Alloimmunization & Sickle Cell Disease

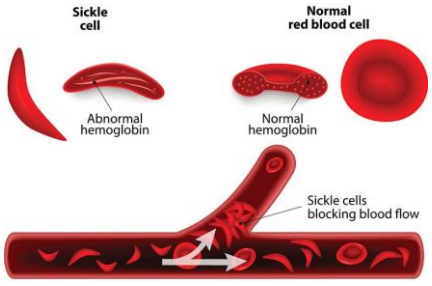
Objectives:

1. **Discuss alloimmunization rates for Sickle Cell Disease (SCD) patients compared to other groups of patients.**
2. **Describe the benefits and challenges of antigen-matching protocols for SCD patients.**
3. **Explain how a SCD patient might develop alloantibodies to an antigen present on his/her cells.**

Quick lesson:

SCD:

- Gene mutation results in variant hemoglobin molecule
  - Sickle shaped RBCs
  - Chronic anemia
  - Micro-occlusions in capillaries of tissues/organs
- Chronically transfused (prophylactic or treatment of acute crisis)



https://www.froedtert.com/sickle-cell-disease/symptoms

What percentage of all patients make alloantibodies? **<5%**

What percentage of SCD patients make alloantibodies?

Much more than the overall population

Some reasons for this: (remember, we still don't know the science of who will make antibody, and who won't)

- Transfusion load? – SCD patients receive many more RBC units than overall population
- Disease state? – chronic inflammation
- Disparity in antigen frequencies between donor base and SCD recipients?

How do we minimize or prevent alloimmunization for SCD patients?

Antigen matching (phenotype matching) programs vary:

- Match for Rh antigens (D,C,E,c,e) & K
- Match for Rh, K, Fy^a
- Full-phenotype matched: Rh, K, Fy, Jk, Ss

"Antigen-matching" means…

Providing units negative for all antigens the patient's cells lack

Practice:

Patient phenotype: D+, C-, E-, c+, e+; K-,k+: Fy(a-b+); Jk(a+b-); S-,s+

1. **What alloantibodies can the patient make? List them:**

2. **Study the phenotypes of the following units. Which units are fully phenotype-matched? (choose all that apply)**
   a) R_Or; K-,k+; Fy(a-b+);Jk(a+b+); S+,s+
   b) R_1R_2; K-,k+; Fy(a-b-); Jk(a+b-); S-,s+
   c) R_Or; K-,k+; Fy(a-b-); Jk(a+b-); S-,s+
   d) rr; K-,k+; Fy(a-b+); Jk(a+b-); S-,s+

Answers: 1. Anti-C, Anti-E, Anti-K, Anti-Fy^a, Anti-Jk^b, Anti-S. **2.** c,d

Most antigen-matching protocols include at least Rh and K. Let's look at Rh haplotypes:

	Fisher-Race Haplotype	Modified Weiner Haplotype	Prevalence (%)		
			Caucasian	African descent	Asian
Rh positive	DCe	R_1	42	17	70
	DcE	R_2	14	11	21
	Dce	R_O	4	44	3
	DCE	R_Z	<0.01	<0.01	1
Rh negative	ce	r	37	26	3
	Ce	r'	2	2	2
	cE	r''	1	<0.01	<0.01
	CE	r^y	<0.01	<0.01	

Table adapted from Technical Manual

In locations where a majority of donors are Caucasian, procuring enough antigen-matched units for SCD patients is challenging!

Many SCD patients: R_OR_O (D+, E-, C-)

Ways to address this challenge:

- Recruitment of minority donors
- Recruitment of R_O donors
- Mass scale phenotyping/genotyping of donors to identify R_O donors

D-negative units are often transfused to SCD patients because…

D-negative units are likely to be C-, E-

Antigen-matching Protocols for SCD Patients	
Benefits	**Challenges**
• Prevent exposure to foreign antigens • Prevent alloimmunization	• Large demand for R_Or & R_OR_O units • Small percentage of donors might meet that criteria • Use of D-negative units for SCD patients (D-negative units always in short supply)

Case study: surprising antibodies made by SCD patients

- SCD patient, 8 year old male
- Prophylactic transfusion schedule
  - Transfused every 4 weeks
  - Antigen-matching strategy: Match Rh, K
- Patient's phenotype:
  - D+, C+, E-, c+, e+: K-

1. **What is the patient's probable genotype?**
   a) R_OR_O
   b) rr
   c) R_1R_1
   d) R_1R_O

2. **Given the antigen matching strategy (match Rh, K), what type of units will be transfused?**
   a) E-, c-, K- units
   b) E-, C-, K- units
   c) E-, K- units
   d) E- units

Antibody screen results:

		Rh					Kell		Duffy		Kidd		MNS				Results		
		D	C	E	c	e	K	k	Fy^a	Fy^b	Jk^a	Jk^b	M	N	S	s	5' RT	LISS 37C	LISS IAT
SCI	R_1R_1	+	+	0	0	+	0	+	+	+	+	+	+	+	+	+	0	0	2+
SCII	R_2R_2	+	0	+	+	0	+	+	0	+	0	+	0	+	0	+	0	0	0

Case study (continued)

Antibody panel:

		Rh					Kell		Duffy		Kidd		MNS				Results
		D	C	E	c	e	K	k	Fy^a	Fy^b	Jk^a	Jk^b	M	N	S	s	LISS IAT
1	R_1R_1	+	+	0	0	+	0	+	+	+	+	+	+	+	+	+	2+
2	R_1R_1	+	+	0	0	+	+	+	0	+	0	+	0	+	0	+	2+
3	R_2R_2	+	0	+	+	0	0	+	+	0	+	+	+	0	+	+	0
4	R_0r	+	0	0	+	+	0	+	0	0	+	0	+	+	+	0	0
5	r'r	0	+	0	+	+	0	+	+	0	+	0	+	+	0	0	2+
6	r"r	0	0	+	+	+	0	+	0	+	+	+	0	+	0	+	0
7	rr	0	0	0	+	+	+	+	0	+	+	0	+	0	+	+	0
8	rr	0	0	0	+	+	0	+	+	+	0	+	0	+	+	+	0
9	rr	0	0	0	+	+	0	+	+	+	0	+	+	0	0	+	0
10	R_1R_1	+	+	0	0	+	0	+	+	0	+	+	+	+	+	0	2+
11	R_0r	+	0	0	+	+	+	+	0	0	+	+	0	+	+	+	0
Auto																	0

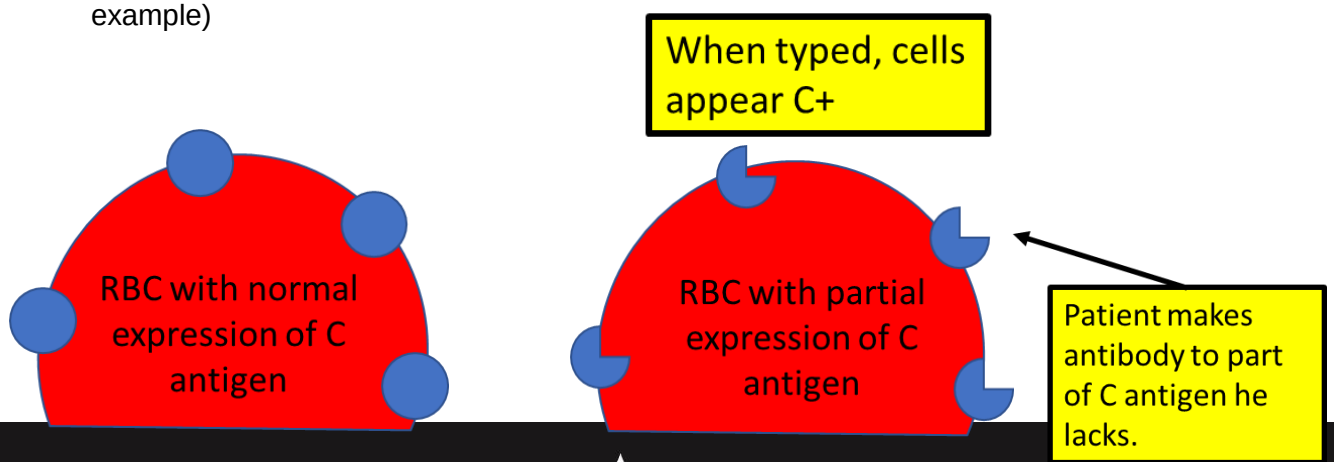
3. **Which antibody seems to be present in the patient's plasma?**
   a) Anti-D
   b) Anti-C
   c) Anti-K
   d) Anti-Fy^a

4. **Wait. The patient's cells tested C+. Is this *auto*antibody?**
   a) Yes, that is the only reasonable explanation.
   b) No, the autocontrol is not positive!

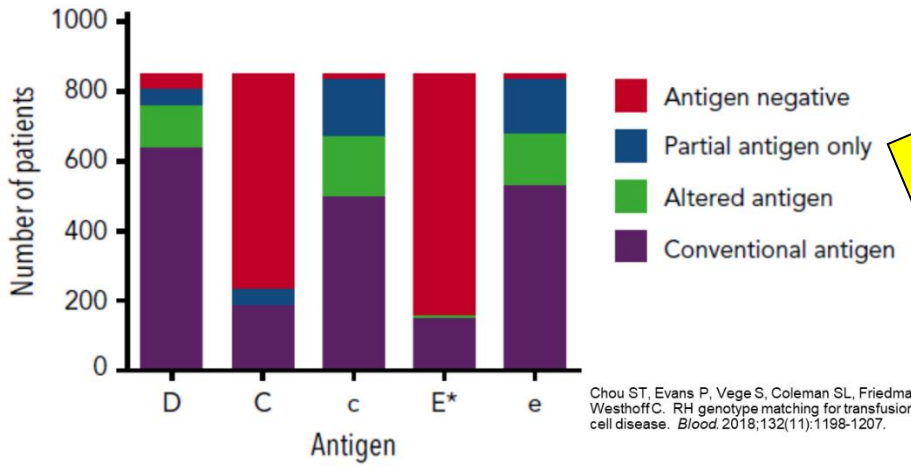
Answers: 1. d **2**. c **3**. b **4**. b

SCD Patients and Variant Antigens:

- There are MANY variant alleles of *RHD* and *RHCE* genes
- Variant alleles are more prevalent in individuals of African descent
- May code for antigens with weak or partial expression (like weak D and partial D, for example)



Variant alleles in SCD population are NOT uncommon!



Chou ST, Evans P, Vege S, Coleman SL, Friedman DF, Keller M, Westhoff C. RH genotype matching for transfusion support in sickle cell disease. *Blood*. 2018;132(11):1198-1207.

Even when we "antigen-match" for SCD patients, if they have variant Rh antigens, we are still exposing them to foreign epitope(s).

Genomic testing can determine if a patient has variant alleles

Assessing Understanding:

1. **Which of the following is true regarding alloimmunization rates of SCD patients compared to overall patient population?**
    a. Alloimmunization rates are lower due to SCD patients being immunocompromised.
    b. Alloimmunization rates are lower due to unknown causes.
    c. Alloimmunization rates are higher due to infrequent transfusion episodes
    d. Alloimmunization rates are higher due to increased transfusion load.

2. **What is the purpose of antigen matching protocols for SCD patients?**
    a. To prevent TACO.
    b. To prevent iron overload.
    c. To prevent alloimmunization.
    d. To prevent transfusion-transmitted diseases.

3. **Choose the best explanation for why some SCD patients make Rh antibodies to antigens that are EXPRESSED on their own cells, and despite antigen-matching protocols.**
    a. Because donor units are often mistyped for Rh antigens.
    b. Because patients might have variant alleles that code for partial Rh antigens.
    c. Because samples get mixed up in the lab.
    d. Because they are transfused ABO incompatible units.

Answers: 1. d **2**. c **3**. b