Effective Treatment for Thalassemia, Sickle Cell Disease and Hemophilia in the Absence of a Local Clinic

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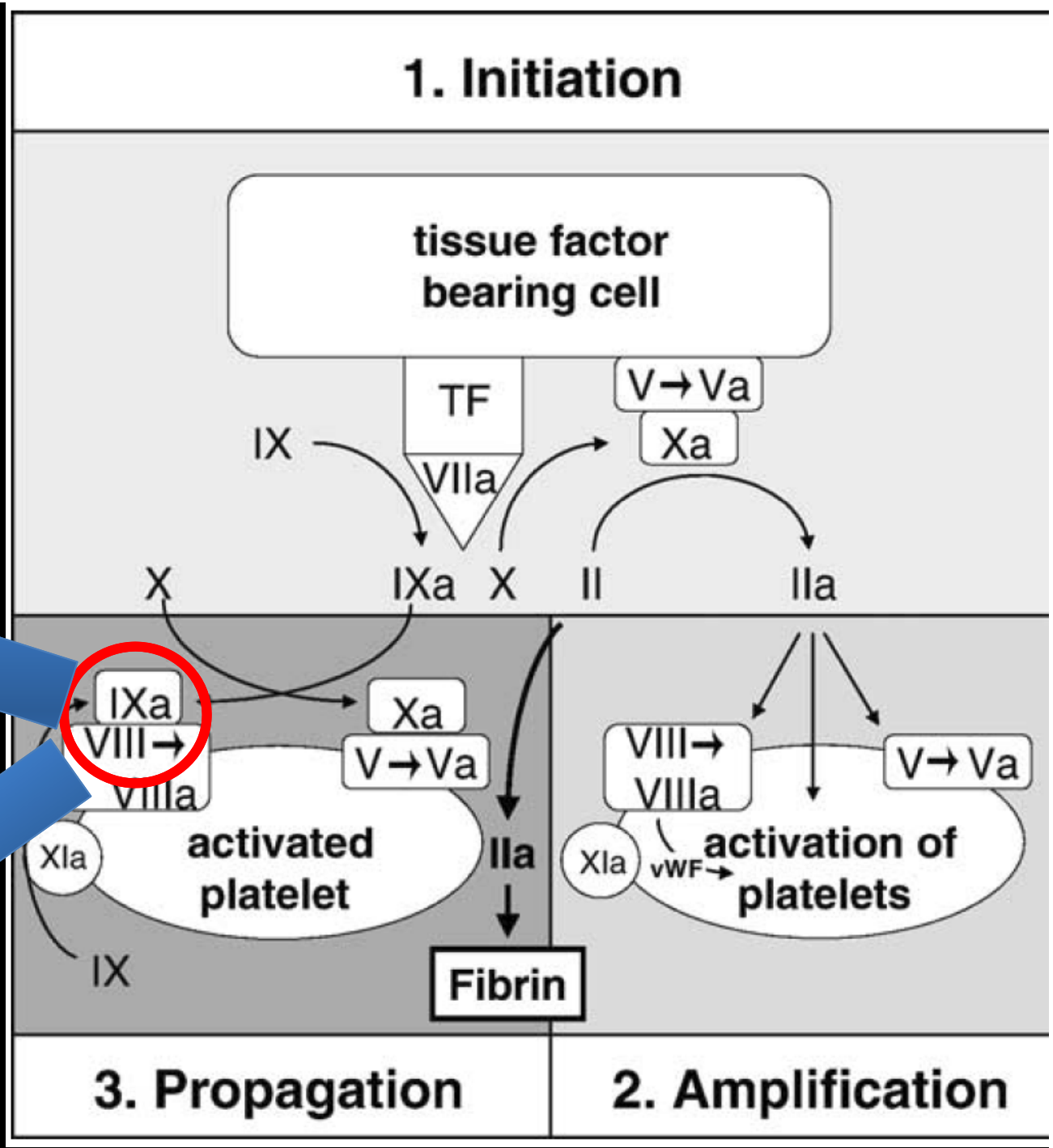
Hartmann, Trans Med Rev 2006;20, 230-241

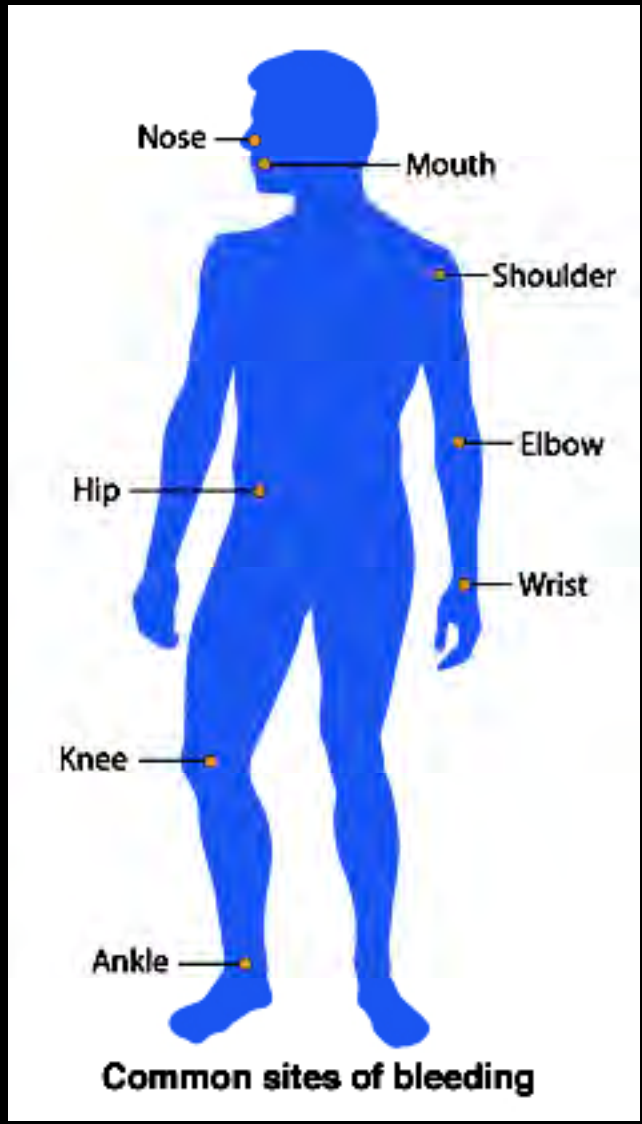


Hemophilia A
- FVIII deficiency
- 1:5 000 males

Hemophilia B
- FIX deficiency
- 1:30 000 males

Hemophilia: Clinical Manifestations

- Musculoskeletal bleeding
  - Hemarthrosis
  - Intra-muscular hematoma
- Mouth bleeding, epistaxis
- Intracranial bleeding
- Bleeding with trauma, procedures, surgery
- Menorrhagia (including symptomatic carriers)



http://www.koate-dviusa.com

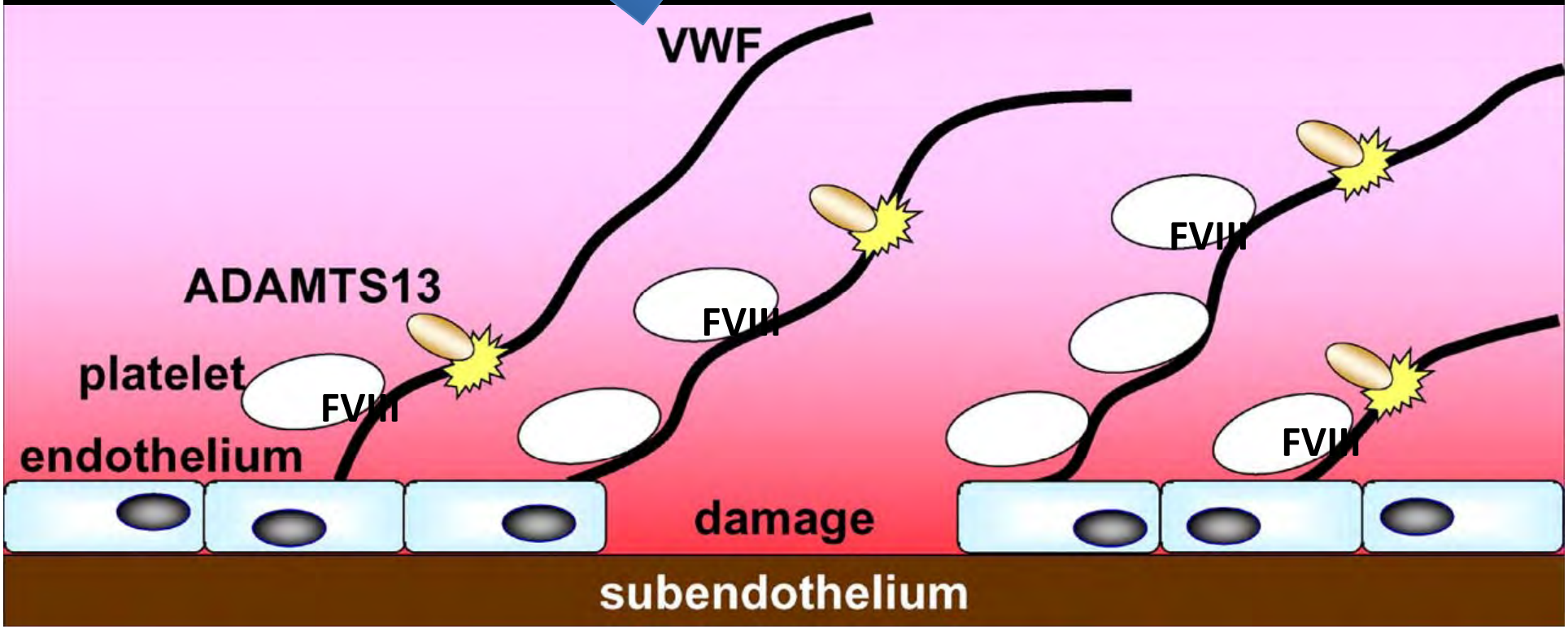
Hemophilia: Clinical Manifestations

- Severe < 0.01 U/mL (<1%)
  - frequent, spontaneous, life-threatening with trauma or surgery
- Moderate 0.01 - 0.05 U/mL (1-5%)
  - provoked by minor trauma, serious with trauma or surgery
- Mild > 0.05 U/mL (>5%)
  - mild symptoms, can be asymptomatic aside from trauma or surgery

Bowen, Blood 2010;115::2565

Von Willebrand Disease

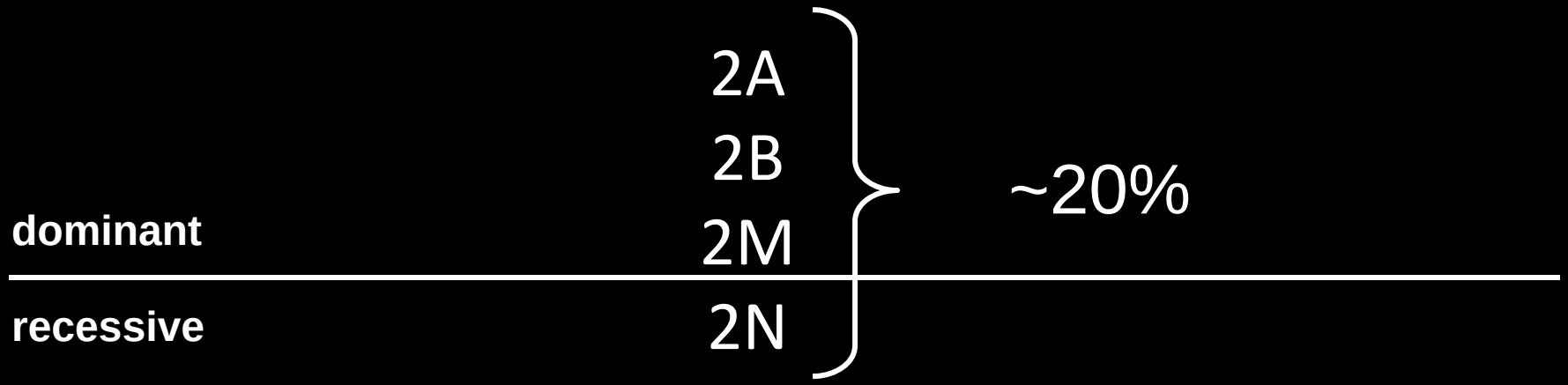
- vWF deficiency/dysfunction
- 1:1000 (symptomatic), M=F



vWD: Classification

Type 1 - mild/moderate quantitative trait ~80%

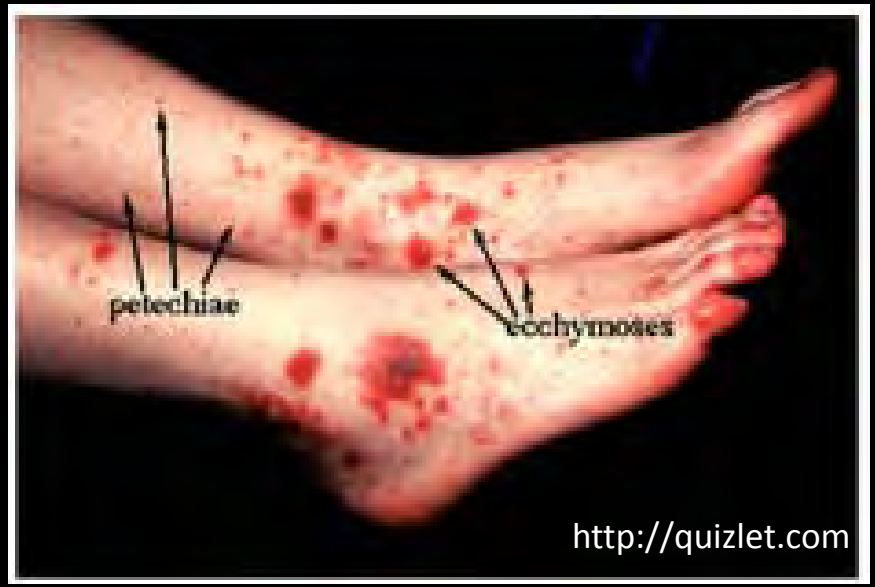
Type 2 - qualitative traits



Type 3 - severe quantitative trait ~ 1 per million

vWD: Clinical Manifestations

- Mucocutaneous
  - Menorrhagia
  - Epistaxis
  - Bruising
  - Excessive bleeding from minor wounds
  - GI bleeding
  - Oral cavity/post-dental procedure
  - Post-operative
  - Post-partum
- Musculoskeletal (Type 3)
  - Resembles FVIII deficiency
  - Hemarthrosis
  - Soft tissue, muscle hematomas



Hemophilia/vWD: Principles of Treatment

- Specific factor replacement
  - FVIII (Kogenate FS, Helixate FS, Advate, Xyntha)
  - FIX (Benefix)
  - vWF (Humate P, Wilate)
- DDAVP
  - Recruitment of endogenous vWF, which indirectly also increases FVIII levels
  - Used for mild hemophilia A and type 1 vWD
- Topical agents to promote fibrin clot formation (eg., thrombin)
- Anti-fibrinolytic agents (eg., tranexamic acid) to stabilize clots
- Ancillary strategies: rest, cold, anti-inflammatories, OCP (menorrhagia)

FactorFirst

Delay in the restoration of hemostasis to the patient with hemophilia or von Willebrand disease may be life or limb-threatening.

- Triage based on bleeding severity; do not wait for factor levels before starting treatment
  - Limb/life-threatening = Head and neck; chest, abdomen, pelvis, spine; iliopsoas and hip; massive vaginal hemorrhage; extremity muscle compartments; fractures or dislocations; deep laceration; uncontrolled bleeding
  - Moderate/minor: nose (epistaxis) ; mouth/gums; joints (hemarthroses); menorrhagia; abrasions and superficial lacerations

http://www.hemophilia.ca/en/

TREATMENT FOR LIFE OR LIMB-THREATENING BLEEDS

PATIENT MUST RECEIVE PRODUCT URGENTLY

Hemophilia A: (all severities)
Recombinant factor VIII concentrate 40-50 units/kg

Hemophilia B: (all severities)
Recombinant factor IX concentrate 100-120 units/kg >15 yrs
Recombinant factor IX concentrate 135-160 units/kg <15 yrs
The dosage for recombinant factor IX is substantially higher because of its lower recovery, particularly in children.

Von Willebrand Disease:
A VW factor concentrate containing factor VIII such as Humate-P 60-80 Ristocetin cofactor units/kg

It is critical to raise the factor level to 80-100% urgently for all life or limb-threatening bleeds.

http://www.hemophilia.ca/en/

TREATMENT FOR MODERATE/ MINOR BLEEDS

PATIENT MUST RECEIVE PRODUCT WITHIN 30 MINUTES WHENEVER POSSIBLE

Hemophilia A: (severe/moderate)
Recombinant factor VIII concentrate 20-30 units/kg

Hemophilia A: (mild)
Desmopressin (Octostim/DDAVP) 0.3 mcg/kg (max. 20 mcg)–SC/IV

Hemophilia B: (severe/moderate/mild)
Recombinant factor IX concentrate 35-50 units/kg >15 yrs
Recombinant factor IX concentrate 50-70 units/kg <15 yrs
The dosage for recombinant factor IX is substantially higher because of its lower recovery, particularly in children.

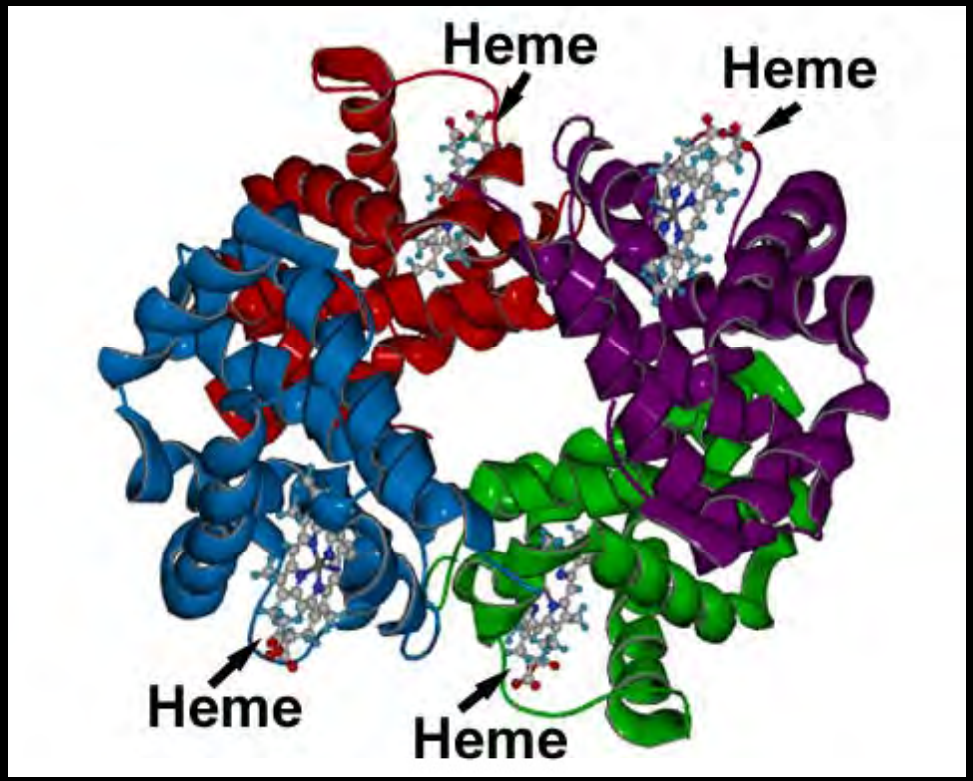
Von Willebrand Disease:
Type 1 and Type 2A or 2B known to have used desmopressin safely and effectively – (Octostim/DDAVP) 0.3 mcg/kg (max. 20 mcg)–SC/IV

For patients not responding to desmopressin (such as Type 3 or Type 2B) use a VW factor concentrate containing factor VIII such as Humate-P 60-80 Ristocetin cofactor units/kg

For mucosal bleeds in all above add:
Tranexamic Acid (Cyklokapron) 25 mg/kg po tid 1-7 days (contraindicated if hematuria)

http://www.hemophilia.ca/en/

- Must be able to
  - Describe the bleeding disorder accurately
  - Recognize of different types of bleeds, and best ways to treat them
  - Prepare and infuse factor concentrate safely;
  - Store product safely
  - Dispose of equipment safely
  - Know when to contact the HTC for help
  - Keep a regular routine of attending clinics at the HTC
  - Keep accurate treatment records and submit them at agreed intervals
- Liaise with patient's HTC to confirm eligibility

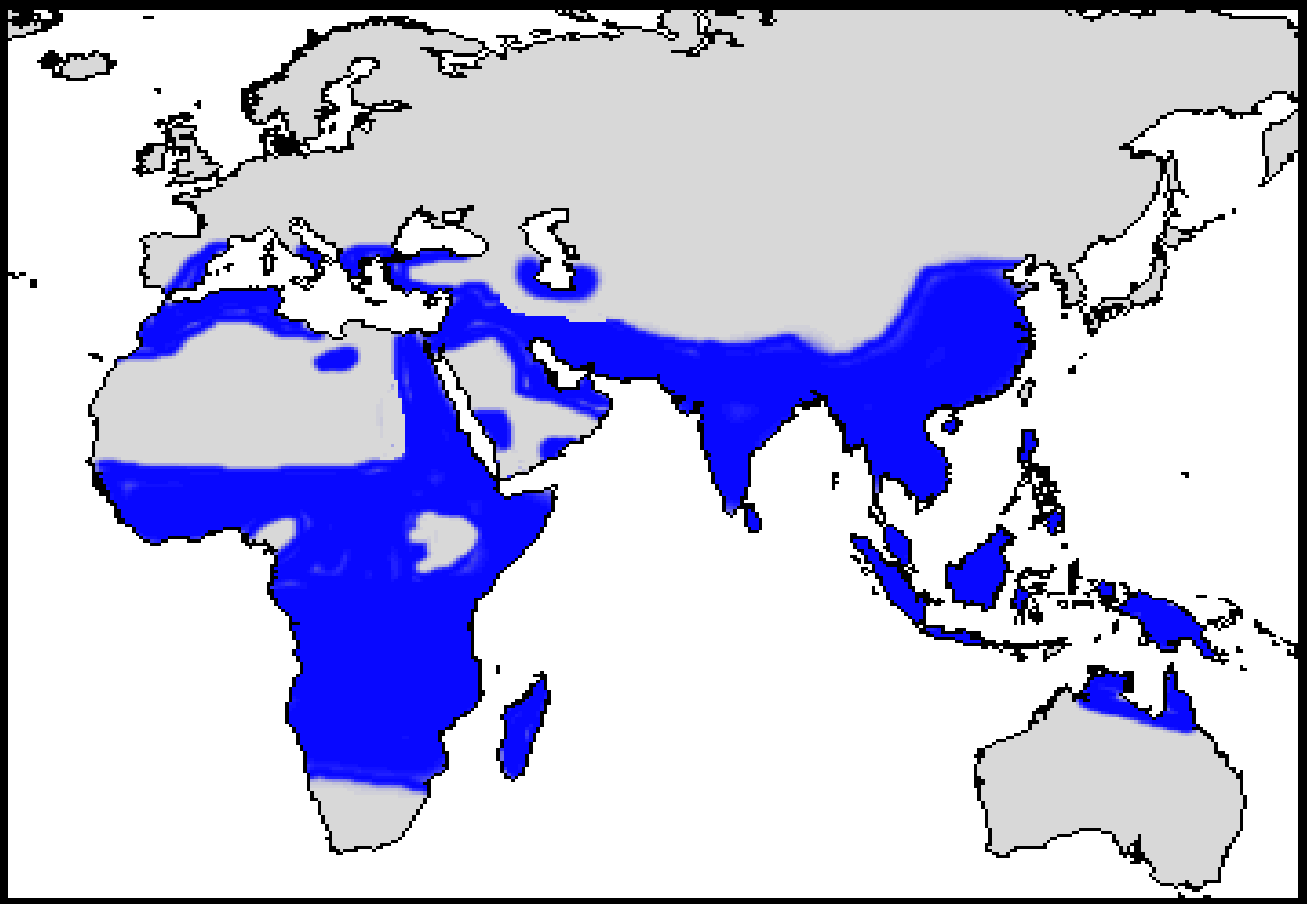


Structure of hemoglobin

- 4 globin chains (2 x alpha and 2 x beta), each containing heme group which binds O_2
- When deoxygenated, Hgb exists in "taut" configuration, with beta globin chains held apart with ionic bonds
- With oxygen binding, ionic bonds broken, beta globin chains move together and Hgb adopts "relaxed" configuation

- Quantitative defect: **thalassemia** (eg., alpha thalassemia, beta thalassemia
- Qualitative defect: hemoglobinopathy (eg., **sickle cell disease**)

http://www.chemistry.wustl.edu/~courses/genchem/Tutorials/Hemoglobin/images/hhemo_rib1.jpg



1. Modell, Bull of the WHO 2008;86:480–487.
2. Eaton JW, et al., eds. Sickle cell disease: basic principles & clinical practice. New York: Raven Press Ltd. 1994.

- Hgb disorders =world's most common genetic disease (sickle cell >> thal)
- 1% of couples worldwide at risk for having affected child
- Population distribution mirrors P. falciparum malaria edemicity
- Most individuals born in low-resource settings die before age 5

Alpha Thalassemia

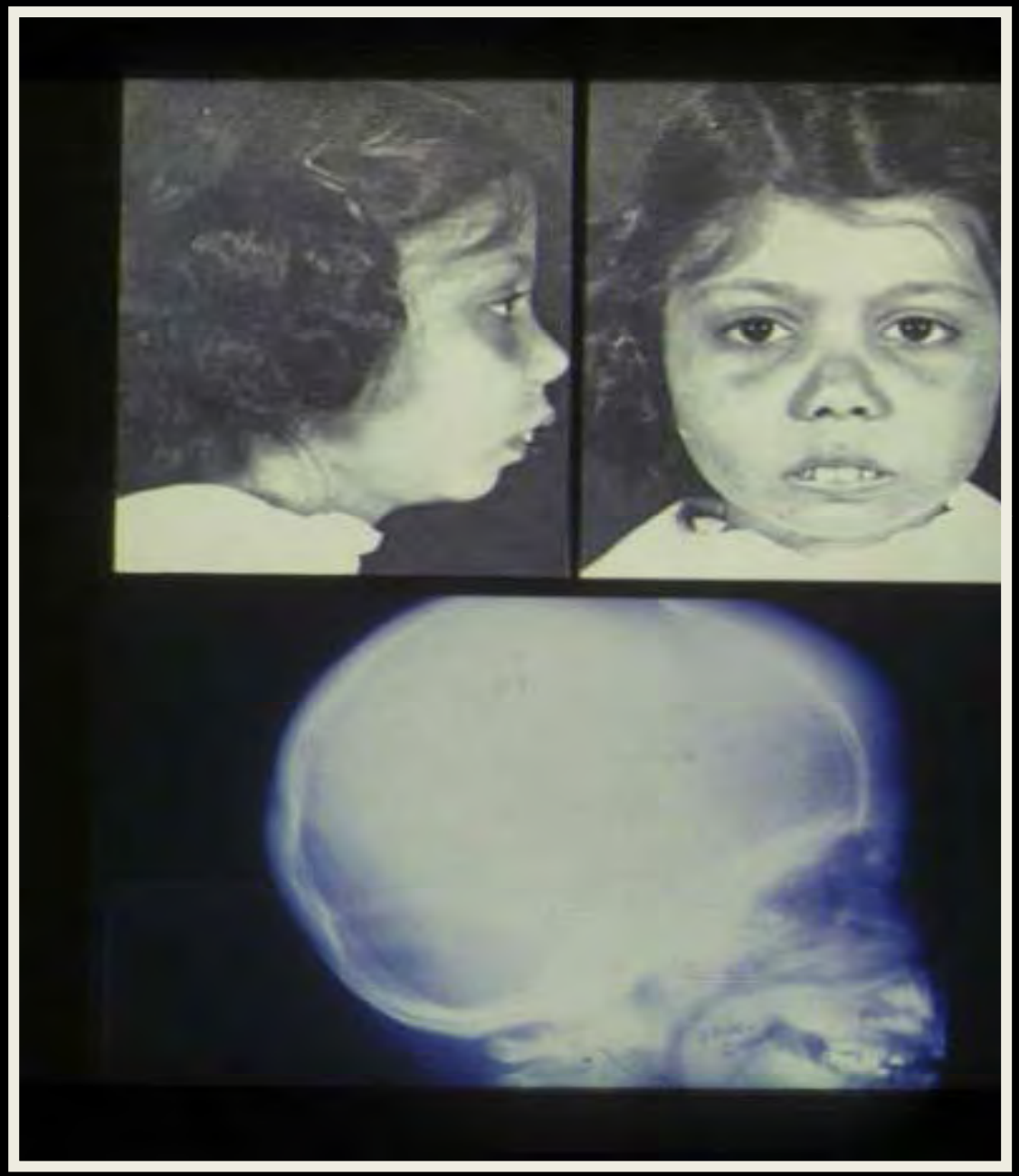
Disease	Phenotype	Hgb	Genotype
Alpha thal minima (Alpha-thal trait 2)	Normal	A	αα/ α-
Alpha thal minor (Alpha-thal trait 1)	Mild microcytic anemia	A	αα/ -- (cis) α-/ α- (trans)
HgbH disease (alpha thal major)	Moderate microcytic anemia	A, H	α-/ --
Hgb Barts disease (fetal hydrops)	Stillbirth	Barts, Portland	-- / --

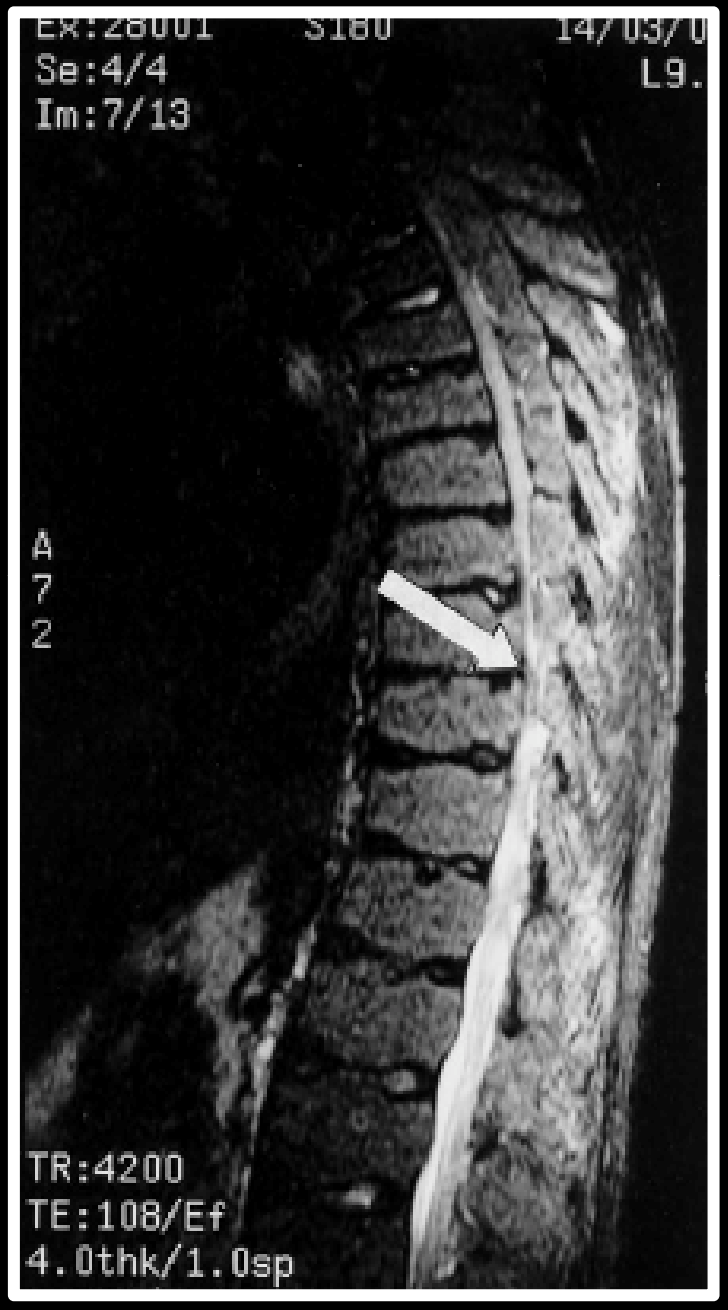
- Generally a benign disease; average baseline Hgb = 90-100 g/L
- Oxidative stress (infection, fever, sulpha meds, etc) and pregnancy increase transfusion requirements
- Goal of transfusion = prevention of symptomatic anemia (eg., keep Hgb > 70-80 g/L)

Beta Thalassemia

Disease	Phenotype	Hgb	Genotype
Beta-thal minor (Beta-thal trait)	Mild microcytic anemia	A, A2, F	ß$^{+}$/ß ß^{o}/ß
Beta-thal intermedia	Moderate microcytic anemia	A, A2, F	TMaj with mitigators TMin with exacerbators
Beta-thal major (Cooley's anemia)	Severe microcytic anemia	(A), A2, F	ß^{o}/ß^{o} ß^{o}/ß$^{+}$ ß$^{+}$/ß$^{+}$

- Lifelong transfusion support required (typically 3-4 RBC units/week in adults)
- Goal of transfusion is <u>suppression of marrow hyperplasia</u> (eg., keep Hgb > 90-100 g/L)

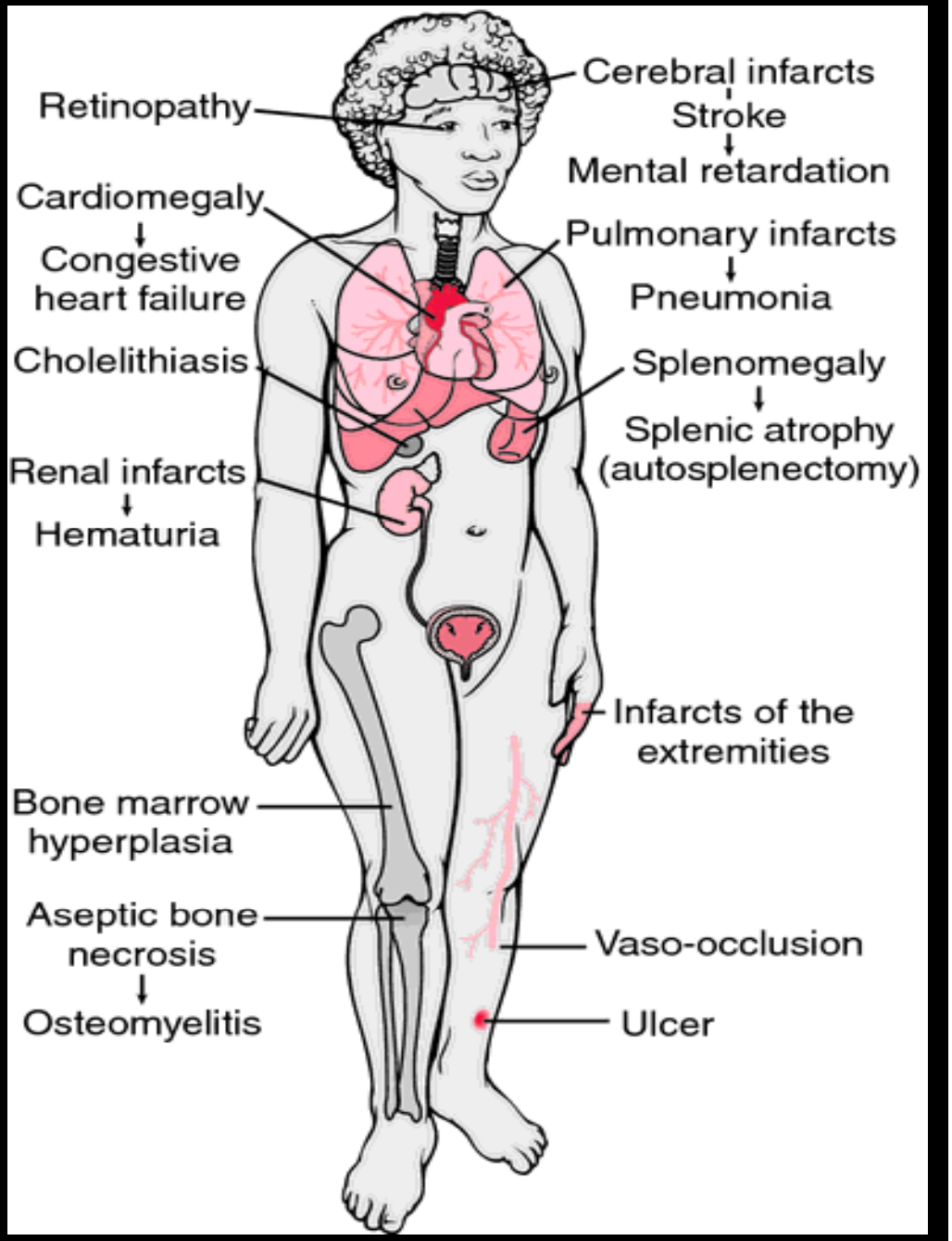




Chehal, Spine 2003;28:E245

Sickle Cell Disease

Genotype	HgbS	Typical clinical severity
$ß^S/ß^A$	20-30%	Asymptomatic
$ß^S/ß^C$	50%	Mild-moderate
$ß^S/ß^+$	70-85%	Moderate
$ß^S/ß^°$, $ß^S/ß^S$	90-95%	Severe



http://medical-dictionary.thefreedictionary.com

Indications for transfusion therapy in sickle cell disease

Generally accepted	Possibly effective	Not indicated
Acute cerebrovascular accident	Preoperative/preprocedural, in which relative ischemia might be induced, such as operations involving general anesthesia and cerebral angiography	Compensated anemia
Primary and secondary stroke prevention	Recurrent or persistent priapism	Infections other than aplastic anemia
Retinal artery occlusion	Advanced pulmonary or cardiac disease, such as pulmonary hypertension and heart failure	Uncomplicated acute painful crisis
Acute and recurrent splenic sequestration	Progressive renal failure	Minor surgeries without anesthesia
Intrahepatic cholestasis	Unusually frequent or severe painful crisis	Nonsurgically managed aseptic necrosis
Acute chest syndrome	Pregnancy with exacerbation of anemia, especially if symptomatic	Uncomplicated pregnancy
Aplastic crisis	—	—
Acute blood loss (eg, traumatic splenic rupture)	—	—

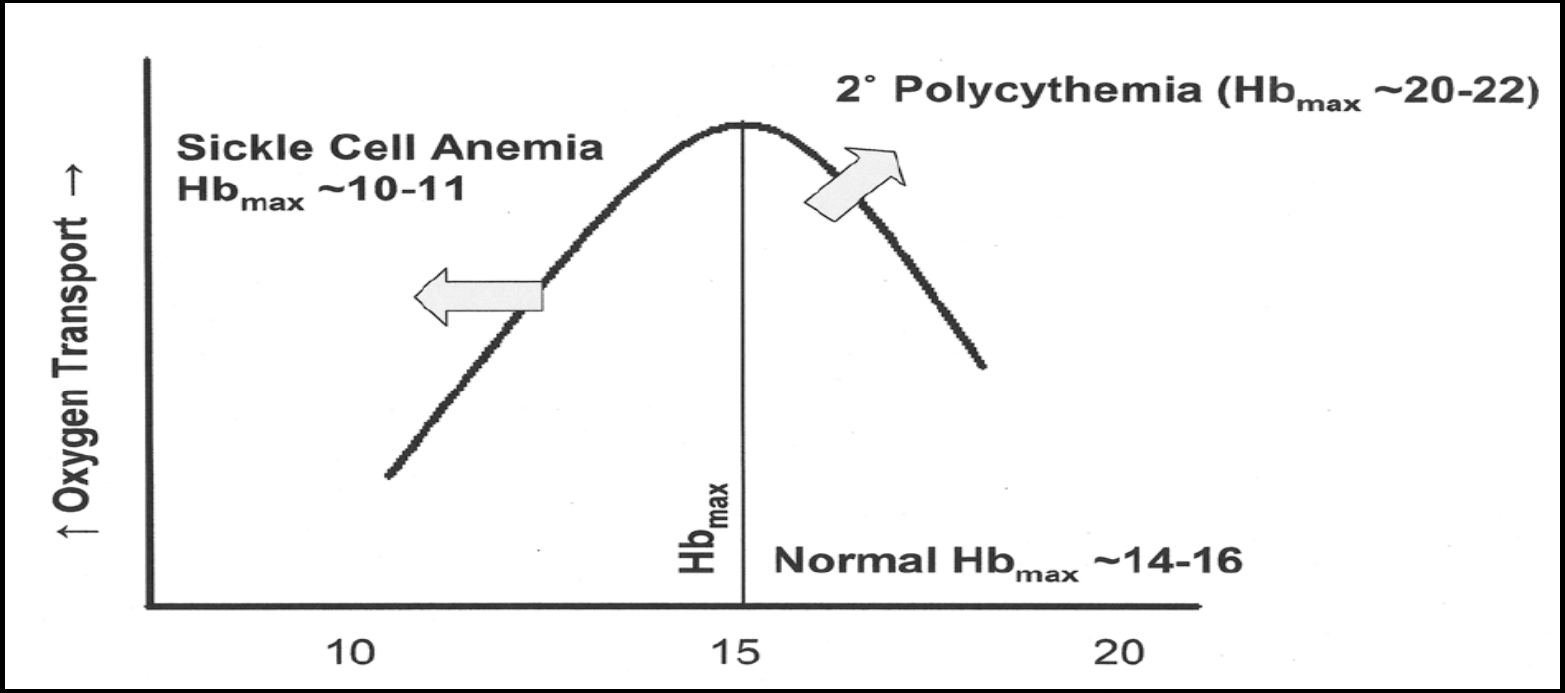
Wanko, Hem Onc Clinics of NA 2005;19:803

- What seem like symptoms of anemia may in fact reflect medication effects (eg., fatigue), hypovolemia (eg., tachycardia, hypotension), or other disease (eg., dyspnea)
- As per NIH Guidelines, prophylactic transfusions to prevent complications of anemia in sickle cell disease not advised unless Hgb < 50 g/L!

→

In patients hospitalized for pain episodes and other events, the Hb concentration may fall well below the admission value. If the patient is stable and the reticulocyte count high (>20 percent or >250,000/μL), transfusions can be deferred. In general, patients should be transfused if there is sufficient physiological derangement to result in heart failure, dyspnea, hypotension, or marked fatigue. Such symptoms tend to occur during an acute illness when hemoglobin falls under 5 g/dL. Patients with an acute event associated with falling hemoglobin can die suddenly from cardiovascular collapse and should be monitored closely.

- While diluting HgbS with HgbA will improve blood viscosity, increasing Hgb to exceed 100-110 g/L will worsen it
- Excessive transfusion risks **hyperviscosity syndrome**: hypertension, congestive heart failure, confusion, stroke, possibe worsening of vaso-occlusive pain
- Achieving a desired HgbS% (eg., <30%) without exceeding a total hemoglobin of 100-110 g/L often requires an <u>exchange transfusion</u>



Swerdlow, Hematology 2006;48

Alloimmunization

- Approx 25% of patients with SCD will become alloimmunized from transfusion
- In part due to differences in antigen expression between typical donor and sickle cell patient

Table 3. Average Frequencies of RBC Alloantibodies Made By Transfused Patients With SCD

Antibody	Average frequency (%)
Anti-E	21
Anti-K	18
Anti-C	14
Anti-Le^a	8
Anti-Fy^a	7
Anti-Jk^b	7
Anti-D	7
Anti-Le^b	7
Anti-S	6
Anti-Fy^b	5
Anti-M	4
Anti-E	2
Anti-C	2

Josephson CJ, TMR 2007;21:118

RH gene complex	Antigens expressed	Gene frequency in the US population: Caucasians	Gene frequency in the US population: African Americans
R_0	cDe	0.04	0.44
r	ce	0.37	0.26
R_1	Cde	0.42	0.17
R_2	cDE	0.14	0.11
r′	Ce	0.02	0.02
r″	cE	0.01	<0.01
R_z	CDE	<0.01	<0.01
r_y	CE	<0.01	<0.01

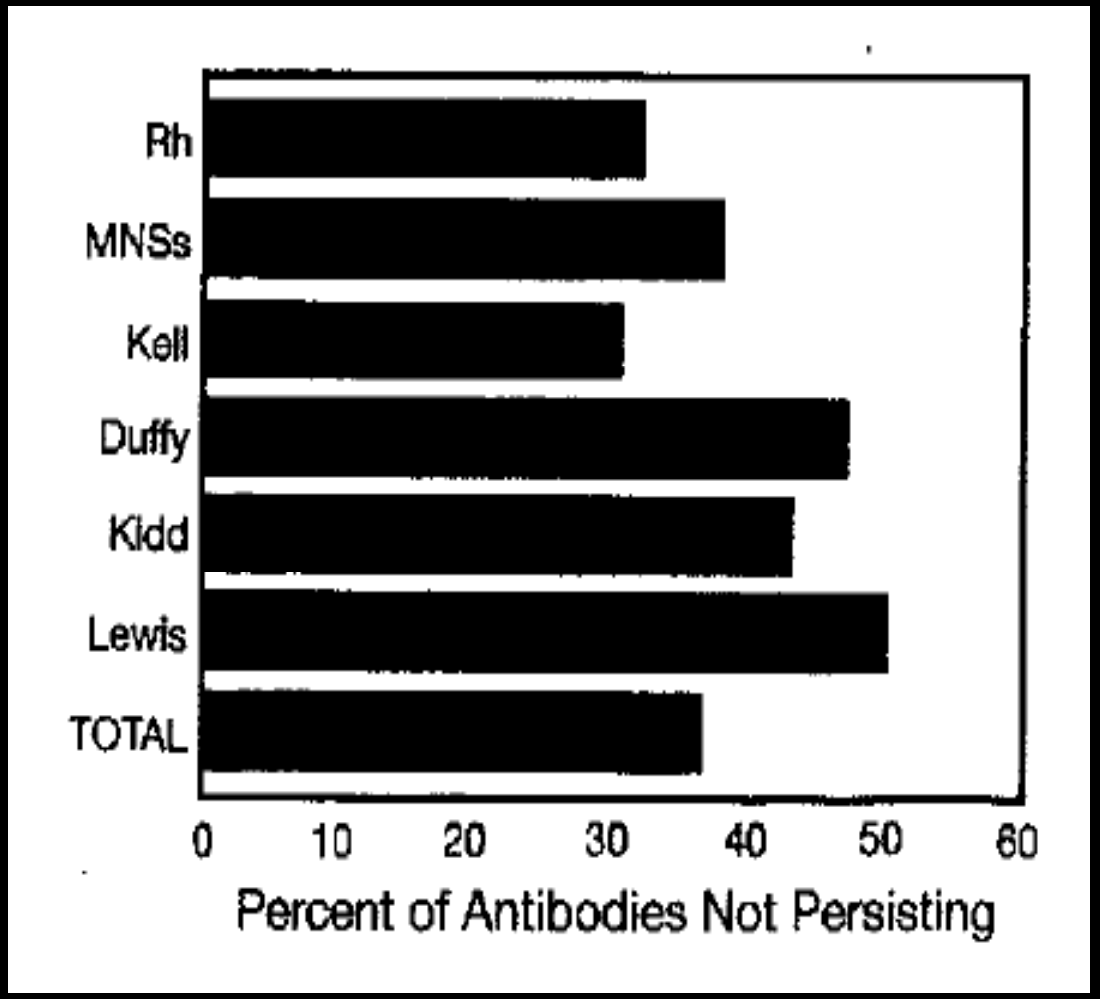
Blood group	Antigens expressed	Antigen frequency (%): Caucasians	Antigen frequency (%): African Americans
Kell	K	9.0	2.0
	k	99.8	>99.9
	Kp^a	2.0	<0.1
	Js^a	<0.1	20.0
	Js^b	>99.9	99.0
Kidd	Jk^a	77.0	92.0
	Jk^b	74.0	49.0
MNS	M	78.0	70.0
	N	72.0	74.0
	S	55.0	31.0
	s	89.0	97.0
	S-s-U-[1]	0	1.0
Duffy	Fy^a	66.0	10.0
	Fy^b	83.0	23.0
	Fy(a-b-)[1]	<0.01	68.0

[1] Null phenotypes in the MNS and Duffy blood group systems.

Wanko, Hem Onc Clinics of NA 2005;19:803

Detection of Alloantibodies

- In patients with sickle cell disease, 30-50% of antibodies will be undetectable on at least one occasion one year after they were first observed
- Episodic transfusions in different hospitals increases risk of DHTRs and possibly hyperhemolysis (Hgb worse after transfusion)



Vichinsky E, Semin in Hematol 2001;1(S1):14

Prevention of Alloimmunization

- Prophylactic matching decr alloimmunization/DHTR

Matching protocol	% of immunizations that would have been prevented beyond ABO/D matching	% of transfused SCD who would never make an antibody	Frequency of required phenotype in Caucasians
Rh (C,c,D,E,e)	37.2%	82.3%	15%

- Extensive matching (beyond Rh/Kell) usually reserved for patiets who have already made an antibody

Castro, Transfusion 2002;42:684

Are we ready to start genotyping?

- In some cases, tells us what we already suspected (eg., Fy^{b}-negative units not required for $Fy(^{a-b-})$ patients due to GATA-box mutations
- In some cases, tells us what we could have found out through other means (eg., you can phenotype a transfused sickle patient using hypotonic saline lysis)
- In some cases, tells us what we don't really want to know! (eg., patients are missing high-frequency antigens like hr^{B} which we would have a hard time matching for if they ever made an antibody to it)

Are we ready to start genotyping?

- But in some cases, this information is crucial
  - Patients we think are C+ are actually partial C (up to 28% of sicklers!)
  - Patients with antibodies to antigens we don't have typing sera for (eg., anti-V)

- Many centres are now routinely genotyping their sickle cell patients, and blood collection agencies are creating genotype databases of their donors

	Hemophilia/vWD	Thalassemia/Sickle Cell
Product Requirements?	❑ Which specific product do they use? ❑ How much would be needed to treat a life-threatening bleed?	❑ What antibodies have they already made? ❑ What degree of prophylactic antigen-matching is required? ❑ Other requirements (eg., washed?)
Goals of therapy?	❑ On-demand vs prophylactic factor replacement? ❑ Does patient qualify for home-infusion protocol?	❑ Prevention of symptomatic anemia? ❑ Prevention of marrow hyperplasia? ❑ Dilution of HgbS%?
Supportive care?	❑ Are adjunct meds available (tranexamic acid, DDAVP)?	❑ Does patient require monitoring for toxicities for adjunct meds (hydroxyurea, iron chelation)?
When to obtain heme consult?	❑ ***After*** treating a bleeding episode (“Factor First”) ❑ Prior to any surgical procedure	❑ ***Before*** transfusing RBCs (unless on chronic transfusion program) ❑ Prior to any surgical procedure

Parting Thoughts

Patients with congenital clotting disorders or hemoglobinopathies are usually affiliated with comprehensive care programs at hospitals with 24/7 specialist coverage

DON'T BE AFRAID TO CALL!

Patients themselves often know how they need to be managed

LET THEM HELP YOU!

The blood bank needs to be kept in the loop if specialized products will be required

HAVE PRODUCTS STOCKED IN ADVANCE!

Don’t Need It After All?

RBCS WITH EXTENDED TYPING

CLOTTING FACTOR CONCENTRATES

University Health Network

Leading with Innovation
Serving with Compassion
ST. MICHAEL'S HOSPITAL
A teaching hospital affiliated with the University of Toronto

THANK-YOU


Canadian Blood Services


ORBCoN
Ontario Regional Blood Coordinating Network