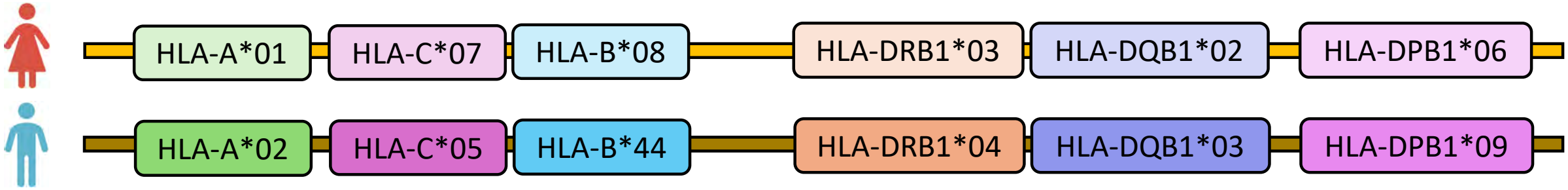
- The table above indicates the **order of importance** of which loci to match:

A, B, C, DR > DQ, DP

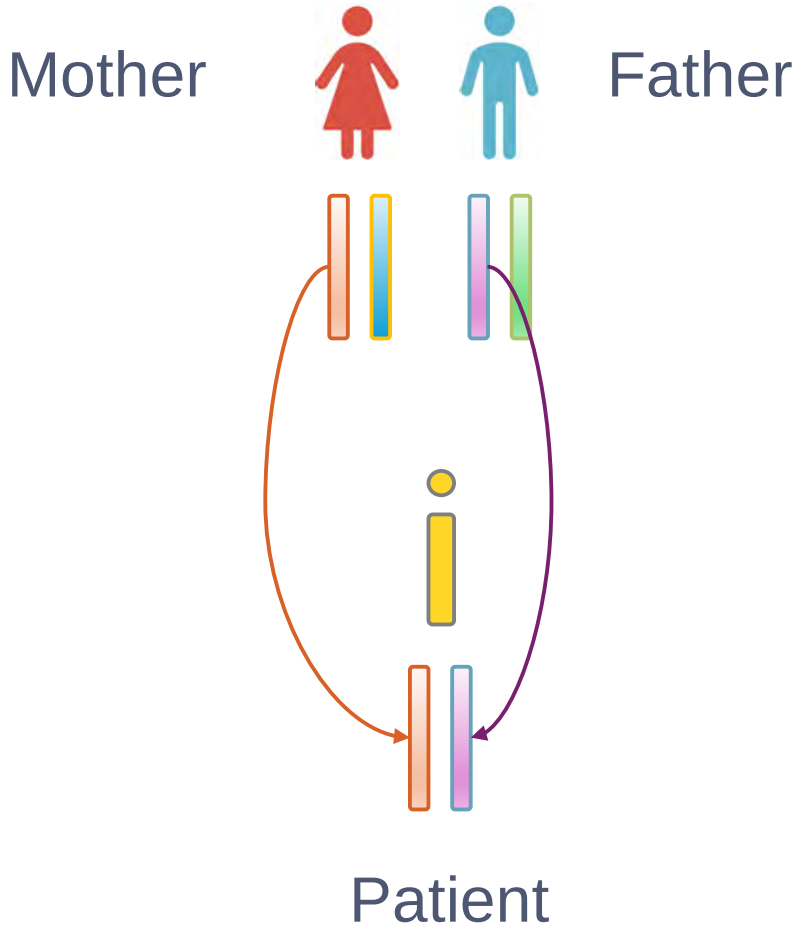
HLA Mismatches (MMs) pose an increased risk for **Graft versus Host Disease (GVHD)**

HLA genes are inherited as a haplotype

- The HLA genes are on same chromosome (Chr. 6) and get inherited together
- One haplotype from mom
- One haplotype from dad
- HLA-genes are **co-dominantly expressed** (like RBC antigens)



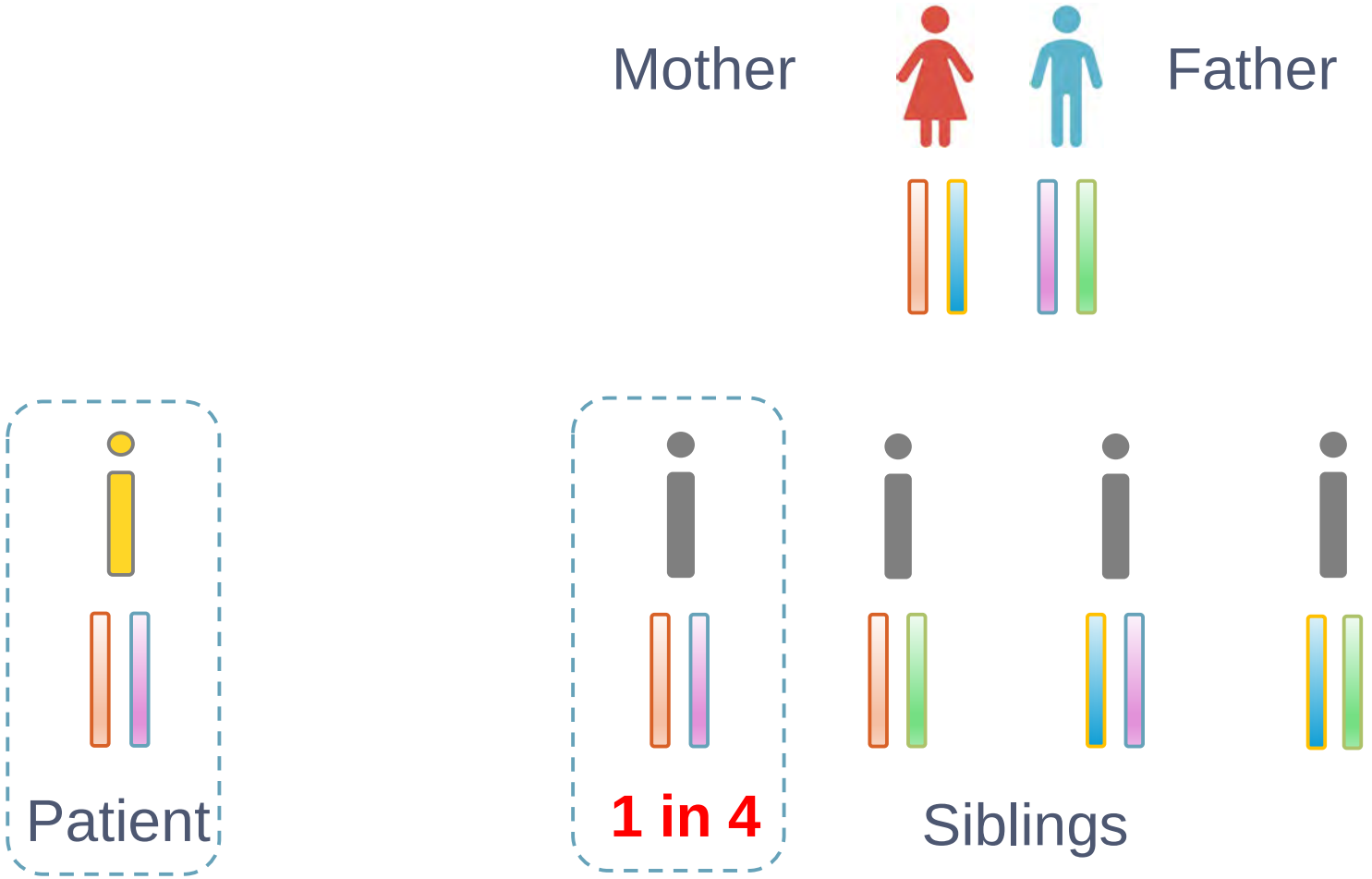
Haploidentical = Sharing one identical haplotype



Therefore, by definition, you have to be **related** to be haploidentical to someone

Parents and offspring are automatically haploidentical

HLA-Matched (10/10) Related Donor Only in Siblings – 1 in 4 chance

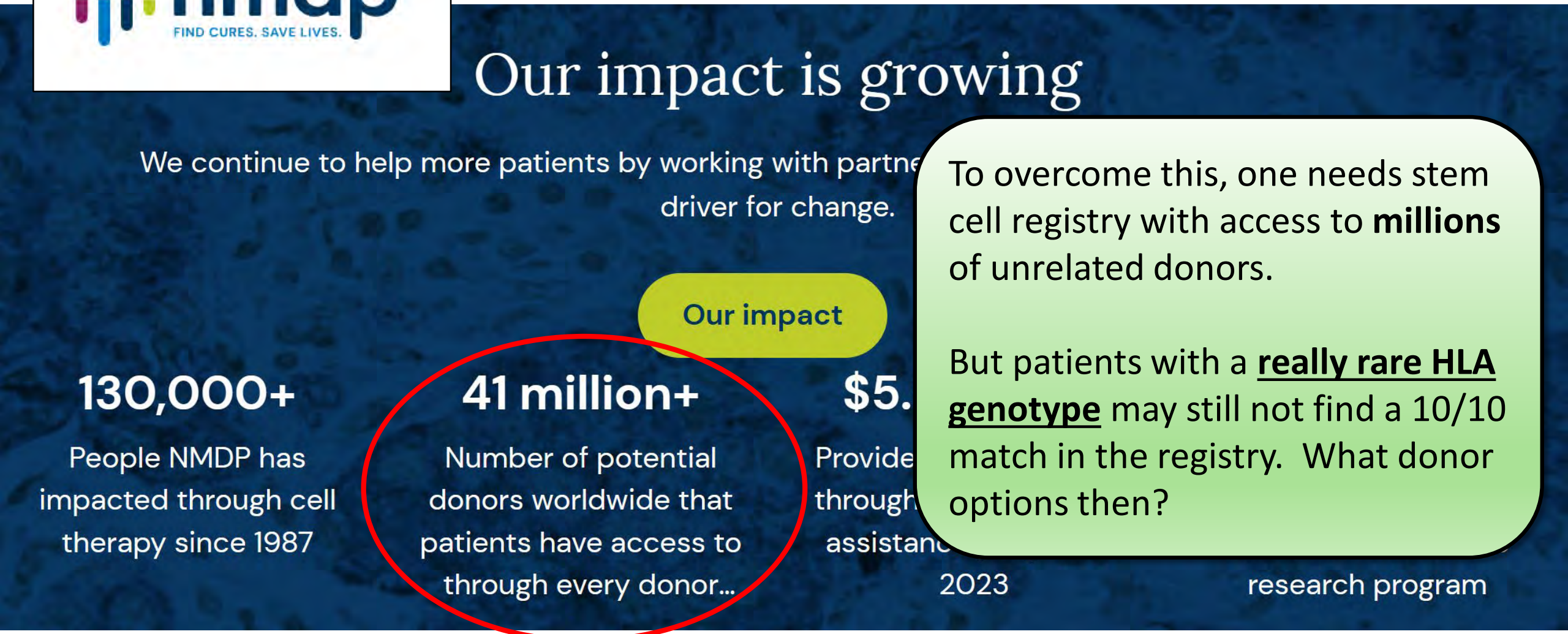


HLA-Matched (10/10) - Unrelated Donor (MUD)

- **HLA is highly polymorphic**
- This means the odds of a 10/10 HLA-Matched Unrelated Donor (MUD), per unrelated donor, are significantly less!

#	*HLA-A*	*HLA-B*	*HLA-C*	*HLA-DRB1*	*HLA-DQB1*	*HLA-DQA1*	*HLA-DPB1*	*HLA-DPA1*
Alleles	8472	10183	8750	3751	2771	847	2762	740
Proteins	4949	6073	4723	2422	1658	407	1583	361
Nulls	445	364	385	133	122	21	145	31

https://hla.alleles.org/nomenclature/stats.html (last accessed 10/15/2024)



To overcome this, one needs stem cell registry with access to **millions** of unrelated donors.

But patients with a **really rare HLA genotype** may still not find a 10/10 match in the registry. What donor options then?

https://www.nmdp.org/ (last accessed 10/15/2024)

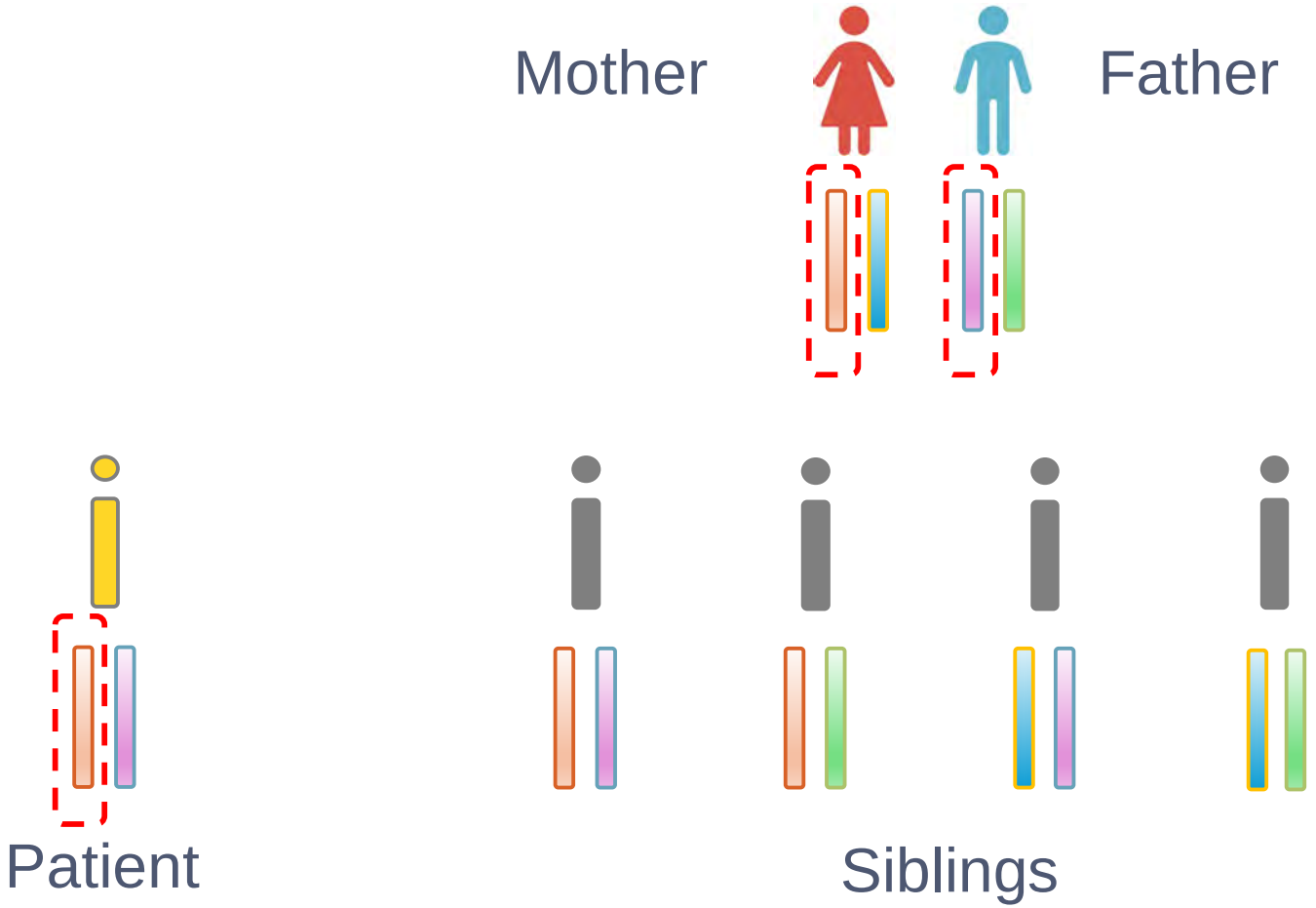
What are the alternatives to an HLA matched donor (related or unrelated)?

1. HLA-Mismatched Unrelated Donor (e.g. 9/10 match)

2. Haploidentical (Related) donor

3. Cord blood (CB) units (less stringent matching requirements - looking for 6/6 match rather than 10/10 match)

Haploidentical Donor Options



Odds per relation?

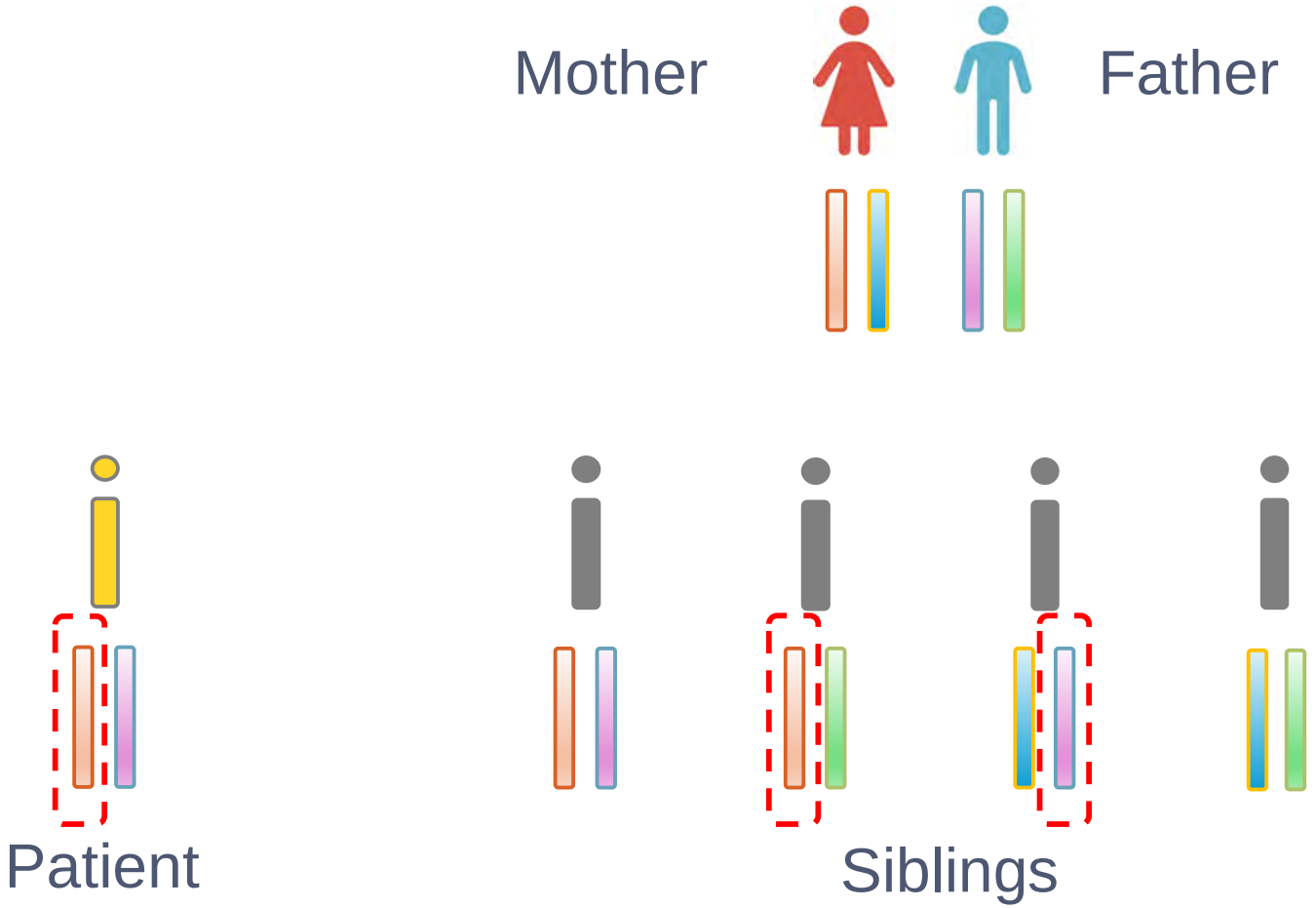
- Parent = 1 in 1 (100%)
- Offspring = 1 in 1 (100%)

- Sibling = 2 in 4 (50%)

- Grandparents, grandchildren, aunts, uncles, nieces, nephews = 1 in 4 (25%)

Etc...

Haploidentical Donor Options



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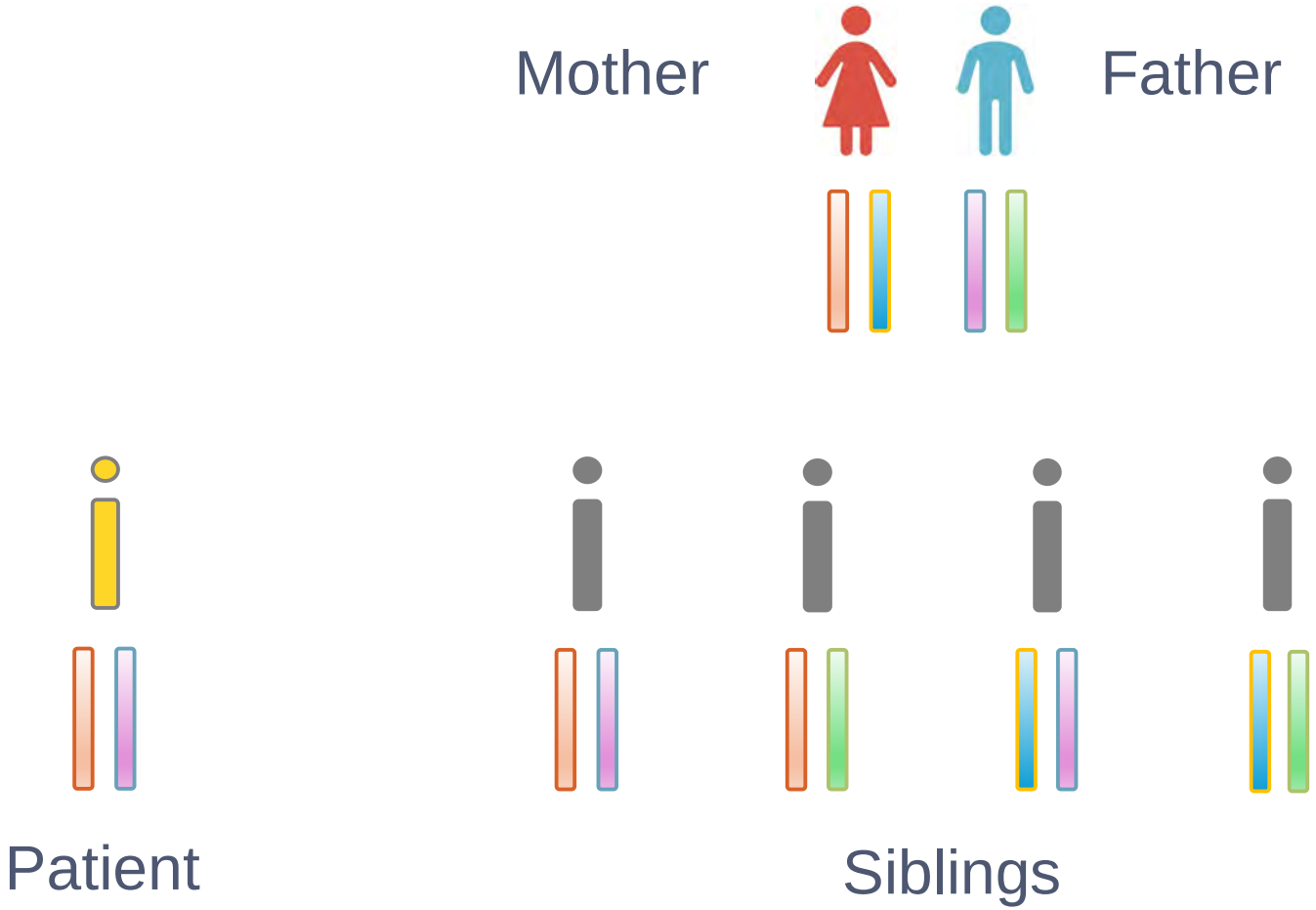
Etc...

Haploidentical Donor Options



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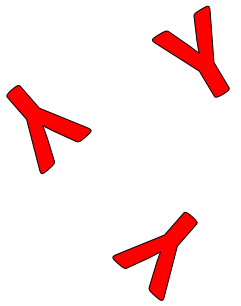
- Sibling = 2 in 4 (50%)
- Grandparents, grandchildren, aunts, uncles, nieces, nephews = 1 in 4 (25%)

Etc...

Newer regimens have improved the success rate of HLA mismatched donors

- This includes 9/10 mismatched unrelated & haploidentical donors
- This means **we are seeing more HPCTs proceeding with mismatched HLA donors** over the past 2 decades
- **BUT...** having HLA-mismatched donors means patients can make **DONOR SPECIFIC ANTIBODIES** against the mismatched antigen



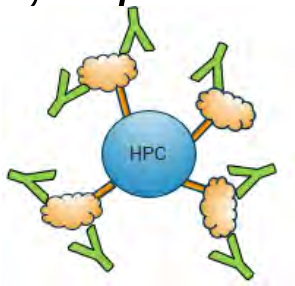
- HLA antibodies develop due to alloimmunization after sensitizing events (transfusion, transplant, pregnancy)
  - **Mothers are especially disadvantaged** because they have increased odds being exposed to their haploidentical donor offspring during pregnancy ☹

Pandey P, Pande A, Mandal S, Devra AK, Sinha VK, Bhatt AP, Mishra S. Effects of different sensitization events on HLA alloimmunization in renal transplant cases; a retrospective observation in 1066 cases. Transpl Immunol. 2022 Dec;75:101680. doi: 10.1016/j.trim.2022.101680. Epub 2022 Jul 29. PMID: 35908630.
Picascia A, Grimaldi V, Sabia C, Napoli C. Comprehensive assessment of sensitizing events and anti-HLA antibody development in women awaiting kidney transplantation. Transpl Immunol. 2016 May;36:14-9. doi: 10.1016/j.trim.2016.03.002. Epub 2016 Mar 22. PMID: 27013139.

DSAs are associated with poorer transplant outcomes

(has been observed with unrelated, haploidentical, cord HPCTs)

- **Engraftment/Recovery issues**
  - **Primary Graft Failure**
  - **Graft rejection**
    - Immune-mediated rejection of donor cells by residual host cells due to genetic differences between donor and recipient
  - Secondary Graft Failure (loss of graft after initial engraftment)
  - **Delayed Engraftment/Recovery**
- **Transplant Associated Mortality**
- **Decreased Overall Survival**



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3. Ciurea SO, Thall PF, Milton DR, Barnes TH, Kongtim P, Carmazzi, Y, et al. Complement-binding donor-specific anti-HLA antibodies, and risk of primary graft failure in hematopoietic stem cell transplantation., Biol Blood Marrow Transplant. 2015;21:1392–8.
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INTERNATIONAL STANDARDS FOR HEMATOPOIETIC CELLULAR THERAPY PRODUCT COLLECTION, PROCESSING, AND ADMINISTRATION

FACT FOUNDATION FOR THE ACCREDITATION OF CELLULAR THERAPY

JACIE Joint Accreditation Committee ISCT | EBMT

FACT & ASHI accreditation standards require a policy/procedure for addressing HLA antibody testing for HLA-mismatched donors & recipients

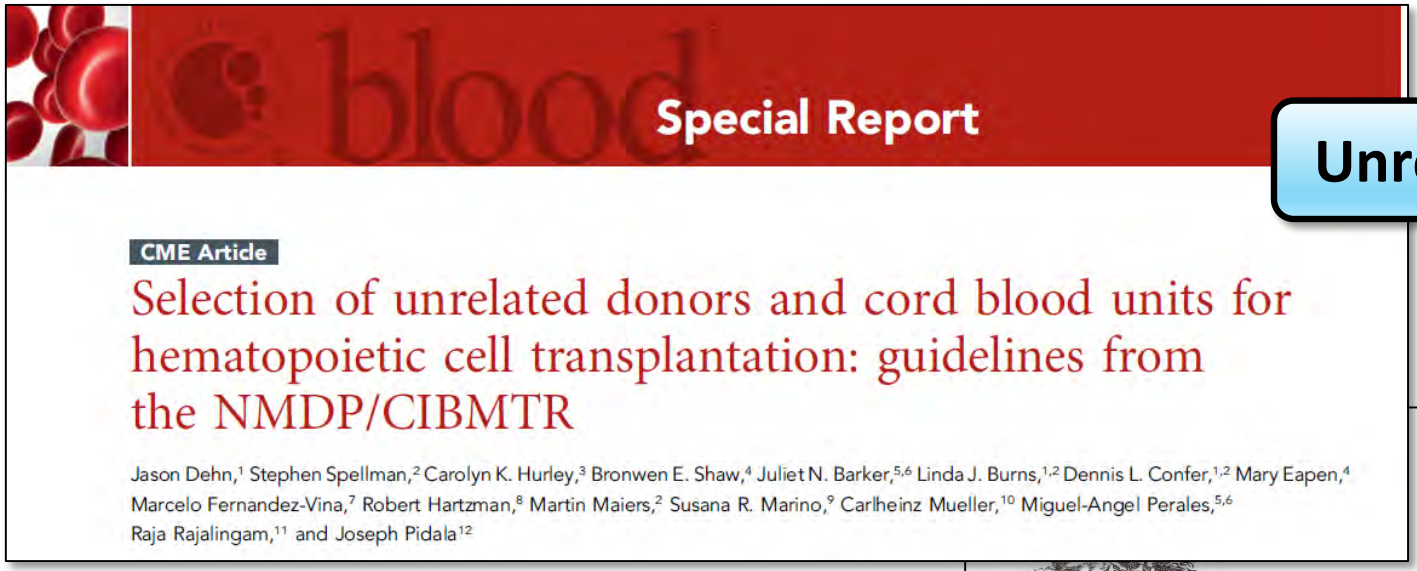
B6.4.14.4 There shall be a policy or Standard Operating Procedure for anti-HLA antibody testing for mismatched donors and recipients.

D.5.3.3 Blood, Bone Marrow and Hematopoietic Cell Transplantation (HCT)

D.5.3.3.1.6 Have a policy for HLA antibody testing for mismatched donors and recipients.

Eighth Edition FACT-JACIE International Standards for Hematopoietic Cellular Therapy Product Collection, Processing and Administration, Version 8.1. https://www.factglobal.org/standards/hct-standards/ (last accessed 10/18/2024)
2024 ASHI Standards with Guidance. https://www.ashi-hla.org/page/standards (last accessed 10/18/2024)

Unrelated donors (2019)



blood

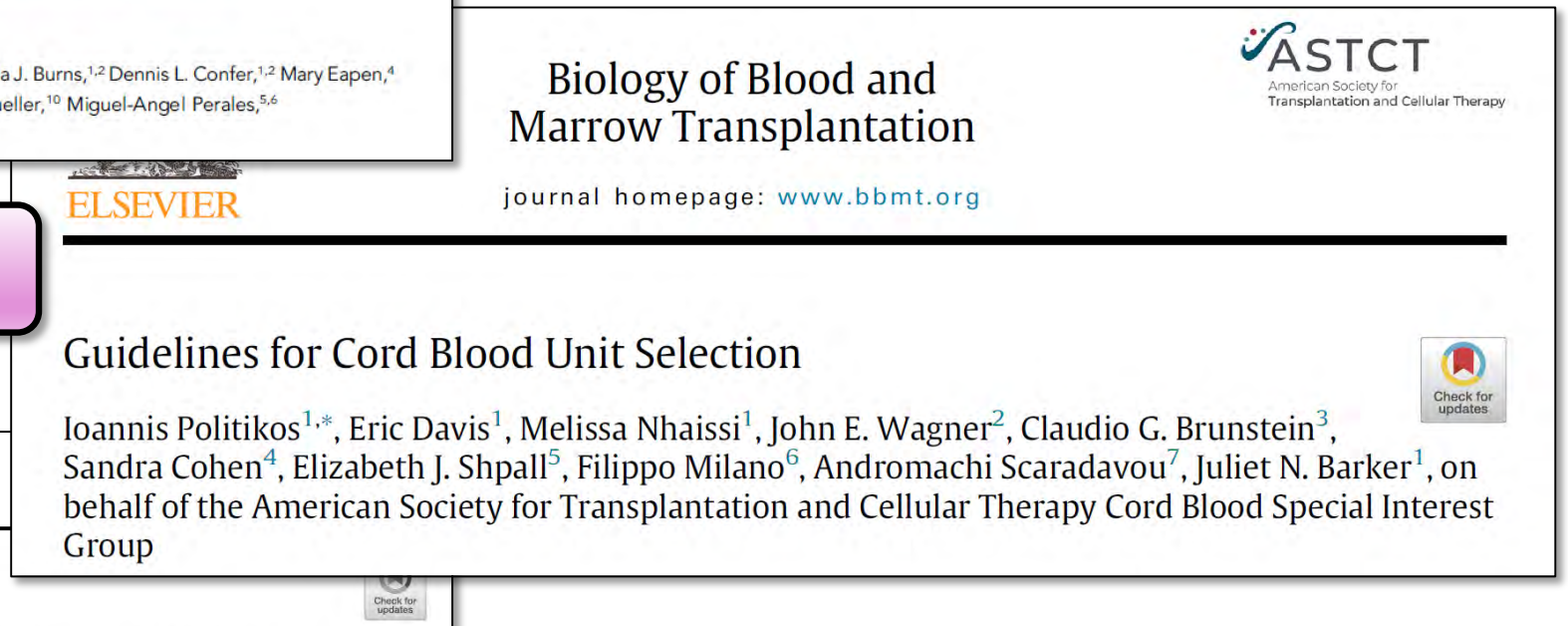
Special Report

CME Article

Selection of unrelated donors and cord blood units for hematopoietic cell transplantation: guidelines from the NMDP/CIBMTR

Jason Dehn,[1] Stephen Spellman,[2] Carolyn K. Hurley,[3] Bronwen E. Shaw,[4] Juliet N. Barker,[5,6] Linda J. Burns,[1,2] Dennis L. Confer,[1,2] Mary Eapen,[4] Marcelo Fernandez-Vina,[7] Robert Hartzman,[8] Martin Maiers,[2] Susana R. Marino,[9] Carlheinz Mueller,[10] Miguel-Angel Perales,[5,6] Raja Rajalingam,[11] and Joseph Pidala[12]

Cord Blood Units (2020)



Biology of Blood and Marrow Transplantation

ASTCT American Society for Transplantation and Cellular Therapy

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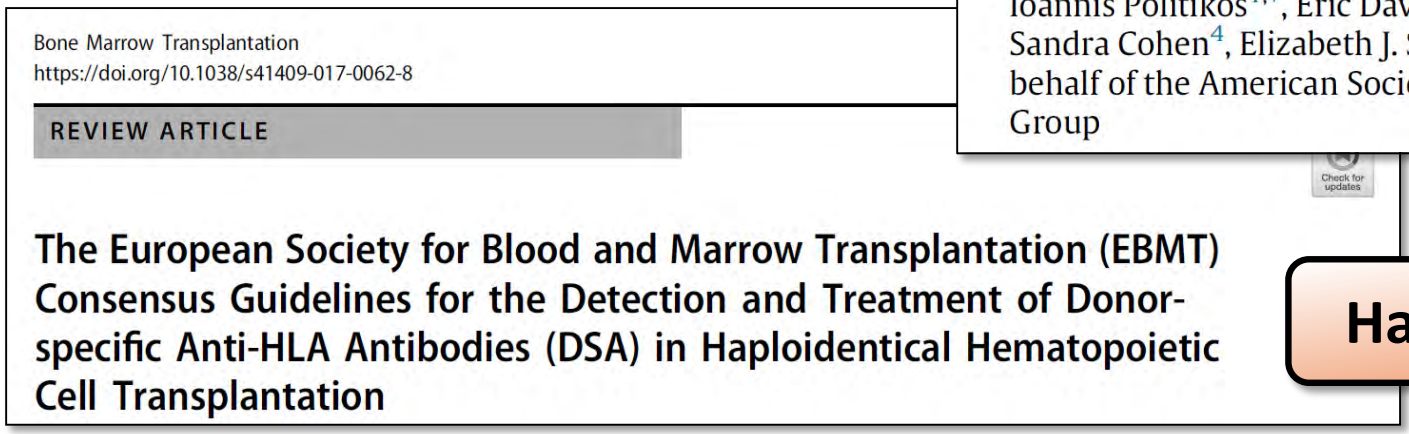
journal homepage: www.bbmt.org

Guidelines for Cord Blood Unit Selection

Ioannis Politikos[1,*], Eric Davis[1], Melissa Nhaissi[1], John E. Wagner[2], Claudio G. Brunstein[3], Sandra Cohen[4], Elizabeth J. Shpall[5], Filippo Milano[6], Andromachi Scaradavou[7], Juliet N. Barker[1], on behalf of the American Society for Transplantation and Cellular Therapy Cord Blood Special Interest Group

Check for updates

Haploidentical donors (2018)



Bone Marrow Transplantation
https://doi.org/10.1038/s41409-017-0062-8

REVIEW ARTICLE

The European Society for Blood and Marrow Transplantation (EBMT) Consensus Guidelines for the Detection and Treatment of Donor-specific Anti-HLA Antibodies (DSA) in Haploidentical Hematopoietic Cell Transplantation

Dehn J, Spellman S, Hurley CK, Shaw BE, Barker JN, Burns LJ, Confer DL, Eapen M, Fernandez-Vina M, Hartzman R, Maiers M, Marino SR, Mueller C, Perales MA, Rajalingam R, Pidala J. Selection of unrelated donors and cord blood units for hematopoietic cell transplantation: guidelines from the NMDP/CIBMTR. Blood. 2019 Sep 19;134(12):924-934. doi: 10.1182/blood.2019001212. Epub 2019 Jul 10. Erratum for: doi: 10.1182/blood.2019002898. PMID: 31292117; PMCID: PMC6753623.

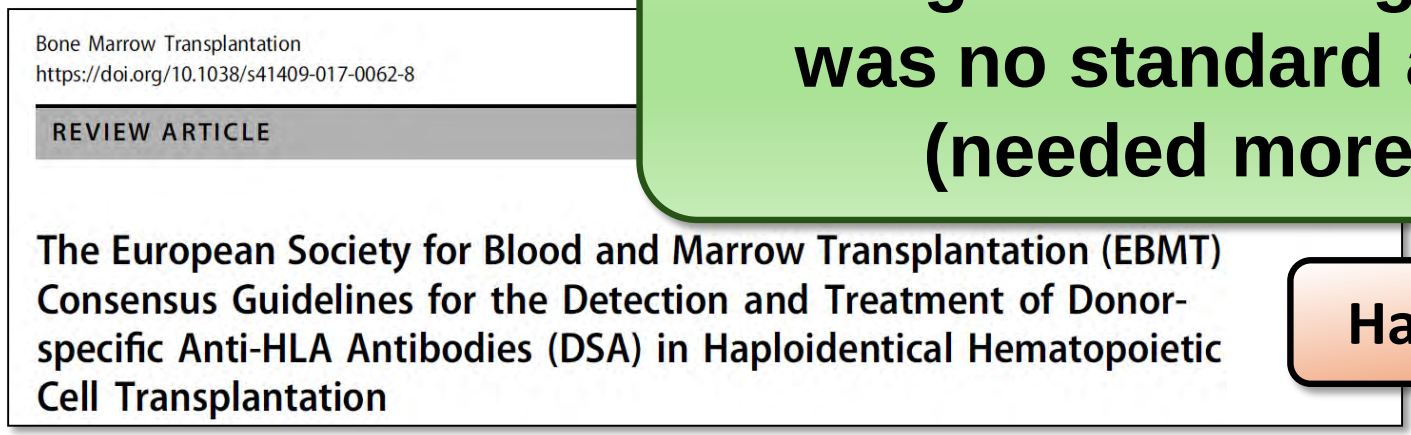
Politikos I, Davis E, Nhaissi M, Wagner JE, Brunstein CG, Cohen S, Shpall EJ, Milano F, Scaradavou A, Barker JN; American Society for Transplantation and Cellular Therapy Cord Blood Special Interest Group. Guidelines for Cord Blood Unit Selection. Biol Blood Marrow Transplant. 2020 Dec;26(12):2190-2196. doi: 10.1016/j.bbmt.2020.07.030. Epub 2020 Jul 28. PMID: 32736011.

Ciurea, S.O., Cao, K., Fernandez-Vina, M. et al. The European Society for Blood and Marrow Transplantation (EBMT) Consensus Guidelines for the Detection and Treatment of Donor-specific Anti-HLA Antibodies (DSA) in Haploidentical Hematopoietic Cell Transplantation. Bone Marrow Transplant 53, 521–534 (2018). https://doi.org/10.1038/s41409-017-0062-8

Unrelated donors (2019)

All acknowledge the consideration of DSAs in donor selection and have various comments on attempting desensitization in various DSA settings - but recognized there was no standard approach (needed more data)

Cord Blood U



Haploidentical donors (2018)

Dehn J, Spellman S, Hurley CK, Shaw BE, Barker JN, Burns LJ, Confer DL, Eapen M, Fernandez-Vina M, Hartzman R, Maiers M, Marino SR, Mueller C, Perales MA, Rajalingam R, Pidala J. Selection of unrelated donors and cord blood units for hematopoietic cell transplantation: guidelines from the NMDP/CIBMTR. Blood. 2019 Sep 19;134(12):924-934. doi: 10.1182/blood.2019001212. Epub 2019 Jul 10. Erratum for: doi: 10.1182/blood.2019002898. PMID: 31292117; PMCID: PMC6753623.
Politikos I, Davis E, Nhaissi M, Wagner JE, Brunstein CG, Cohen S, Shpall EJ, Milano F, Scaradavou A, Barker JN; American Society for Transplantation and Cellular Therapy Cord Blood Special Interest Group. Guidelines for Cord Blood Unit Selection. Biol Blood Marrow Transplant. 2020 Dec;26(12):2190-2196. doi: 10.1016/j.bbmt.2020.07.030. Epub 2020 Jul 28. PMID: 32736011.
Ciurea, S.O., Cao, K., Fernandez-Vina, M. et al. The European Society for Blood and Marrow Transplantation (EBMT) Consensus Guidelines for the Detection and Treatment of Donor-specific Anti-HLA Antibodies (DSA) in Haploidentical Hematopoietic Cell Transplantation. Bone Marrow Transplant 53, 521–534 (2018). https://doi.org/10.1038/s41409-017-0062-8

Desensitization: “The strategy of eliminating or decreasing pre-existing HLA alloantibody”

- Ideally should be multi-pronged approach:

    1. Stop Making the Antibody (e.g. rituximab)
    2. Remove the Antibody already made (e.g. plasma exchange)
    3. Interfere with Antibody’s effectiveness (e.g. IVIG)

- See both monotherapies and polytherapies reported in the literature

Choi AY, Manook M, Olaso D, Ezekian B, Park J, Freischlag K, Jackson A, Knechtle S, Kwun J. Emerging New Approaches in Desensitization: Targeted Therapies for HLA Sensitization. Front Immunol. 2021 Jun 11;12:694763. doi: 10.3389/fimmu.2021.694763. PMID: 34177960; PMCID: PMC8226120.

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Transplantation and Cellular Therapy 000 (2024) 1–16

Hot off the press! (2024)

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Transplantation and Cellular Therapy

journal homepage: www.astctjournal.org

Guideline

ASTCT Consensus Recommendations on Testing and Treatment of Patients with Donor-specific Anti-HLA Antibodies

Piyanuch Kongtim[1], Pongthep Vittayawacharin[1], Jun Zou[2], Samer Srour[3], Brian Shaffer[4], Roman M. Shapiro[5], Ankur Varma[6], Joseph McGuirk[7], Bhagirathbhai R. Dholaria[8], Shannon R. McCurdy[9], Amy E. DeZern[10], Nelli Bejanyan[11], Asad Bashey[12], Sabine Furst[13], Luca Castagna[14], Jacopo Mariotti[15], Annalisa Ruggeri[16], Rebeca Bailen[17], Takanori Teshima[18], Huang Xiao-Jun[19], Carmen Bonfim[20], Fleur Aung[21], Kai Cao[21], Paul A. Carpenter[22], Mehdi Hamadani[23], Medhat Askar[24,25], Marcelo Fernandez-Vina[26], Alin Girnita[27], Stefan O. Ciurea[1,*]

Kongtim P, Vittayawacharin P, Zou J, Srour S, Shaffer B, Shapiro RM, Varma A, McGuirk J, Dholaria BR, McCurdy SR, DeZern AE, Bejanyan N, Bashey A, Furst S, Castagna L, Mariotti J, Ruggeri A, Bailen R, Teshima T, Xiao-Jun H, Bonfim C, Aung F, Cao K, Carpenter PA, Hamadani M, Askar M, Fernandez-Vina M, Girnita A, Ciurea SO. ASTCT Consensus Recommendations on Testing and Treatment of Patients with Donor-specific Anti-HLA Antibodies. Transplant Cell Ther. 2024 Sep 10:S2666-6367(24)00654-7. doi: 10.1016/j.jtct.2024.09.005. Epub ahead of print. PMID: 39260570.

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Guideline

ASTCT Consensus Recommendations on Testing and Treatment of Patients with Donor-specific Anti-HLA Antibodies

10.1 – Regarding Desensitization

For DSA < 20,000 MFI, recommend combination of:

10.1. Summary and Recommendations

- *Multimodality pretransplant desensitization should be used to decrease DSA (Figure 1):*
  - *For DSA up to 20,000 MFI, plasmapheresis, rituximab, IVIG and infusion of donor-derived HLA antigen (either irradiated buffy coat for the corresponding HLA class I and II or platelet transfusions for corresponding HLA class I only) are recommended.*
  - *For DSA >20,000 MFI, patients may require antibody titration (due to bead saturation), and an alternative donor without corresponding HLA should be selected, or else should be treated using an investigational approach.*
  - *For DSA 2,000-10,000 MFI in haploidentical HSCT or 1,000- 10,000 MFI in CBT, additional data are needed to determine that patients with these lower DSA levels can be treated with a lower intensity desensitization protocol, such as rituximab with IVIG.*

MFI = mean fluorescent intensity (semi-quantitative measure of Ab)

Kongtim P, Vittayawacharin P, Zou J, Srour S, Shaffer B, Shapiro RM, Varma A, McGuirk J, Dholaria BR, McCurdy SR, DeZern AE, Bejanyan N, Bashey A, Furst S, Castagna L, Mariotti J, Ruggeri A, Bailen R, Teshima T, Xiao-Jun H, Bonfim C, Aung F, Cao K, Carpenter PA, Hamadani M, Askar M, Fernandez-Vina M, Girnita A, Ciurea SO. ASTCT Consensus Recommendations on Testing and Treatment of Patients with Donor-specific Anti-HLA Antibodies. Transplant Cell Ther. 2024 Sep 10:S2666-6367(24)00654-7. doi: 10.1016/j.jtct.2024.09.005. Epub ahead of print. PMID: 39260570.

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Guideline

ASTCT Consensus Recommendations on Testing and Treatment of Patients with Donor-specific Anti-HLA Antibodies

10.1 – Regarding Desensitization

For DSA < 20,000 MFI, recommend combination of:

1. Plasmapheresis

10.1. Summary and Recommendations

- *Multimodality pretransplant desensitization should be used to decrease DSA (Figure 1):*
  - *For DSA up to 20,000 MFI, plasmapheresis, rituximab, IVIG and infusion of donor-derived HLA antigen (either irradiated buffy coat for the corresponding HLA class I and II or platelet transfusions for corresponding HLA class I only) are recommended.*
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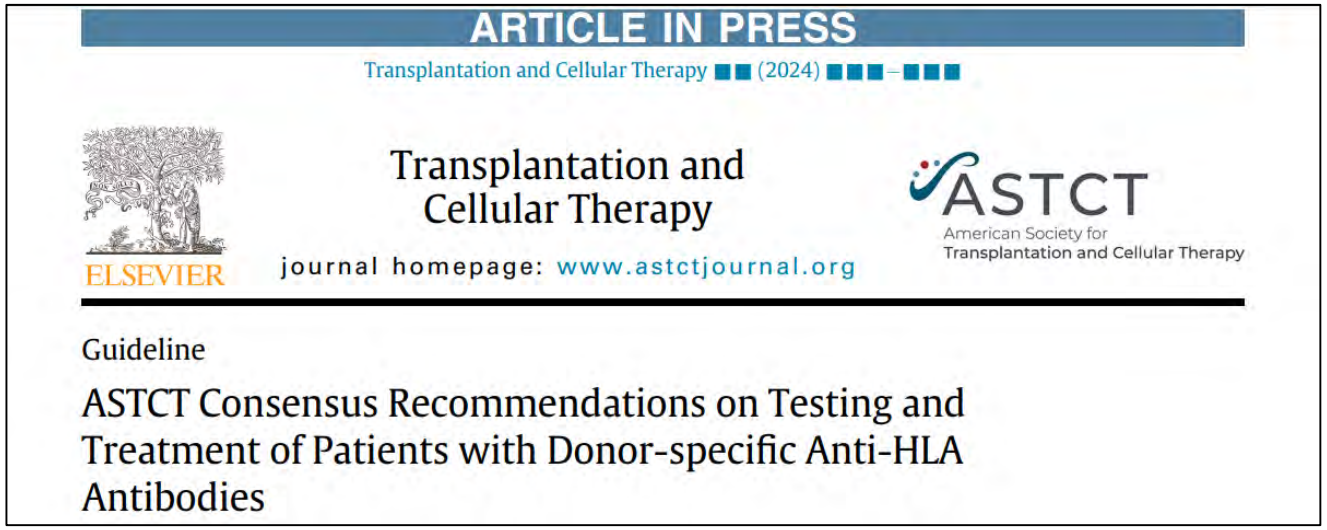

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Transplantation and Cellular Therapy ■■ (2024) ■■■–■■■

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Transplantation and Cellular Therapy

journal homepage: www.astctjournal.org

ASTCT
American Society for Transplantation and Cellular Therapy

Guideline

ASTCT Consensus Recommendations on Testing and Treatment of Patients with Donor-specific Anti-HLA Antibodies

10.1 – Regarding Desensitization

For DSA < 20,000 MFI, recommend combination of:

1. Plasmapheresis
2. Rituximab (anti-CD20)

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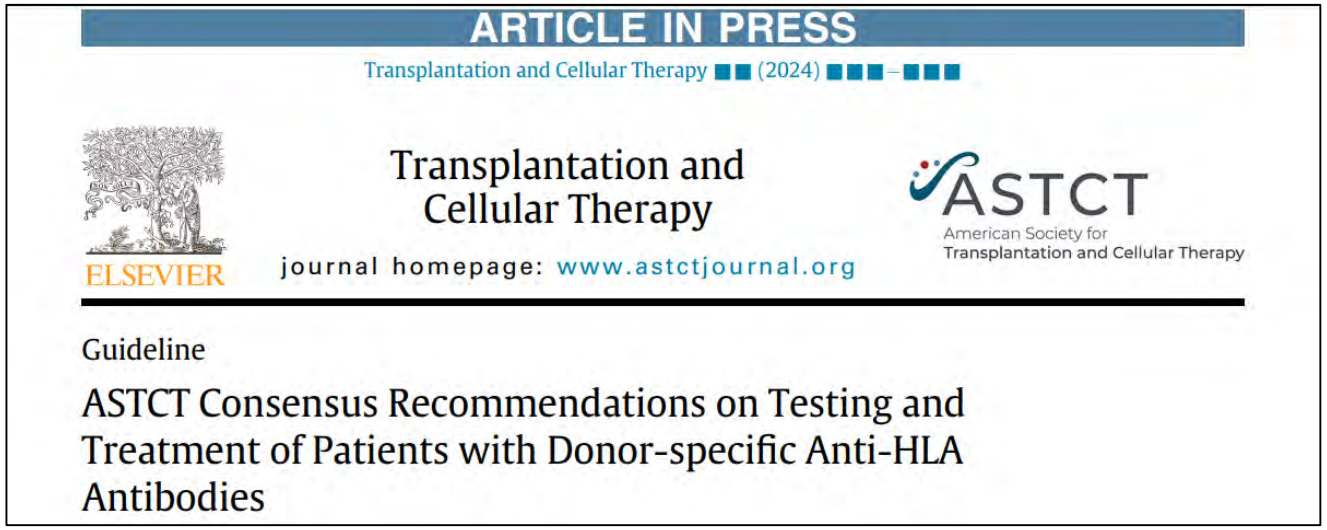
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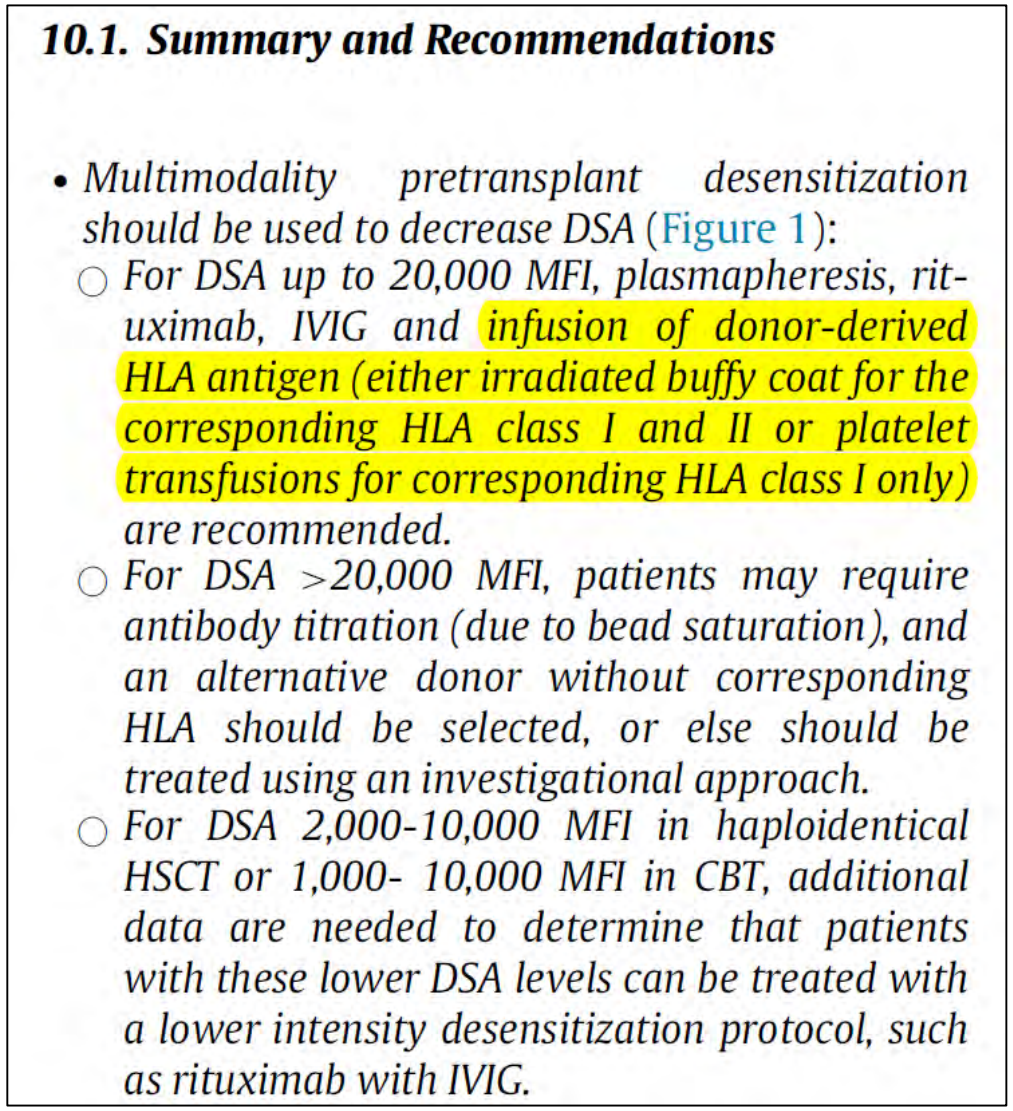

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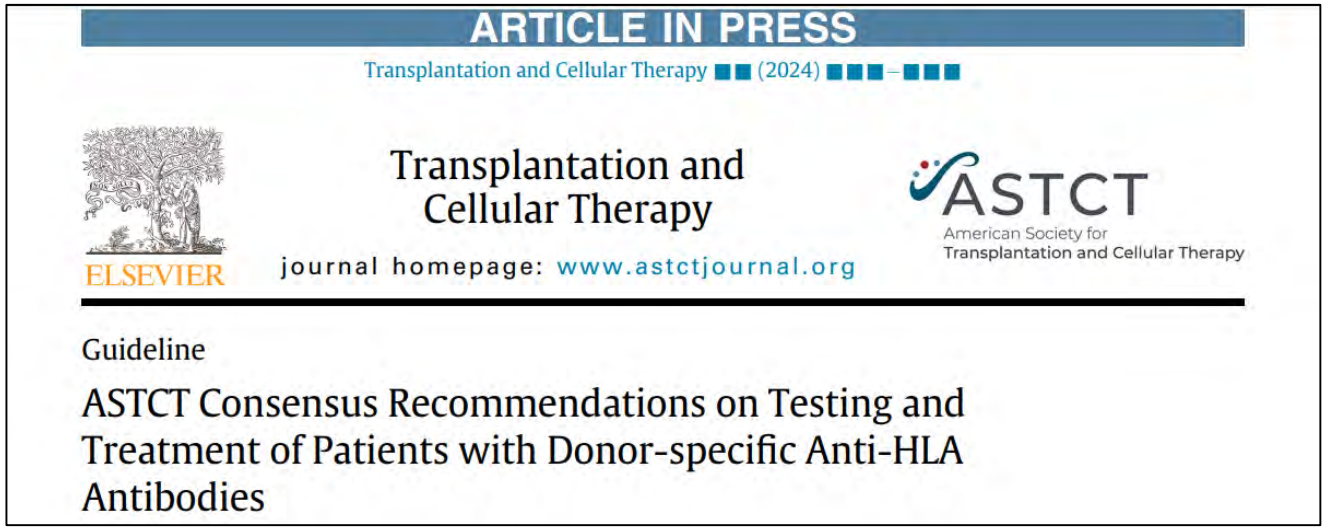

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with these lower DSA levels can be treated with a lower intensity desensitization protocol, such as rituximab with IVIG.

The idea is antibody removal through *in vivo* adsorption (depending on semantics, can be considered as Ab blocking/neutralization)

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Infusion/Transfusion of HLA-Typed Platelets

Platelets express HLA-A and HLA-B

All reports have been from outside US
(mainly Europe, Asia)

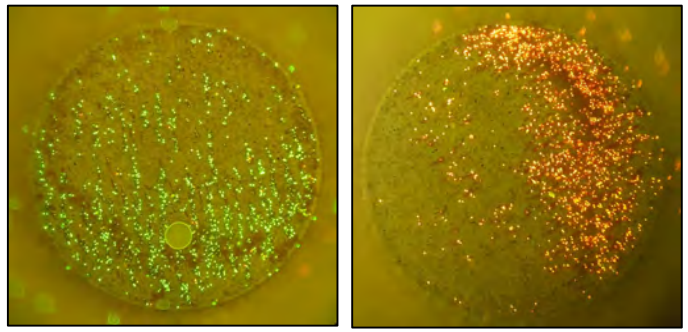
0041-1337/02/7308-1280/0
TRANSPLANTATION
Vol. 73, 1280–1285, No. 8, April 27, 2002
Printed in U.S.A.

POSITIVE SERUM CROSSMATCH AS PREDICTOR FOR GRAFT FAILURE IN HLA-MISMATCHED ALLOGENEIC BLOOD STEM CELL TRANSPLANTATION

HELLMUT D. OTTINGER,[1,2] VERA REBMANN,[1] KERSTIN A. PFEIFFER,[1] DIETRICH W. BEELEN,[2] BERNHARD KREMENS,[3] VOLKER RUNDE,[2] ULRICH W. SCHAEFER,[2] AND HANS GROSSE-WILDE[1,4]

Institute of Immunology, Departments of Bone Marrow Transplantation, and Paediatric Haematology, Oncology and Endocrinology, University Hospital of Essen, 45122 Essen, Germany

- 30 patients transplanted with **(+) complement dependant cytotoxicity (CDC) B-cell and/or T-cell cross match**
- 2 of 30 attempted desensitization = TPE + **"mismatched" platelets**
  - Details of regimen and definition of "mismatch" not specified
- *Note: Used different definition of reaching "Engraftment" by Day 28:*
  - *Self-sustained PMN > 1x10^3 /µL*
  - *Untransfused platelet count > 2x10^4 /µL (= 20,000/µL)*



Live cells Dead cells
(photos by Deanna C Fang)

Ottinger HD, Rebmann V, Pfeiffer KA, et al. Positive serum crossmatch as predictor for graft failure in HLA-mismatched allogeneic blood stem cell transplantation. *Transplantation.* 2002;73(8):1280-1285

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- Patient #1 – IgM & IgG cytotoxic Anti-B44
  - → successfully ↓ DSA, (-) XM before transplant
  - → engraftment → long-term overall survival ☺
- Patient #2 – IgG Anti-A24
  - → persistent DSA, (+) XM before transplant
  - → failed to engraft → died at Day 31, bleeding ☹

- Implications:
  - If can successfully decrease DSA and achieve (-) XM prior to transplant → better outcome.

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Bone Marrow Transplant. 2012 Apr;47(4):508-15. doi: 10.1038/bmt.2011.131. Epub 2011 Jun 20.

Risk and prevention of graft failure in patients with preexisting donor-specific HLA antibodies undergoing unmanipulated haploidentical SCT.

Yoshihara S[1], Maruya E, Taniguchi K, Kaida K, Kato R, Inoue T, Fujioka T, Tamaki H, Ikegame K, Okada M, Soma T, Hayashi K, Fujii N, Onuma T, Kusunoki Y, Saji H, Ogawa H.

Author information

1 Division of Hematology, Department of Internal Medicine, Hyogo College of Medicine, Hyogo, Japan. yoshihar@hyo-med.ac.jp

- Prospective study, 01/2008 → 03/2010
- 11 (+) DSA / 79 haploidentical SCT
- 6/11 – no desensitization → 3/6 engrafted (50%)
- 5/11 – desensitization → 5/5 engrafted (100%)
  - **2/5 – Platelet transfusion only (40 units, Day -1)**
    - from healthy related donors expressing Ag corresponding to DSA
  - 2/5 – TPE + Rituximab
  - 1/5 – Bortezomib + dexamethasone
    - (pt had anti-DR4 DSA)

Yoshihara S, Maruya E, Taniguchi K, et al. Risk and prevention of graft failure in patients with preexisting donor-specific HLA antibodies undergoing unmanipulated haploidentical SCT. *Bone Marrow Transplant.* 2012;47(4):508-515.

Vox Sang. 1998;75(4):308-17.

The official requirements for platelet concentrates.

Engelfriet CP[1], Reesink HW, Snyder EL, Dzik WH, Masse M, Naegelen C, Brand A, Williamson L, Knipe J, Bruce M, Woodfield DG, Sekiguchi S, Myllylä G, Sabliński J, Zupańska B.

Author information

1 Central Laboratory of The Netherlands, Red Cross Blood Transfusion Service, Amsterdam.

- Japan: "One Unit" of Platelet Concentrate Derived from 200ml of whole blood (WB)
  - **Requirement - Must contain > 2 x 10^{10} platelets**
  - If from WB → Can obtain 1 or 2 units (from 200 or 400ml, respectively)
  - If from Apheresis (usual method) → Can obtain 5, 10, 15, or 20 units
- United States: Platelet Unit Requirements (*)
  - If from WB (pre-pooled) - must contain > 5.5 x 10^{10} plts (> 90% units)
  - 1 apheresis unit must contain > 3 x 10^{11} plts (> 75% units, with 95% CI)
  - Nowadays, "1 unit" is usually refers to an "apheresis" unit

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(*) Standards for AABB. Standards for Blood Banks and Transfusion Services, 34th edition.

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1 apheresis platelet unit in USA

~ 15 platelet units in Japan

↓

40 platelet units in Japan

~ 2.7 apheresis platelet units in USA

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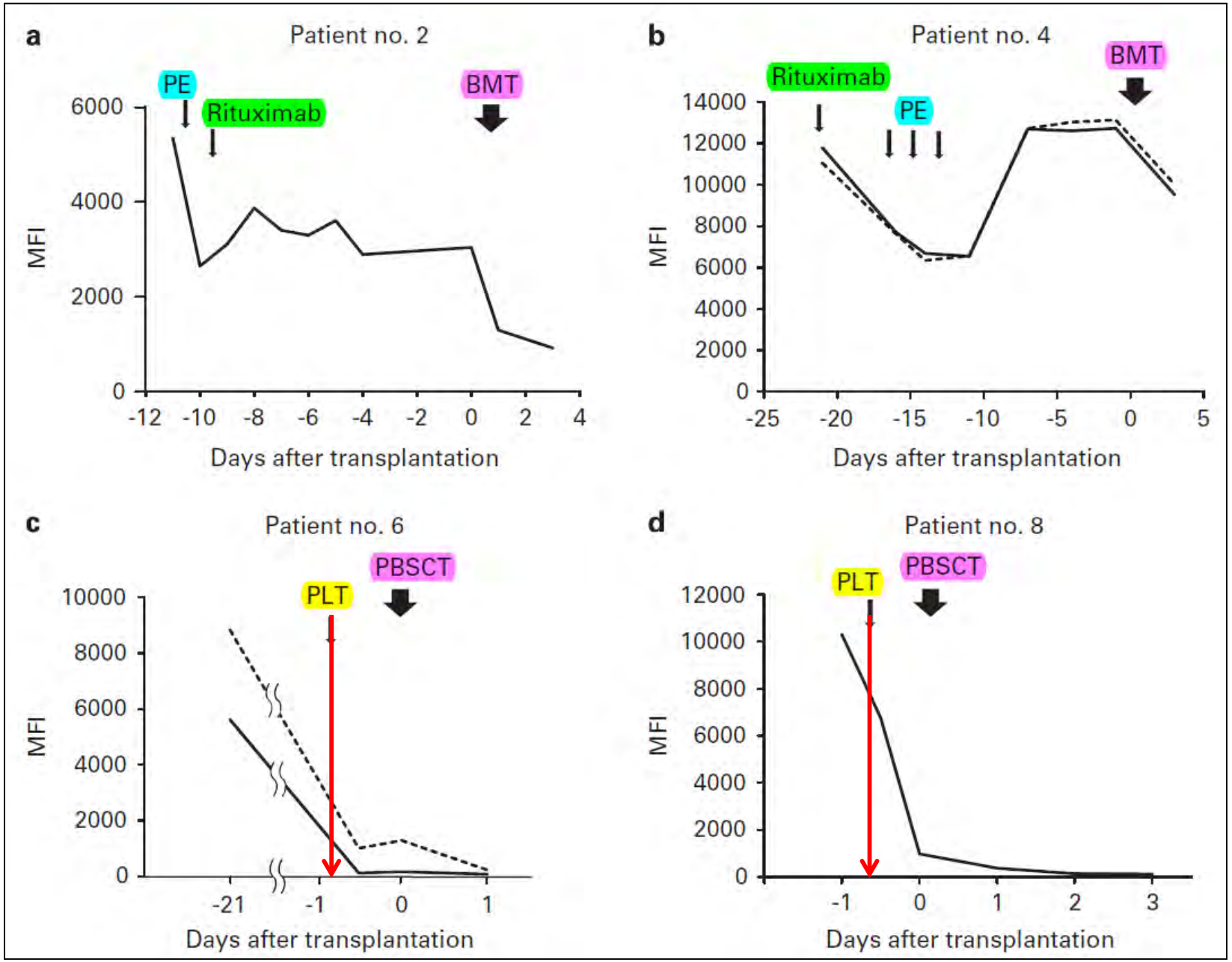

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Platelet transfusion alone appeared to be **more effective** at decreasing DSA MFIs than TPE + Rituximab combined.

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Engraftment times:	Neutrophil	Platelet
• **Platelets only (#1)**	**Day 10**	**Day 19**
• **Platelets only (#2)**	**Day 10**	**Day 17**
• PE + Rituximab (#1)	Day 15	Day 35
• PE + Rituximab (#1)	Day 24	Day 32
• Bortezomib + Dexameth.	Day 11	Day 51

Consider which regimen option a patient would prefer....

Fig. 1 Yoshihara S, Maruya E, Taniguchi K, et al. Risk and prevention of graft failure in patients with preexisting donor-specific HLA antibodies undergoing unmanipulated haploidentical SCT. *Bone Marrow Transplant.* 2012;47(4):508-515.

Bone Marrow Transplant. 2017 May;52(5):794-796. doi: 10.1038/bmt.2017.10. Epub 2017 Feb 6.

Effective desensitization of donor-specific HLA antibodies using platelet transfusion bearing targeted HLA in a case of HLA-mismatched allogeneic stem cell transplantation.

Yamashita T[1,2], Ikegame K[1], Kojima H[3], Tanaka H[3], Kaida K[1], Inoue T[1], Ogawa H[1].

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2 Department of Hematology, Nephrology and Rheumatology, Graduate School of Medicine, Akita University, Akita, Japan.
3 HLA Foundation Laboratory, Kyoto, Japan.

- 41 year old woman, h/o 2 failed SCTs, needing 3rd transplant
- Enrolled in HLA full mismatch trial → Cousin as donor (1/8 match)
- After cousin was selected, new DSA emerged post-transfusion
  - Anti-B*40:02 [B61] (8103 "titer" – *meant mfi?*)
- Desensitization
  1. Rituximab (Day -10)
  2. IVIG (Days -8 to -5)
  3. **DSA-PC (- 6 hours, pre-stem cell infusion, over 3 hrs)**
     - **20 units (324ml, 3.86 x 10^{11} plt [~ 1.3 US apheresis plt])**
     - Platelet donor is an HLA-matched sister of the stem cell donor

Desensitization	MFI
Originally	5562
Rituximab	4136
IVIG	No Δ
Preconditioning	2962
Platelet	267

Yamashita T, Ikegame K, Kojima H, Tanaka H, Kaida K, Inoue T, Ogawa H. Effective desensitization of donor-specific HLA antibodies using platelet transfusion bearing targeted HLA in a case of HLA-mismatched allogeneic stem cell transplantation. Bone Marrow Transplant. 2017 May;52(5):794-796. doi: 10.1038/bmt.2017.10. Epub 2017 Feb 6. PMID: 28165448.

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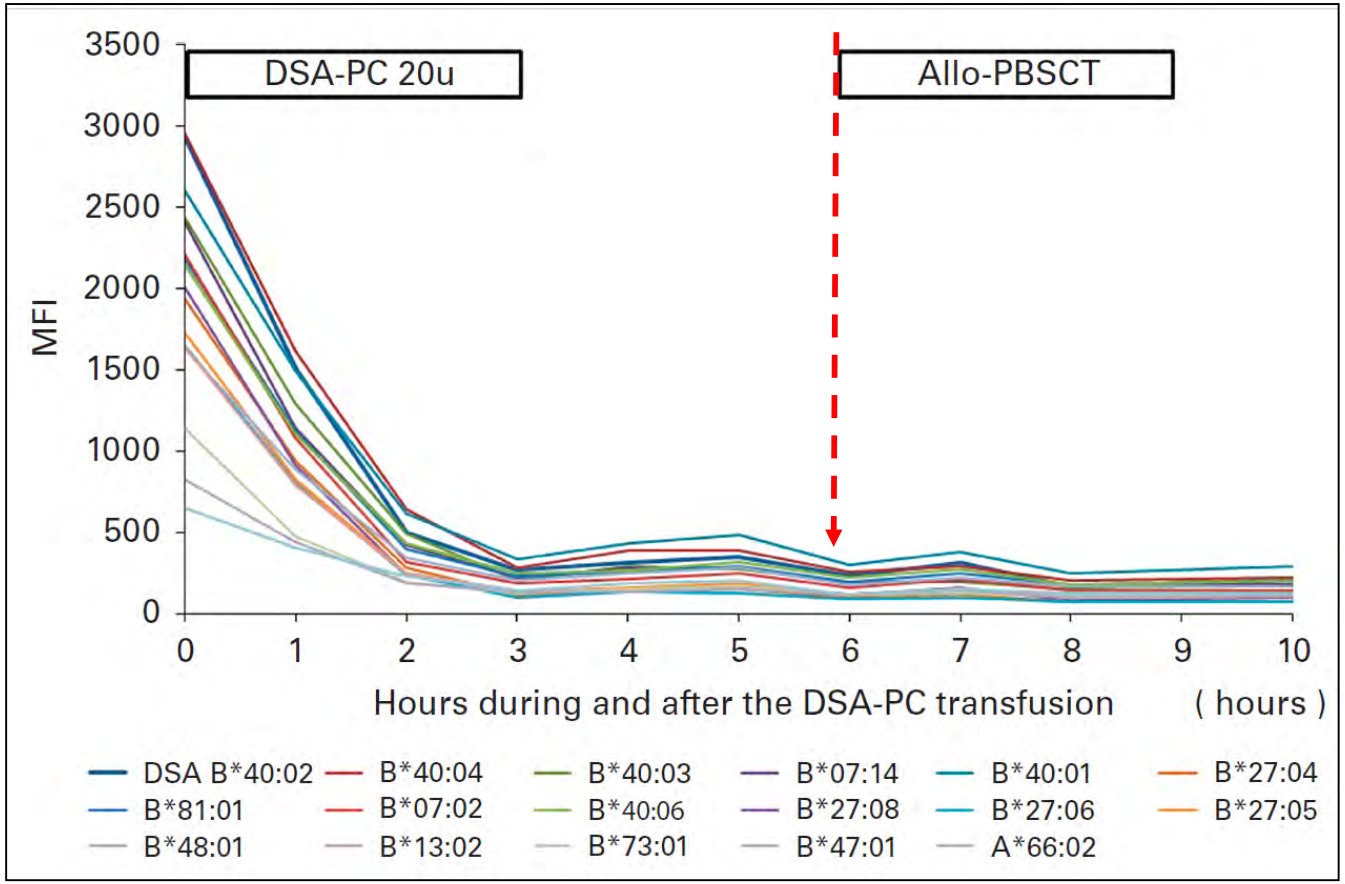
Can see immediate effect platelet transfusion → DSA (-) by end of transfusion



OUTCOMES

Day 9

→ Neutrophil engraftment ☺

→ Complete donor chimerism

Day 17

→ Complete donor chimerism

12 Months

→ Still in Complete Remission

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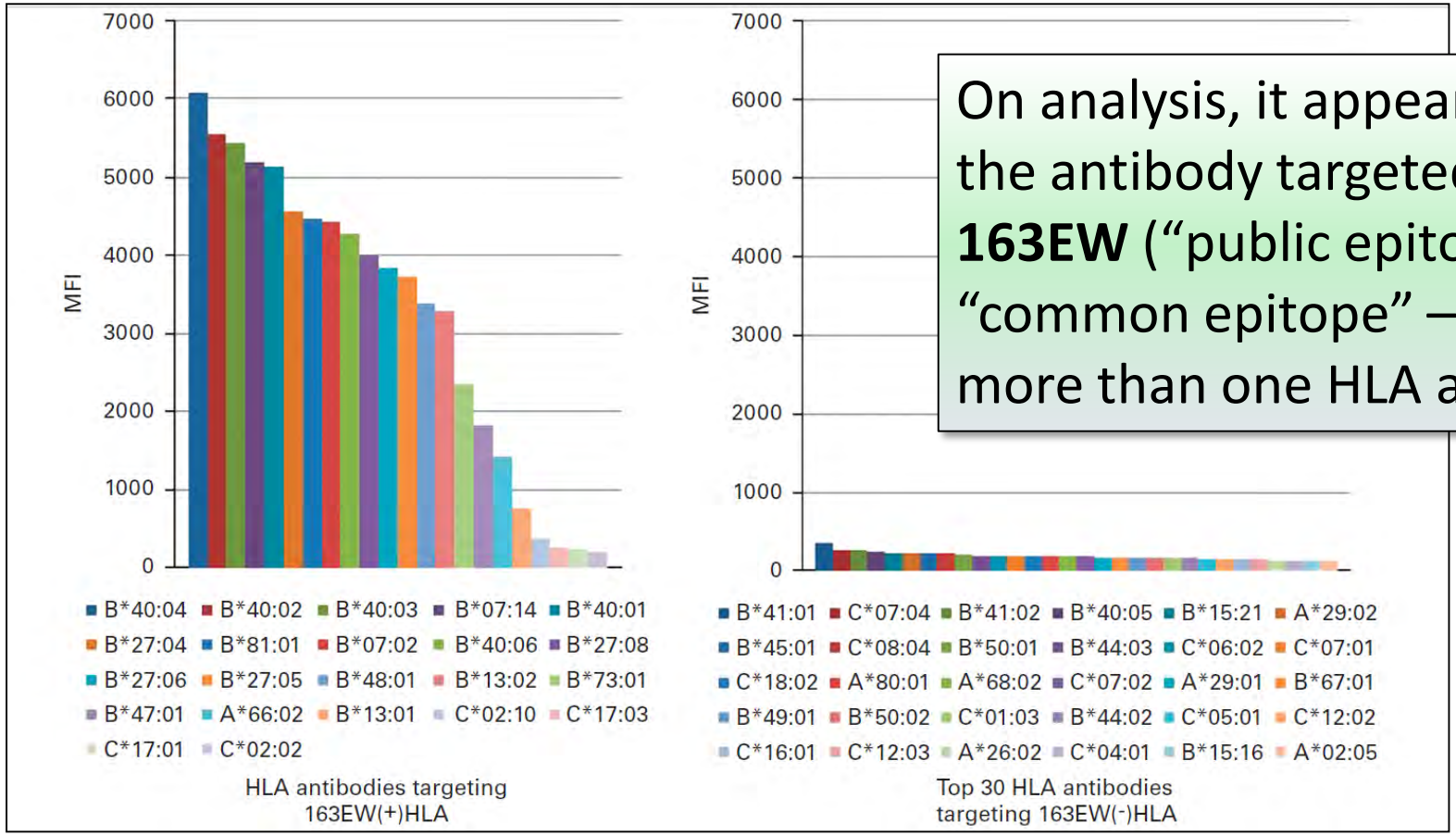

On analysis, it appeared that the antibody targeted **epitope 163EW** (“public epitope” or “common epitope” – shared by more than one HLA antigen)

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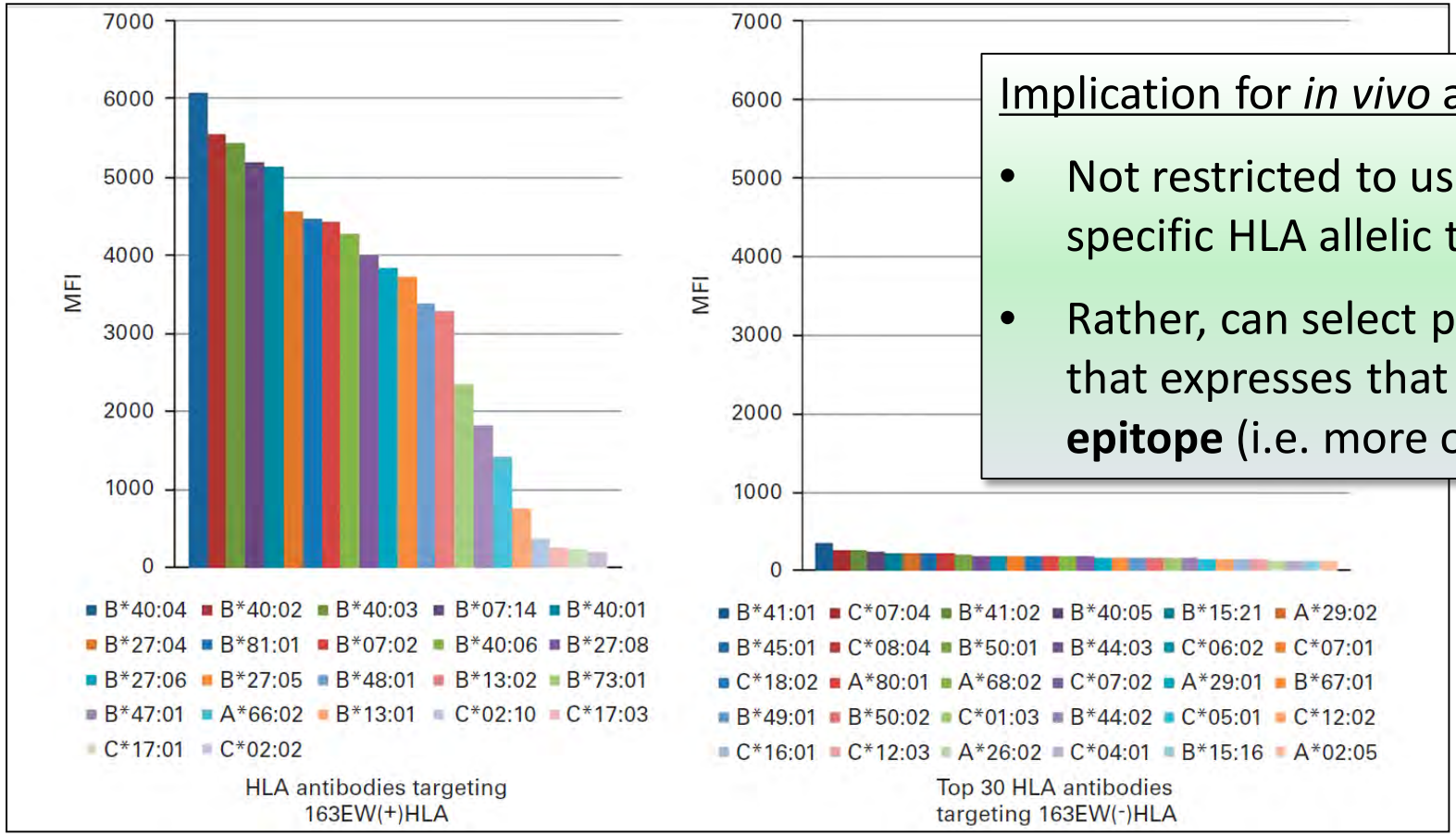

Implication for *in vivo* adsorptions:

- Not restricted to using platelet of specific HLA allelic type.
- Rather, can select platelet (donor) that expresses that common **epitope** (i.e. more options) ☺


供者特异性HLA抗体对单倍体相合造血干细胞植入的影响 - 中华血液学杂志
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点赞 0
分享 0
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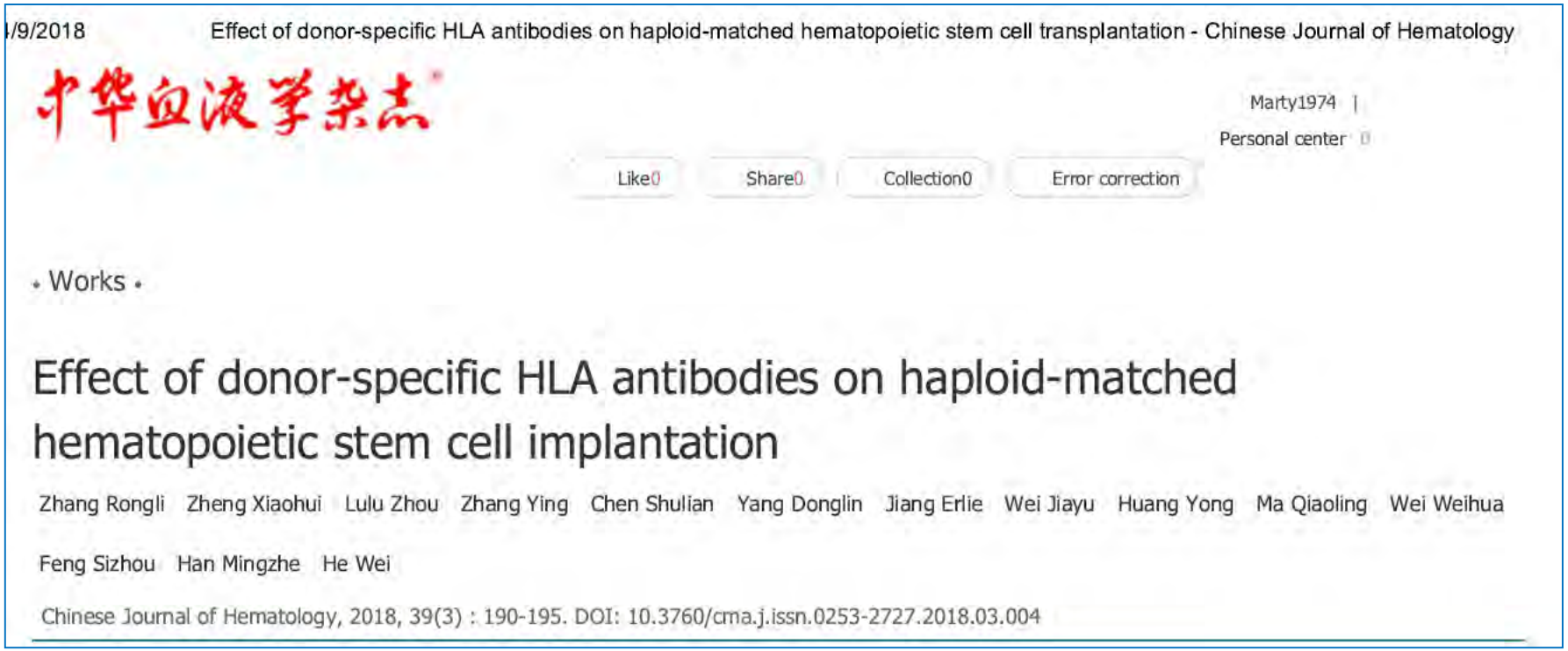
中华血液学杂志, 2018,39(3) : 190-195. DOI: 10.3760/cma.j.issn.0253-2727.2018.03.004


1/9/2018 Effect of donor-specific HLA antibodies on haploid-matched hematopoietic stem cell transplantation - Chinese Journal of Hematology
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Effect of donor-specific HLA antibodies on haploid-matched hematopoietic stem cell implantation
Zhang Rongli Zheng Xiaohui Lulu Zhou Zhang Ying Chen Shulian Yang Donglin Jiang Erlie Wei Jiayu Huang Yong Ma Qiaoling Wei Weihua
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Zhang R, He Y, Yang D, et al. Combination treatment of rituximab and donor platelets infusion to reduce donor-specific anti-HLA antibodies for stem cells engraftment in haploidentical transplantation. J Clin Lab Anal. 2020;34(7):e23261. doi:10.1002/jcla.23261.

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DOI: 10.1002/jcla.23261

RESEARCH ARTICLE

WILEY

Combination treatment of rituximab and donor platelets infusion to reduce donor-specific anti-HLA antibodies for stem cells engraftment in haploidentical transplantation

Rongli Zhang | Yi He | Donglin Yang | Erlie Jiang | Qiaoling Ma | Aiming Pang | Weihua Zhai | Jialin Wei | Sizhou Feng | Mingzhe Han

- N = 78 consecutive haploidentical-HPCT pts (6/2016 - 03/2018)
- 9 of 78 had (+) DSA
- First 4 DSA (+) pts had same conditioning regimen as (-) DSA cohort, no desensitization → only 1/4 (25%) engraftment
  - 2 of 3 w failed engraftment → 2nd transplant w/ desensitization → 100% engrafted
- Next 5 DSA (+) pts had desensitization → 100% engraftment
  - DSA to HLA Class I only → **Platelets (day -1) only**
  - DSA to HLA Class I & II → **Platelets (day -1)** + Rituximab (day -21 to -14)
    - **"Two therapeutic amounts" of donor apheresis platelets 3-5 x 10^{11}** (*per unit or total?*)

Zhang R, He Y, Yang D, et al. Combination treatment of rituximab and donor platelets infusion to reduce donor-specific anti-HLA antibodies for stem cells engraftment in haploidentical transplantation. J Clin Lab Anal. 2020;34(7):e23261. doi:10.1002/jcla.23261.

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    - **"Two therapeutic amounts" of donor apheresis platelets 3-5 x 10^{11}** (*per unit or total?*)

Platelet infusion appears to be sufficient for desensitization when you just have DSA to HLA Class I

Zhang R, He Y, Yang D, et al. Combination treatment of rituximab and donor platelets infusion to reduce donor-specific anti-HLA antibodies for stem cells engraftment in haploidentical transplantation. J Clin Lab Anal. 2020;34(7):e23261. doi:10.1002/jcla.23261.

Bone Marrow Transplantation (2018) 53:791–794
https://doi.org/10.1038/s41409-018-0220-7

CORRESPONDENCE

Depletion of donor-specific anti-HLA A2 alloantibodies in a hematopoietic cell transplant recipient using directed mismatched platelet transfusions

Bernd M. Spriewald[1] · Christian Bach[1] · Juergen Zingsem[2] · Julian Strobel[2] · Julia Winkler[1] · Andreas Mackensen[1] · Wolf Roesler[1]

- 53 year old F, AML with intermediate genetic risk & induction failure.
- 9/10 donor identified → (+) DSA to HLA-A2, (+) CDC XM
- Desensitization = Rituximab x 4, Bortezomib x 4, **HLA-A2 (+) platelet transfusions x 7 days (Days -7, -5, - 3, -2, -1, 0 + 0)** [Av. = 3.2 x 10^{11} plt/unit]
- **DSA testing:**
  - **Before and 2-3 hours after each platelet transfusion until Day (-)1**
  - Days +7, +15

Spriewald, B.M., Bach, C., Zingsem, J. *et al.* Depletion of donor-specific anti-HLA A2 alloantibodies in a hematopoietic cell transplant recipient using directed mismatched platelet transfusions. *Bone Marrow Transplant* **53,** 791–794 (2018). https://doi.org/10.1038/s41409-018-0220-7

A2-PT	= HLA-A2 Plt
R	= Rituximab
B	= Bortezomib

- Outcome
  - Day 7 = last platelet transfusion ☺
  - Day 10 = Engraftment ☺
  - Day 30 = 100% chimerism
  - Remained in complete remission after 1 year
    - DSA remained (-)ve
  - Only complication:
    - Brief episode of Grade II acute upper GI GVHD

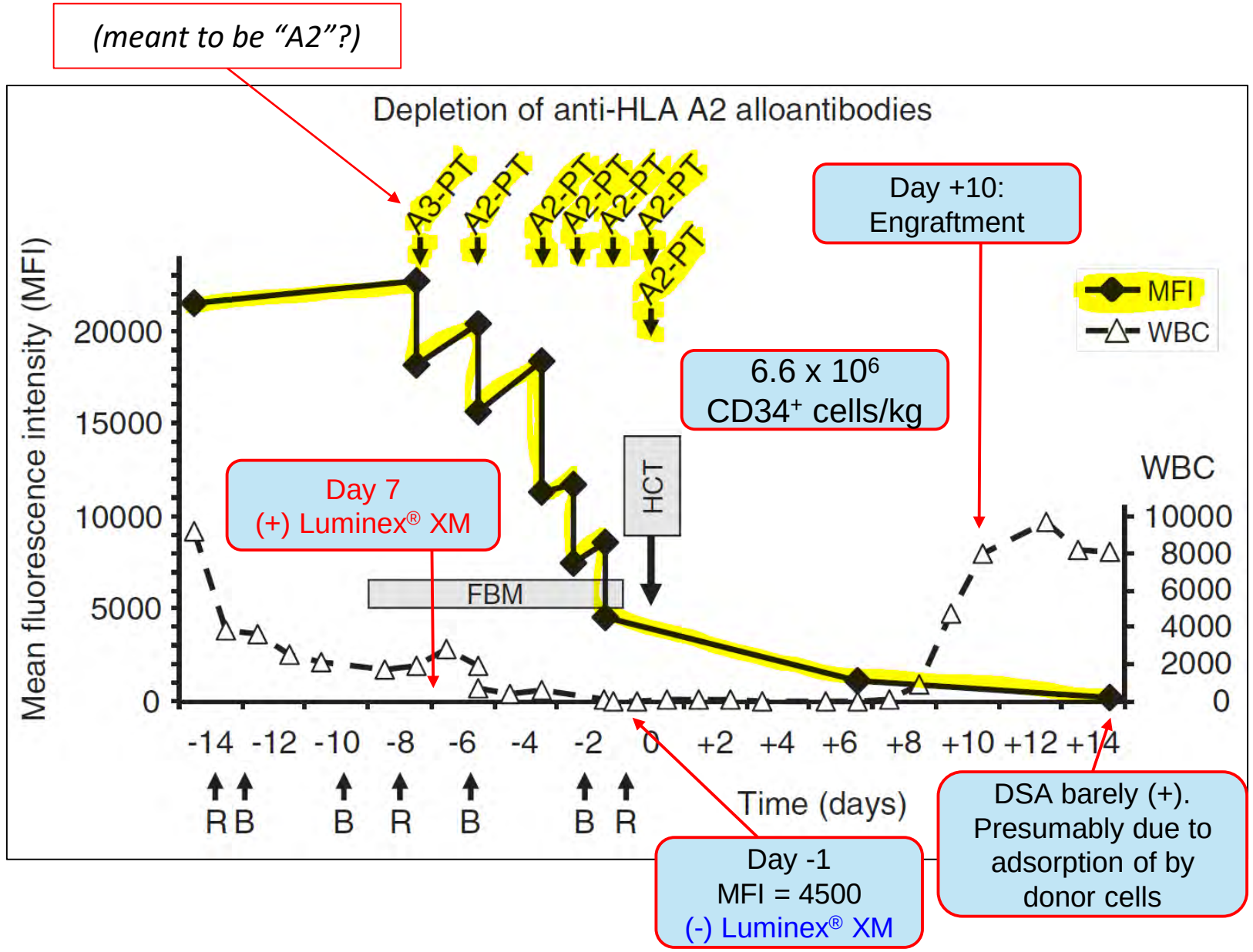
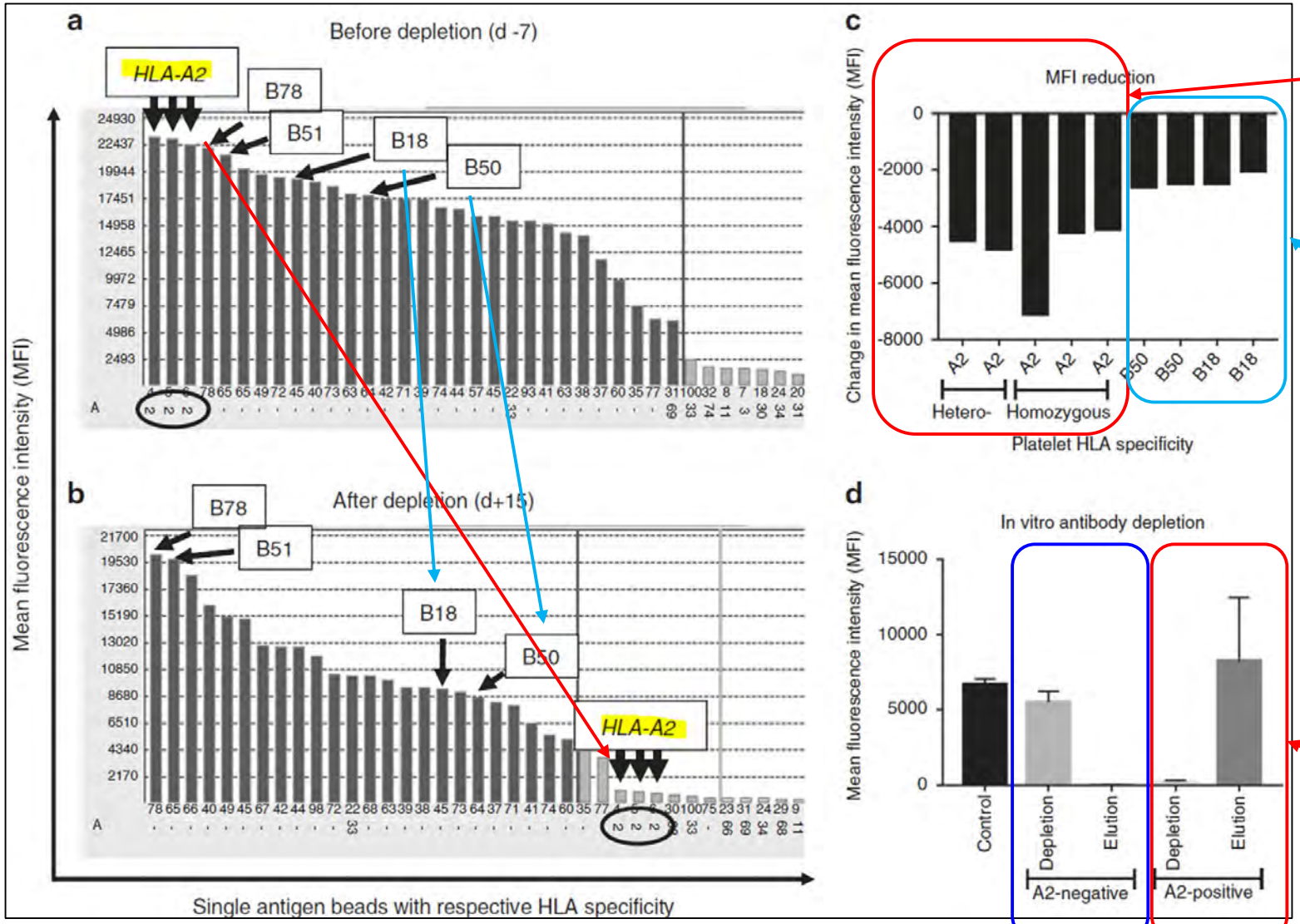


Fig. 2. Spriewald, B.M., Bach, C., Zingsem, J. *et al.* Depletion of donor-specific anti-HLA A2 alloantibodies in a hematopoietic cell transplant recipient using directed mismatched platelet transfusions. *Bone Marrow Transplant* **53,** 791–794 (2018). https://doi.org/10.1038/s41409-018-0220-7

UC San Diego Health



MFI drop with the 1st 5 platelet transfusions
(*Did not assess with last 2 due to confounding effect of HLA-A2 stem cells)*

Note: When platelets expressed HLA-B50 and -B18, those antibodies did not drop as much as with HLA-A2

Demonstrating the *in vitro* adsorptive effects of HLA-A2 platelets on DSA MFI levels *(no effect seen with HLA-A2-negatve platelets)*

Spriewald, B.M., Bach, C., Zingsem, J. *et al.* Depletion of donor-specific anti-HLA A2 alloantibodies in a hematopoietic cell transplant recipient using directed mismatched platelet transfusions. *Bone Marrow Transplant* **53,** 791–794 (2018). https://doi.org/10.1038/s41409-018-0220-7

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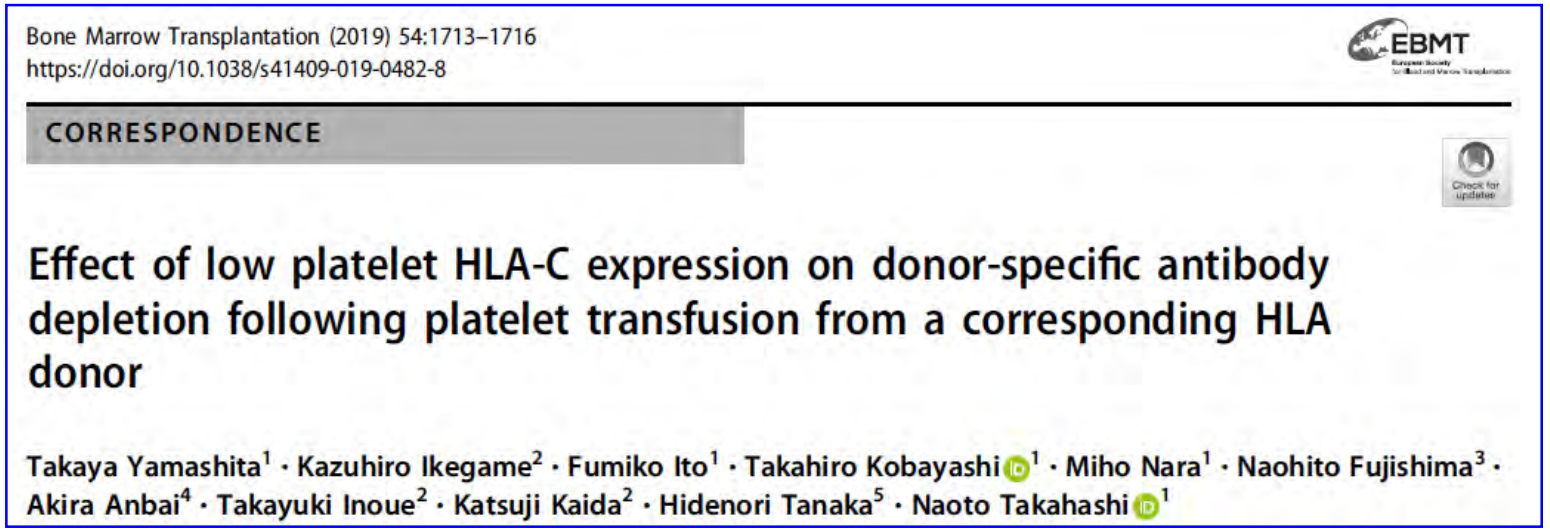
Take Home

1. This is a case where **depletion of DSA was used without TPE or IA**
2. *In vitro* demonstration of platelet adsorptive effect on anti-HLA (Ab)
3. No transfusion reactions ☺
4. Not a consistent difference between homozygous (n=3) and heterozygous (n=2) HLA-A2 platelets on MFI drop (~4000-5000 MFI)
5. 5 platelet transfusions brought DSA >20,000 MFI → 4500 MFI

Spriewald, B.M., Bach, C., Zingsem, J. *et al.* Depletion of donor-specific anti-HLA A2 alloantibodies in a hematopoietic cell transplant recipient using directed mismatched platelet transfusions. *Bone Marrow Transplant* **53,** 791–794 (2018). https://doi.org/10.1038/s41409-018-0220-7



Bone Marrow Transplantation (2019) 54:1713–1716
https://doi.org/10.1038/s41409-019-0482-8

CORRESPONDENCE

Effect of low platelet HLA-C expression on donor-specific antibody depletion following platelet transfusion from a corresponding HLA donor

Takaya Yamashita[1] · Kazuhiro Ikegame[2] · Fumiko Ito[1] · Takahiro Kobayashi[1] · Miho Nara[1] · Naohito Fujishima[3] · Akira Anbai[4] · Takayuki Inoue[2] · Katsuji Kaida[2] · Hidenori Tanaka[5] · Naoto Takahashi[1]

- 54 year old woman with therapy-related AML,
- **Broadly and strongly sensitized to HLA**
- Haploidentical son as donor
- Desensitization
  - Day (-10) = Rituximab, 375mg/m2
  - Day (-9 to -6) = IVIG x 4 days
  - Day 0 (-6 hr.s) = **20 units of platelets (4.4 x 10^{11} plts), from husband**
- **Measured MFI every hour**

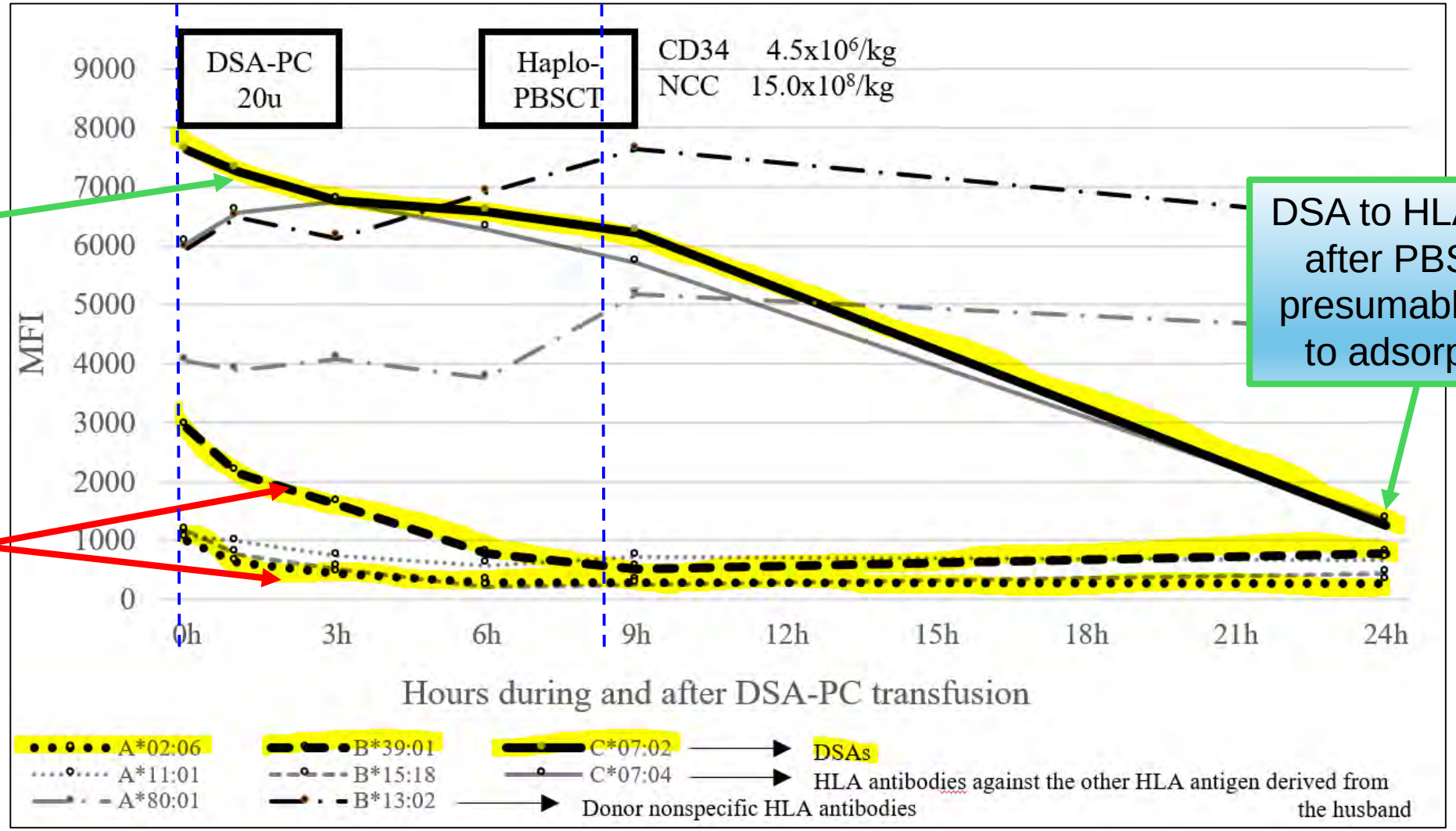
Yamashita, T., Ikegame, K., Ito, F. *et al.* Effect of low platelet HLA-C expression on donor-specific antibody depletion following platelet transfusion from a corresponding HLA donor. *Bone Marrow Transplant* **54,** 1713–1716 (2019). https://doi.org/10.1038/s41409-019-0482-8

	A	*B*	*C*	*DRB1*
Patient	**31:01**	**51:01**	**14:02**	**04:05**
	---	**54:01**	**01:02**	**09:01**
Son (donor)	**31:01**	**51:01**	**14:02**	**04:05**
	02:06	**39:01**	**07:02**	**15:01**
Admission	**mfi = 10347**	**mfi = 5349**	**mfi = 16403**	
Day (-)10	**mfi = 1227**	**mfi = 3817**	**mfi = 9549**	
Ritux, IVIG (& conditioning)	**mfi = 999**	**mfi = 2910**	**mfi = 7631**	
After Platelets	**mfi = 297**	**mfi = 782**	**mfi = 6572**	
After HSCT	**mfi < 1500**	**mfi < 1500**	**mfi < 1500**	

Yamashita, T., Ikegame, K., Ito, F. *et al.* Effect of low platelet HLA-C expression on donor-specific antibody depletion following platelet transfusion from a corresponding HLA donor. *Bone Marrow Transplant* **54,** 1713–1716 (2019). https://doi.org/10.1038/s41409-019-0482-8

Platelets less effective with DSA to HLA-C ☹

Platelets more effective with DSA to HLA-B ☺



DSA to HLA-C ☹ after PBSCT, presumably due to adsorption

Yamashita, T., Ikegame, K., Ito, F. *et al.* Effect of low platelet HLA-C expression on donor-specific antibody depletion following platelet transfusion from a corresponding HLA donor. *Bone Marrow Transplant* **54,** 1713–1716 (2019). https://doi.org/10.1038/s41409-019-0482-8

Flow cytometry analysis of different levels of expression of HLA-A, vs. HLA-B vs. HLA-C depending on the cell *(Fig 1.b, n = 7 healthy donors)*

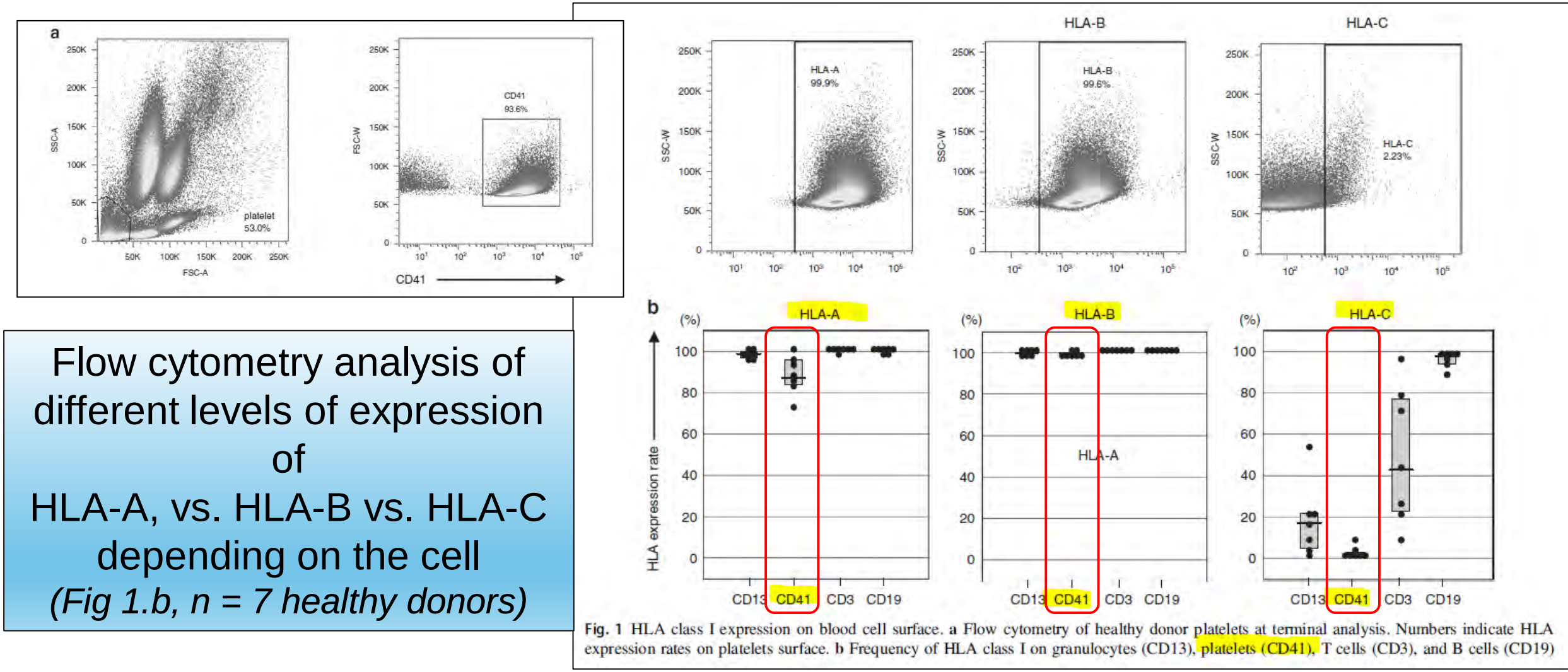
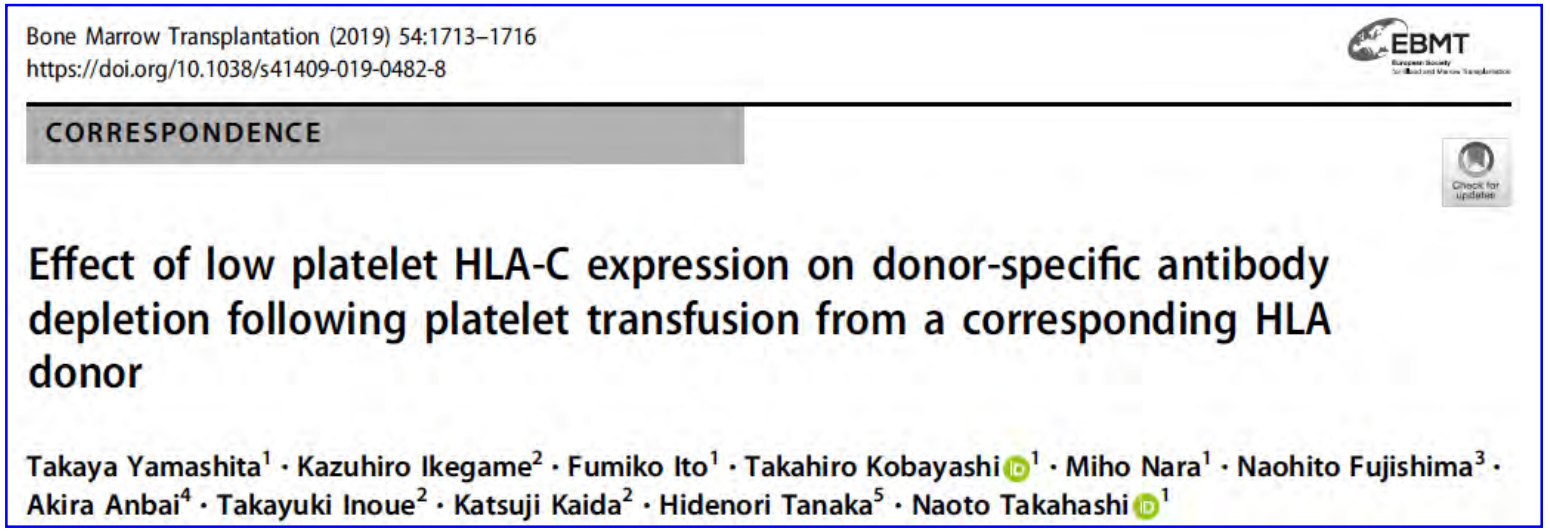


Fig. 1 HLA class I expression on blood cell surface. **a** Flow cytometry of healthy donor platelets at terminal analysis. Numbers indicate HLA expression rates on platelets surface. **b** Frequency of HLA class I on granulocytes (CD13), platelets (CD41), T cells (CD3), and B cells (CD19)

Yamashita, T., Ikegame, K., Ito, F. *et al.* Effect of low platelet HLA-C expression on donor-specific antibody depletion following platelet transfusion from a corresponding HLA donor. *Bone Marrow Transplant* **54,** 1713–1716 (2019). https://doi.org/10.1038/s41409-019-0482-8



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- Outcome = PMN engraftment at Day 11 ☺
- Authors' Take Home:
  - Platelet are <u>not</u> effective for DSA to HLA-C
  - Level of HLA-C expression on stem cells is uncertain
  - But HLA-C has lower expression on other cells examined, so maybe DSA to HLA-C is less of a concern.
    - This is an area for further study.

Q. Could infusion of WBCs be an alternative solution for DSAs to HLA-C?

Yamashita, T., Ikegame, K., Ito, F. *et al.* Effect of low platelet HLA-C expression on donor-specific antibody depletion following platelet transfusion from a corresponding HLA donor. *Bone Marrow Transplant* **54,** 1713–1716 (2019). https://doi.org/10.1038/s41409-019-0482-8

HLA-Typed irradiated WBCs (irradiated buffy coat)

WBCs express HLA Class I (A, B, **C**) and Class II **DR, DQ, DP**)

[vs platelets which only express HLA Class I (A, B)]

ELSEVIER

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

Biology: Biomarkers

Complement-Binding Donor-Specific Anti-HLA Antibodies and Risk of Primary Graft Failure in Hematopoietic Stem Cell Transplantation

Stefan O. Ciurea [1,*], Peter F. Thall [2], Denái R. Milton [2], Titus H. Barnes [3], Piyanuch Kongtim [1], Yudith Carmazzi [3], Asdrúbal A. López [3], Dianne Y. Yap [3], Uday Popat [1], Gabriela Rondon [1], Benjamin Lichtiger [3], Fleur Aung [3], Vahid Afshar-Kharghan [4], Qing Ma [1], Marcelo Fernández-Viña [5], Richard E. Champlin [1], Kai Cao [3]

[1] *Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, Texas*
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[3] *Department of Pathology and Laboratory Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas*
[4] *Department of Benign Hematology, The University of Texas MD Anderson Cancer Center, Houston, Texas*
[5] *Department of Pathology, Stanford University, Palo Alto, California*

Ciurea SO, Thall PF, Milton DR, et al. Complement-Binding Donor-Specific Anti-HLA Antibodies and Risk of Primary Graft Failure in Hematopoietic Stem Cell Transplantation. *Biol Blood Marrow Transplan*t. 2015;21(8):1392-1398.

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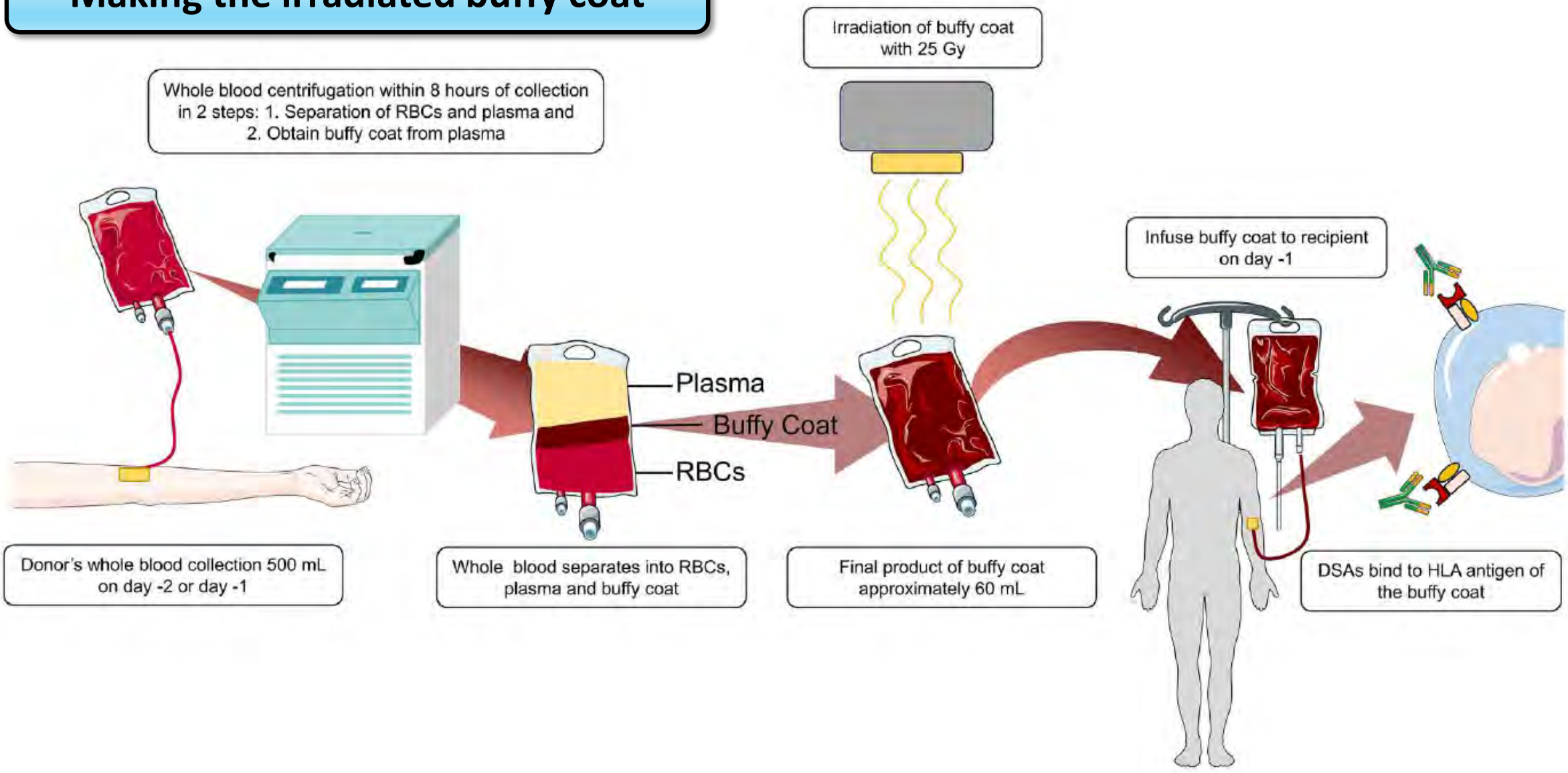
- 22 (+) DSA of 122 haploidentical transplants
  - **09/2005 – 09/2013**
- 12 of 22 → desensitization
  - 7 of 12 → TPE + Rituximab + IVIG
  - 5 of 12 → TPE + Rituximab + IVIG + **irradiated buffy coat infusions (from same HSC donor)**

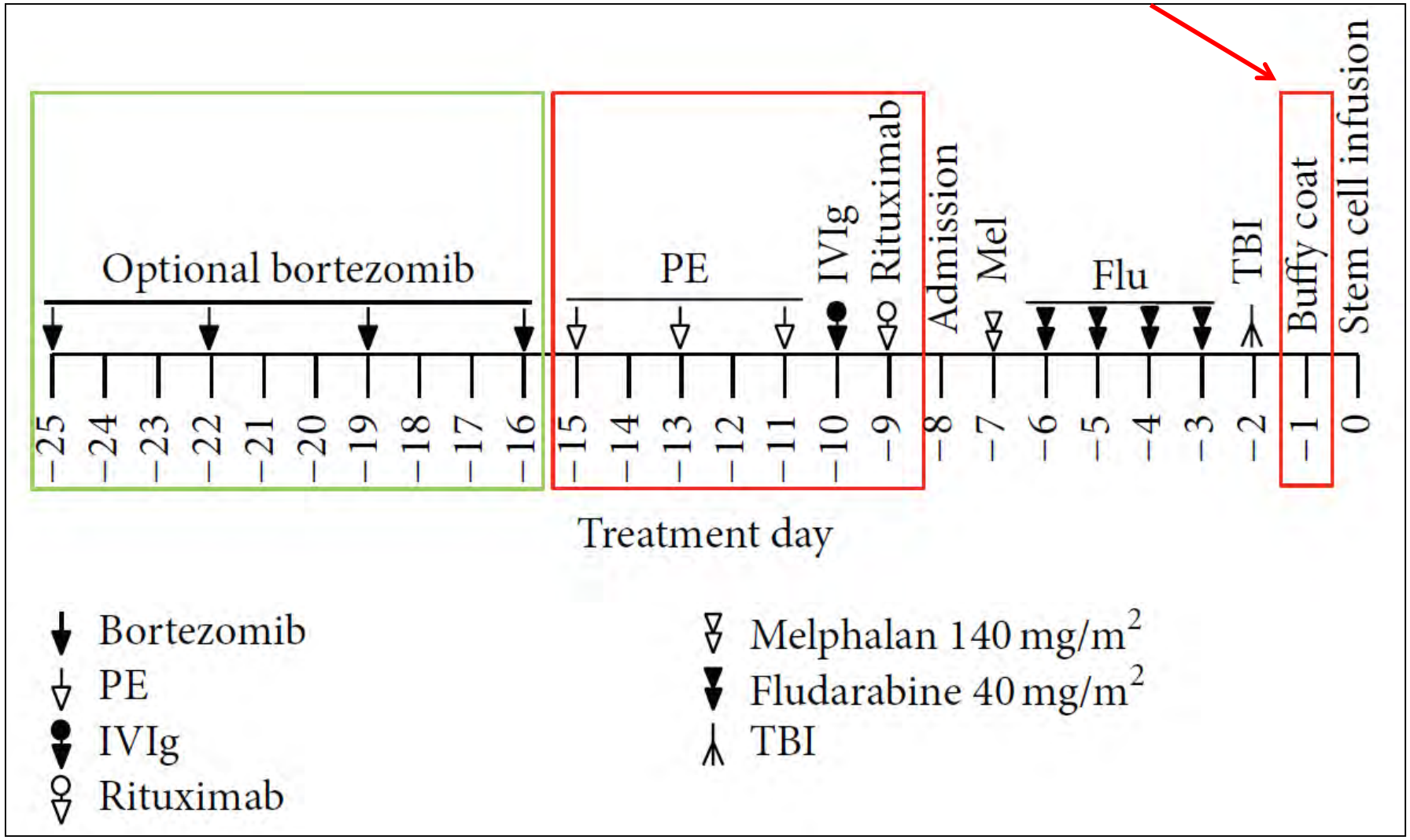
Ciurea SO, Thall PF, Milton DR, et al. Complement-Binding Donor-Specific Anti-HLA Antibodies and Risk of Primary Graft Failure in Hematopoietic Stem Cell Transplantation. *Biol Blood Marrow Transplan*t. 2015;21(8):1392-1398.

Making the irradiated buffy coat



Pongthep Vittayawacharin, Piyanuch Kongtim & Stefan O. Ciurea (2024) Future directions in haploidentical hematopoietic stem cell transplantation, Hematology, 29:1, 2366718, DOI: 10.1080/16078454.2024.2366718

5 of 12 got irradiated buffy coat infusions (from same donor) on Day (-1), collected from 500ml whole blood



Kongtim P, Cao K, Ciurea SO. Donor Specific Anti-HLA Antibody and Risk of Graft Failure in Haploidentical Stem Cell Transplantation. Adv Hematol. 2016;2016:4025073. doi: 10.1155/2016/4025073. Epub 2016 Jan 24. PMID: 26904122; PMCID: PMC4745275.

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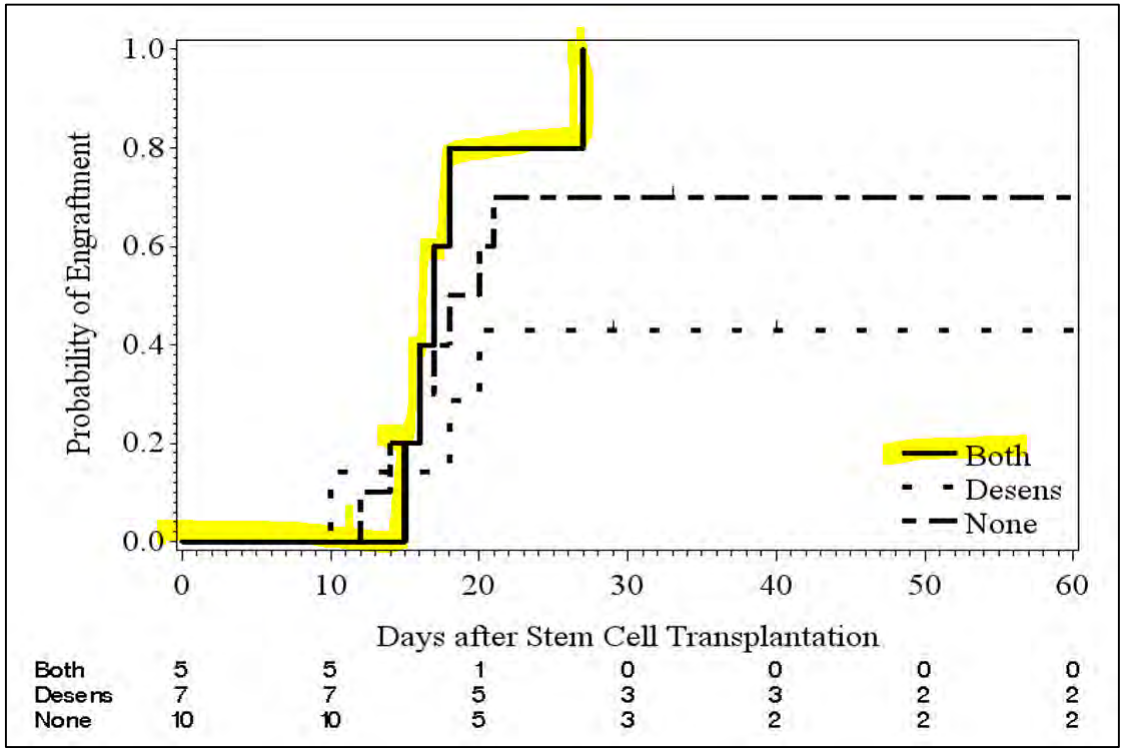
Desensitization **with buffy coat appeared to give better chance and rate of engraftment** (compared to without buffy coat)

Table 2
Associations between GF, C1q Status, and Treatment

Covariate	GF		Fisher's Exact Test *P*
	Yes (n = 7)	No (n = 15)	
C1q at transplant, n (%)			.0003
Positive	5 (100)	0	
Negative	1 (6)	15 (94)	
Nonassessable	1	0	
DSA levels at transplant, n (%)			.0039
>5000	7 (64)	4 (36)	
≤5000	0	11 (100)	
Treatment, n (%)			.14
None	3 (30)	7 (70)	
Desensitization alone	4 (57)	3 (43)	
Desensitization with buffy coat	0	5 (100)	

GF indicates graft failure; DSA, donor-specific anti-HLA antibodies.



REGULAR ARTICLE

blood advances

Treatment of allosensitized patients receiving allogeneic transplantation

Stefan O. Ciurea,[1,2,*] Monzr M. Al Malki,[3,*] Piyanuch Kongtim,[2] Jun Zou,[4] Fleur M. Aung,[4] Gabriela Rondon,[1] Julianne Chen,[1] Michiko Taniguchi,[5] Salman Otoukesh,[3] Auayporn Nademanee,[3] Stephen J. Forman,[3] Richard Champlin,[1] Ketevan Gendzekhadze,[5,†] and Kai Cao[4,†]

[1]Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Hematopoietic Cell Transplantation and Cellular Therapy Program, Division of Hematology-Oncology, The University of California Irvine, Irvine, CA; [3]Department of Hematology and Hematopoietic Cell Transplantation, City of Hope, Duarte, CA; [4]Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX; and [5]HLA Laboratory, City of Hope, Duarte, CA

- 37 (+) DSA, (+) desensitization, haploidentical transplants patients
  - 27 from MD Anderson (UTMDACC); 10 from City of Hope (COH)
  - From **11/2010 – 01/2019**
- Desensitization = IVIG + Rituximab + TPE
  - → 27 of 37 (73%) also **had irradiated donor buffy coat infusion (Day -1)**
- 345 control patients (no DSA) from UTMDACC from same time period for comparison

Ciurea SO, Al Malki MM, Kongtim P, Zou J, Aung FM, Rondon G, Chen J, Taniguchi M, Otoukesh S, Nademanee A, Forman SJ, Champlin R, Gendzekhadze K, Cao K. Treatment of allosensitized patients receiving allogeneic transplantation. Blood Adv. 2021 Oct 26;5(20):4031-4043. doi: 10.1182/bloodadvances.2021004862. PMID: 34474478; PMCID: PMC8945639.

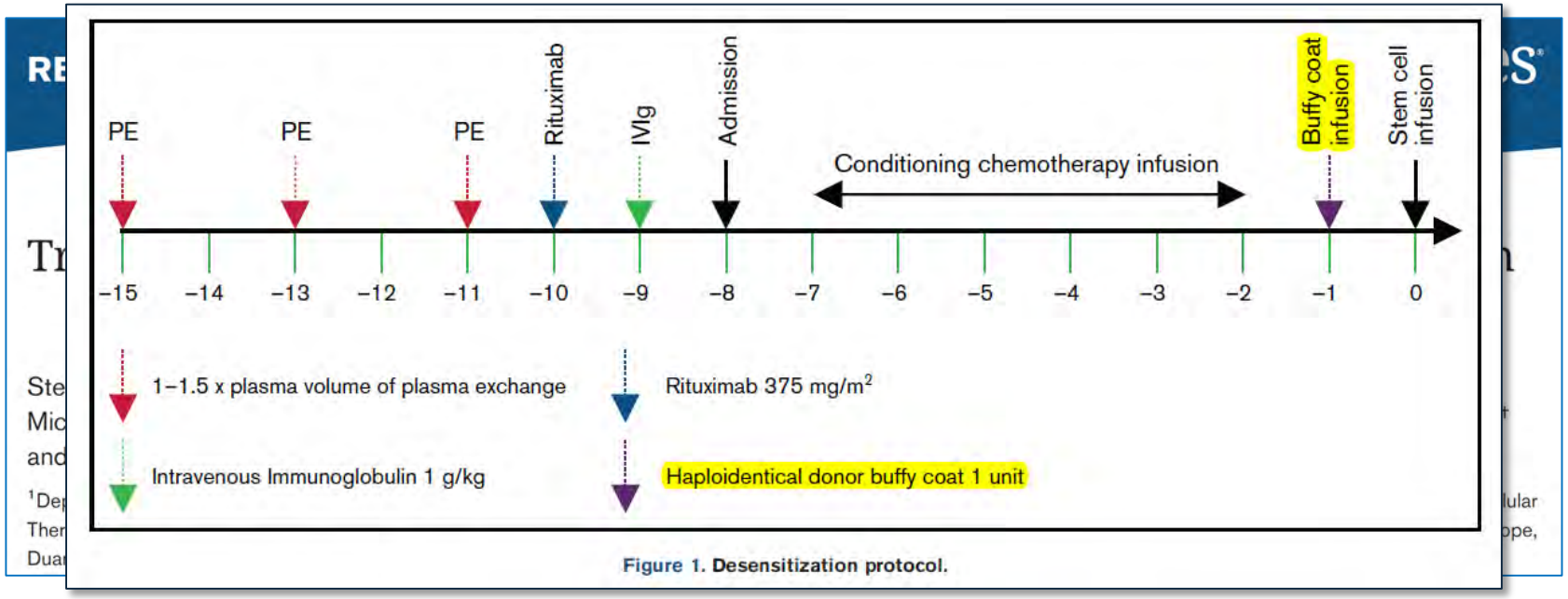


Figure 1. Desensitization protocol.

- 37 (+) DSA, (+) desensitization, haploidentical transplants patients
  - 27 from MD Anderson (UTMDACC); 10 from City of Hope (COH)
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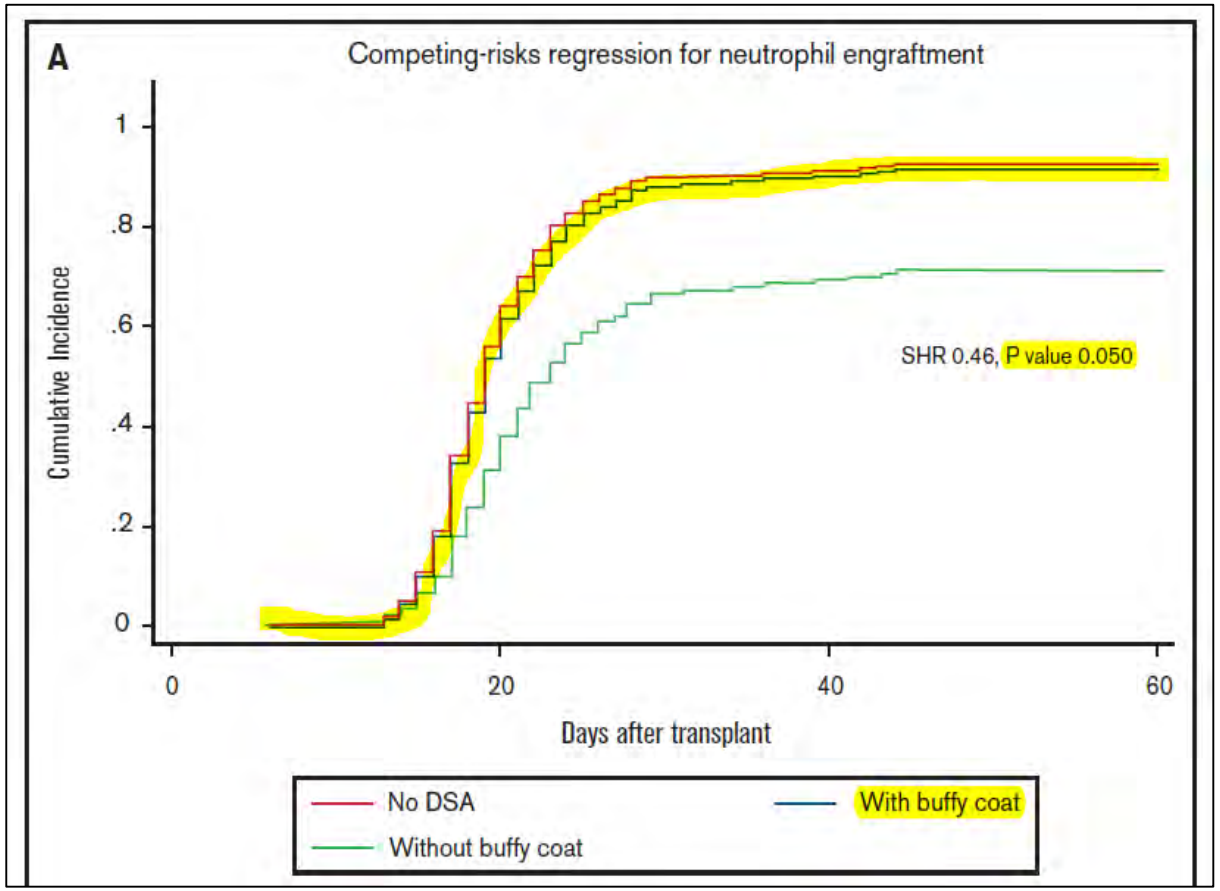

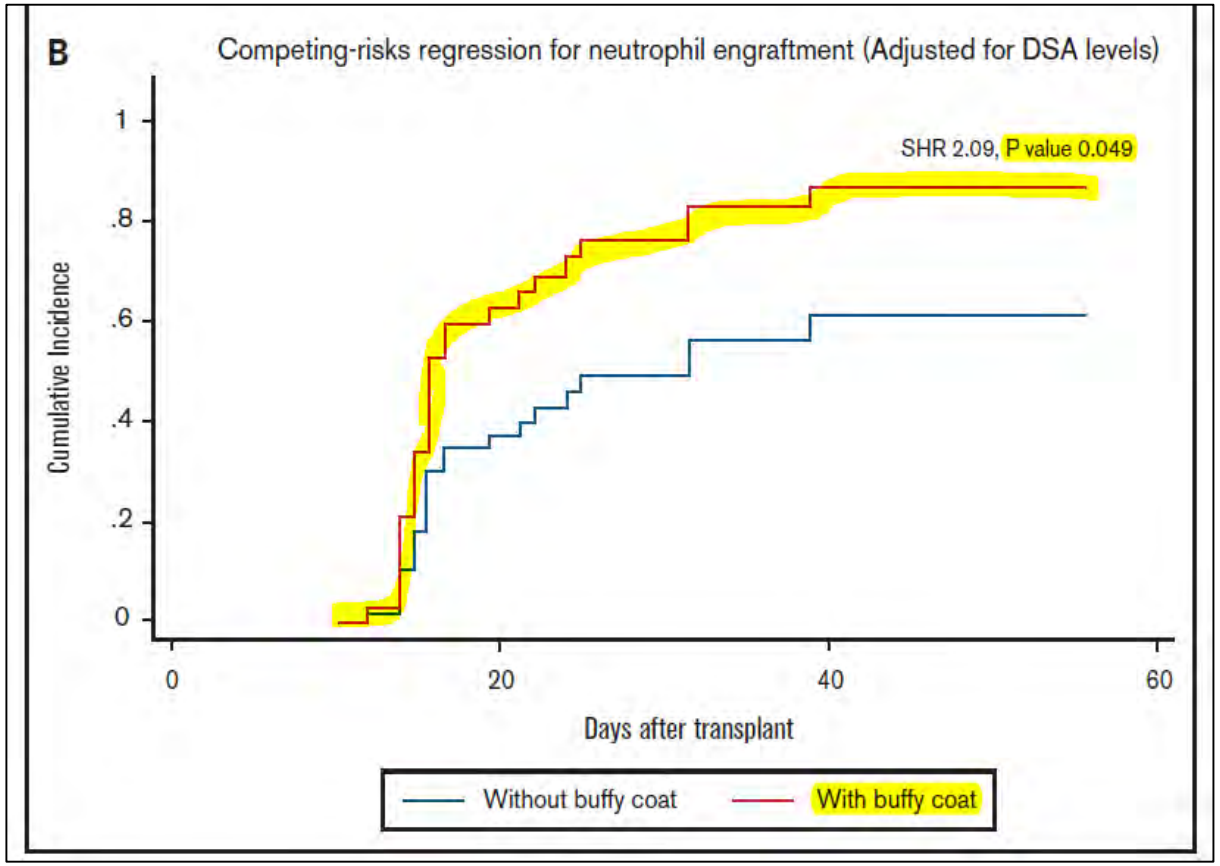

- **Now had statistical significance** for effect of **desensitization + buffy coat** on:
  1. Rate of neutrophil engraftment (speed), and
  2. Chance of neutrophil engraftment (%)
- Desens. **(+) buffy coat** → comparable engraftment to pts with (-) DSA
- Desens. **(-) buffy coat** → worse outcomes, even when adjusted for DSA levels

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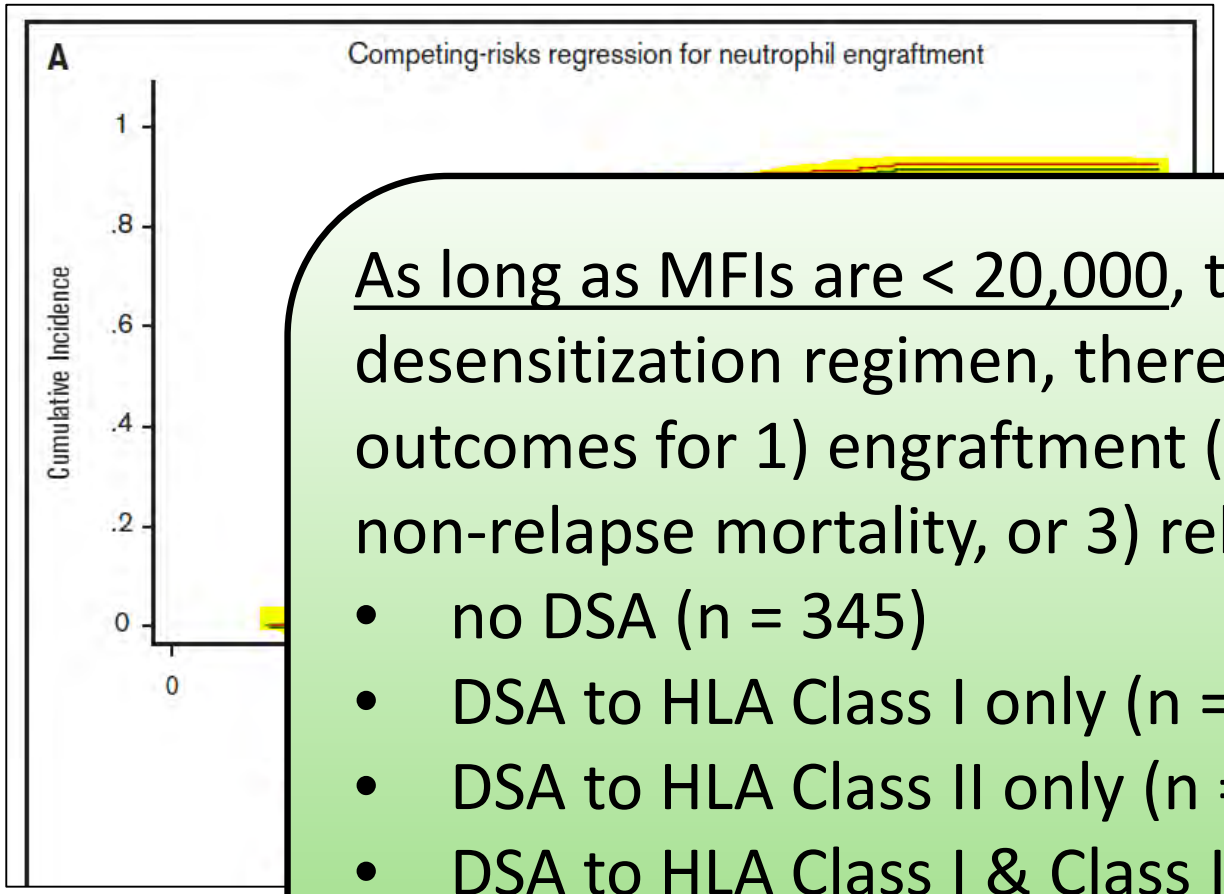

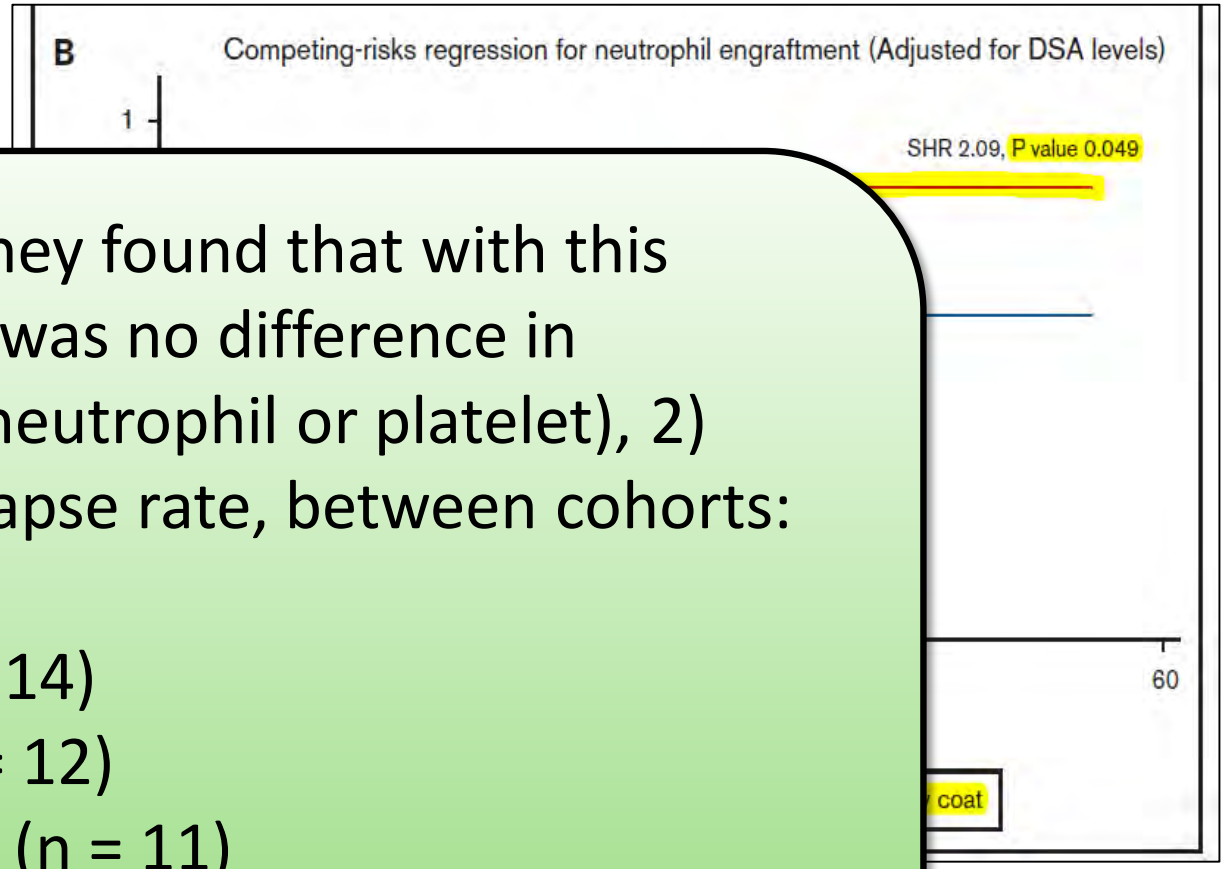

As long as MFIs are < 20,000, they found that with this desensitization regimen, there was no difference in outcomes for 1) engraftment (neutrophil or platelet), 2) non-relapse mortality, or 3) relapse rate, between cohorts:

- no DSA (n = 345)
- DSA to HLA Class I only (n = 14)
- DSA to HLA Class II only (n = 12)
- DSA to HLA Class I & Class II (n = 11)

→ Inference that buffy coat desensitization is effective with both Class I and/or II DSA

- **Now h** **oat** on:
  1. Ra
  2. Cha
- Desens. **(+) buffy coat** → comparable engraftment to pts with (-) DSA
- Desens. **(-) buffy coat** → worse outcomes, even when adjusted for DSA levels

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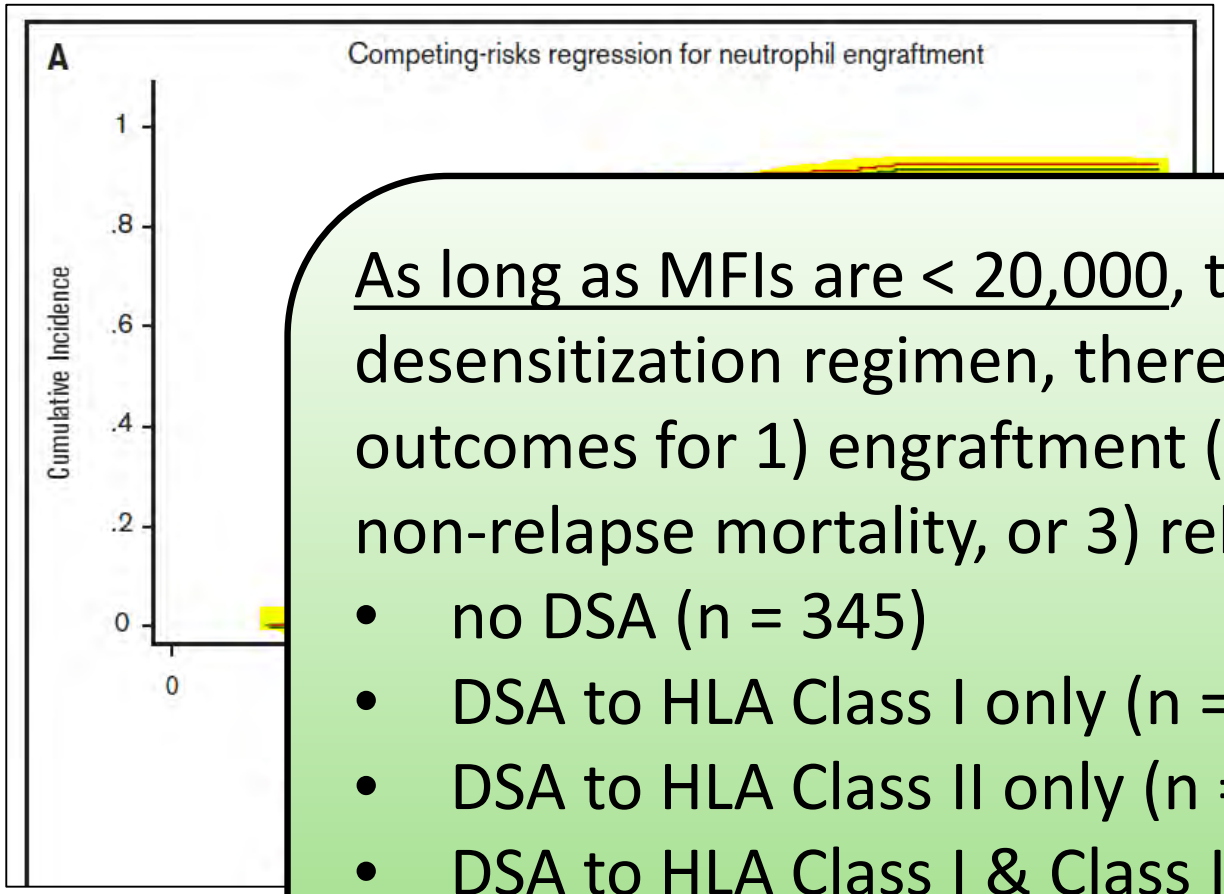

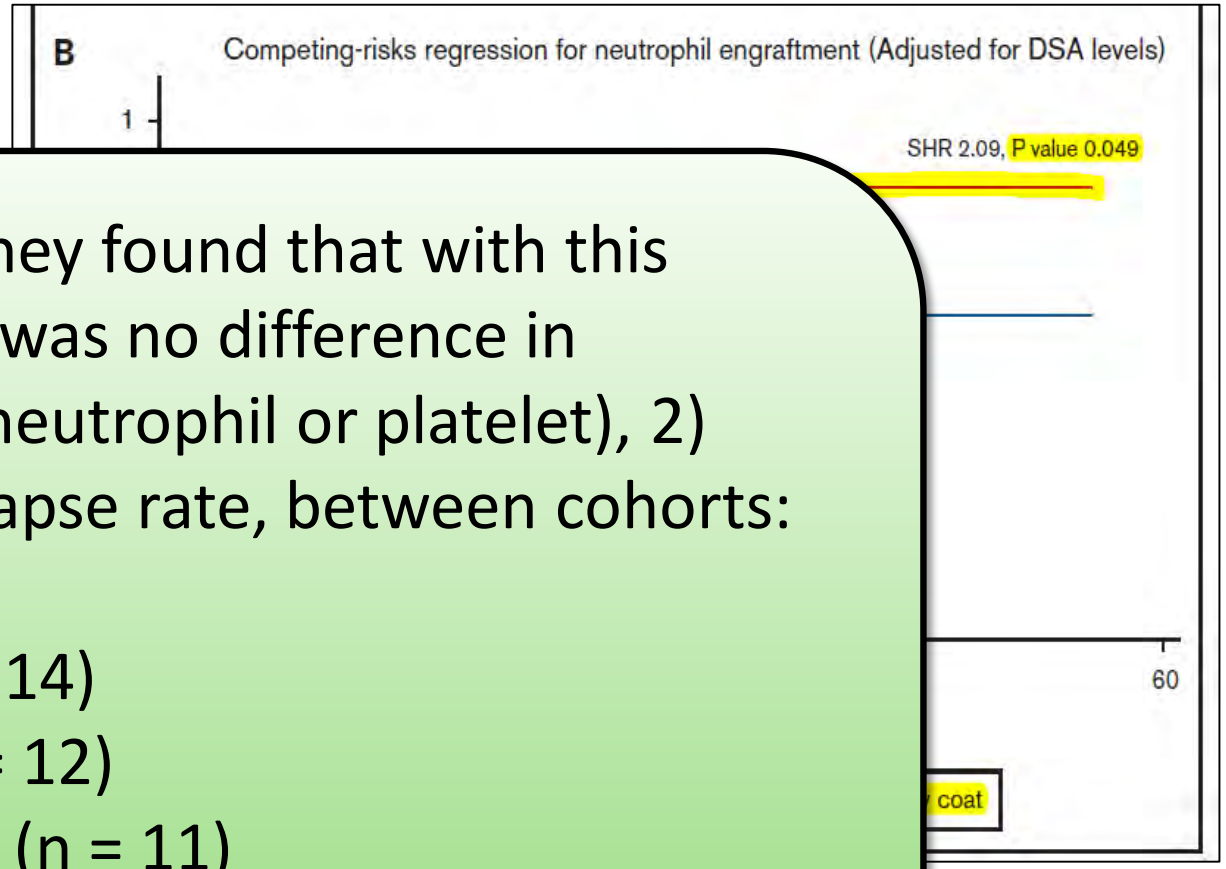

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- **Now h** **oat** on:
  1. Ra
  2. Cha
- Desens. **(+) buffy coat** → comparable outcomes to pts w/o DSA
- Desens. **(-) buffy coat** → worse outcomes, even when adjusted for DSA levels

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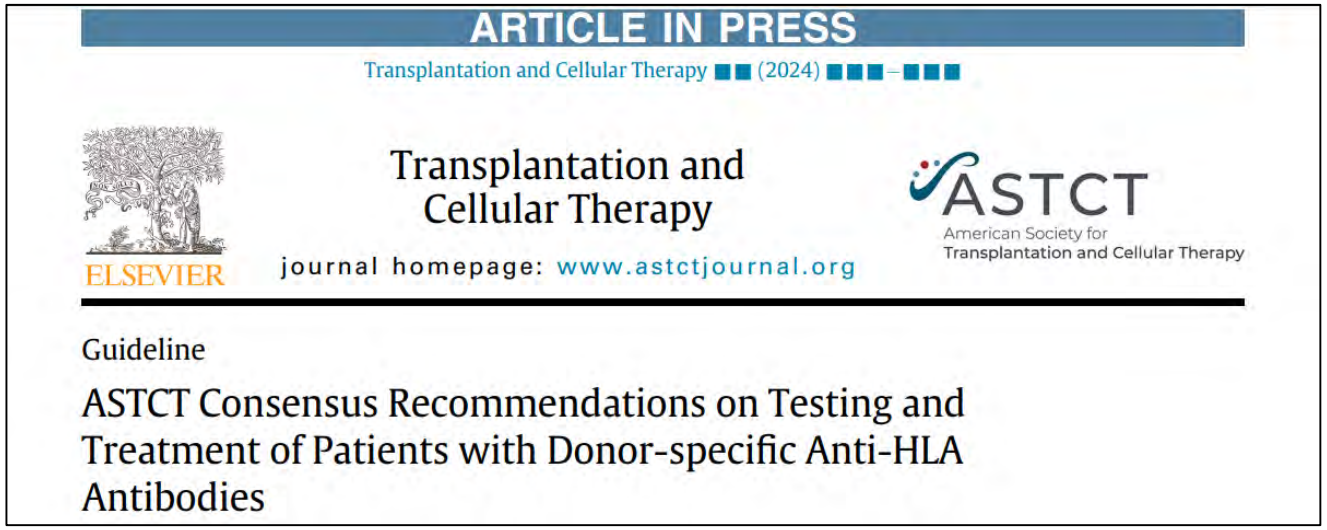

10.1 – Regarding Desensitization

For DSA < 20,000 MFI, recommend combination of:

1. Plasmapheresis
2. Rituximab (anti-CD20)
3. IVIG
4. **Infusion of donor-derived HLA**
   - **Platelets (for HLA Class I only DSA)**
   - **Irradiated buffy coat (for HLA Class I and/or II DSA)**

10.1. Summary and Recommendations

- *Multimodality pretransplant desensitization should be used to decrease DSA (Figure 1):*
  - *For DSA up to 20,000 MFI, plasmapheresis, rituximab, IVIG and infusion of donor-derived HLA antigen (either irradiated buffy coat for the corresponding HLA class I and II or platelet transfusions for corresponding HLA class I only) are recommended.*
  - *For DSA >20,000 MFI, patients may require antibody titration (due to bead saturation), and an alternative donor without corresponding HLA should be selected, or else should be treated using an investigational approach.*
  - *For DSA 2,000-10,000 MFI in haploidentical HSCT or 1,000- 10,000 MFI in CBT, additional data are needed to determine that patients with these lower DSA levels can be treated with a lower intensity desensitization protocol, such as rituximab with IVIG.*

Kongtim P, Vittayawacharin P, Zou J, Srour S, Shaffer B, Shapiro RM, Varma A, McGuirk J, Dholaria BR, McCurdy SR, DeZern AE, Bejanyan N, Bashey A, Furst S, Castagna L, Mariotti J, Ruggeri A, Bailen R, Teshima T, Xiao-Jun H, Bonfim C, Aung F, Cao K, Carpenter PA, Hamadani M, Askar M, Fernandez-Vina M, Girnita A, Ciurea SO. ASTCT Consensus Recommendations on Testing and Treatment of Patients with Donor-specific Anti-HLA Antibodies. Transplant Cell Ther. 2024 Sep 10:S2666-6367(24)00654-7. doi: 10.1016/j.jtct.2024.09.005. Epub ahead of print. PMID: 39260570.

Take Home Points

1. Patient can make DSAs against mismatched donor HLA antigens
2. DSAs have a detrimental effect on HSC transplant outcomes
3. Transfusion of HLA-typed cellular products as (part of) desensitization strategy to decrease DSA levels via *in vivo* adsorption
4. The latest **2024 ASTCT consensus statement recommends including infusion of donor-derived HLA (platelets or WBCs) in desensitization regimens when DSAs < 20,000 MFI.** This can affect:
    a. Transfusion medicine services
    b. Cellular therapy lab services (especially if WBCs are cryopreserved)

UC San Diego Health

Thank you for your time

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