Hemoglobinopathies in obstetrics and gynecology

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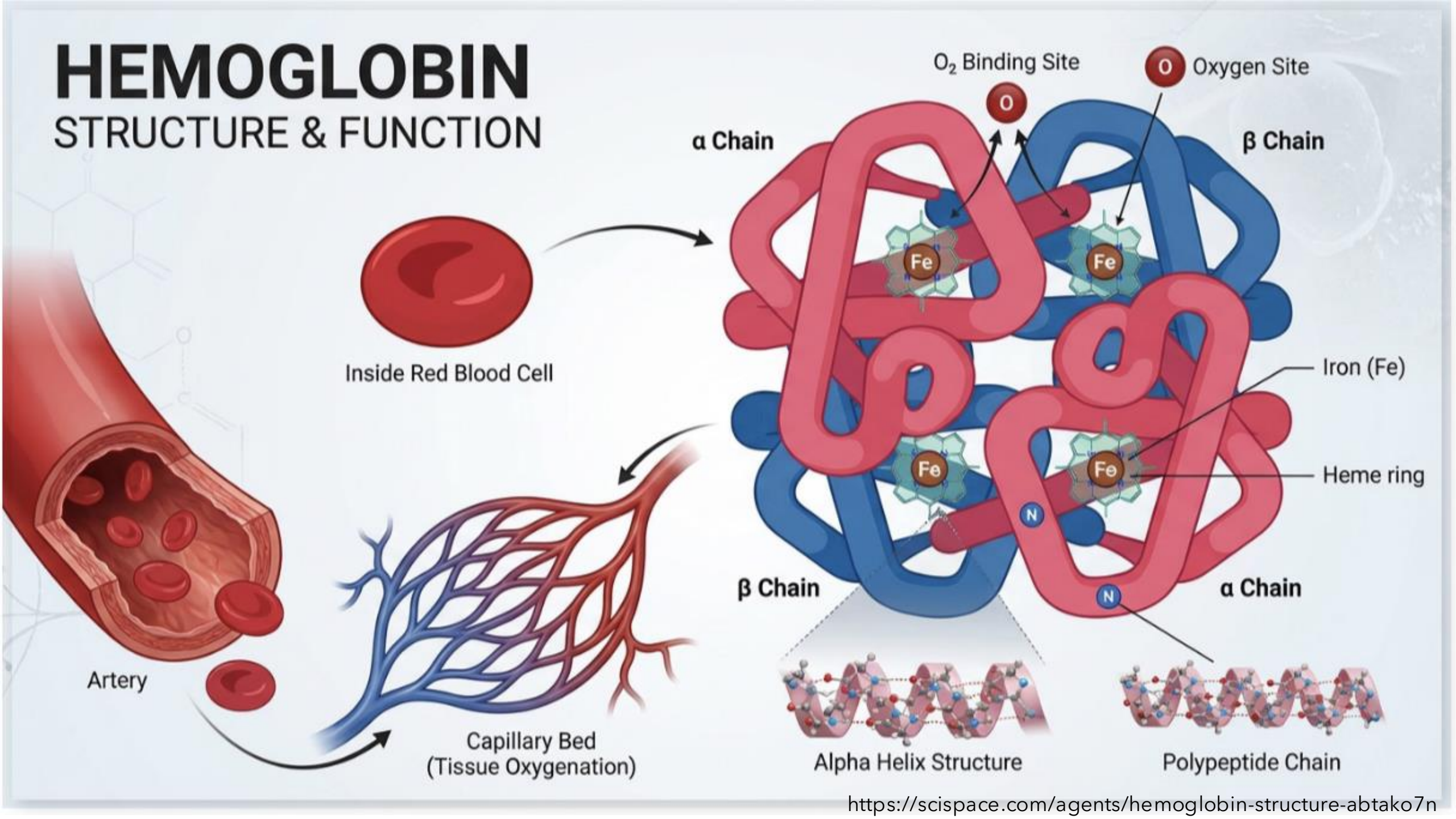
Hemoglobinopathy

Inherited disorders characterized by abnormal structure or production of hemoglobin

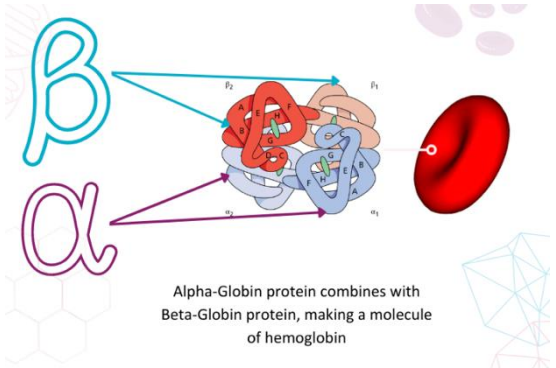
- Impairment of oxygen delivery
- Dysfunctional Iron metabolism
- Vasoocclusion

HEMOGLOBIN
STRUCTURE & FUNCTION



https://scispace.com/agents/hemoglobin-structure-abtako7n

Beta Globin Genes



Alpha Globin Genes

b1

b2

a1

a2

a3

a4

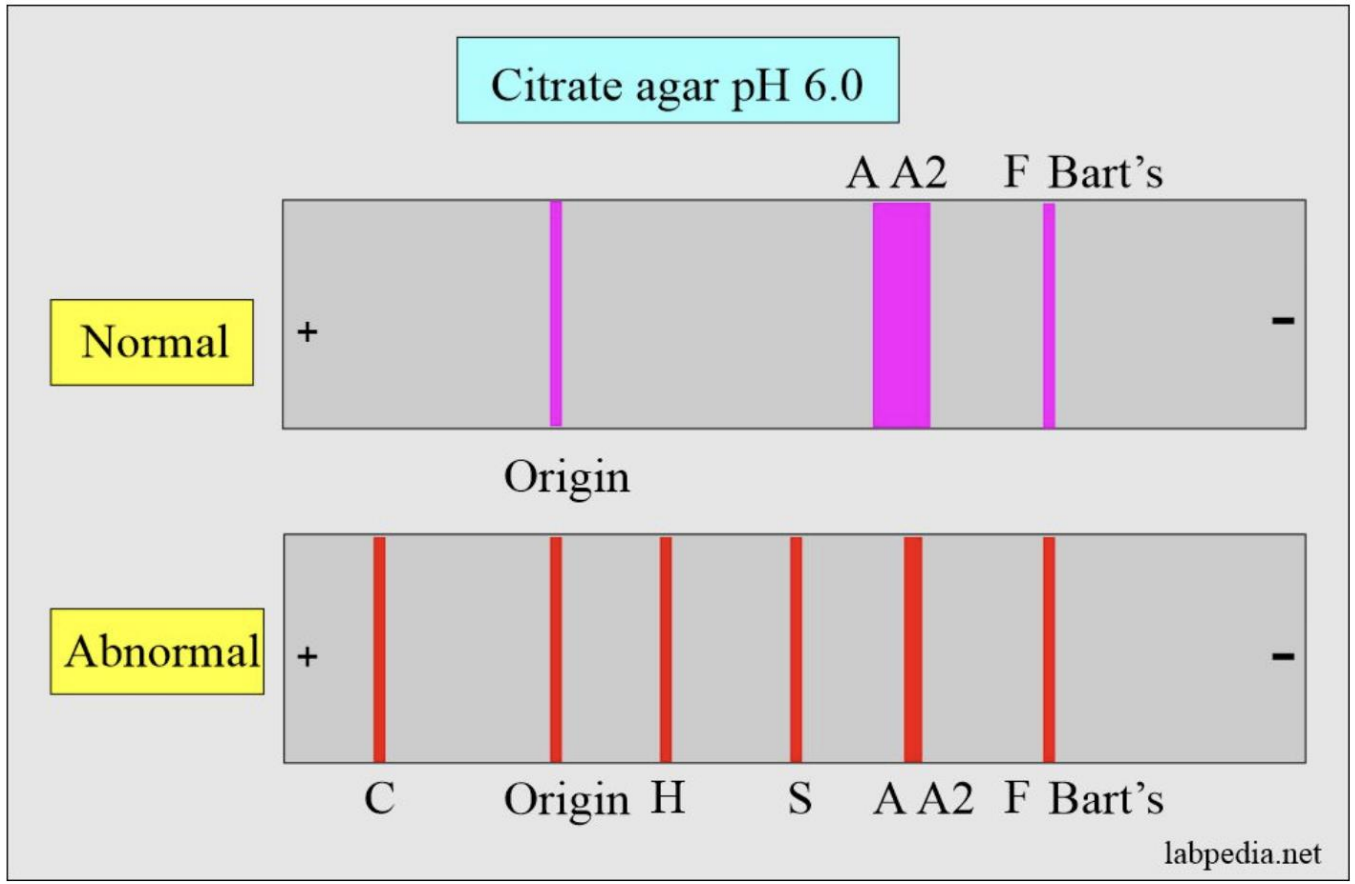
Hemoglobin Protein

Chromosome 11

Chromosome 16

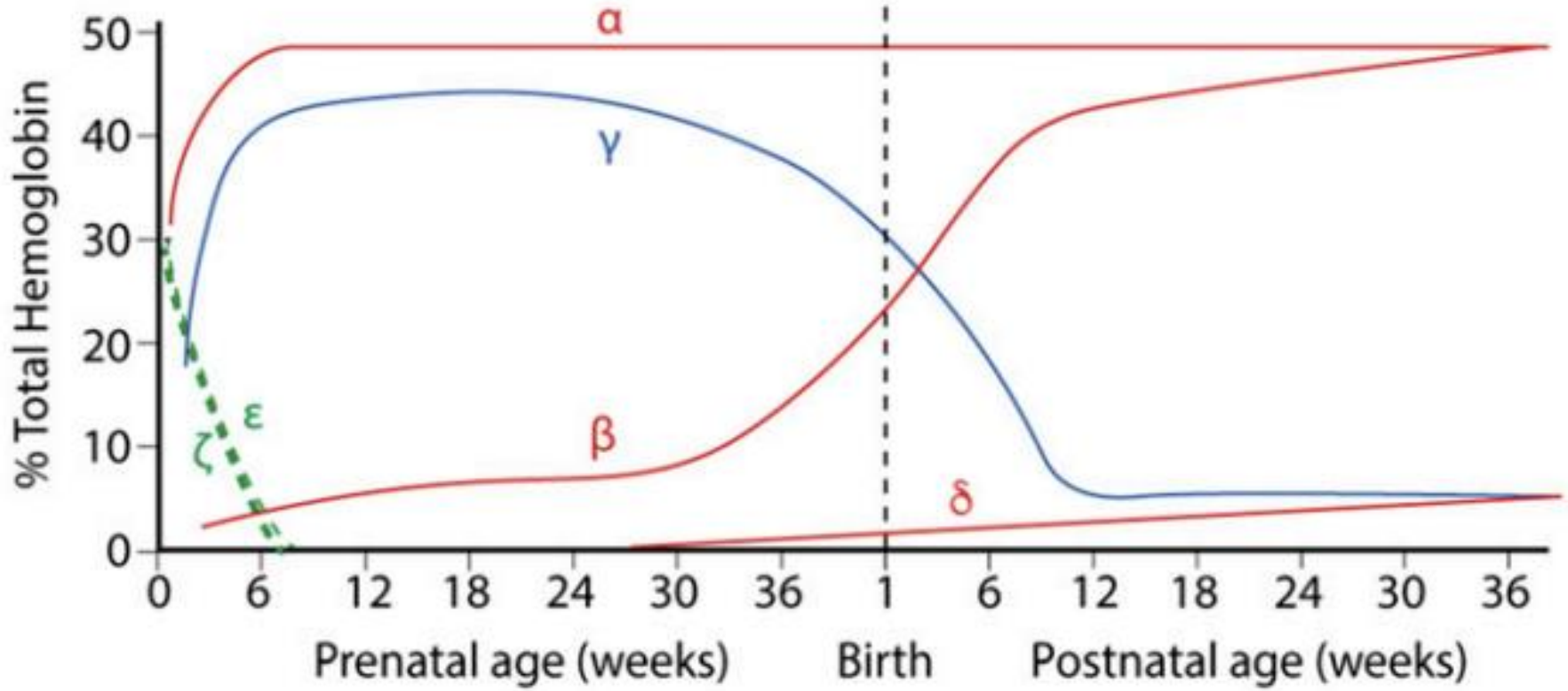
https://sickle.bwh.harvard.edu/thal_inheritance.html

Name	Component α -β Like subunit
A	α_2 β_2
A2	α_2 δ_2
F	α_2 γ_2
Portland	ξ_2 γ_2 (1ST 8 wks of I.U.life)
Gower 1	ξ_2 ε_2
Gower 2	α_2 ε_2
H	β_4
Bart's	γ_4



Hb electrophoresis on citrate medium

https://labpedia.net/haemoglobin-hb-electrophoresis/



Main site of haematopoeisis

Yolk sac — Fetal Liver — Bone Marrow

Prenatal age (weeks)		Post-natal age (weeks)
0-8 weeks	8-40 weeks	>24 weeks
$\zeta_2\varepsilon_2$ Hb Gower I $\alpha_2\varepsilon_2$ Hb Gower II $\zeta_2\gamma_2$ Hb Portland I	$\alpha_2\gamma_2$ HbF	$\alpha_2\beta_2$ HbA

King et al. NEJM 2018

Alpha thalassemia

Beta thalassemia

Sickle cell disease

Hb C disease

Hb E disease

HbX*

High affinity hemoglobinopathies

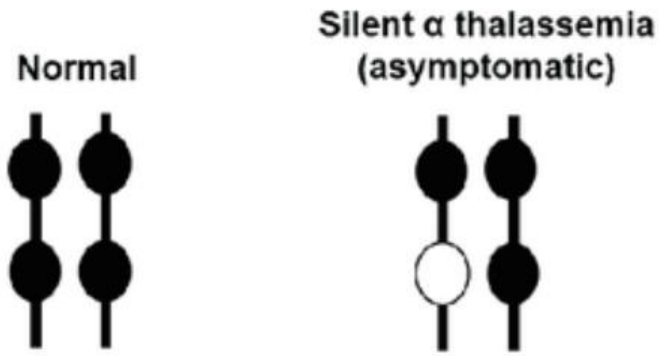
TABLE 1

Prevalence of hemoglobinopathy gene carriers in the world's population (1–3, 6, e1, e2)

Region	Gene carriers
Africa	5 to 30%
Arab nations	5 to 40% Up to 60% regionally
Central Asia and India	10 to 20%
South-East Asia	5 to 40% Up to 70% regionally
USA and Central America	5 to 20%
Italy	7 to 9%
Greece	6 to 7%
Turkey	7 to 10%
Germany, Great Britain, Portugal, Spain, France, the Netherlands, Belgium, Scandinavian countries	Among total population: 0.5 to 1% Among immigrants: 5%
Albania, the former Yugoslavia, Croatia, Bosnia-Herzegovina, Bulgaria	2 to 5%
Russia	Rare
Transcaucasia	Up to 5%

Kohn et al. Dtsch Arztebl Int 2011; 108(31–32): 532–40

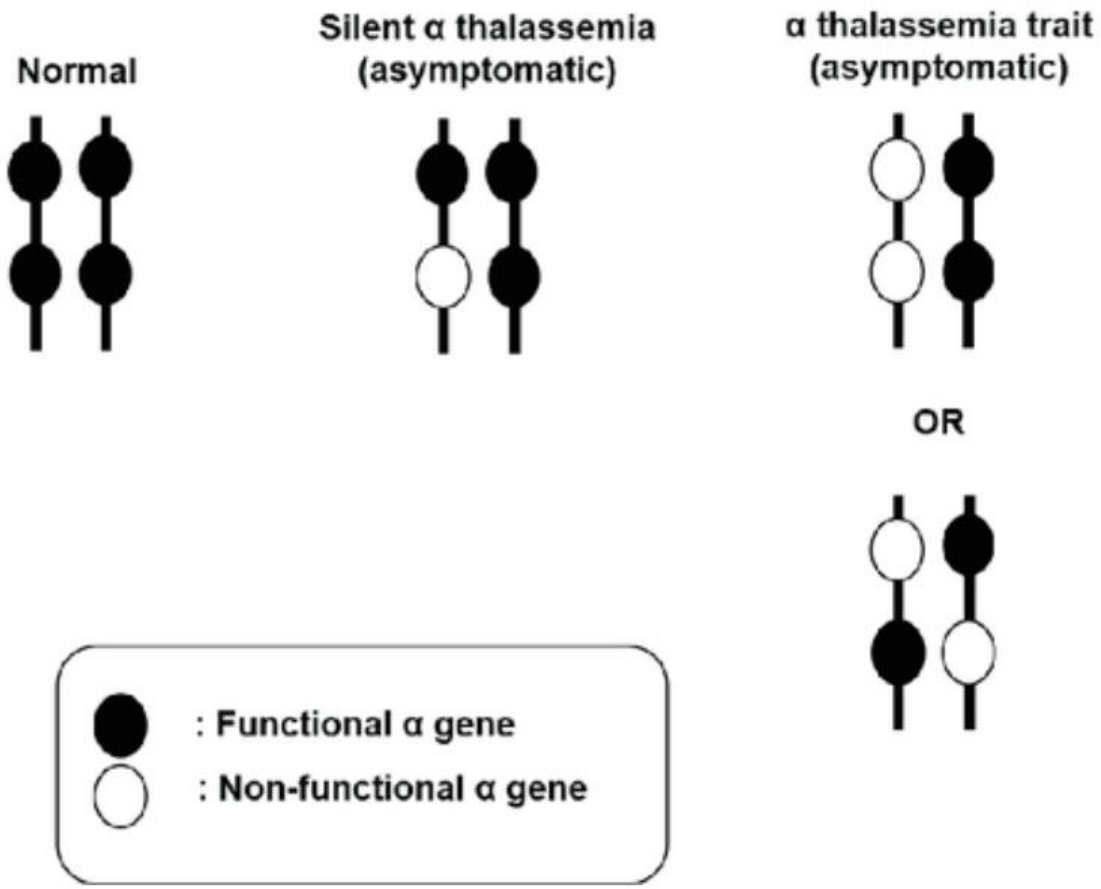
Alpha Thalassemia



Phenotypic expression and types of α-thalassemia.

Normal Hemoglobin
Mild Microcytosis
Requires genetic testing for diagnosis

Alpha Thalassemia



Phenotypic expression and types of α-thalassemia.

Mild Anemia
Mild Microcytosis
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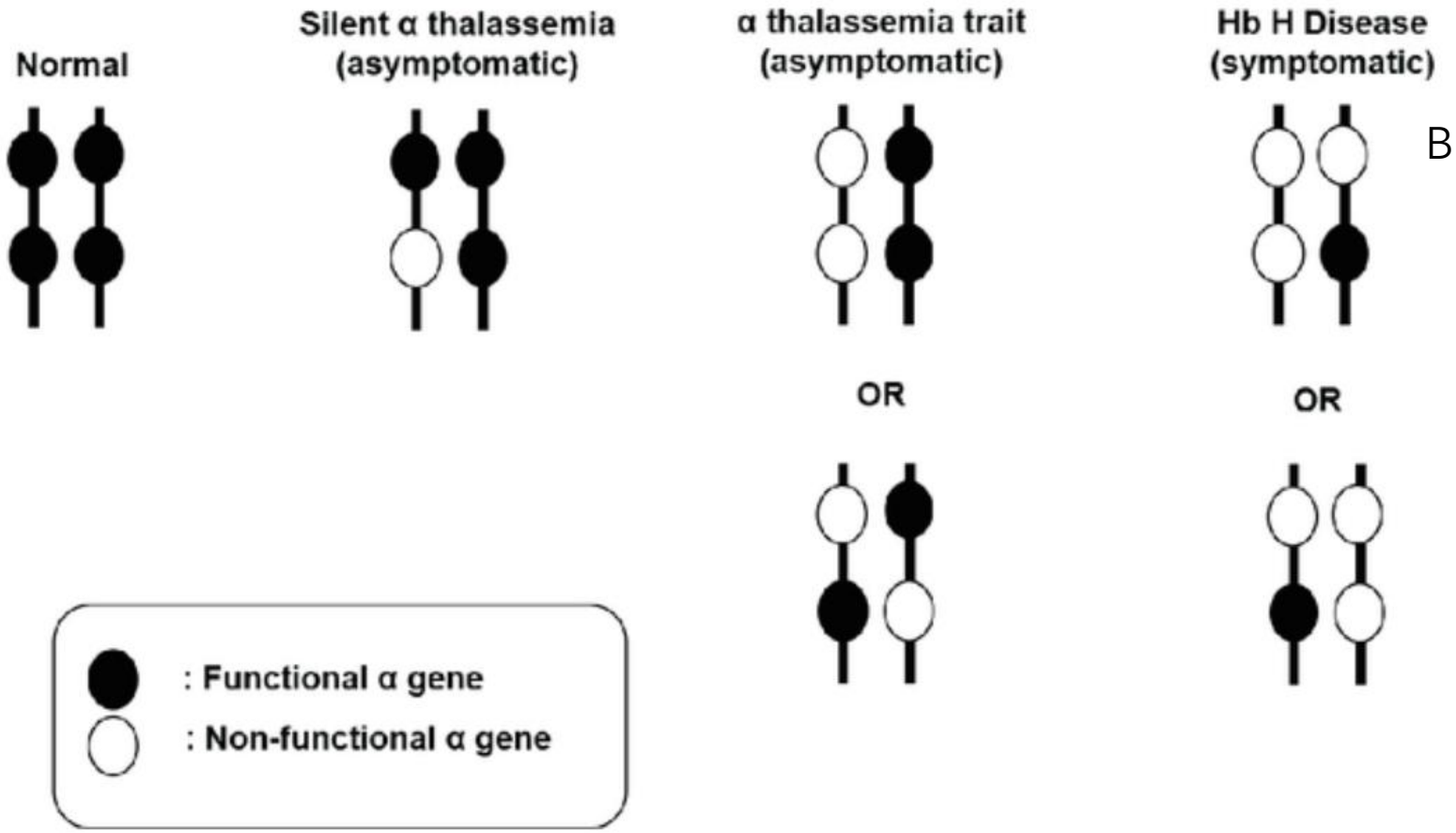
Alpha Thalassemia



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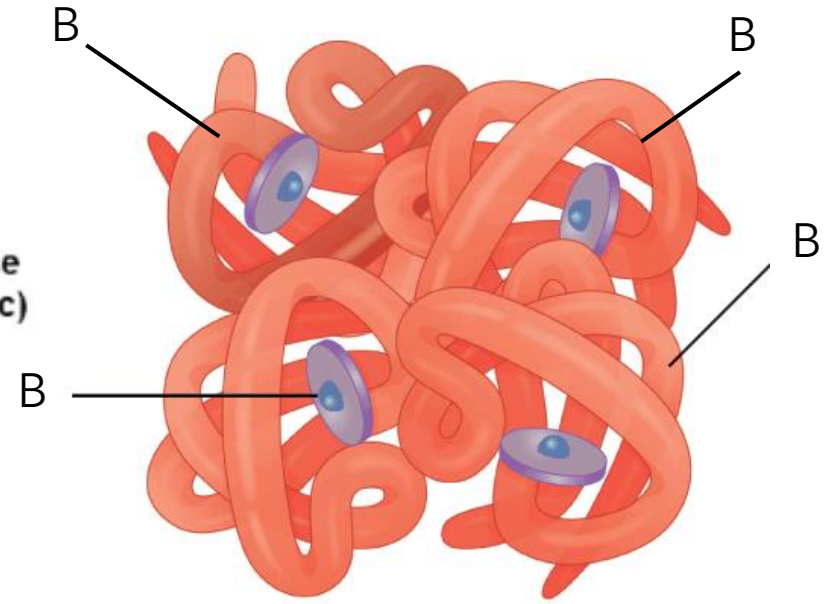
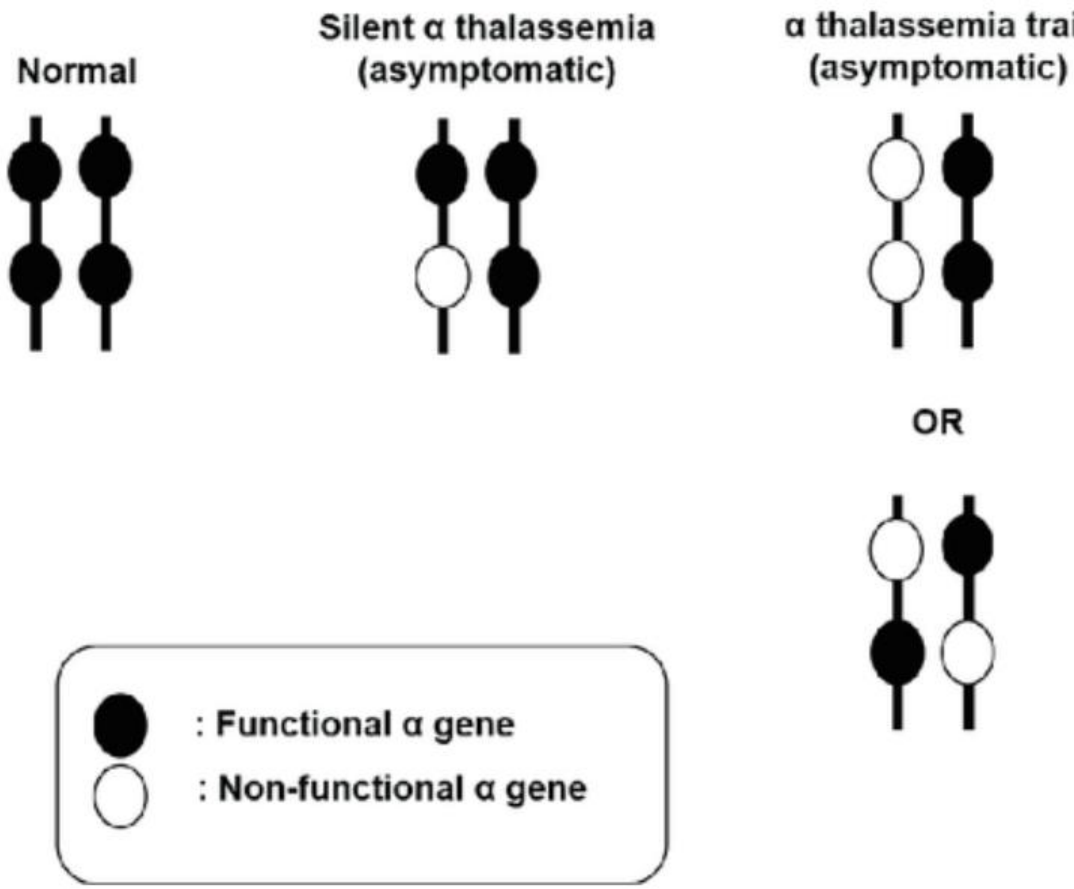


Moderate microcytic anemia (Hb 8-10g/dL)
Hemolysis

Alpha Thalassemia



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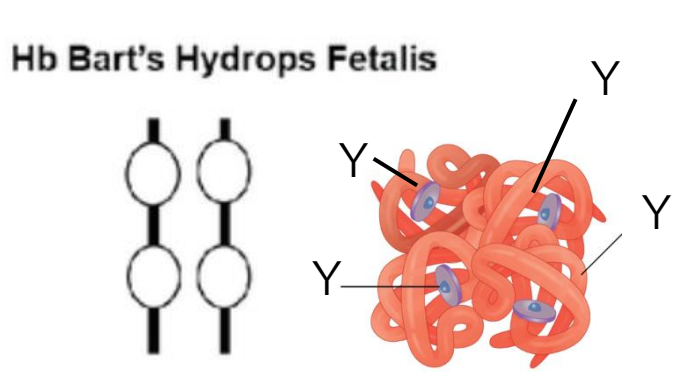
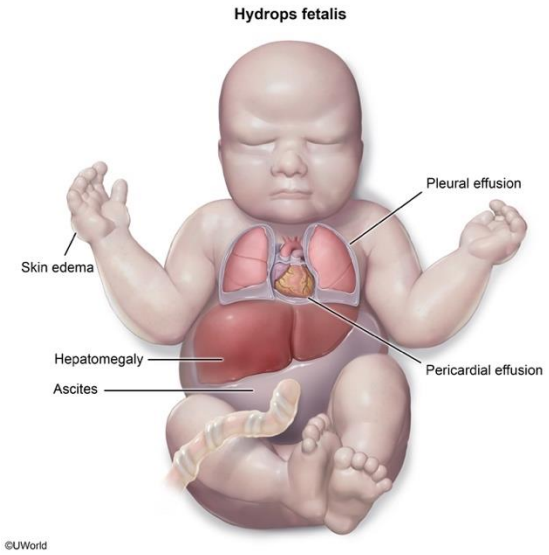


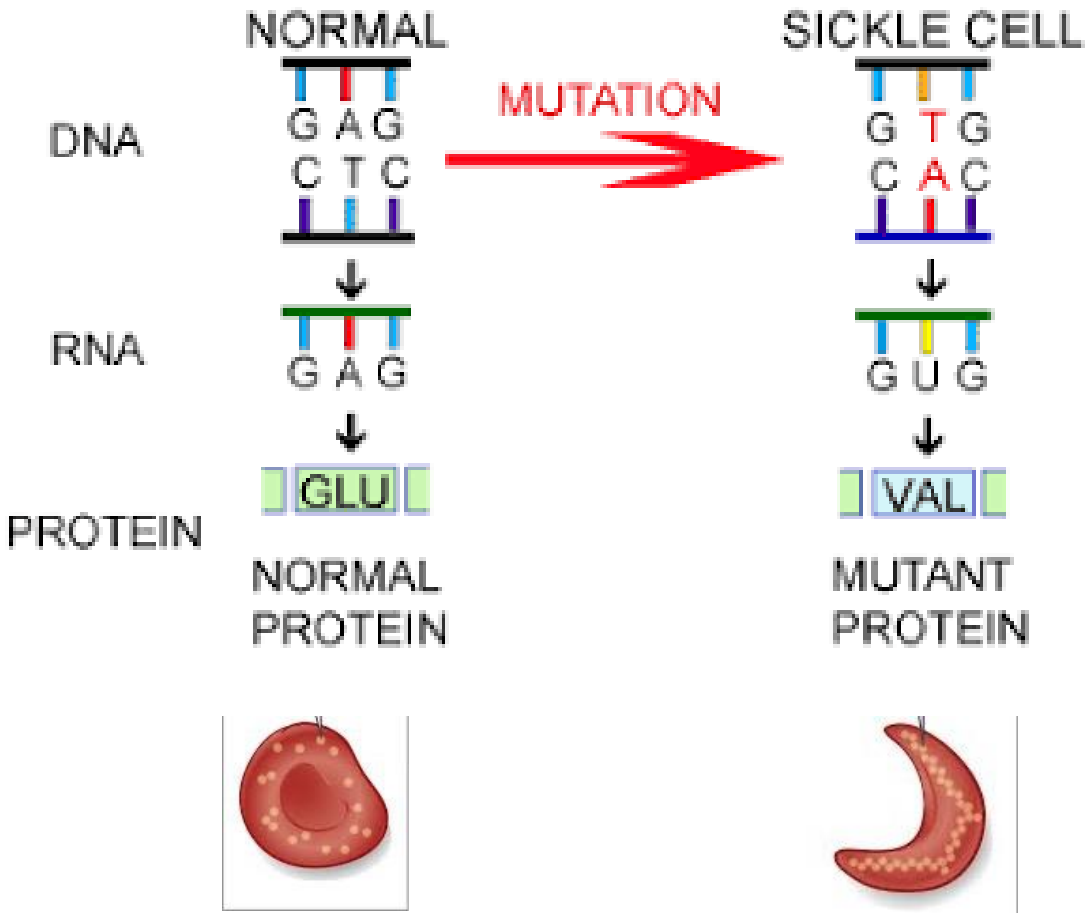


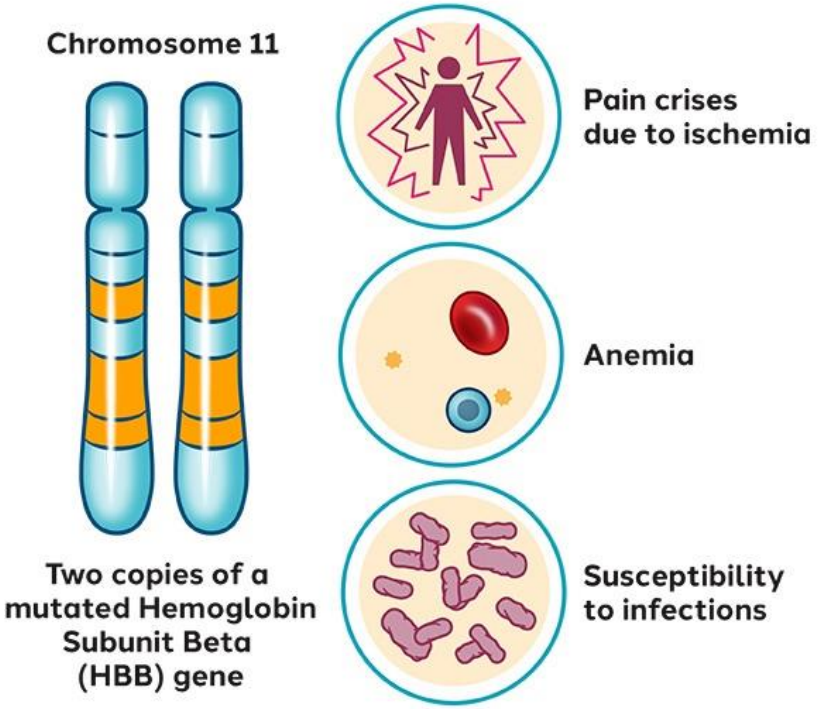
Beta Thalassemia

Nomenclature	Genotype	Phenotype
β Thal Minor (β Thal Trait)	β/β^{+} or β/β^{0}	Mild Anaemia (Hb>9) Microcytosis ~55-75fL ↑ HbA_2(3.5-5%)
β Thal Intermedia (Non-Transfusion Dependent Thal)	β^{0}/β^{+} (Mild Variants) or β^{+}/β^{+}	Jaundice, Splenomegaly Mod Anaemia (Hb ~7) Microcytosis ~55-70fL ↑ HbA_2 (1-2%), ↑ HbF (~60%) EMH, Iron Overload
β Thal Major (Transfusion Dependent Thal)	β^{0}/β^{+} (Severe Variants) Or β^{0}/β^{0}	Jaundice, Splenomegaly Severe Anaemia (Hb 3-7) Microcytosis ~55-60fL No HbA, ↑ HbF (~90%) EMH, Iron Overload Bone Deformities

LearnHaem

Sickle Cell Disease





https://www.sangamo.com/programs/clinical-trials/sickle-cell-disease/

Hemoglobin C
Hemoglobin E

Hemoglobin	Point mutation position	Amino acid substitution	Codon and base substitution
HbS	Beta 6	Glu → Val	GAG → GUG
HbC	Beta 6	Glu → Lys	GAG → AAG
HbE	Beta 26	Glu → Lys	GAG → AAG

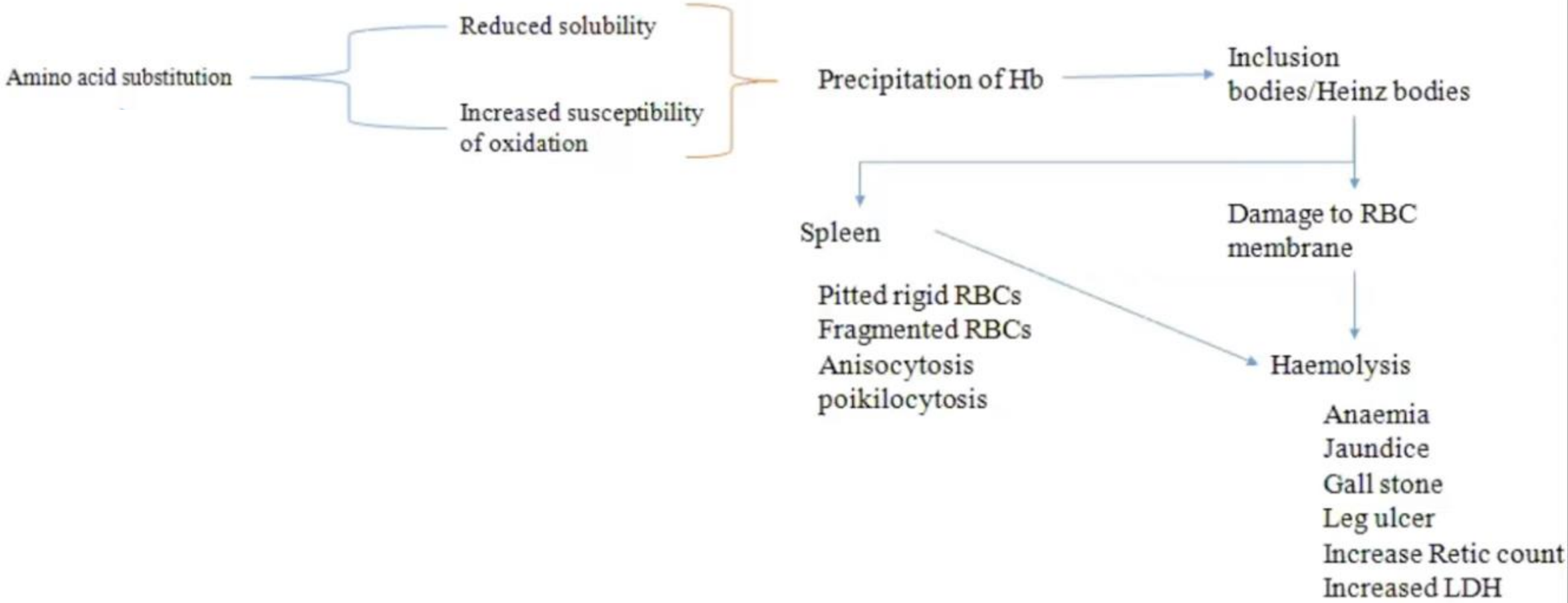
TABLE 3

Diagnoses, gene types, hematological findings, and cardinal symptoms of the main hemoglobin disorders (2, 3, 10, 13)

Diagnosis	Gene type	Red blood cell (RBC) count	Hemoglobin pattern	Cardinal symptoms
Sickle-cell disease	HbSS	Hb 6 to 9 g/dL Normochromic sickle cells Positive hemolysis parameters	HbS = 55 to 90% HbA_2 >3.5% HbF = <10 to >20%	Sickle-cell crises/pain crises Acute organ syndromes Chronic hemolytic anemia
HbS heterozygosity	HbAS	Normal	HbS = 35 to 40% HbA_2 ≥3.5%	No apparent illness
Sickle-cell β^+-thalassemia	HbS β^+-thalassemia	Hb 9 to 12 g/dL Hypochromia, microcytosis	HbS >55% HbF >20% HbA_2 >3.5%	Variable, mild sickle-cell disease
Sickle-cell β^0-thalassemia	HbS β^0-thalassemia	Hb 6 to 10 g/dL Hypochromia, microcytosis	HbS >80% HbF <20% HbA_2 >3.5%	Severe sickle-cell disease
HbSC disease	HbSC	Hb 10 to 13 g/dL Target cells MCV <75 fl	HbS ≈ 50% HbC ≈ 50% HbF <5%	Weak symptoms of sickle-cell disease Chronic hemolytic anemia
HbC disease	HbCC	Hb 10 to 12 g/dL Target cells MCV <75 fl MCHC >35 g/dL	HbC >95% HbA_2 ≈ 2.5% HbF ≈ 0.5%	Pain crises Organ events Chronic hemolytic anemia
HbC heterozygosity	HbAC	Normal	HbC ≈ 50% HbA ≈ 47% HbA_2 = 3%	No apparent disease
HbE heterozygosity	HbAE	Hb normal or slightly low Hypochromia	HbE = 25 to 35%	Mild, hypochromic anemia
HbE disease	HbEE	Hb 10 to 14 g/dL High RBC count MCH 20 pg MCV 65 fl Target cells	HbE >95% HbA_2 ≈ 2.5% HbF <3%	Mild anemia Hemolysis caused by infections/ medical drugs

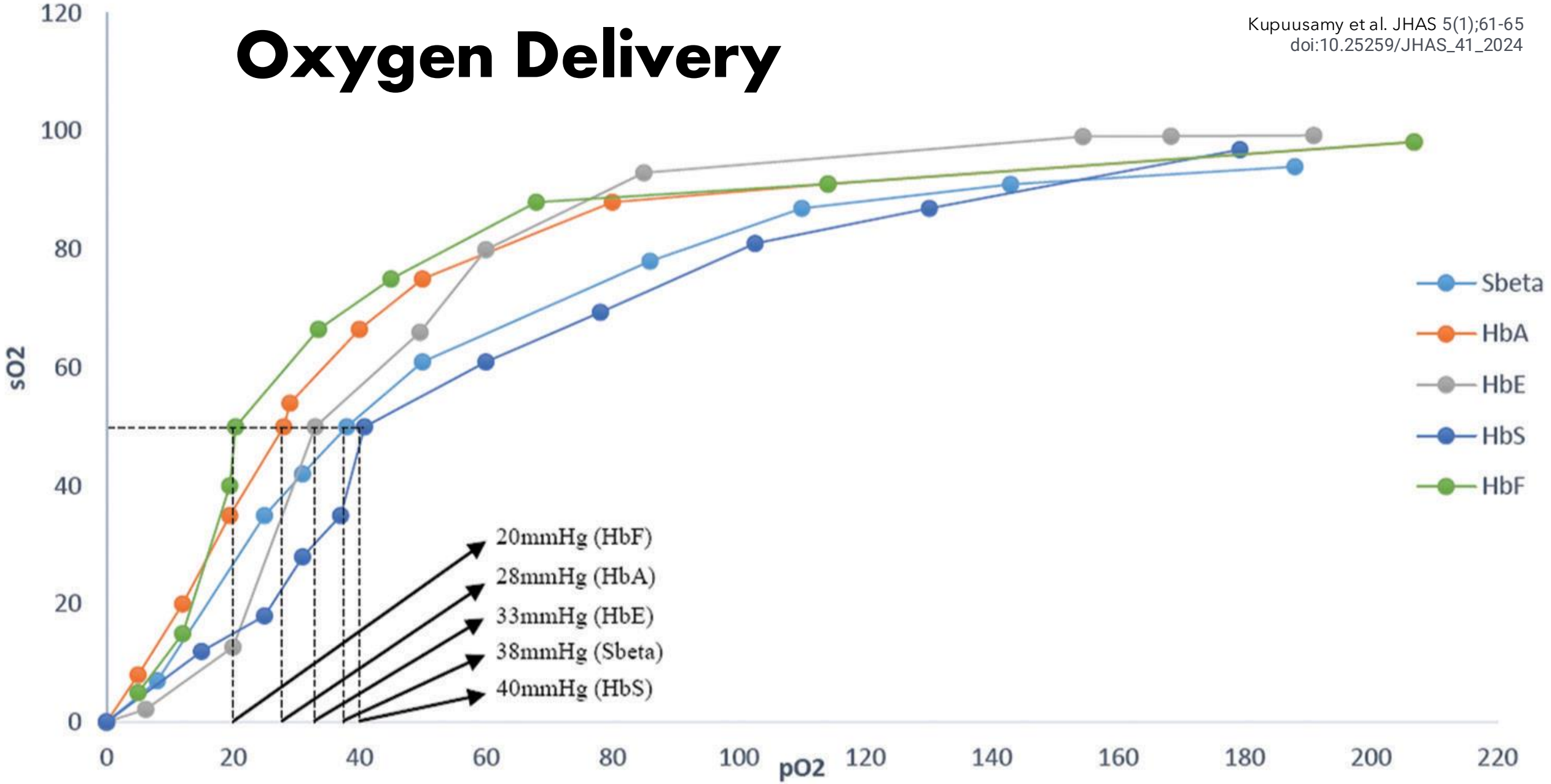
Kohn et al. Dtsch Arztebl Int 2011; 108(31–32): 532–40

Unstable Hemoglobins

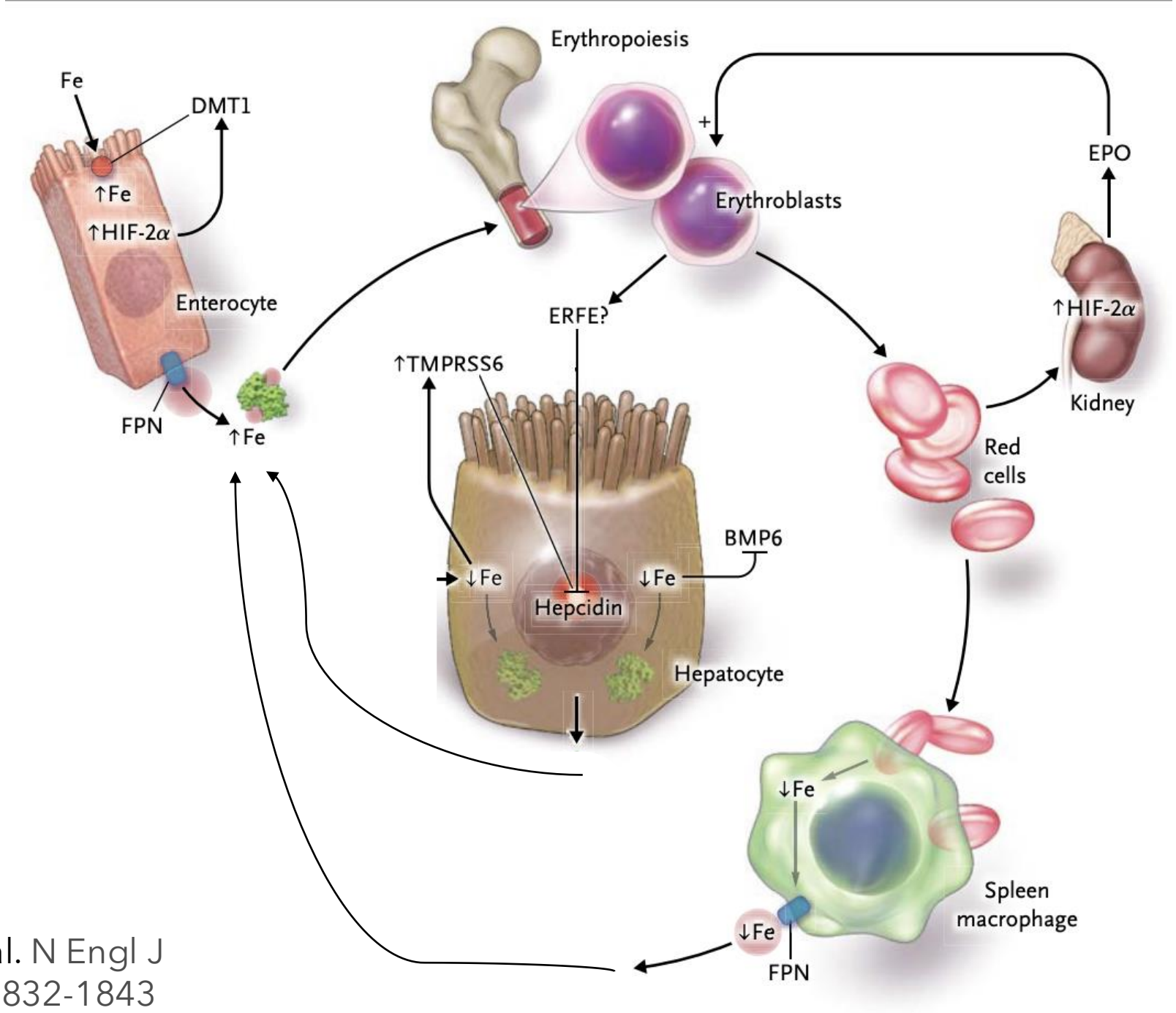


Oxygen Delivery

Kupuusamy et al. JHAS 5(1);61-65
doi:10.25259/JHAS_41_2024

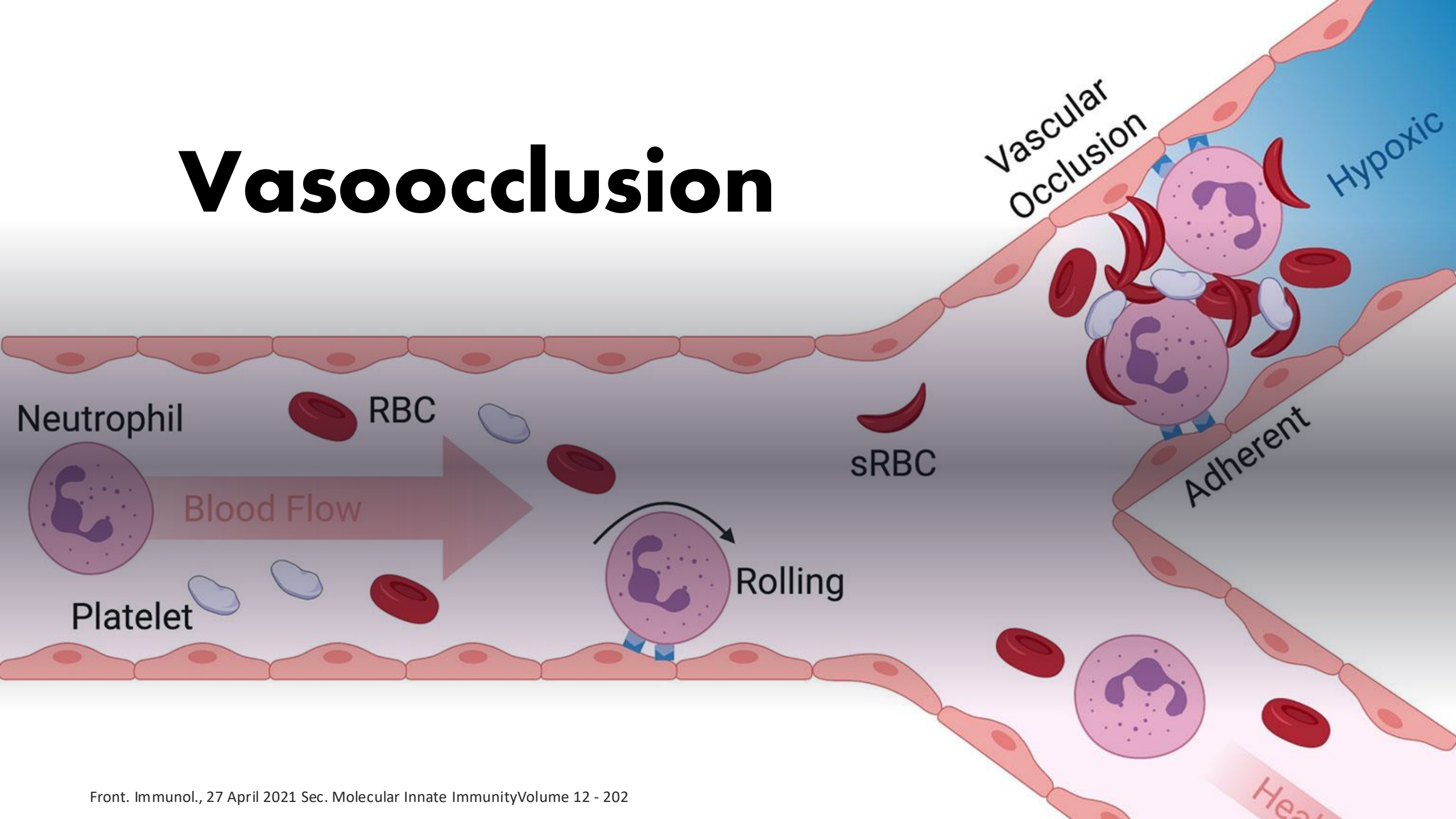


IRON OVERLOAD



Camaschella et al. N Engl J Med 2015;372:1832-1843

Vasoocclusion



Front. Immunol., 27 April 2021 Sec. Molecular Innate ImmunityVolume 12 - 202

Vasoocclusive Complications

Acute

- Acute chest
- Infections
- Cholecystitis
- Stroke
- Splenic sequestration
- Priapism
- Vasoocclusive crisis

Chronic

- Pulmonary HTN
- Iron overload
- Renal disease
- Avascular necrosis
- Retinopathy
- Leg ulcers

High affinity hemoglobinopathies

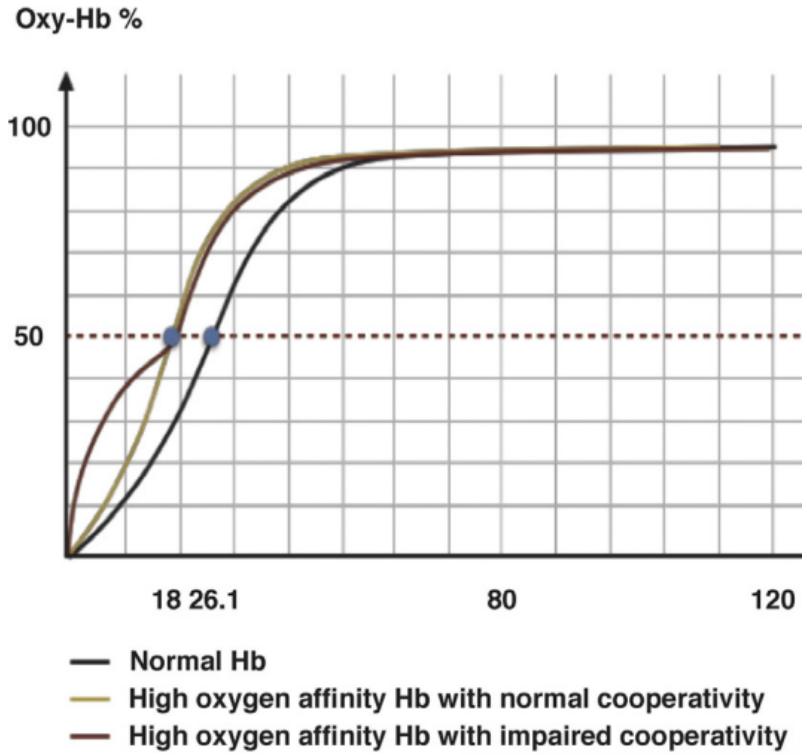
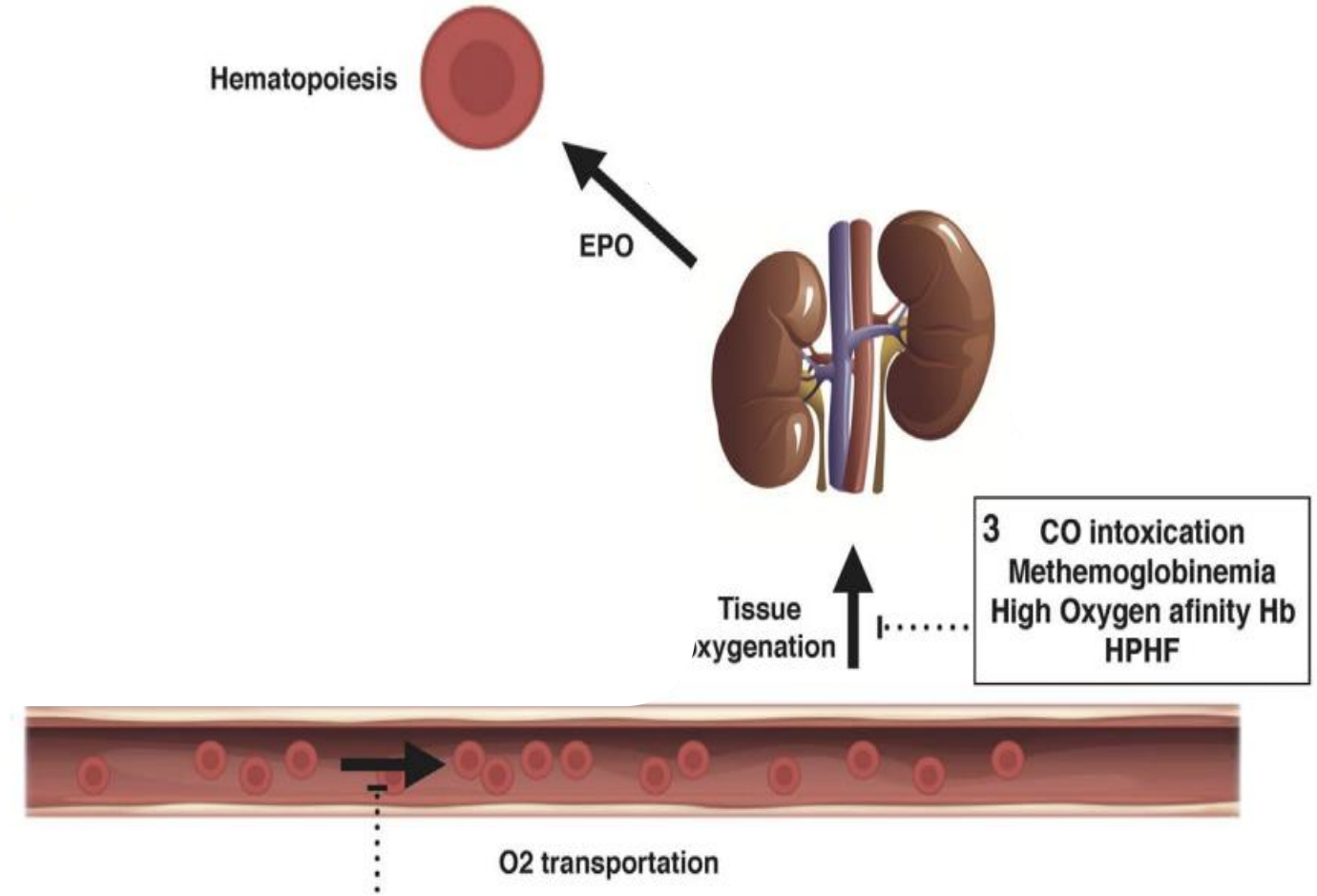
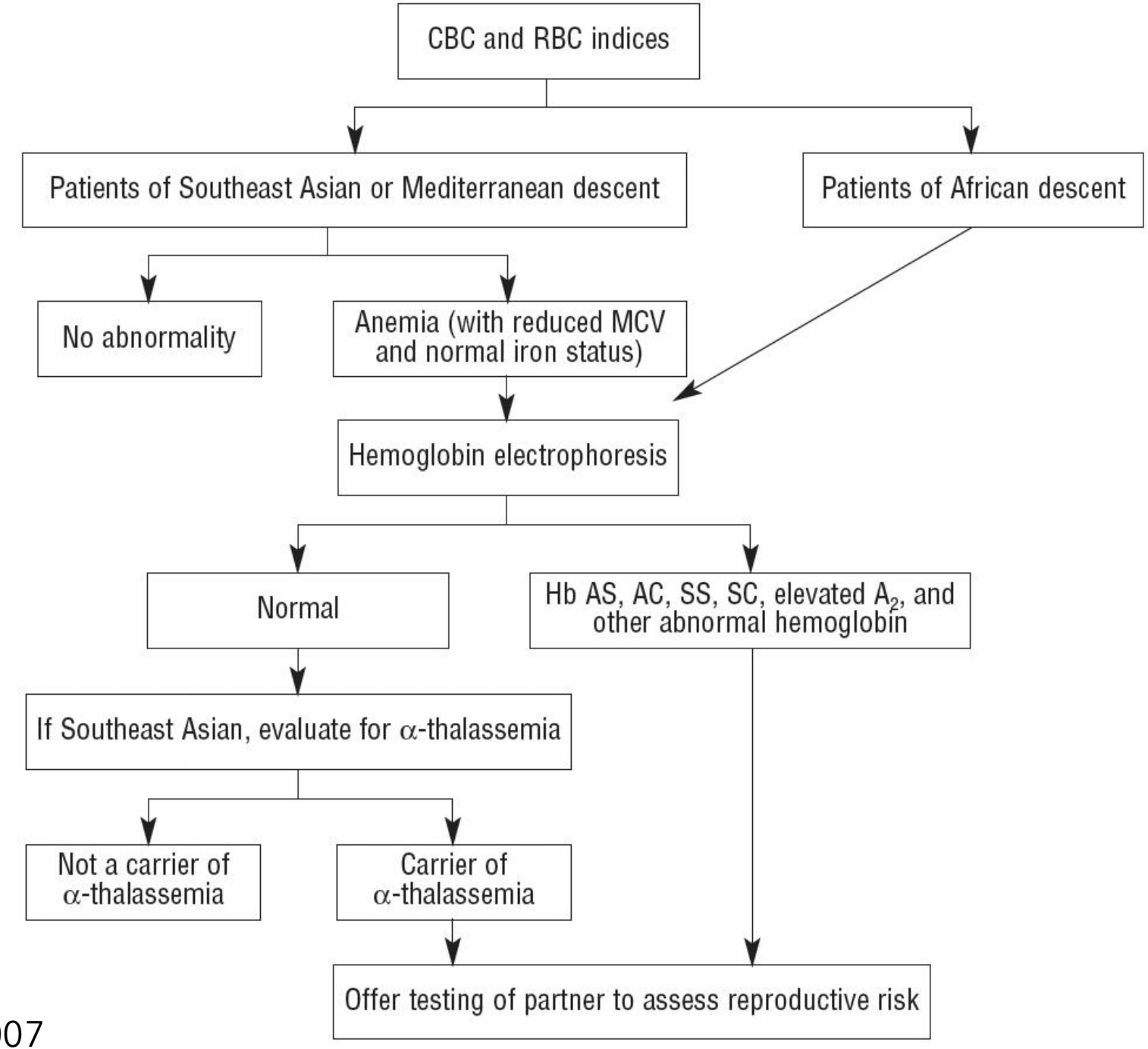


Fig. 1. Oxygen dissociation curves according Hb's O2 affinity and



Hemoglobinopathy Screening



ACOG practice bulletin. 2007

Hemoglobinopathy Diagnosis

Hemoglobin electrophoresis, isoelectric focusing, or high performance liquid chromatography

Genetic testing

Oxygen dissociation curves

Sickle cell solubility screening test

Considerations in the pregnant patient

Avoidance of factors that precipitate vasoocclusive/pain crises: Cold, heavy physical exertion, dehydration, stress
Folic acid supplementation: 4mg daily
Care in centers with expertise in mgt of sickle cell complications
Hb >10 (Hb SS and B thal) and Hb S < 40%*
Consideration to exchange transfusion 4-6 weeks prior to delivery*
Avoid Hydroxyurea and iron chelation (3 months prior to conception)
Aspirin with increased risk for pre-eclampsia, anticoagulation with history of stroke/VTE and inpatient ppx

Considerations for neonates

Sickle cell Disease

+ Serial ultrasounds and antepartum fetal testing
+ Monitoring for post natal opioid withdrawal
+ Monitoring for signs/symptoms of acute ischemic stroke
+ Referral to hematology

Hb barts Hydrops fetalis

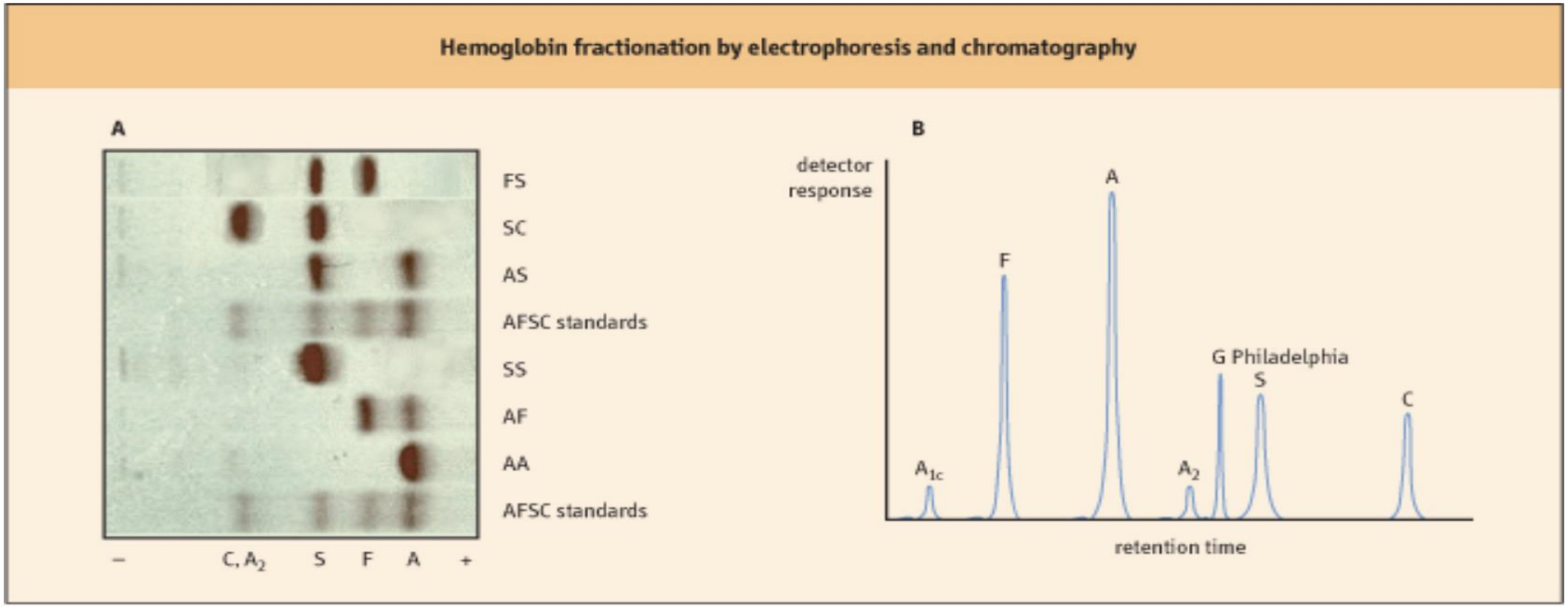
+ Prevention through screening
+ Intrauterine bone marrow transplantation? CRISPR?

B thalassemia Major

+ Early initiation of transfusion/possibly intrauterine

Newborn screening

NEWBORN SCREEN RESULT	PRESUMED DIAGNOSIS
FA	Normal
FAS	Sickle cell trait
FS	Sickle cell anemia: Hemoglobin SS or hemoglobin S/β^0 thalassemia
FSA	Hemoglobin S/β^+ thalassemia
FSC	Hemoglobin SC disease
F	Transfusion-dependent β-thalassemia (β-thalassemia major)
FA Barts	Hemoglobin H disease



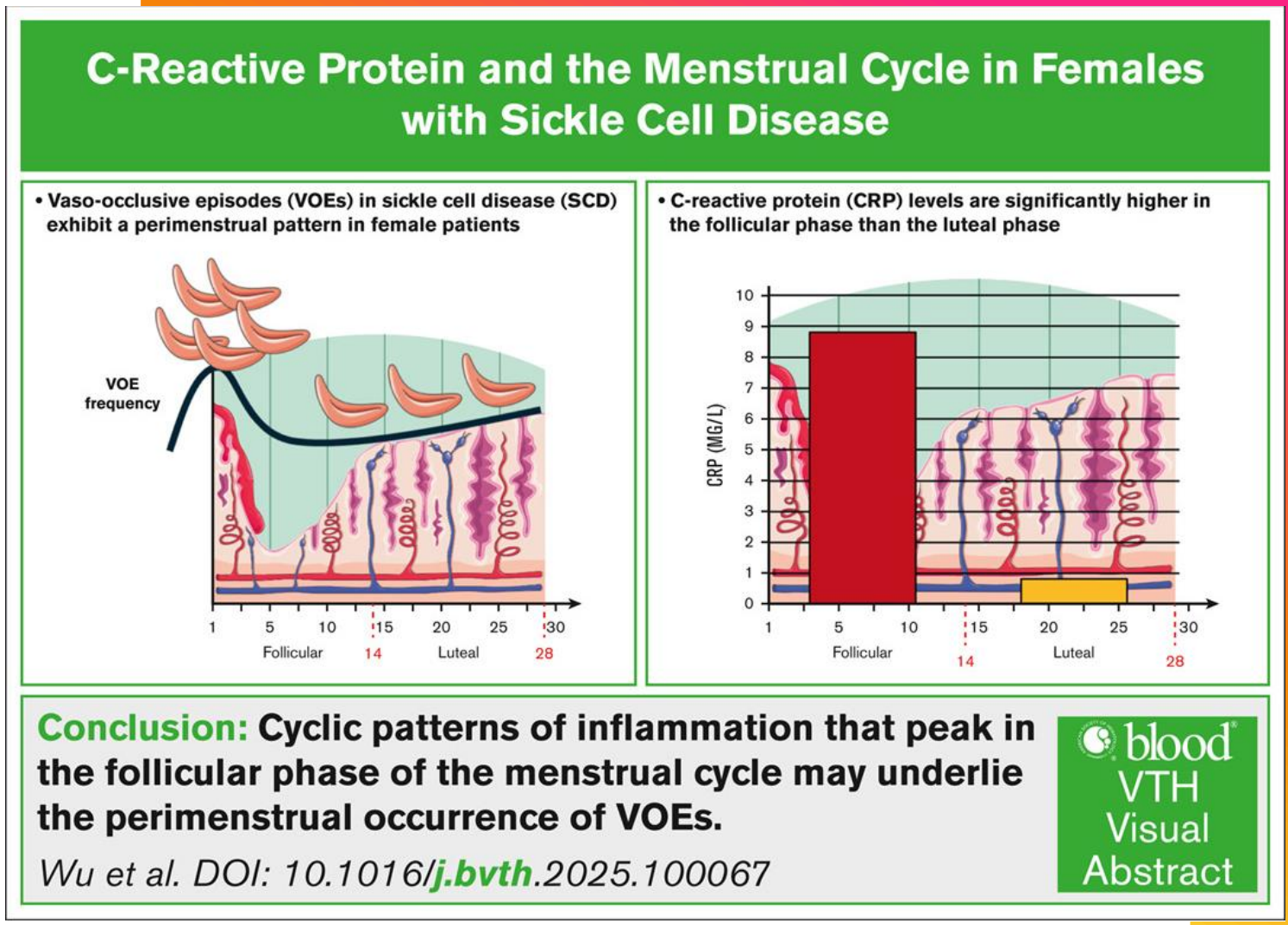
Hb SS and contraceptives/HRT/GAHT

Condition	Sub-Condition	Cu-IUD	LNG-IUD	Implant	DMPA	POP	COC
Age		Menarche to <20 yrs:2	Menarche to <20 yrs:2	Menarche to <18 yrs:1	Menarche to <18 yrs:2	Menarche to <18 yrs:1	Menarche to <40 yrs:1
		≥20 yrs:1	≥20 yrs:1	18-45 yrs:1	18-45 yrs:1	18-45 yrs:1	≥40 yrs:2
				>45 yrs:1	>45 yrs:2	>45 yrs:1	
Obesity	a) Body mass index (BMI) ≥30 kg/m²	1	1	1	1	1	2
	b) Menarche to <18 years and BMI ≥ 30 kg/m²	1	1	1	2	1	2
Smoking	a) Age <35	1	1	1	1	1	2
	b) Age ≥35, <15 cigarettes/day	1	1	1	1	1	3
	c) Age ≥35, ≥15 cigarettes/day	1	1	1	1	1	4
Dysmenorrhea	Severe	2	1	1	1	1	1

King et al. Mediterr J Hematol Infect Dis 2020; 12; e2020032

Other gynecologic considerations

+ 30-40% HMB
+ Sexual dysfunction and dyspareunia are also common
+ NSAIDs can be safely used for dysmenorrhea



Hematologic Treatment

- Hydroxyurea

  No evidence that it decreases pain during menstruation (no impact on CRP). Can not be used during pregnancy

- Simple or Exchange transfusions

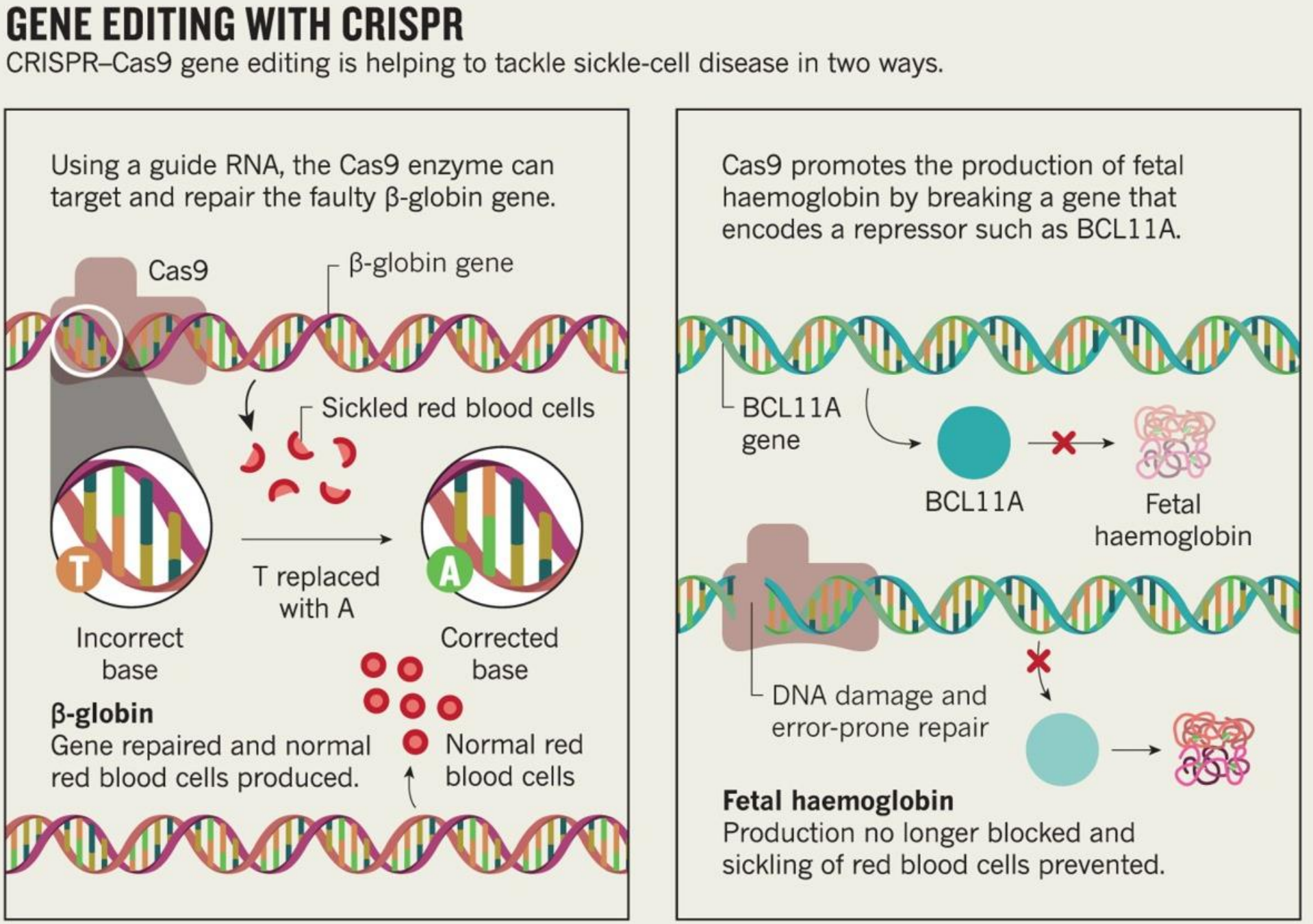
  Only available treatment during pregnancy

- Voxelotor – withdrawn from market
- Crizanlizumab – P selectin inhibitor

  Can not be used during pregnancy

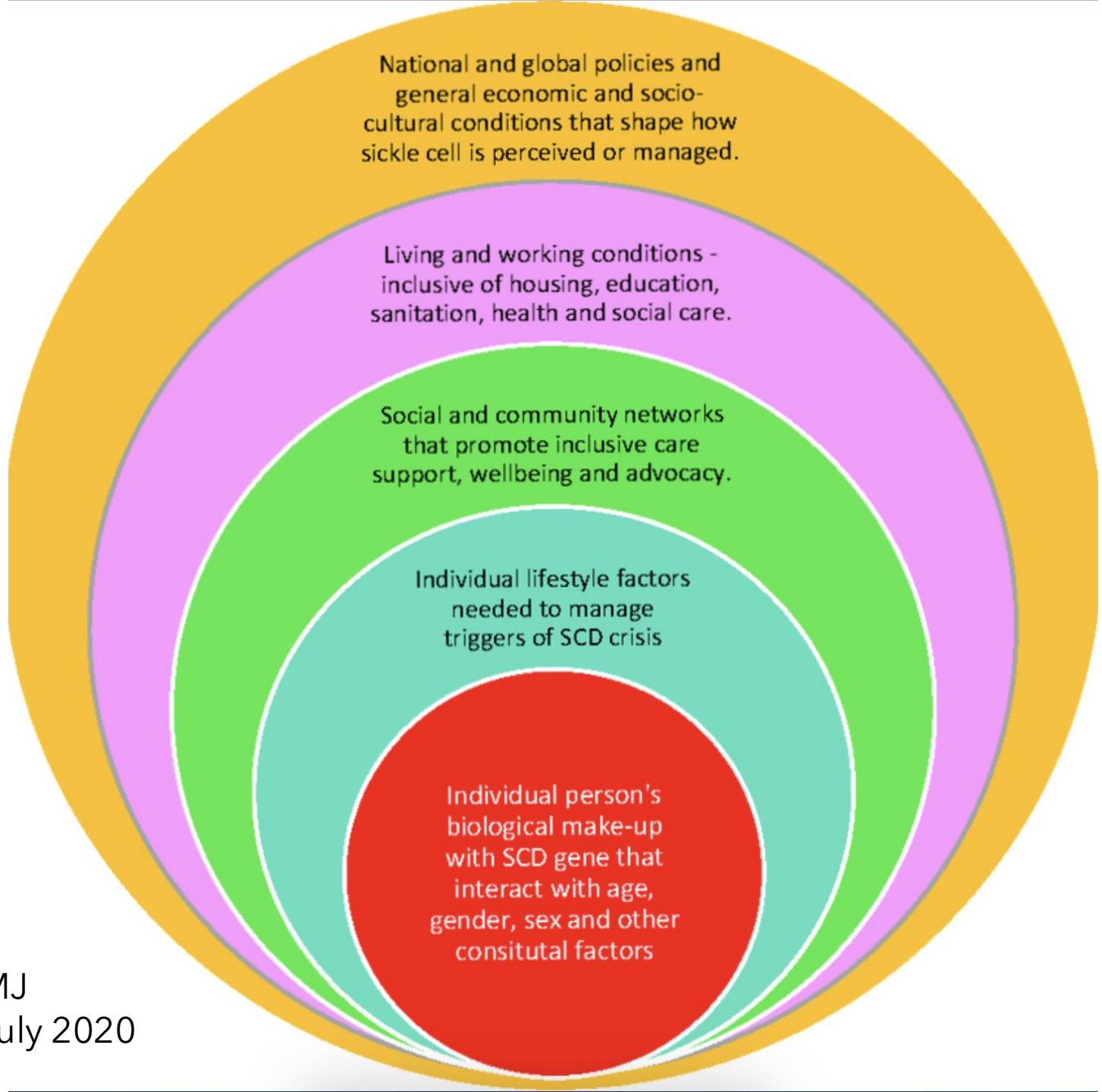
- L-glutamine – amino acid powder

BMT and Gene Therapies



Bourzac et al. Nature **549**, pagesS28–S30 (2017)

Intersectionality and determinants of health in sickle cell disease



Berghs et al. BMJ global health. July 2020