Transfusion Management of Sickle Cell Disease

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14th Pan Arab Conference, Doha, Qatar
November 30, 2024

Disclosures

- Advisory panel, Pfizer

Objectives

Discuss red cell therapy and alloimmunization risk in SCD

Discuss the role of molecular testing for transfusion support

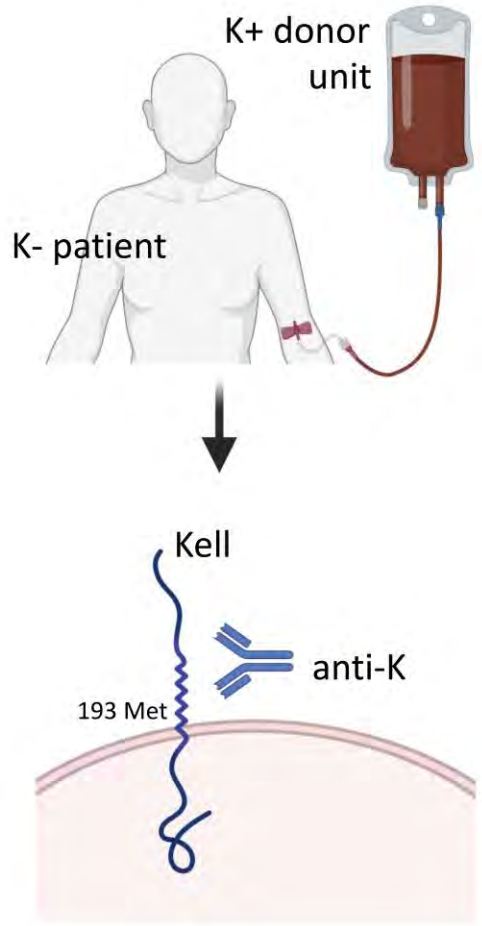
Discuss management of patient who are challenging to transfuse

Red cell therapy for sickle cell disease

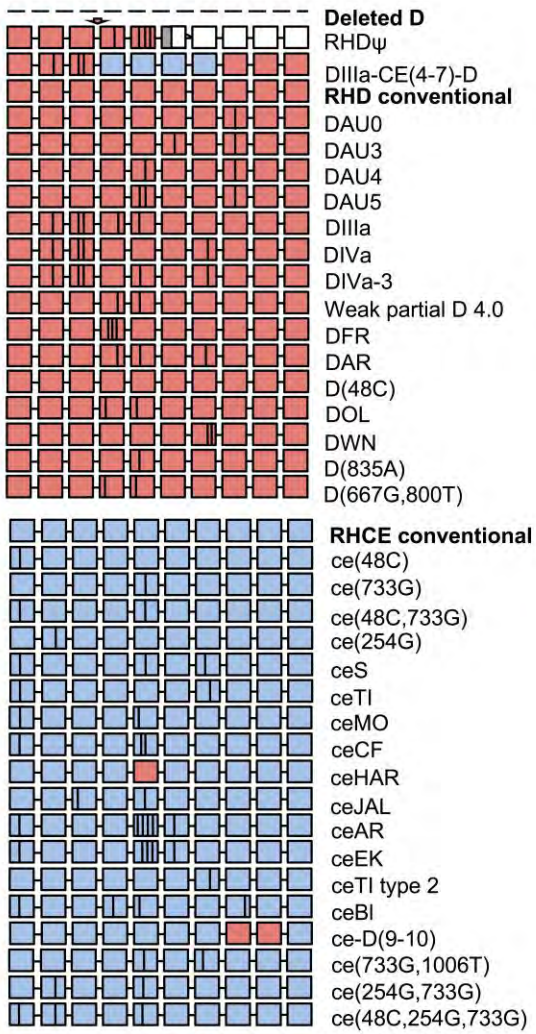
- Remains a major therapeutic option
  - Prevention of stroke most common indication for chronic RBC therapy
  - Pre-requisite for curative therapy
  - Supportive care for HSCT
- Alloimmunization remains a frequent complication, posing unique challenges to:
  - Identify sufficient red cell units to support individuals with multiple antibodies
  - Support those with history of multiple DHTRs or hyperhemolysis

Alloimmunization risk factors

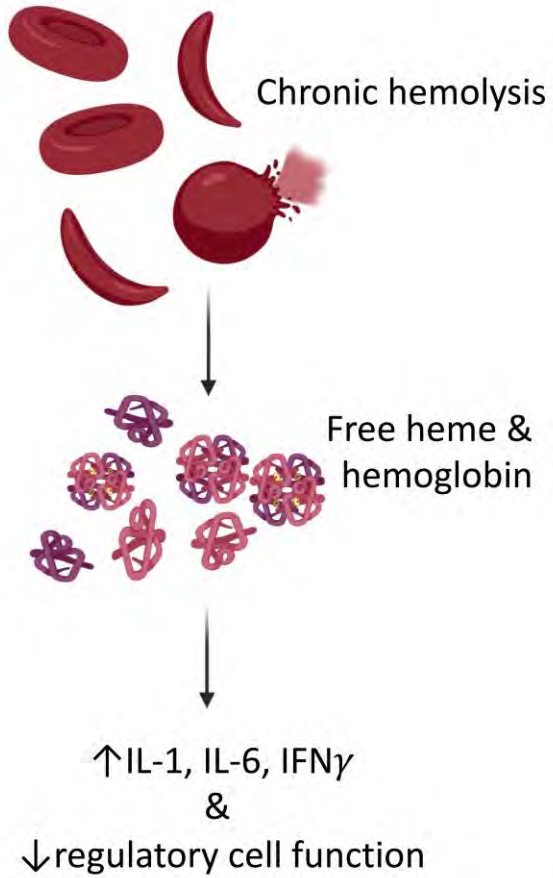
Recipient-donor red cell antigen mismatch



RH genetic diversity



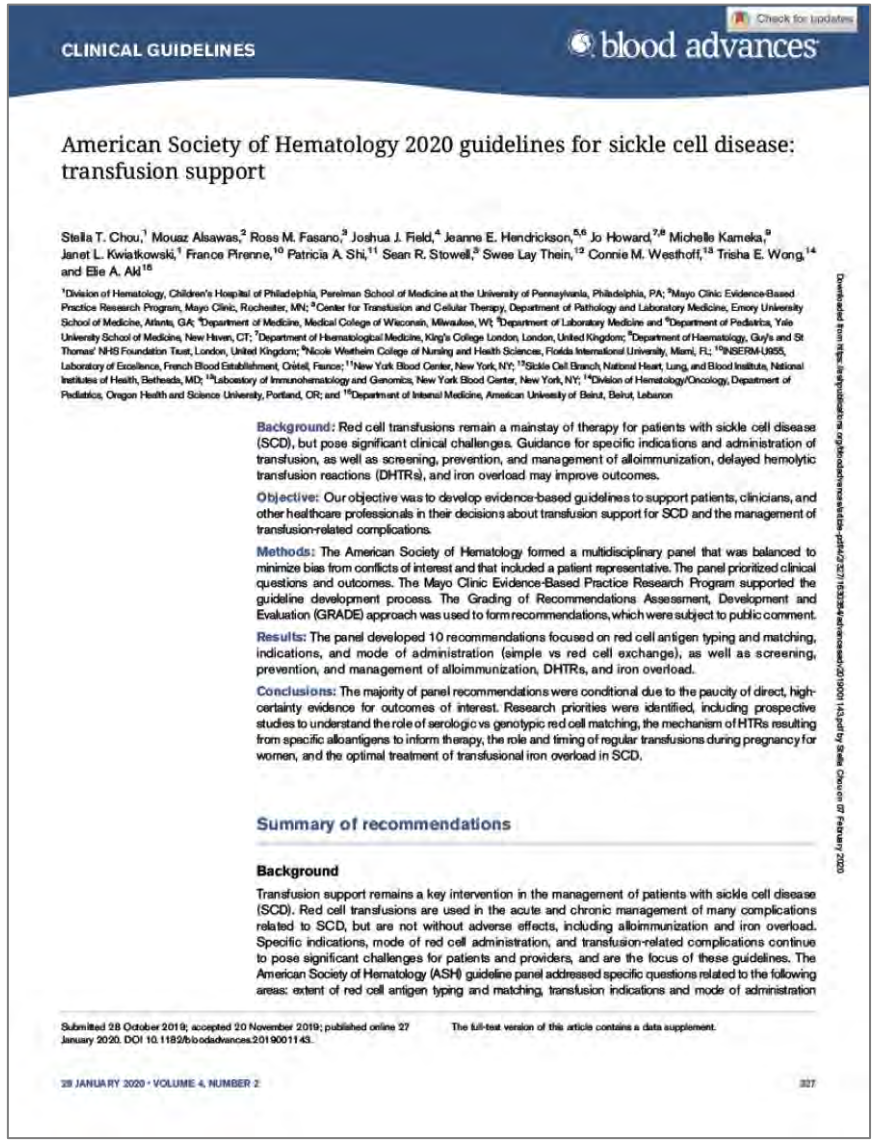
Chronic inflammation and immune system dysregulation



Linder & Chou Haematologica 2021

ASH CLINICAL PRACTICE GUIDELINES
SICKLE CELL DISEASE (SCD)

Prophylactic red cell antigen matching



CLINICAL GUIDELINES

blood advances

American Society of Hematology 2020 guidelines for sickle cell disease: transfusion support

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Background: Red cell transfusions remain a mainstay of therapy for patients with sickle cell disease (SCD), but pose significant clinical challenges. Guidance for specific indications and administration of transfusion, as well as screening, prevention, and management of alloimmunization, delayed hemolytic transfusion reactions (DHTRs), and iron overload may improve outcomes.

Objective: Our objective was to develop evidence-based guidelines to support patients, clinicians, and other healthcare professionals in their decisions about transfusion support for SCD and the management of transfusion-related complications.

Methods: The American Society of Hematology formed a multidisciplinary panel that was balanced to minimize bias from conflicts of interest and that included a patient representative. The panel prioritized clinical questions and outcomes. The Mayo Clinic Evidence-Based Practice Research Program supported the guideline development process. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to form recommendations, which were subject to public comment.

Results: The panel developed 10 recommendations focused on red cell antigen typing and matching, indications, and mode of administration (simple vs red cell exchange), as well as screening, prevention, and management of alloimmunization, DHTRs, and iron overload.

Conclusions: The majority of panel recommendations were conditional due to the paucity of direct, high-certainty evidence for outcomes of interest. Research priorities were identified, including prospective studies to understand the role of serologic vs genotypic red cell matching, the mechanism of HTRs resulting from specific alloantigens to inform therapy, the role and timing of regular transfusions during pregnancy for women, and the optimal treatment of transfusional iron overload in SCD.

Summary of recommendations

Background

Transfusion support remains a key intervention in the management of patients with sickle cell disease (SCD). Red cell transfusions are used in the acute and chronic management of many complications related to SCD, but are not without adverse effects, including alloimmunization and iron overload. Specific indications, mode of red cell administration, and transfusion-related complications continue to pose significant challenges for patients and providers, and are the focus of these guidelines. The American Society of Hematology (ASH) guideline panel addressed specific questions related to the following areas: extent of red cell antigen typing and matching, transfusion indications and mode of administration

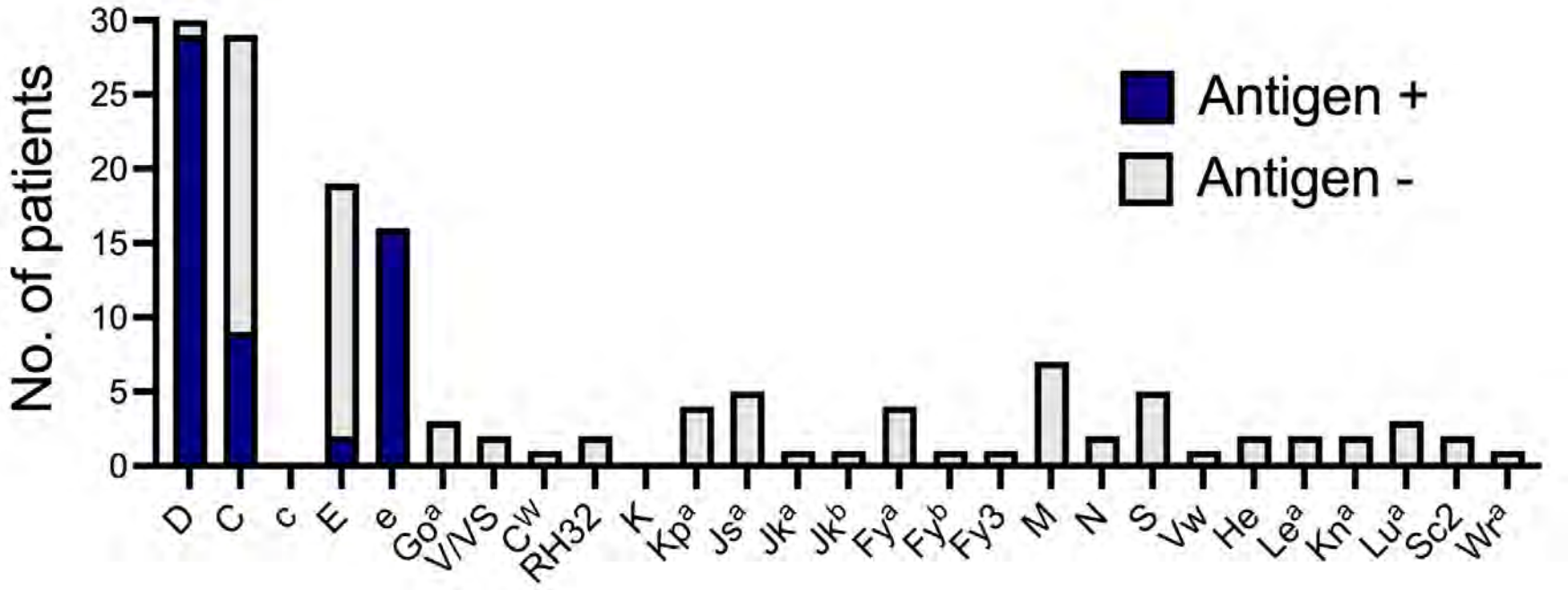
Submitted 28 October 2019; accepted 20 November 2019; published online 27 January 2020. DOI 10.1182/bloodadvances.2019001143.

The full-text version of this article contains a data supplement.

- Recommends prophylactic red cell antigen matching for Rh (C, E or C/c, E/e) and K antigens for all patients with SCD *(**strong** recommendation)*
- Single arm studies pooled showed significantly lower alloimmunization rate with Rh, K or extended matching:
  - ABO/D matched: **1** antibody per 50 units transfused
  - Rh (C/E or C/c, E/e) and K matched: **1** antibody per 250 units transfused

Chou Blood Advances 2020

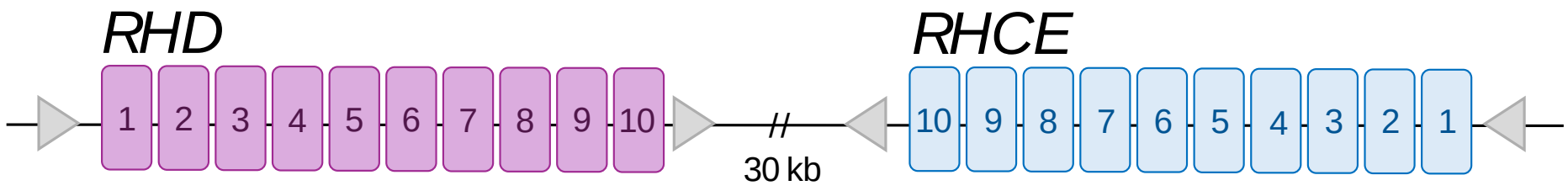
Rh alloimmunization despite prophylactic Rh and K matching from Black donors

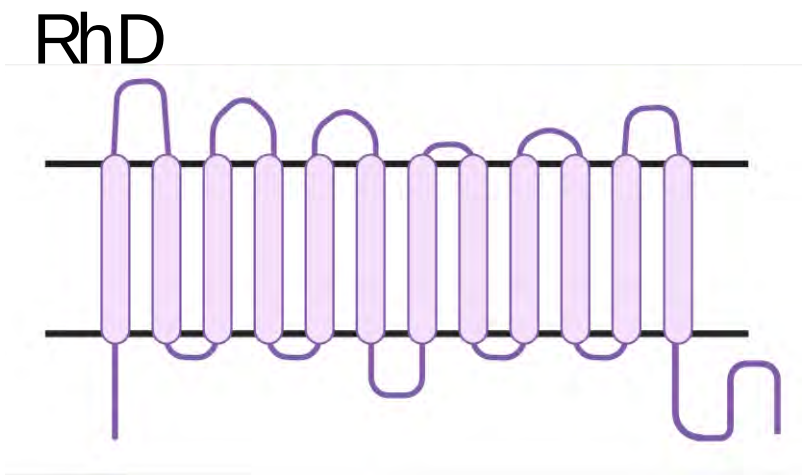


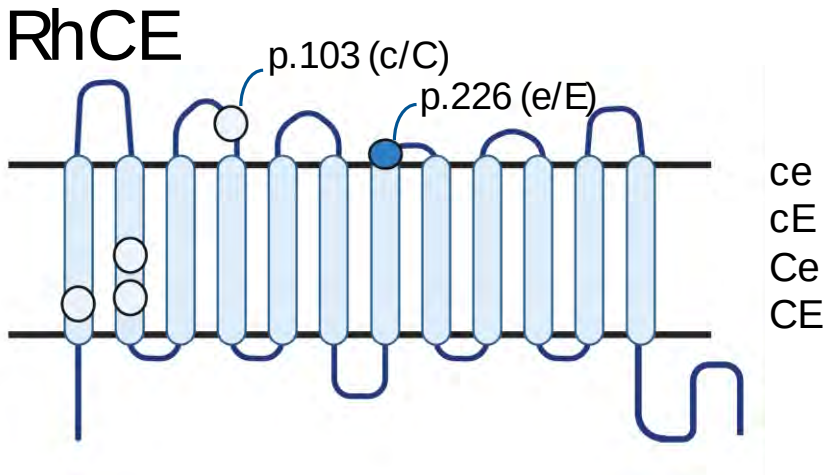
- Rh antibodies most common (66%)
- 30% of Rh antibodies attributed to patient's RH genotype
- Remainder "unexplained" –> Rh variants on donor red cells an underappreciated risk factor
- *RH* diversity in patients *and* donors of African descent contribute to Rh alloimmunization

Chou & Westhoff, Blood 2013

Rh blood group system: immunogenic and complex

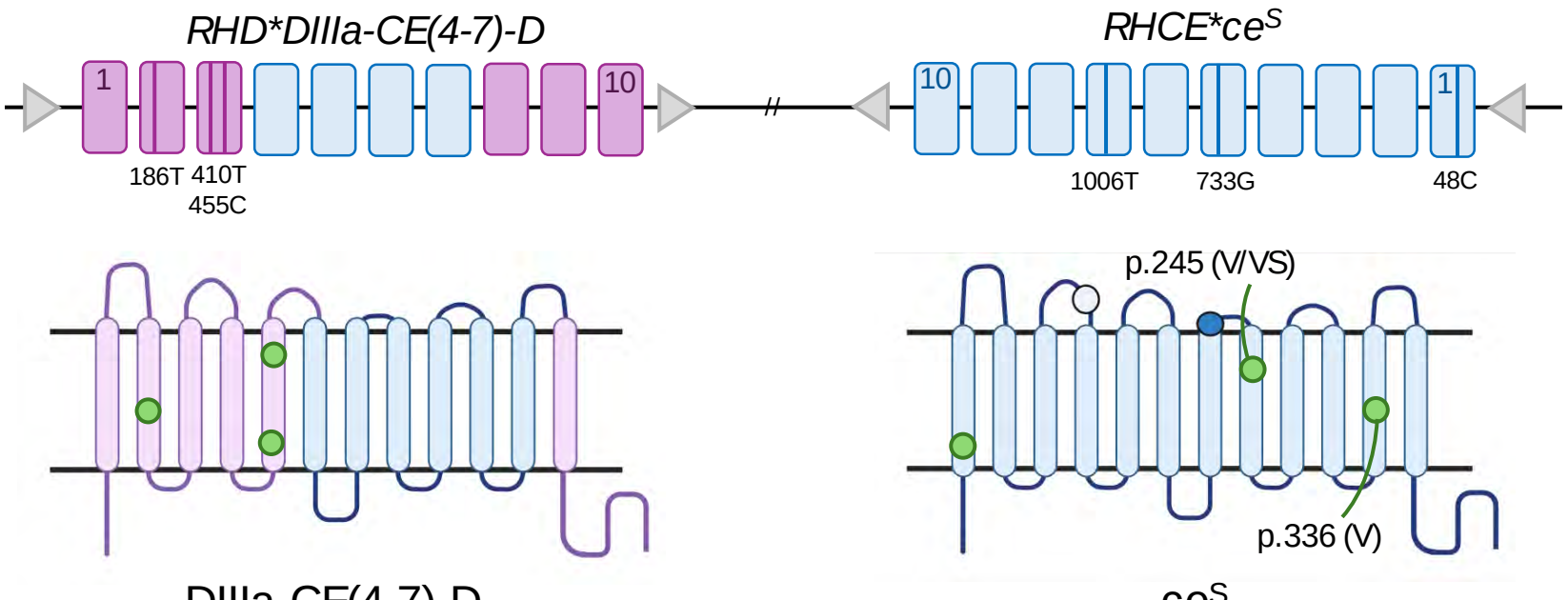






- Most immunogenic after ABO system
- Duplicated gene family – highly homologous
- Highly polymorphic with >500 *RHD* and >150 *RHCE* alleles reported

Rh variants are common in African Blacks



DIIIa-CE(4-7)-D

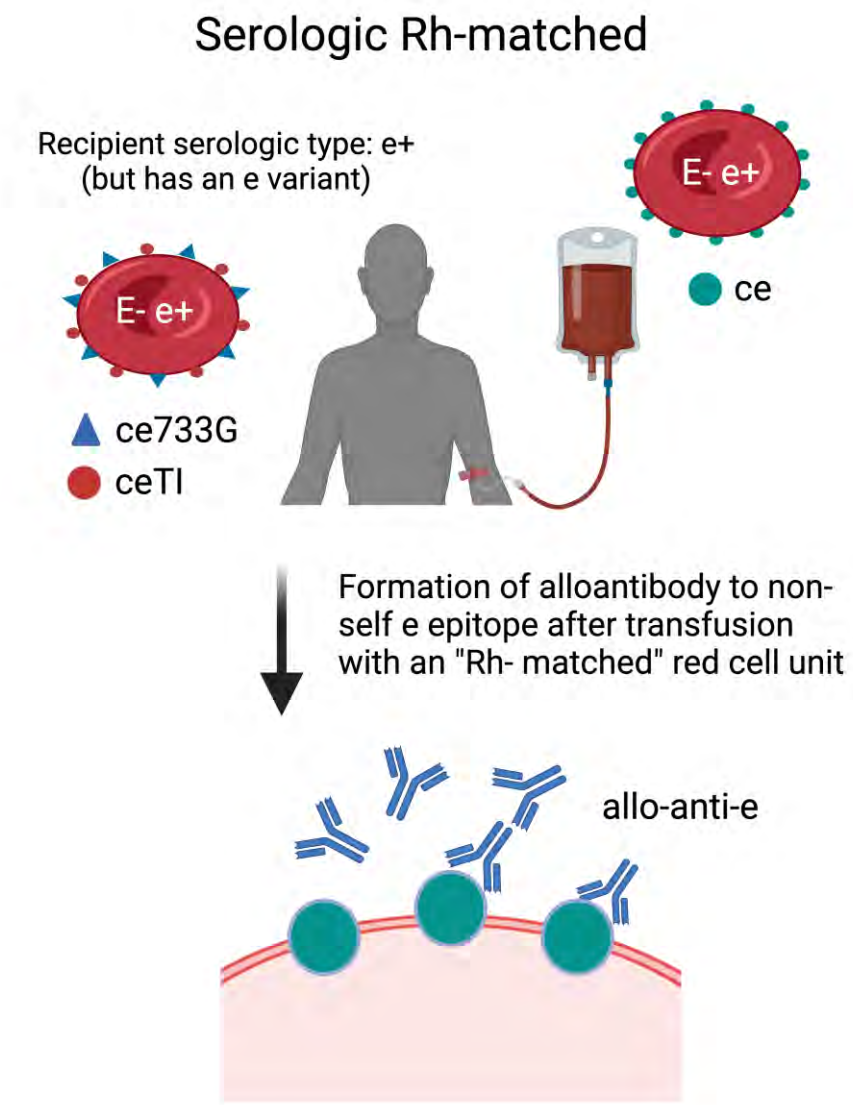
D-, partial C+

ceS

partial c+, E-, partial e+, Hr^B-, hr^B-, V+, VS+

- Variant alleles encode partial antigens, cause loss of high prevalence antigens and/or generate novel antigens
- *RH* variants occur in ~1% Europeans vs ~90% patients and donors of African descent

Rh alloimmunization despite “Rh-matched” RBCs



Chou & Hendrickson, Blood 2024

Rh alloimmunization in sickle cell disease

- Despite Rh (D, C, E) matching, Rh antibodies are the most common
  - *RH* diversity in ***patients and donors*** contributes to alloimmunization
  - Rh alloimmunization may lead to need for RBCs with rare or uncommon phenotypes
  - Prevention may be the best strategy

How can molecular testing improve transfusion management?

HEA profile

Blood Group	Antigen	Result	Comments
Rh	c	+	
	C	0	
	e	+	
	E	0	
	V	+	
	VS	+	
Kell	K	0	
	k	+	
	Kp^a	0	
	Kp^b	+	
	Js^a	0	
	Js^b	+	
Duffy	Fy^a	0	
	Fy^b	(0)*	Not at risk for anti-Fyb.
Kidd	Jk^a	0	
	Jk^b	+	
MNS	M	+	
	N	0	
	S	0	
	s	+	
	U	+	
Lutheran	Lu^a	0	
	Lu^b	+	
Diego	Di^a	0	
	Di^b	+	
Colton	Co^a	+	
	Co^b	0	
Dombrock	Do^a	+	
	Do^b	+	
	Hy	+	
	Jo^a	+	
Landsteiner-Wiener	LW^a	+	
	LW^b	0	
Scianna	Sc1	+	
	Sc2	0	

Red cell antigen genotype

- Genotype predicted extended red cell antigen (HEA) profile performed at first visit
- Used to guide prophylactic Rh (C, E or C/c, E/e) and K matched transfusions
- Informs antibody evaluation when a patient has a new positive antibody test

Comprehensive RH genotype

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SAMPLE: [redacted]

Date received: 06/06/2024
Sample Date: 05/29/2024

HISTORY: African American female. Sickle cell disease. No history of transfusion. Group A positive. No additional RBC phenotype information.

TESTING REQUESTED: CHOP study protocol

DNA TESTING PERFORMED: PreciseType Human Erythrocyte Antigen 1.2 BeadChip DNA *RHD:* Automated RHD BeadChip. Zygosity determination by hybrid Rhesus box detection (associated with *RHD deletion*). Sequencing of *RHD* exons 7 and 8 (to investigate for *RHD*DAU*). *RHCE*: Automated RHCE BeadChip. Sequencing of *RHCE* exon 2 (to investigate for *RHCE*ce254G*).

Human Erythrocyte Antigen Predicted Phenotypes: See page 2.

FY COMMENTS: The sample has the GATA mutation which disrupts the binding site for the erythroid GATA-1 transcription factor resulting in loss of Fy^b expression on the RBCs. Fy^b expression on tissue endothelium is not affected and these individuals would not be expected to make anti-Fy^b.

RH RESULTS: RHD BeadChip: No variants. Hybrid Rhesus box: Negative; however, this marker is discordant for RHD zygosity in samples with *RHCE*ce254G*. *RHD* Sequencing: No variants. RHCE BeadChip: c.48G/C (p.16Trp/Cys), c.733C/G (p.245Leu/Val). *RHCE* Sequencing: c.254C/G (p.85Ala/Gly).

RHD	*RHCE*ce48C 733G*
Deleted *RHD*	*RHCE*ce(254G)*

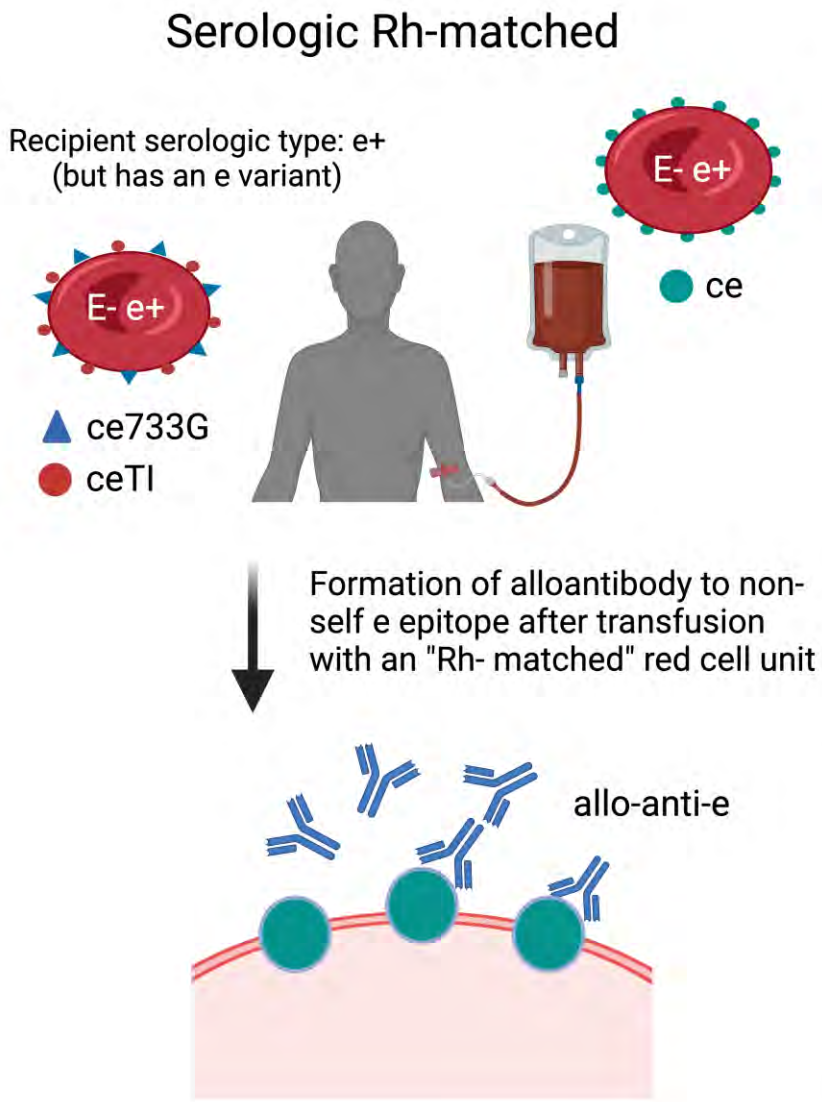
RH alleles

- *RHD* hemizygote, with no changes associated with commonly reported partial D or weak D.
- *RHCE*ce(48C, 733G)* encodes amino acids p.16Cys and p.245Val associated with partial c, partial e, and a V+VS+, hr^B– phenotype.
- *RHCE*ce(254G)* encodes amino acid p.85Gly associated with partial c, partial e, and a hr^B–/$+^w$ CEAG– phenotype

Predicted Rh Phenotype: D+, C– E– c+(partial), e+(partial), V+VS+, hr^B–/$+^w$, hr^S+

- Comprehensive *RH* allele identification for all patients with SCD
- ”High risk” *RH* variants → prophylactic antigen (-) RBCs
  - Patients with alleles encoding partial C
  - Patients with *RHD* alleles encoding partial D

Genotype *RH* matched RBCs for Rh-immunized



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Approach to “difficult to transfuse”

Multiple or severe DHTR w/o ab specificity?

Consider transfusion trial with laboratory monitoring

Consider immunosuppression

Multiple or unexplained Rh antibodies?

Consider comprehensive *RH* genotype

Consider extended matched RBCs

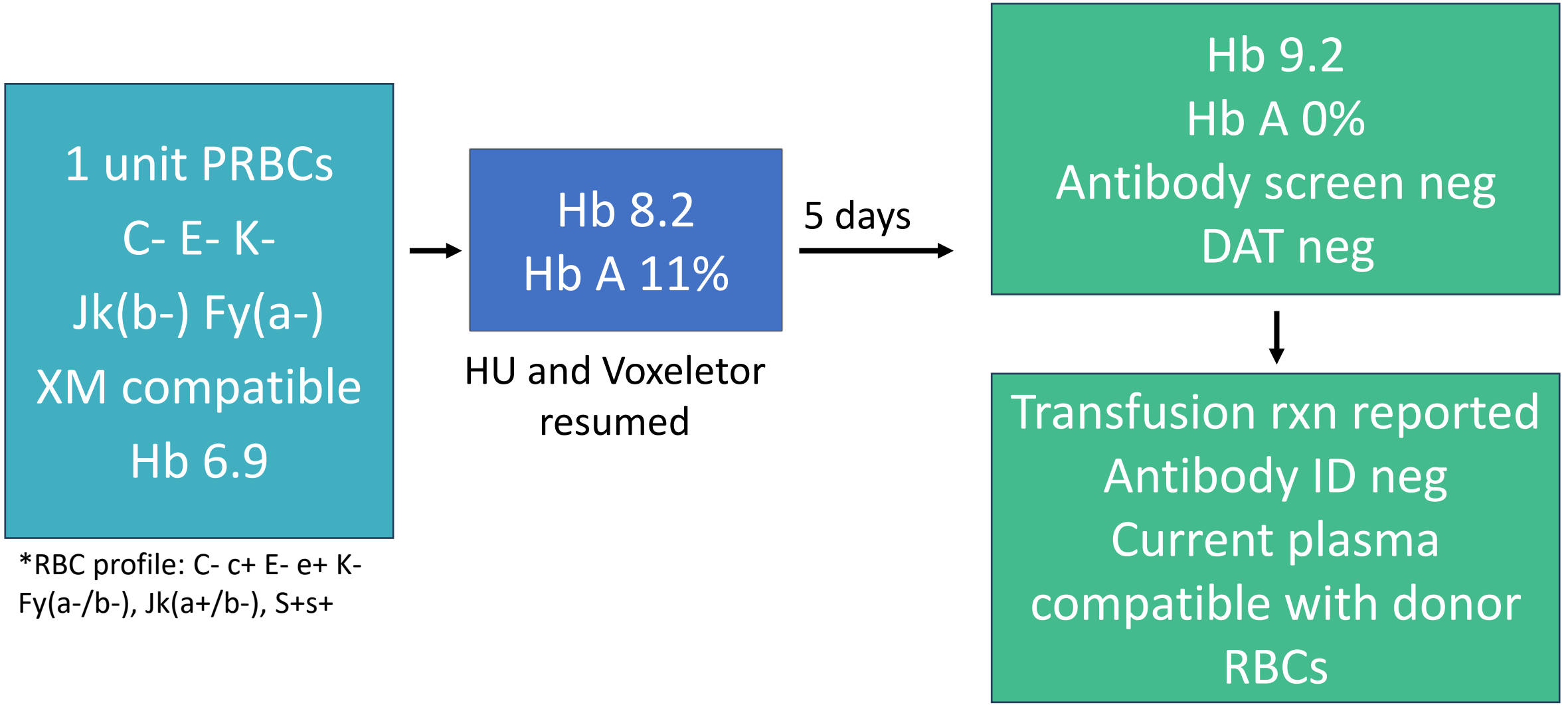
Rh alloimmunized +/- partial Rh antigens?

Consider *RH* genotype matched RBCs

Case 1: “Difficult to transfuse”

- 34 yo male with SCD-SS with h/o multiple DHTRs, seeking gene therapy
  - History of “difficult to transfuse” with multiple DHTRs
  - Known anti-C, -Jk^b, -Fy^a
  - Antigen profile: C- c+ E- e+ K- Jk(a+b-) Fy(a-b-) M+ N- S+ s+
  - *RH* genotype: *RHD-ce; RHD-ce48C*
- Most recent DHTR ~20 months prior
  - Had been transfused C-, E-, K-, Jk(b-), Fy(a-) units compatible in gel
  - Transfusion reaction reported but the antibody screen on pre- and post-transfusion sample negative
  - No antibodies detected in patient’s serum by reacting with a panel of reagent red blood cells

Transfusion trial



*RBC profile: C- c+ E- e+ K- Fy(a-/b-), Jk(a+/b-), S+s+

Treatment and prevention of DHTRs and further alloimmunization

Drug	Dose	Rationale
Recombinant human erythropoietin (EPO)	150 units/kg/d (max 20,000 units/day)	Stimulates erythropoiesis
Intravenous iron	Multiple preparations	Assists with erythropoiesis; may help improve response to EPO
Steroids	1-4 g/kg/d, once daily or divided (max 60 mg/dose) with taper thereafter	Anti-inflammatory
IVIg	0.4-1 g/kg/d (for up to 3-5 days, max cumulative total dose 2 g/kg)	May decrease RBC clearance
Eculizumab	900-1200 mg (if ≥40 kg) or 600 mg (if 10-40 kg); typically, once	Blocks the C5 convertase and decreases complement
Tocilizumab	8 mg/kg/d (max 800 mg/dose), up to 4 days	Blocks the IL-6 receptor and decreases macrophage activation
Rituximab	375 mg/m^2 (max 1000 mg); 2-4 doses over a month	Depletes CD20 expressing B-cells to prevent antibodies of new specificities from being formed

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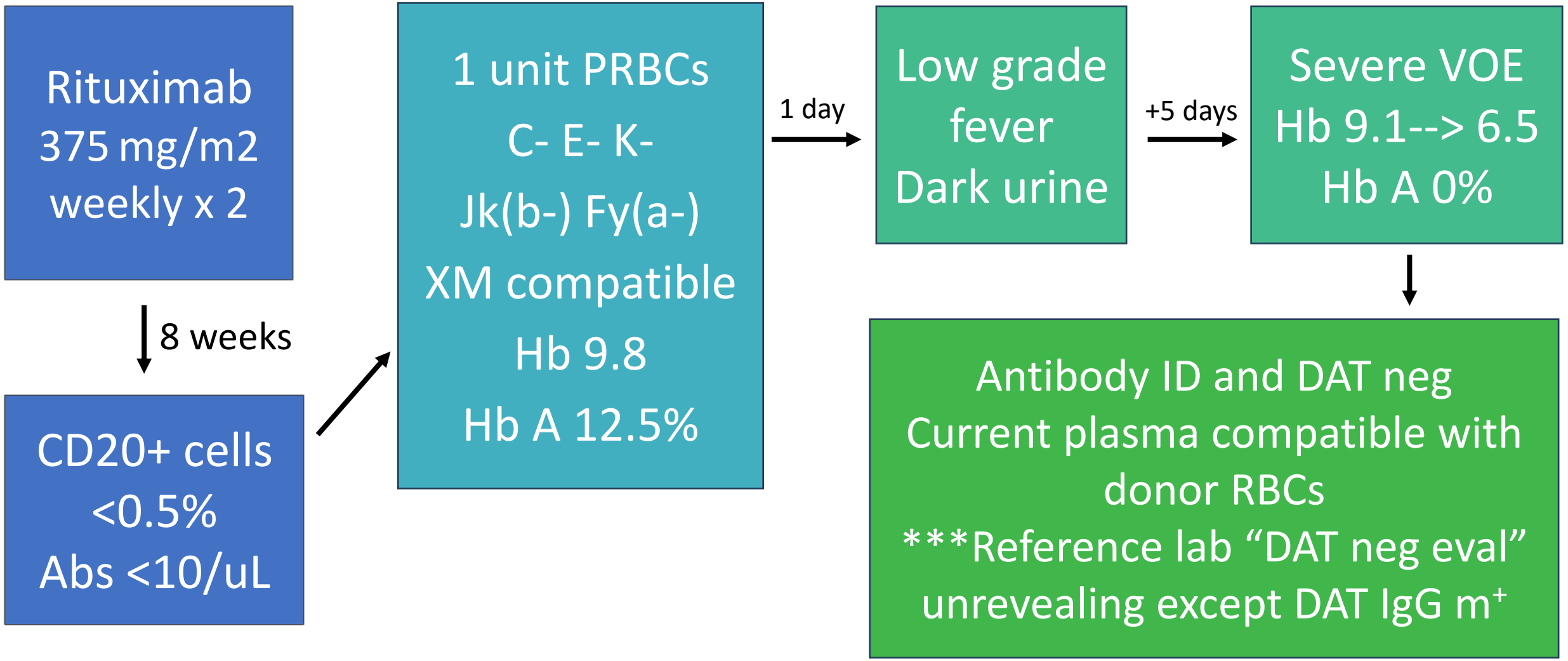
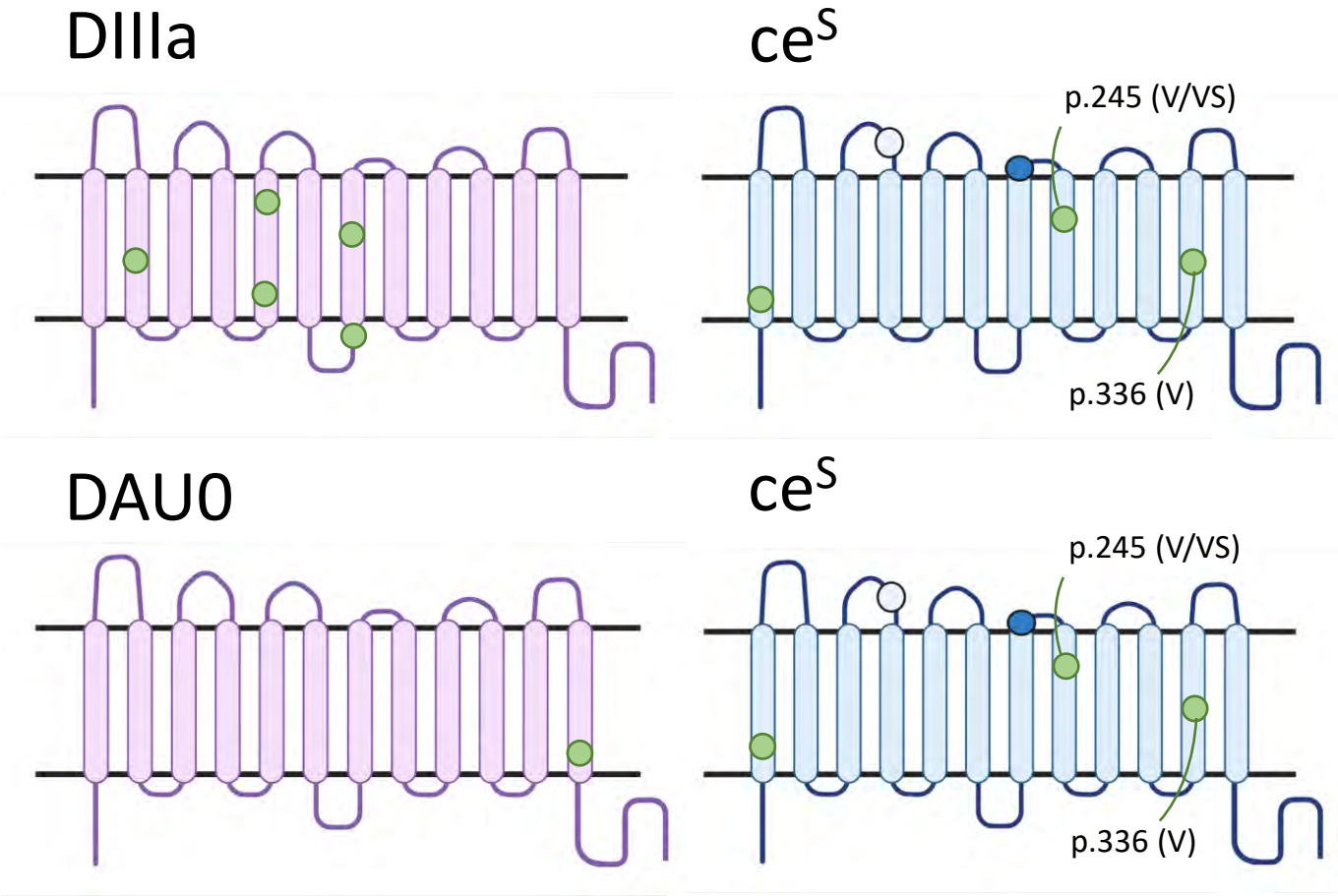
Transfusion trial following immunosuppression



Case 2: “No blood donors”

- 12 yo SCD-SS and autoimmune hepatitis with recurrent splenic sequestration and severe anemia; Hb 4 gm/dL from baseline 7-7.5
  - Difficult to match: anti-C, -Hr^B, -hr^B, and –Lu^a identified in 2016
  - 3 lifetime transfusions: Jan 2011, Mar 2014, Aug 2015 (1 unit each)
  - D+ C- c+ E- e+ K- (Jk(a+b-) Fy(a+b-) M+N+ S-s+)
  - *RH* genotype: *DIIIa-ce^S; DAU0-ce^S*
- Compatible donor match: C-E-K-, hr^B-, Lu^a-
- 8 *RH* genotype matched donors identified nationally
  - Homozygous DIIIa-ce^S and Lu(a-), K-
  - Alternative: identify genotype “compatible” donor units

Molecular testing to guide transfusion

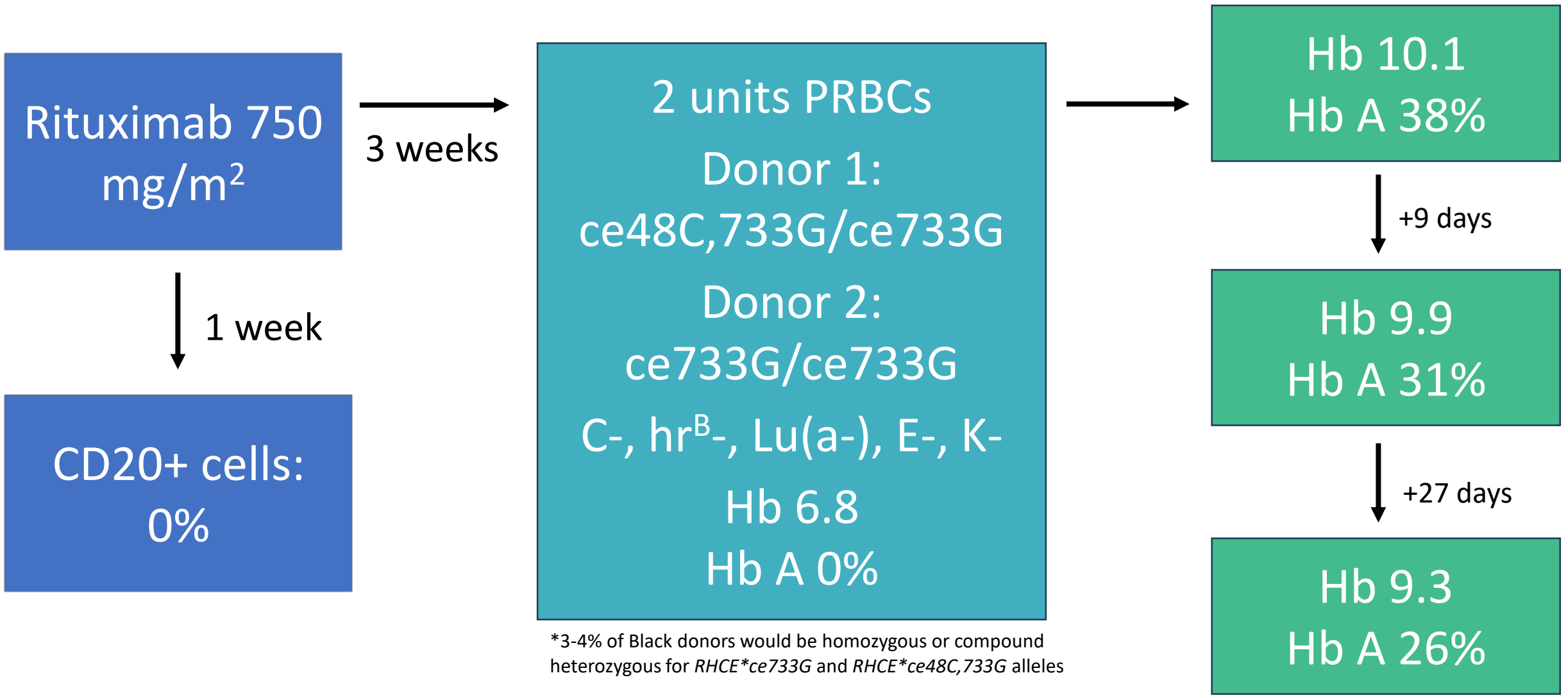


- Treated with HU, Voxeletor
- Recurrent admissions for splenic sequestration with severe anemia, splenectomy recommended
- Transfusion with *RH* genotype "compatible" red cells

Predicted Rh phenotype

D+, C-, partial c+, E-, partial e+, hr^B-, V+, VS+

Transfusion approach



*3-4% of Black donors would be homozygous or compound heterozygous for *RHCE*ce733G* and *RHCE*ce48C,733G* alleles

Summary: preventative measures

- Transfuse judiciously
- Provide prophylactic Rh (C,E or C/c, E/e) and K matched red cells
- Obtain extended RBC antigen genotype, including comprehensive *RH* analysis if possible (alternative: serologic phenotype)
- Obtain complete transfusion history from other hospitals
- Refer complex or antibody negative evaluations to reference labs

Summary: approach for “difficult to transfuse”

- Consider extended matched or *RH* genotype matched red cells for select, challenging cases
- Work closely with blood supplier and reference immunogenomic laboratories
- Consider transfusion trial for most challenging cases, such as those with h/o DHTRs and no antibody specificity
- Consider immunosuppression to prevent further alloimmunization and/or to treat DHTRs

Acknowledgements

Children's Hospital of Philadelphia

Chou Lab
Julia Mewha
*Claire An
Edmund Carvalho
Kaoru Takasaki
Naomi Gunawardena
Sambit Dalui
Jian Meng Fan
Doreen Dong
Jade Nelson

ESC/iPSC core
Deborah French
Guilia Pavani
Paul Gadue
Jean Ann Maguire
Alyssa Gagne

Blood Bank
David Friedman
Judith Mlkvy
Jaleah Hawkins
Lexie Peedin
Jasmine Steele
Pamela Blair

Nursing
Lisa Washington

Apheresis Unit

CURed Clinic

BDMC
Victoria Lazariu

Collaborators

NYBC
Connie Westhoff
Sunitha Vege
Gorka Ochoa
Shaimaa Makrm
Randy Velliquette

American Red Cross
Margaret Keller
Paul Mansfield
Sandy Nance

Patients and families

NIH National Heart, Lung, and Blood Institute

National Blood Foundation
A Program of AABB

Doris Duke Charitable Foundation

American Society of Hematology