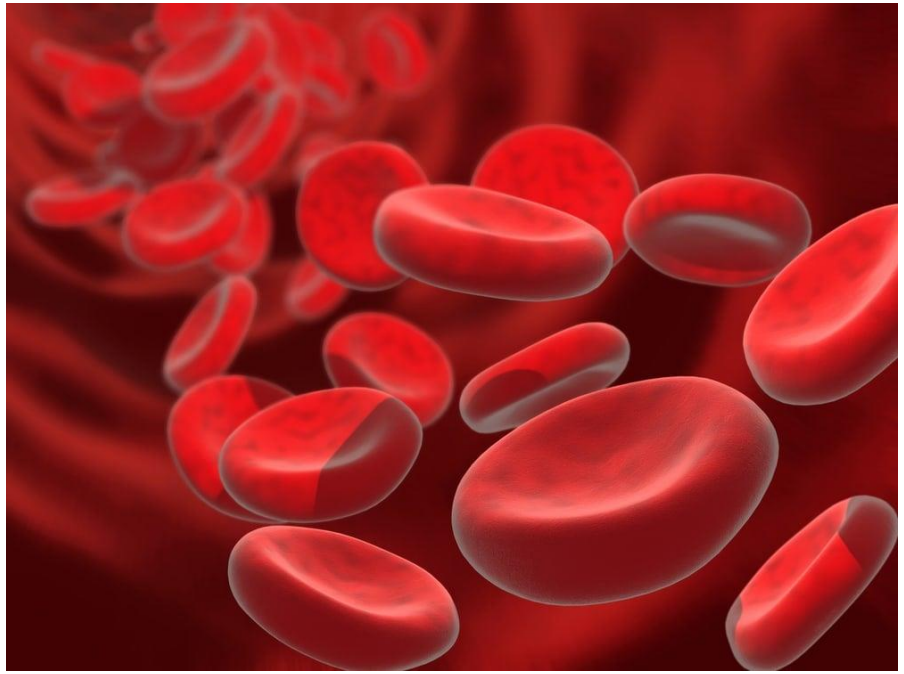
Fred Hutch Cancer Center

UW Medicine

Thalassemias and Hemoglobin Disorders



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Land Acknowledgement

Fred Hutchinson Cancer Center acknowledges the Coast Salish peoples of this land, the land which touches the shared waters of all tribes and bands within the Duwamish, Puyallup, Suquamish, Tulalip and Muckleshoot nations.

DISCLOSURES

Advisory Board – Agios Pharmaceuticals, Sanofi Genzyme, bluebird bio (beti-cel)

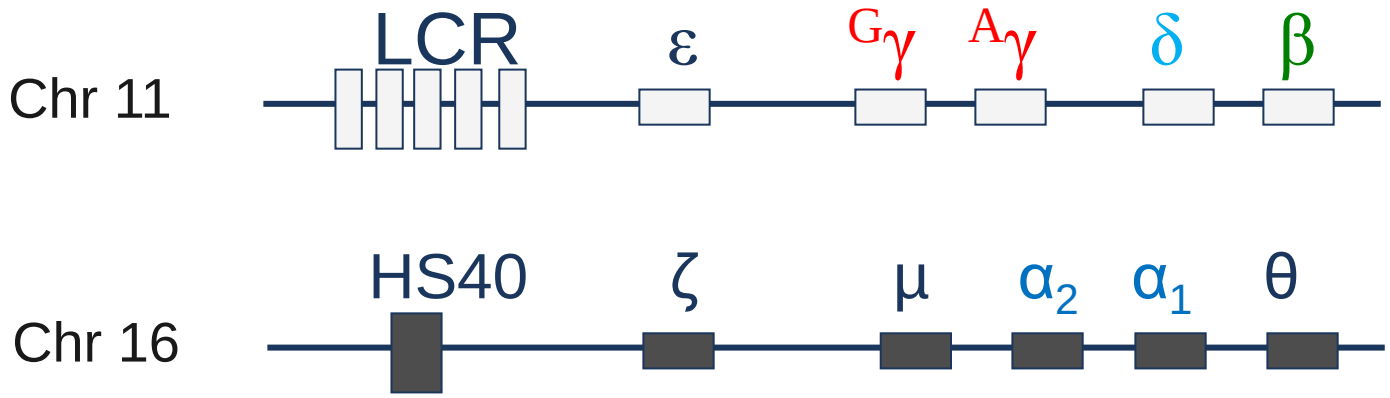
Consultancy – Agios Pharmaceuticals, Sanofi Genzyme

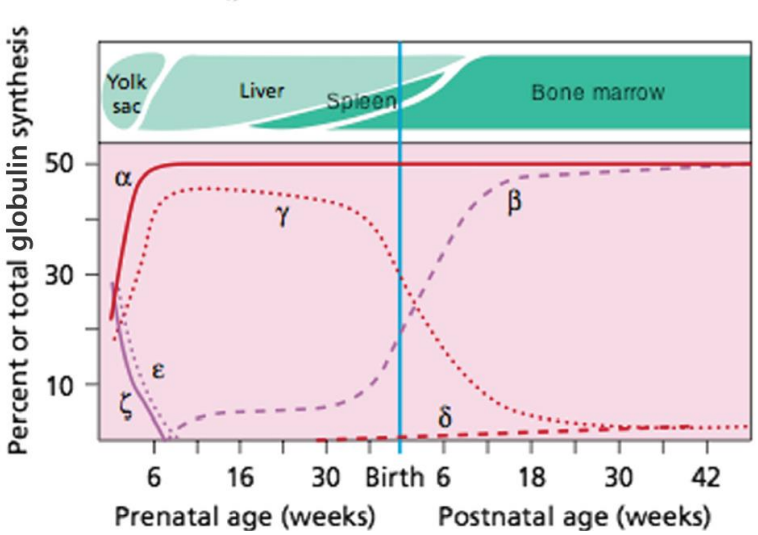
Speaker – Agios Pharmaceuticals

ABIM Hematology exam blueprint

Red blood cell destruction disorders *(15%*		Diagnosis	Testing	Treatment/ Care Decisions	Risk Assessment/ Prognosis/ Epidemiology	Pathophysiology/ Basic Science
Thalassemias						
Alpha thalassemia	LF	⊘	⊘	⊘	⊘	⊘
Beta thalassemia	LF	⊘	⊘	⊘	⊘	⊘
Hemoglobin E disorders	LF	⊘	⊘	✕	✕	✕
Sickle cell disorders *(4.5% of exam)*						
Sickle cell trait		⊘	⊘	⊘	⊘	⊘
Sickle cell anemia (hemoglobin SS disease)		✓	✓	✓	✓	⊘
Hemoglobin SC disease	LF	⊘	⊘	⊘	⊘	⊘
Sickle cell-beta zero and sickle cell-beta plus-thalassemias	LF	⊘	⊘	⊘	⊘	⊘
Non-sickle hemoglobinopathies	LF	⊘	⊘	⊘	✕	✕

Globin genes and hemoglobins





Postembryonic hemoglobin species

A	$\alpha_2\beta_2$	(97%)
A_2	$\alpha_2\delta_2$	(3%)
F	$\alpha_2\gamma_2$	(<1%)

Figure from ASH SAP 2013 Chapter 7.

Hemoglobin disorders

- **Qualitative abnormality: hemoglobinopathies**
  - Amino-acid substitution results in structurally abnormal hemoglobin
    - Hb S, Hb C, Hb D Punjab, Hb E
    - unstable Hb
    - Hb with high or low oxygen affinity
- **Quantitative abnormality: thalassemias and hereditary persistence of fetal hemoglobin**
  - Reduced/absent production of a globin chain;
    - α-thalassemia (reduced or no α-chains, excess β-chains)
    - β-thalassemia (reduced or no β-chains, excess α-chains)
    - HPFH (no production of δ or β-chains, only γ-chains)
- **Combination: thalassemia-hemoglobinopathy**
  - May lead to either phenotype;
    - e.g. sickling disorder in HbS/β-thalassemia, thalassemia in HbE/β thalassemia

ABIM Hematology exam blueprint

- **Thalassemias**
  - β-thalassemia
  - α-thalassemia
  - Hemoglobin E disorders

- **Sickle cell disorders**
  - Sickle cell trait
  - Sickle cell anemia (hemoglobin SS disease)
  - Hemoglobin SC disease and C hemoglobinopathy
  - Sickle cell-β^0 and sickle cell-β^+ thalassemias

- **Non-sickle hemoglobinopathies**
- **Educational resources**

Genetics of thalassemias

β-thalassemias

- expressed several months after birth (requires γ-globin → β-globin switch)
- Predominantly point mutations

α-thalassemias

- Typically expressed earlier (*in utero* and at birth)
- Predominantly gene deletion(s)
  - (-α) or (--) alleles
- Non-deletional: most common is the $\alpha^{CS}\alpha$ allele (Hb Constant Spring)

Distribution of α and β thalassemia

β-thalassemias

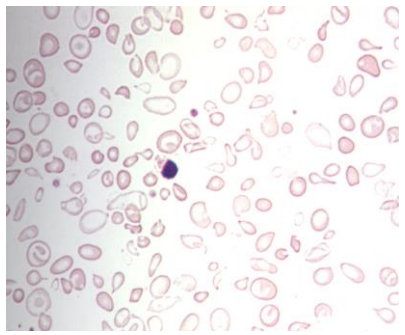
Causative mutations

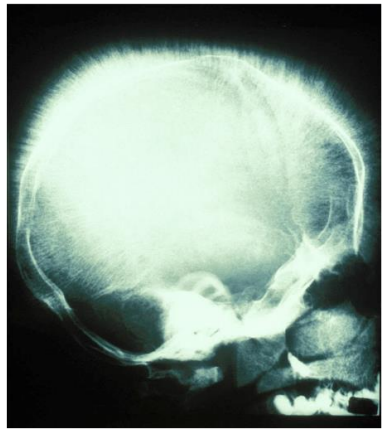
β^0 (null) = No gene product

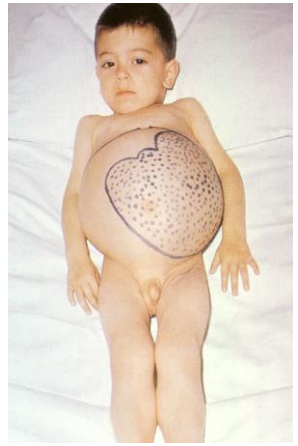
β^+ = reduced production

- **Excess α-globin chains → <u>INEFFECTIVE ERYTHROPOIESIS</u>**
  - α-globin aggregates in erythroid precursors → intramedullary death
  - Signals iron absorption by the gut (relatively low hepcidin) → **<u>IRON OVERLOAD</u>**
- **Excess free intracellular iron:**
  - membrane lipid oxidation and protein damage → phosphatidylserine exposure → **hypercoagulability**
  - decreased RBC deformability and increased clearance from circulation → **<u>HEMOLYSIS</u>**

Pathophysiology and complications of thalassemias







From Guidelines for the Managements of Nontransfusion dependent Thalassemia. Thalassemia International Federation publication 2013.

Hoffbrand & Pettit Color Atlas of Clinical Hematology; © Harcourt, 2000

Clinical classification of β-thalassemias

Clinical Phenotype	Hb (g/dL)	Transf	Clinical features	Most common genotypes
β-thalassemia minor (trait)	**10-12**	**No**	No hemolysis, no splenomegaly, asymptomatic, **RBC>5million**, **HbA_2>3.5%**	**β^0/β or β^+/β**
β-thalassemia intermedia	7-10	+/-	**high Hb F,** bone disease, **transfusion and/or spontaneous** iron overload, splenomegaly*, pulm HTN, leg ulcers	**β^+/β^+ or β^+/β^0**
β-thalassemia major	<7	Age<2y	**>95% HbF**, bone disease, **transfusion** iron overload, splenomegaly*	**β^0/β^0 or β^0/β^+**

*splenomegaly due to increased hemolysis and extramedullary hematopoiesis

Current best supportive care for transfusion-dependent thalassemias

- **Treatment at comprehensive medical center**
  - Hematology, Genetics, Cardiology, Hepatology, Endocrinology, Ob/Gyn

Transfusion therapy

- **Indication: Hb<7g/dL, or Hb 7-10g/dL with symptomatic anemia, poor growth, extramedullary hematopoiesis, or bone disease**
- Adults require 2-3 phenotyped RBC units q 2-4weeks (approx. 50 units/year);
- Goals: keep **pre-transfusion hemoglobin 9.5-10.5 g/dL**

Iron chelation

- Indicated **after 10-20 pRBCs or ferritin>1,000ug/L**
- **Single iron chelator or combination therapy (cardiac involvement)**

Iron chelators

Medication	Dose	Route/form	Comments
Deferoxamine (DFO) (approved as first line for age>2)	50-60mg/kg/d 5-7 days per week **8-12h/day**	**SQ/IV** 8-24h	Local reaction, **hearing loss, retinopathy, growth delay**
Deferiprone (DFP) (approved as second line for age>6)	75-99mg/kg/d divided in 2-3 doses (depends on formulation)	PO tablets	**Neutropenia,** n/v/d, elevated LFTs, **arthropathy**
Deferasirox (DFX) (approved as first line for age>2)	20-40mg/kg/d **q24h**	PO dispersible tablets	**elevated creat**, rash, n/v/d
	14-28mg/kg/d **q24h**	PO tablets or sprinkles	**elevated creat**, rash, n/v/d, less diarrhea (**no lactose**)

β-thalassemia major: additional strategies

- **Splenectomy**
  - Indications: untransfusable due to alloimmunization, severe cytopenias, symptomatic splenomegaly; transfusion requirement >225-250mL/kg/year;
  - **less used than before due to complications**
    - post-op pancreatitis, pleural effusion, portal vein thrombosis;
    - long term risk for sepsis and VTE; need for antibiotic ppx
- **Luspatercept**
  - FDA-approved for transfusion-dependent ß-thalassemia in April 2020;
  - Activin receptor ligand trap → improves ineffective erythropoiesis
  - Dose: 1-1.25mg/kg SQ q 3 weeks
  - >33% reduction in transfusion burden and at least 2 RBC units over 12 weeks in 21.4% patients vs 4.5% on placebo
  - AE: bone pain, headache, asthenia, reports of extramedullary hematopoiesis

Capppellini et al. N Engl J Med 2020; 382(13):1219-31)

β-thalassemia major: allogeneic hematopoietic cell transplantation

Ideally: age<14; HLA-matched sibling donor; no significant iron overload.

- **Pesaro system: predicts post-BMT 3-year OS in children<16yo**

  Adverse factors:

  1. Hepatomegaly >2cm from costal arch
  2. Liver fibrosis on biopsy
  3. Irregular iron chelation

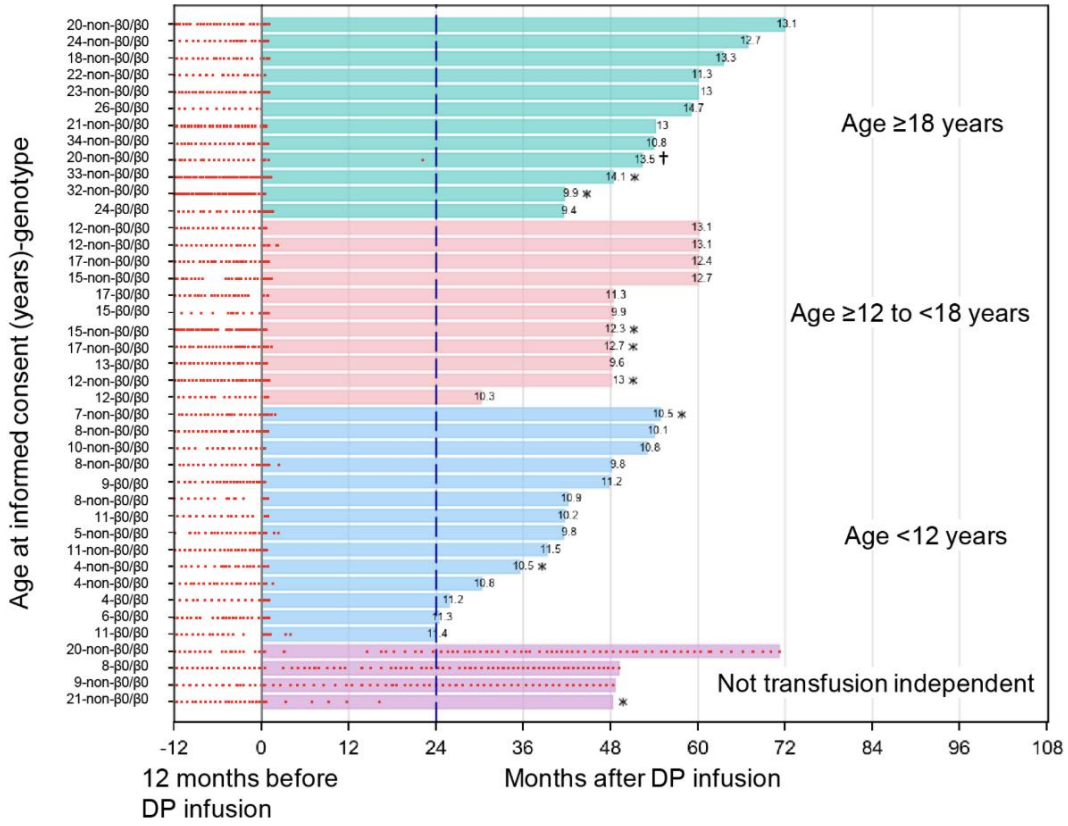
  ➢ Class I: 0 adverse factors → 94%

  ➢ Class II: 1 or 2 adverse factors → 80%

  ➢ Class III: all adverse factors → 61%

Betibeglogene autotemcel (beti-cel): lentiviral-based gene therapy

- approved by FDA in August 2022
- **Autologous transplant of PBSC transduced genetically** to add functional copies of a modified form of the beta globin gene $\beta^{A\text{-}T87Q}$



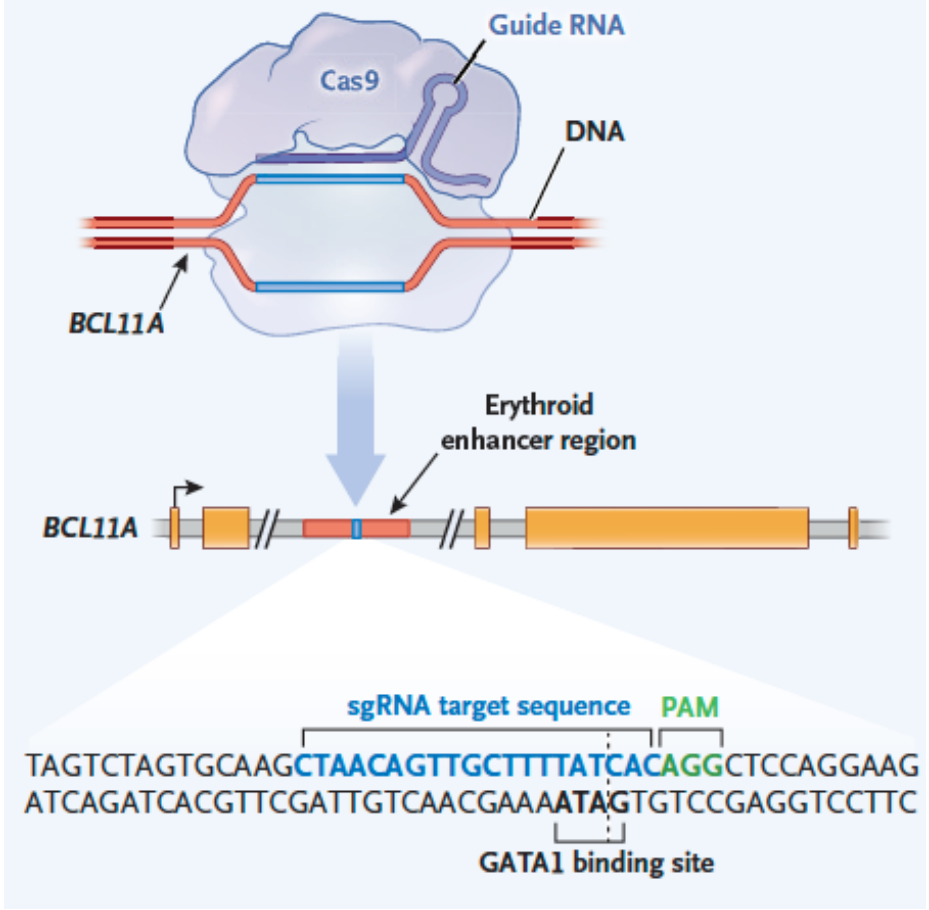
- 37/41 (90%) of patients achieved Hb≥9g/dL for ≥12months (primary endpoint)

J Kwiatowski et al. https://ash.confex.com/ash/2023/webprogram/Paper173869.html

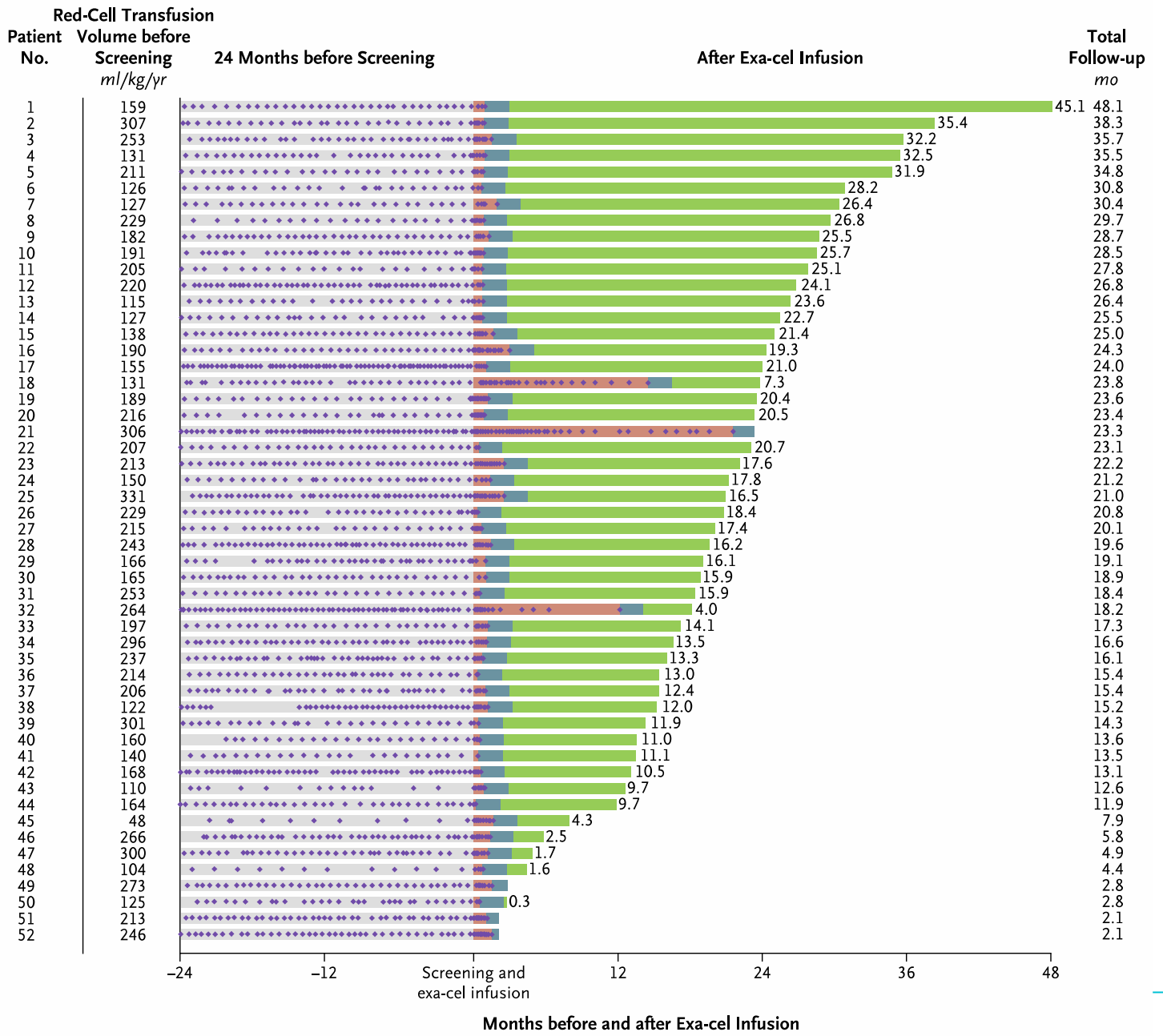
Thompson et al. N Engl J Med. 2018 Apr 19;378(16):1479-1493
F Locatelli et al. N Engl J Med 2022;386:415-427.

Exagamglogene autotemcel (exa-cel) CRISPR-Cas9-based gene therapy

- Approved by FDA in January 2024
- **Autologous transplant of PBSC modified genetically** to disrupt the erythroid-specific enhancer of gamma globin repressor BCL11A



N Engl J Med 2021;384:252-60.



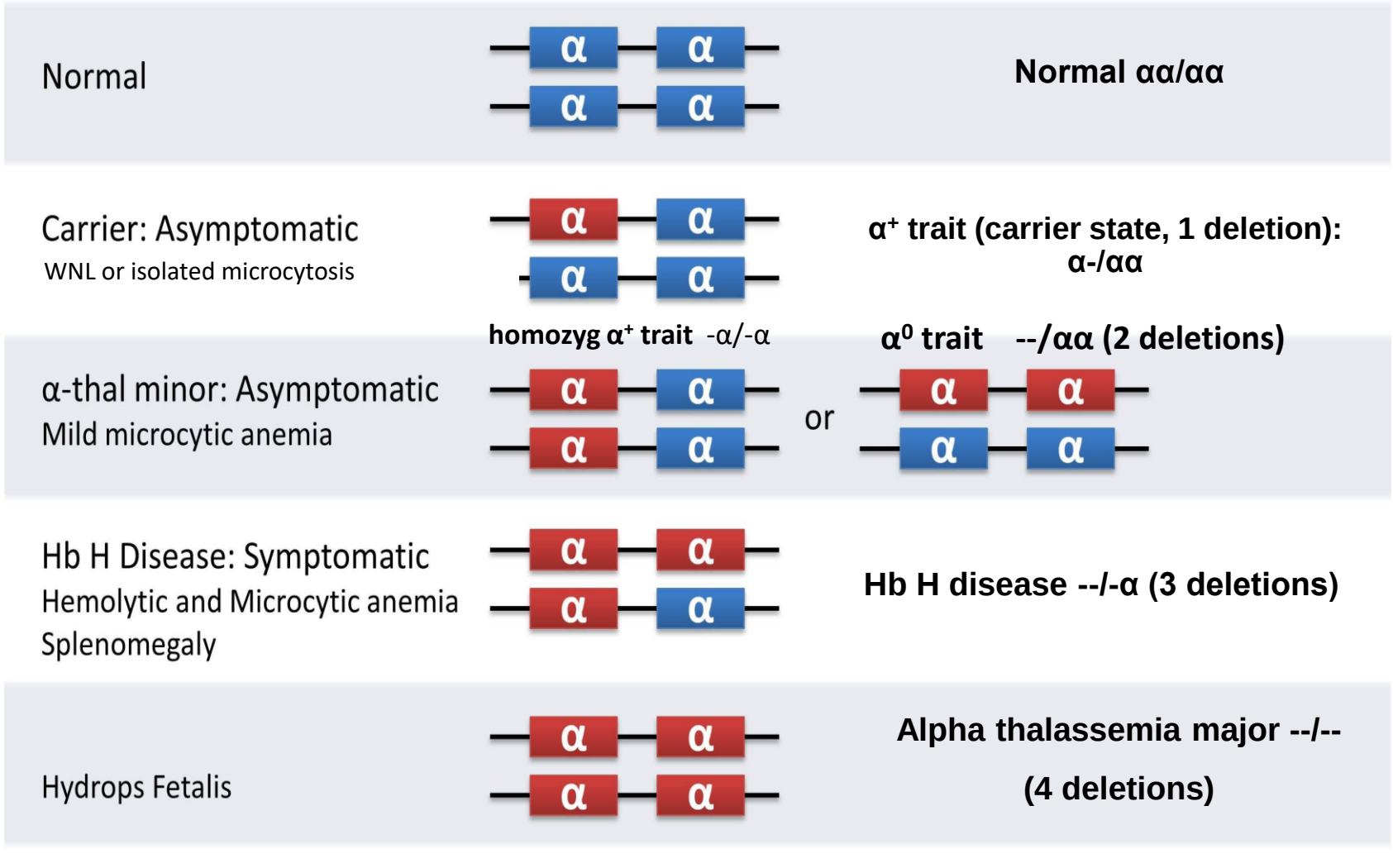
CLIMB THAL-111: primary endpoint

- 48/52 (92%) of patients achieved Hb≥9g/dL for ≥12months (primary endpoint)
- 3 of 4 patients who did not achieve the endpoint had <3mo follow-up
- 1 patient had 84% reduction in transfusion requirement

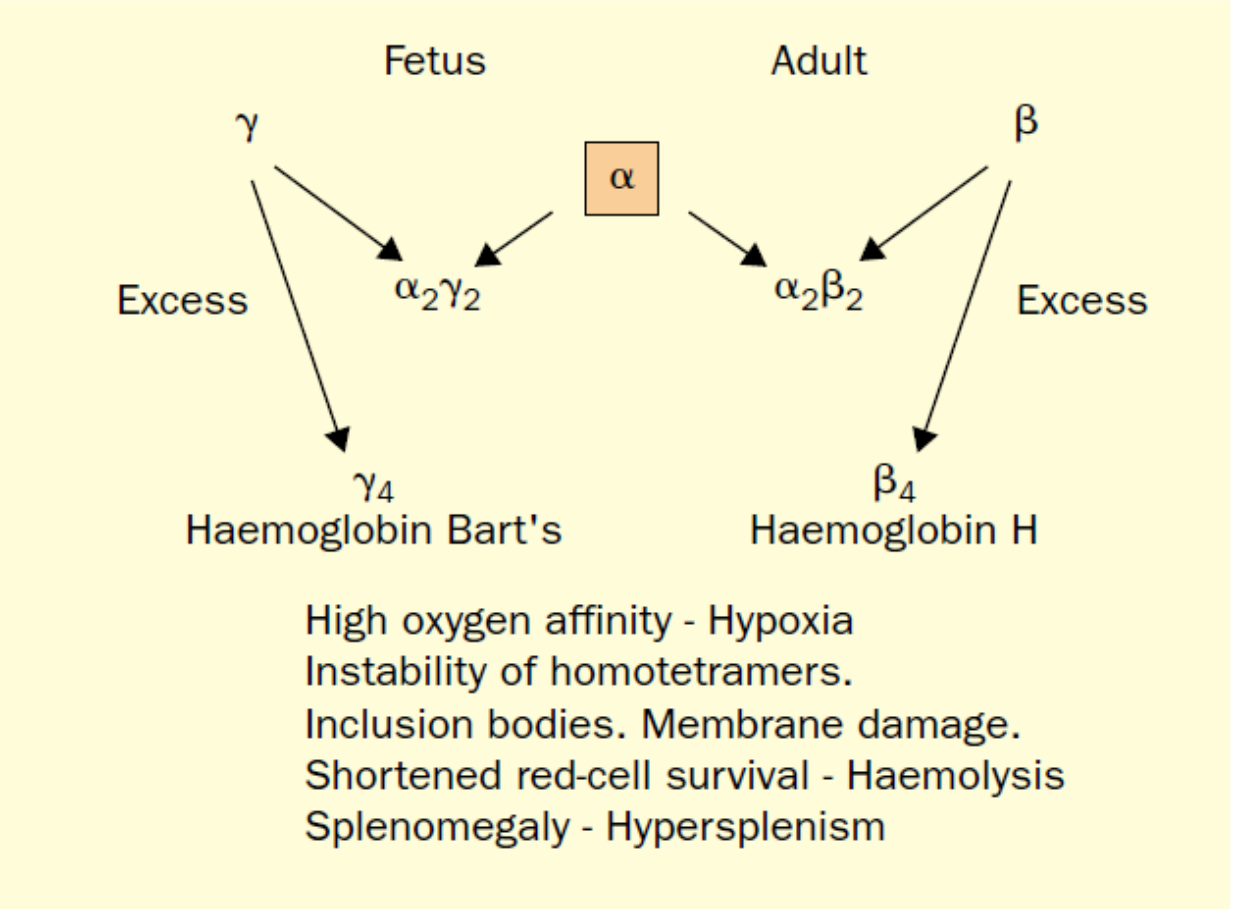
F Locatelli et al. N Eng J Med 2024;390:1663-76

α-thalassemia genetics: mostly deletions

Chromosome 16



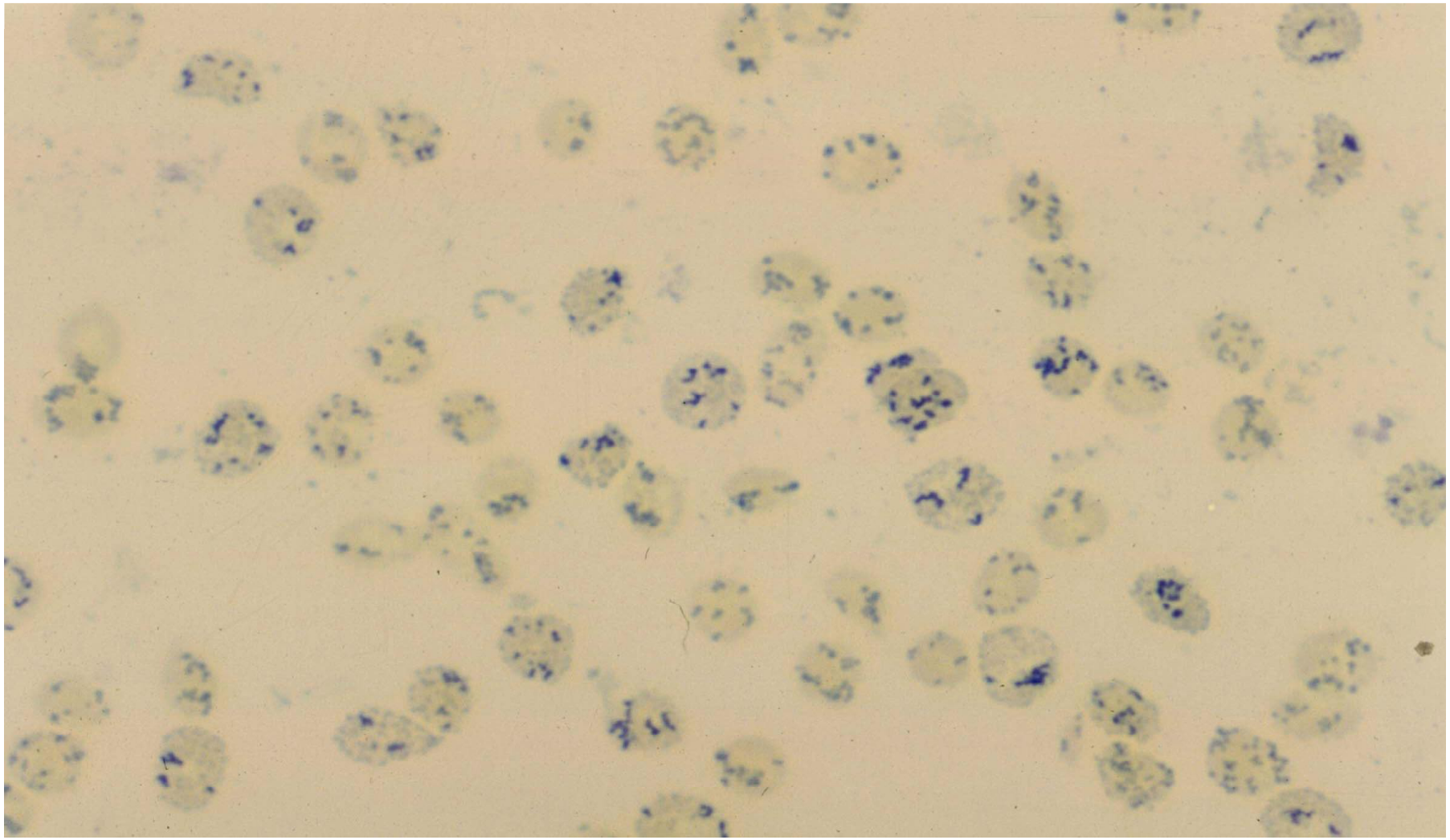
Pathophysiology of α-thalassemias



- excess of γ-like globin chains = γ_4 = Hb Bart's
- excess of β-like globin chains = β_4 = Hb H

Weatherall and Proven. *Lancet* 2000;355:1169-1175

Peripheral blood smear: Hb H inclusions on supravital stain



Courtesy of Dr. Daniel Sabath

Mild α-thalassemias (carrier state αα/α– or trait α–/α–, ––/αα)

KEY ELEMENTS:

1. No hemolysis
2. No anemia (1 deletion) or mild anemia (2 deletions)
3. Borderline microcytosis (1 deletion) or defined microcytosis (2 deletions)
4. Adults have normal hemoglobin electrophoresis

- Newborn screening: may show Hb Bart's
- May have family history of HbH or hydrops
- Adults: confirm with genetic testing for deletion (multiplex PCR screen);
- May find rare HbH inclusions in peripheral blood with supravital stain
- Management: genetic counseling; avoid unnecessary iron supplementation due to microcytosis with or without anemia

More severe α-thalassemias

- **Deletional HbH disease (α-/--) or non-deletional HbH (α-/$\alpha^{T}\alpha$)**
  - Diagnosis: hemolytic anemia with HbH in electrophoresis (5-30%, HbH is unstable)
  - Support: Folate supplementation and RBC transfusions +/-iron chelation if hemolytic exacerbations
  - Splenomegaly may lead to hypersplenism
  - Complications: gallstones, leg ulcers, aplastic crisis due to parvovirus B19

- **Alpha thalassemia major - Hb Bart's hydrops fetalis, (--/--)**
  - screening, prenatal and pre-conception genetic counseling in high-risk populations
  - Diagnosis with hemoglobin electrophoresis in fetal sample
  - Intrauterine transfusions followed by chronic transfusions and iron chelation
  - hematopoietic cell transplantation can be done

α-thalassemia pearls: Hemoglobin Constant Spring

Non-deletional α-thalassemia: Hb Constant Spring

- Most common non-deletional α-thalassemia ($\alpha^{CS}\alpha$ allele)
- Mutation in stop codon of α_2-globin adds 31 aminoacids → unstable globin chain in very small percentage
- **Homozygotes $\alpha^{CS}\alpha/\alpha^{CS}\alpha$** are of intermediate severity between trait and HbH, Hb 10.3, **normal MCV**(88fL), mildly low MCH (26fL)
- Non-deletional **HbH/Constant Spring** $\alpha^{CS}\alpha$/-- is **more severe** than deletional HbH:
  - Lower Hb
  - Higher MCV
  - Earlier presentation

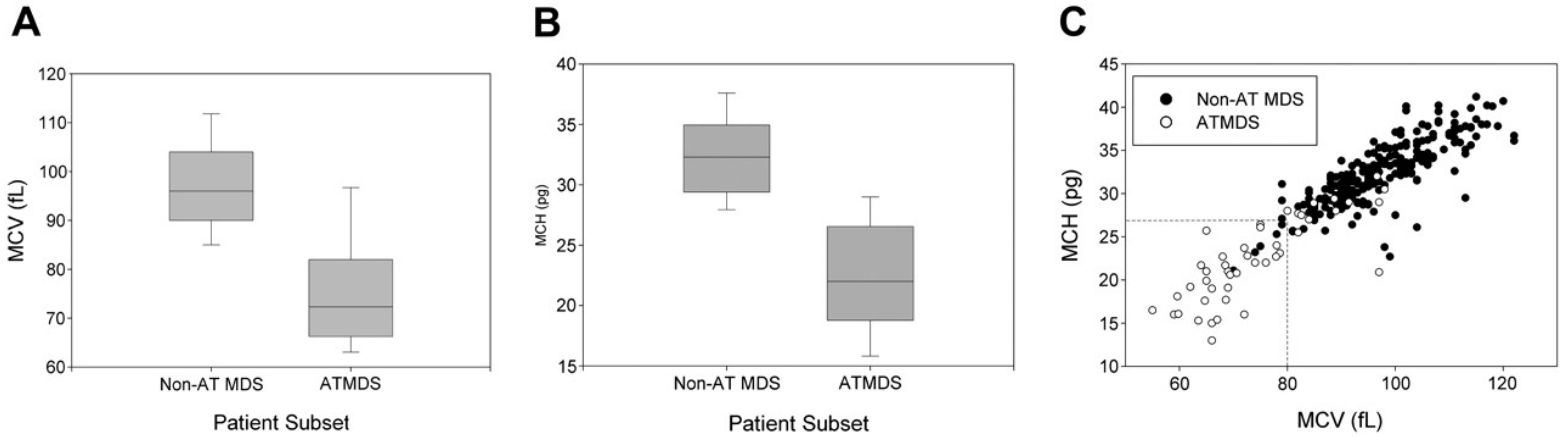
α-thalassemia pearls: rare types

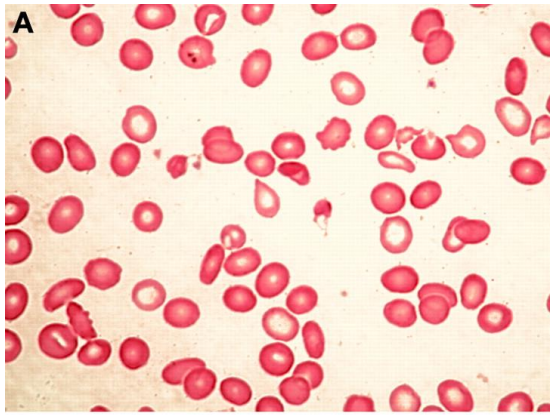
α-thalassemia-intellectual disability syndromes

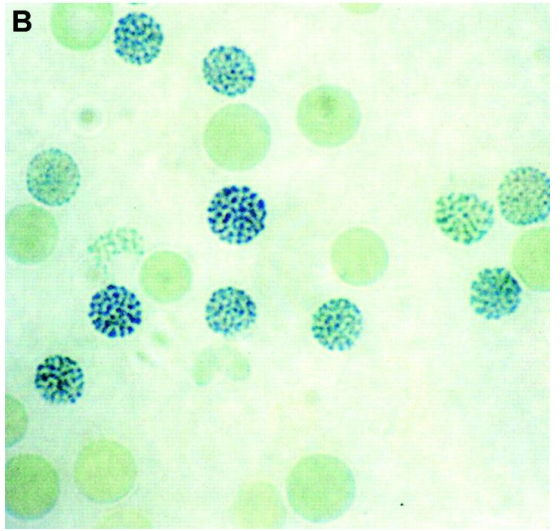
- ATR-16 syndrome: large deletions in α-globin genes on chr 16
- ATR-X syndrome **(α-thalassemia X-linked intellectual disability syndrome)**

α-thalassemia associated with myeloid malignancy (ATMDS)

- acquired α-thalassemia mostly in MDS, rarely in MPN or AML
- low MCV/MCH; HbH inclusions on supravital stain
- ATRX mutations







Steensma et al. Blood, 2005. 05:443-452

ABIM Hematology exam blueprint

- **Thalassemias**
  - β-thalassemia
  - α-thalassemia
  - Hemoglobin E disorders

- **Sickle cell disorders**
  - Sickle cell trait
  - Sickle cell anemia (hemoglobin SS disease)
  - Hemoglobin SC disease and C hemoglobinopathy
  - Sickle cell-β^0 and sickle cell-β^+ thalassemias

- **Non-sickle hemoglobinopathies**
- **Educational resources**

Hemoglobin E causes a thalassemic hemoglobinopathy

- Structure: amino acid substitution *HBB* p.Glu26Lys
- Translation: decreased β^E mRNA production
- α-globin chains precipitate in cytoplasm of erythroid precursors and RBCs → ineffective erythropoiesis
- increased oxidative stress → shortened RBC lifespan

- **2nd most prevalent Hb variant in the world**
  - 30 million worldwide with > 80% in Southeast Asia

Hemoglobin E disorders

Condition	Genotype	Hb EP	Clinical features
Hb E trait	β/β^{E}	HbE 30%	Normal or low MCV
Hb E disease	β^{E}/β^{E}	HbE 90%	**Mild** microcytic anemia
Hb E/β thal **(Very common in SE Asia)**	β^{E}/β^{0} or β^{E}/β^{+}	HbE 40-85% **HbF 10-60%**	**Moderate to severe** microcytic anemia, ineffective erythropoiesis, **spontaneous and transfusion iron overload**
Hb SE disease	β^{S}/β^{E}	HBE 30% HbS 65%	**Mild sickling disorder**, similar to HbS/β^{+} thalassemia

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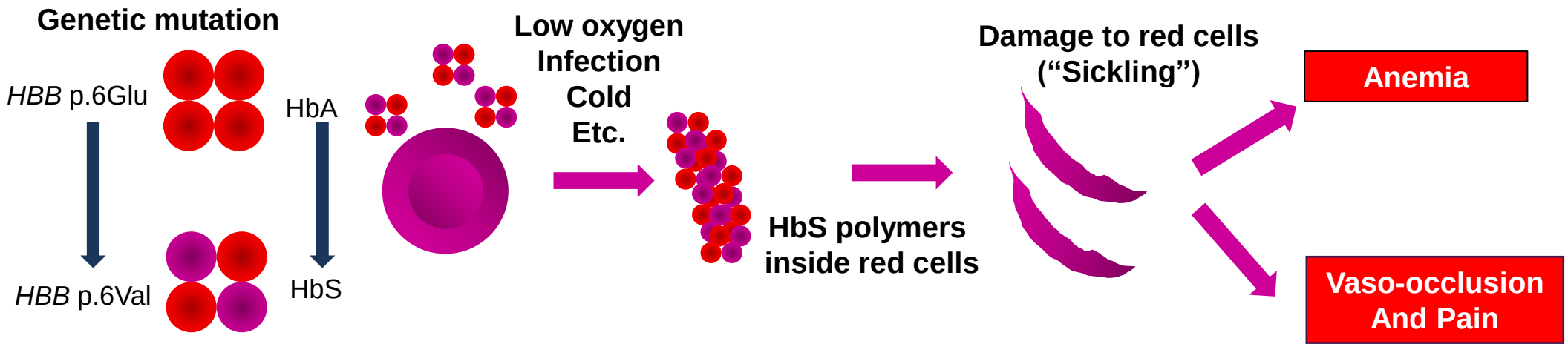
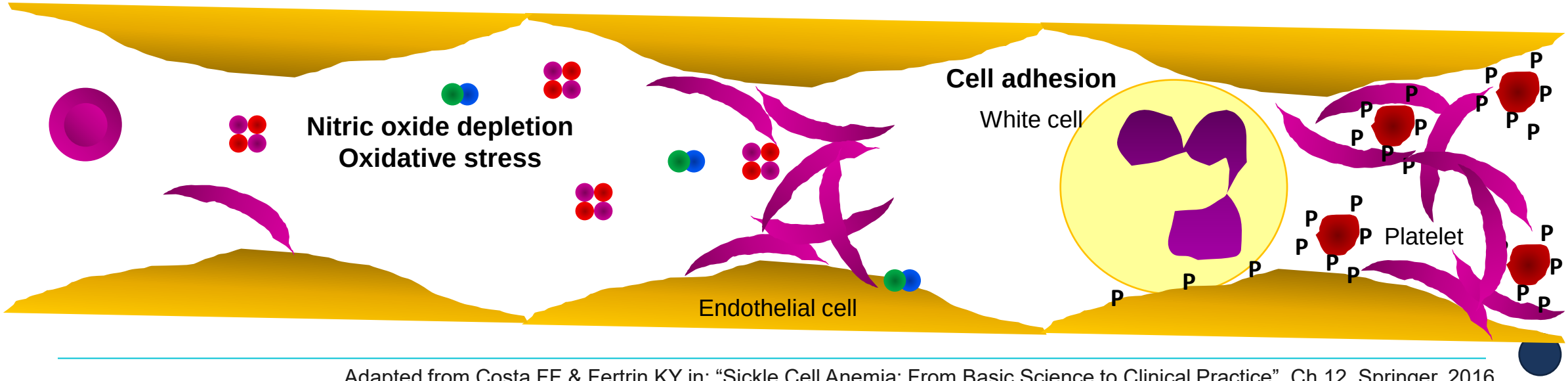
Pathophysiology of sickle cell disease

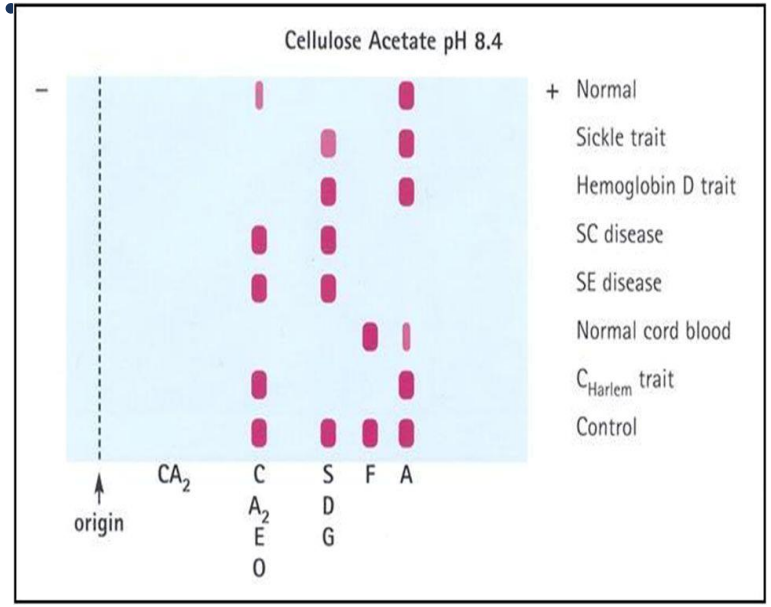


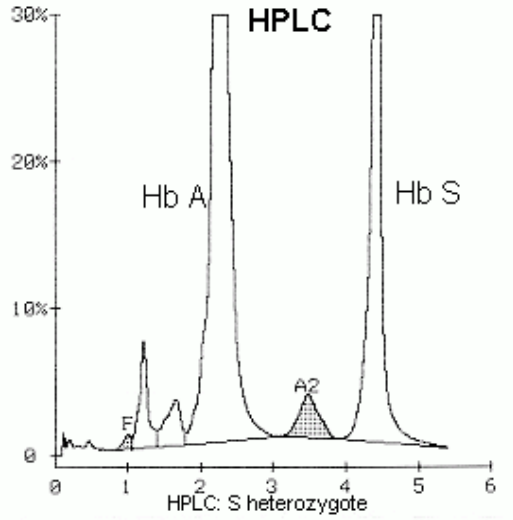


Adapted from Costa FF & Fertrin KY in: "Sickle Cell Anemia: From Basic Science to Clinical Practice", Ch 12, Springer, 2016.

Laboratory diagnosis of sickle cell disease

- HbS solubility test is NOT RECOMMENDED to make a diagnosis of SCD
- CBC to define presence/severity of anemia and MCV
- Hemoglobin electrophoresis
  - cellulose acetate (alkaline pH) - standard
  - citrate agar (acidic pH) – distinguishes HbS/D/G
- **High performance liquid chromatography (HPLC)**
  - **currently most used technique**
  - **Hemoglobins reported from higher to lower**
- Isoelectric focusing (IEF)
  - Commonly used for newborn screening (large sample sizes)
- Molecular biology (rarely utilized for SCD)
  - PCR, gene sequencing is mostly used when the patient is regularly transfused or if a rare genotype is suspected





Sickling syndromes

Table 1. Genotypes of Sickling Syndromes and Their Relative Severities

Genotype	Severity	Characteristics
HbSS	Severe	Most common form
HbSβ⁰	Severe	Clinically indistinguishable from HbSS[6]
HbSO-Arab	Severe	Relatively rare[6]
HbSD-Punjab	Severe	Mostly in northern India[6]
HbSC-Harlem	Severe	Migrates like HbSC, but rare double β-globin mutation[7]
HbCS-Antilles	Severe	Rare double β-globin mutation[8]
HbSC	Moderate	25% of SCD[9]
HbSβ+, Mediterranean	Moderate	5%–16% HbA[6]
HbAS-Oman	Moderate	Dominant rare double β-globin mutation[10]
HbSβ+, African	Mild	16%–30% HbA[6]
HbSE	Mild	HbE found mostly in Southeast Asia[11]
HbS-HPFH	Very mild	Large deletions in β-globin gene complex; > 30% HbF[6]

HbA = hemoglobin A; HbE = hemoglobin E; HbF = fetal hemoglobin; HbS-HPFH = HbS and gene deletion HPFH; HbSC = heterozygous hemoglobin SC; HbSS = homozygous hemoglobin SS; HbSβ⁰ = hemoglobin S-β thalassemia⁰; HbSβ+ = hemoglobin S-β thalassemia+; SCD = sickle cell disease.

Vivien A. Sheehan. Hematology-Oncology 12:1, 2-15

Clinical and laboratory findings in SCD

SCD

	A (%)	S (%)	F (%)	A_2 (%)	C (%)	Clinical severity	Hb (g/dL)	MCV (fL)
Sickle cell anemia (SS)	0	75- 95	<10	<3.5	0	Usually marked	6-9	>80
Sickle-β^0-thal	0	80-92	<20	>3.5	0	Marked to moderate	6-9	<70
Sickle-β^+-thal	5-30	65-90	<20	>3.5	0	Mild to moderate	9-12	<75
Hb SC	0	45-50	1-5	NA	45-50	Mild to moderate	10-15	75-85
Sickle-HPFH	0	<70	>30	<2.5	0	Mostly Asymptomatic	12-14	<80
Sickle trait (AS)	50-60	35-45	<2	<3.5	0	Mostly Asymptomatic	normal	normal
Normal	95-98	0	<1	<3.5	0	Asymptomatic	normal	normal

Modified from Table from ASH SAP Chapter 7 2013.

Sickle cell trait (HbAS)

HbS 35-45%, no anemia and no hemolysis

- May be co-inherited with alpha thalassemia deletion, causing microcytosis

Most affected organ is the kidney:

- Hematuria due to renal papillary necrosis
- Hyposthenuria
- Increased risk for CKD
- Increased risk for UTI
- Renal medullary carcinoma (very rare)

Rare complications:

- Splenic infarction or sequestration (high altitude / scuba diving / severe dehydration)
- Exertional sudden death / rhabdomyolysis
- Higher risk of PE (OR 3.9)
- Traumatic hyphema may lead to acute glaucoma

Tsaras et al. *Am J Med.* 2009;122(6):507-512.

Sickle-beta thalassemias

Clinical manifestations

- Variable degree of anemia depending on genotype
- Significant microcytosis (MCV<75)
- Sickle-β^0 thalassemia is similar to HbSS in severity
- Sickle-β^+ thalassemia can be mild depending on degree of residual HbA production
- Splenomegaly frequent – may have mild thrombocytopenia due to hypersplenism

Management

- Genetic counseling, folate supplementation
  - Sickle-β^0 thalassemia usually managed as HbSS
  - Sickle-β^+ thalassemia can use HU if SCD affecting daily activities, case by case decision

Hemoglobin SC disease

Clinical manifestations

- CBC:
  - Mild/moderate anemia or no anemia with compensated hemolytic state
  - Common co-inheritance of alpha thalassemia deletion with microcytosis
  - May have mild increase in MCHC due to HbC crystals
  - **Sickled cells may be rare; frequent target cells; HbC crystals inside red cells**
- Moderate disease; 30% may have frequent VOC
- Splenomegaly frequent – may have mild thrombocytopenia due to hypersplenism
- Higher incidence of AVN and retinopathy

Management

- Genetic counseling, folate supplementation
- HU: if SCD affecting daily activities, case by case decision

Question

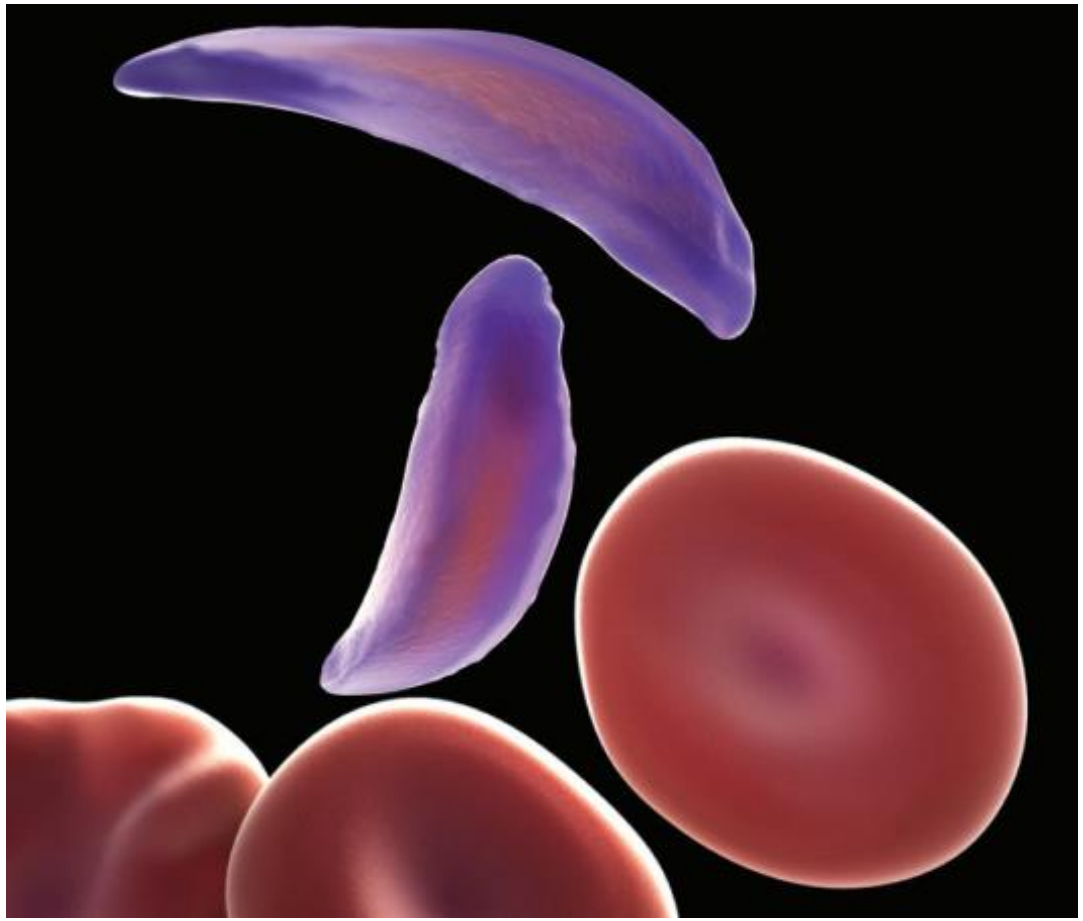
A 47yo woman with sickle cell trait brings her 19- and 21-year-old sons by the same father for evaluation. Neither has ever had a blood transfusion.

You find on hemoglobin HPLC that the younger son has a report of "$ASFA_2$" and the older one has a report for "$SAFA_2$". You suspect:

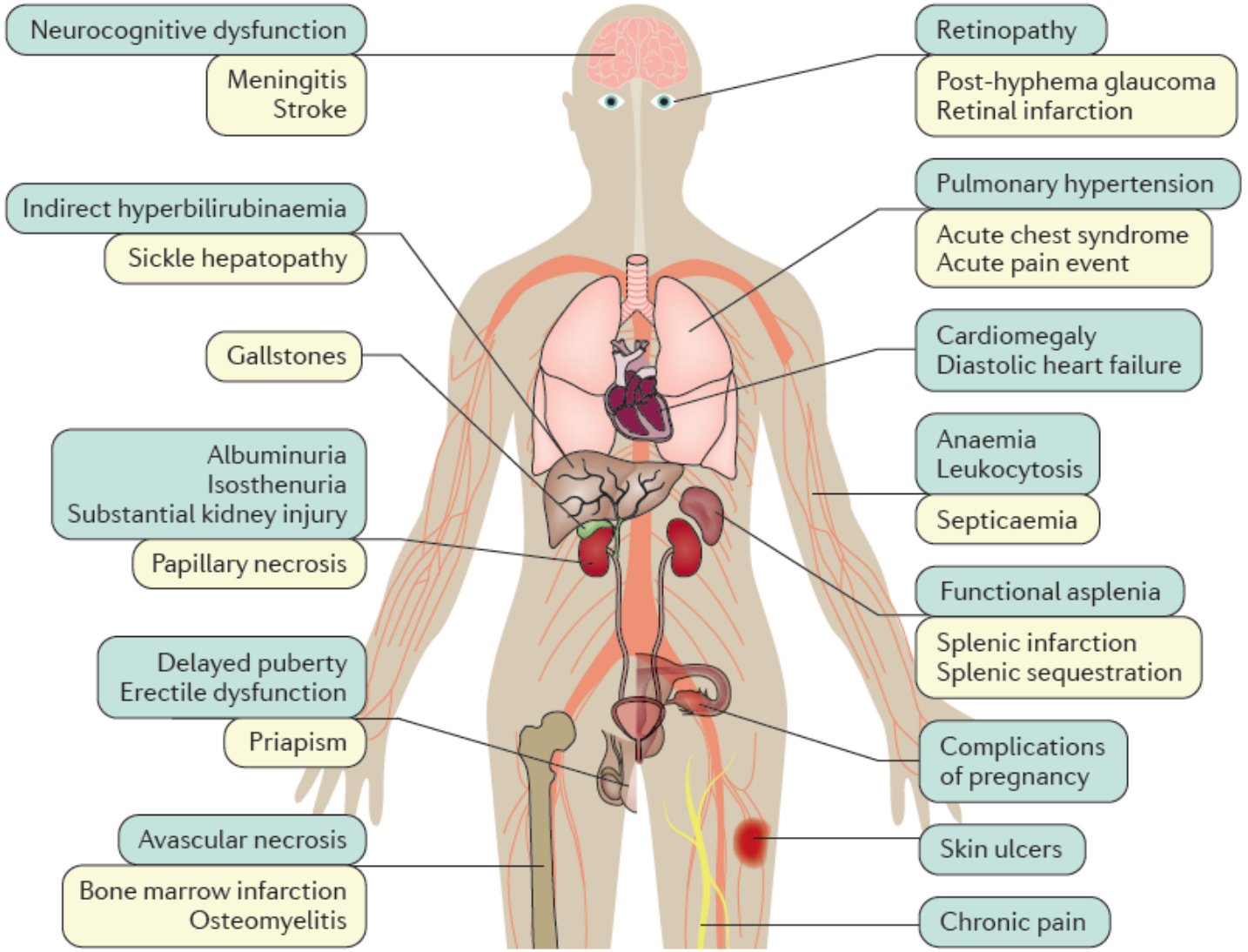
A. Both sons have sickle cell trait
B. One son has sickle cell trait and the other has sickle cell anemia with α-thalassemia
C. One has sickle cell trait and the other has sickle-β-thalassemia
D. Incongruent paternity

Acute manifestations of sickle cell disease (SCD)

- **Vaso-occlusive crisis/episode**
- **Acute chest syndrome**
- **Stroke** (ischemic/hemorrhagic)
- Sequestration (hepatic/splenic)
- Acute intrahepatic cholestasis
- **Aplastic crisis**
- Acute priapism



Sickle cell disease is systemic and progressive



Kato et al. Nat Rev Dis Primers 2018, 4:18010

Question

A 22-yo F with sickle cell anemia (HbSS) presents to the ED with severe chest pain, shortness of breath, and low-grade fever. CXR reveals a RLL infiltrate. SpO2 is 88% on room air, placed on oxygen. She receives broad spectrum antibiotics, IV fluids, a morphine PCA, and 2 units of packed RBCs for Hb 6.5g/dL. Despite these interventions, she remains in respiratory distress and gets transferred to the ICU.

What additional therapy should be initiated at this time?

A. Nitroprusside
B. Albuterol
C. Hydroxyurea
D. RBC exchange
E. Sildenafil

Acute chest syndrome (ACS)

- Leading cause of death and 2nd most common cause of admission in adult SCD patients
- Diagnosis:
  - PMH of SCD
  - Fever
  - Respiratory sx (dyspnea/cough/sputum)
  - New infiltrate on CXR
  - ±Hypoxia
- Triggers:
  - Infection (mostly children)
  - in-situ thrombosis
  - fat emboli (more frequent in adults)

ST Miller. How I treat acute chest syndrome in children with sickle cell disease. Blood 2011; 117(20)

VOC and ACS management

- **VOC:**
  - Aggressive analgesia (include NSAIDs and opioids as needed)
  - Appropriate hydration (PO and/or IV)
  - Check for triggers (infection, dehydration, acidosis)
- **ACS** → also add:
  - Empiric broad-spectrum antibiotics
  - Supplemental oxygen if SpO2<92%
  - Incentive spirometer, bronchodilators PRN
  - **Simple or exchange red cell transfusions**
- **DISCUSS STARTING HYDROXYUREA OUTPATIENT**

ST Miller. How I treat acute chest syndrome in children with sickle cell disease. Blood 2011; 117(20)

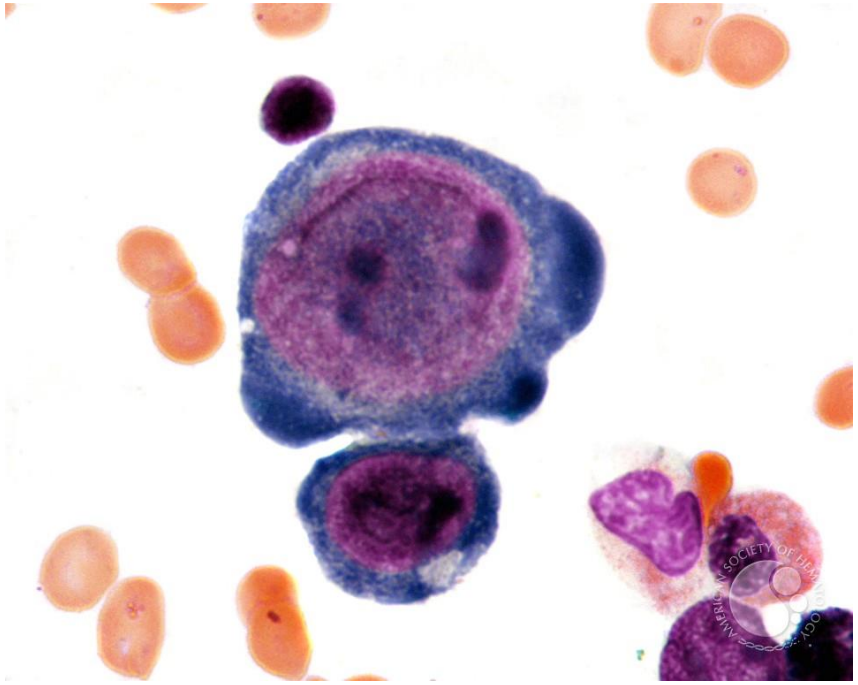
Indications for red cell exchange in SCD

(Prefer automated over manual)

- Abnormal transcranial doppler in children (CBF velocity>200m/s - STOP trial)
- Acute ischemic stroke
  - Goal is HbS<30% prior to next RCE, indefinitely (STOP 2 trial)
- Severe ACS (SpO2<90% despite O_2 supplementation)
- Hepatic sequestration / intrahepatic cholestasis
- Multisystem Organ Failure Syndrome

Question

A 17 yo F with sickle cell anemia presents with profound fatigue and weakness. Her labs show Hb 4.3 g/dL (baseline 7.5 g/dL), MCV 84fL, and retic 1%. Her bone marrow smear shows:



What tests can confirm the etiology?

A. Serum folate and homocysteine
B. Serum B12 and methylmalonic acid
C. IgG and IgM for parvovirus B19
D. PCR for parvovirus B19

Aplastic crisis in SCD

- Cause: parvovirus B19 infection
- May happen in ANY chronic hemolytic anemia
- Diagnosis:
  - Anemia with **reticulocytopenia**
  - Marrow: giant **proerythroblasts** with viral inclusions
  - **PCR+ for parvovirus** (serology is not useful)

- Management: transfusions for support; avoid Hb overcorrection

Question

A 32-yo male with sickle cell anemia (HbSS) is diagnosed with symptomatic gallstones. He is slated for an elective cholecystectomy under general anesthesia. The surgery is considered medium risk. CBC reveals he is at his baseline hemoglobin level of 7.5 g/dL.

Which of the following should be done preoperatively?

A. Start hydroxyurea
B. RBC transfusion to Hb >8g/dL
C. RBC transfusion to Hb >10g/dL
D. RBC exchange transfusion to HbS<30%

TAPS study: evidence for transfusion to Hb>10g/dL up to 10 days prior to low or medium risk surgeries

- 39% (no tx) vs. 15% (transfused) complications (p=0.032)
- **High risk surgeries** NOT included in the study:
  - Cardiothoracic
  - Neurosurgery (included medium risk for: laminectomy, disc or peripheral nerve surgery)
  - GI: hepatectomy, esophagectomy, Whipple's
  - Vasc: aorto-femoral bypass, aorto-iliac endarterectomy
  - Ortho: scoliosis
  - Urology: cystectomy, radical prostatectomy
  - Craniofacial surgery

Howard et al. *Lancet* 2013; 381: 930–38

Transfusion in SCD

→ **Extended RBC antigen profile by genotype (or serology)** for all patients;

→ Prophylactically match for **C/c, E/e, and K** (and HbS-negative);

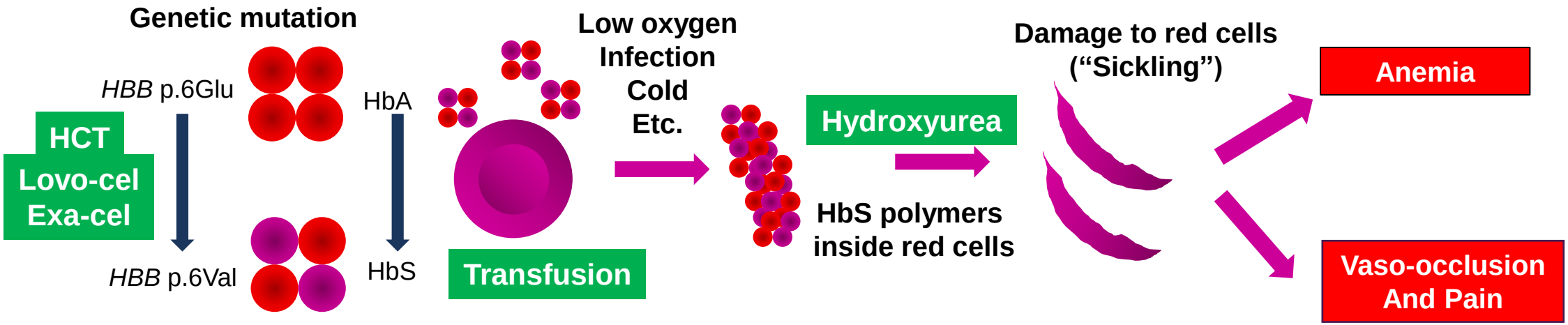
Typical indications:

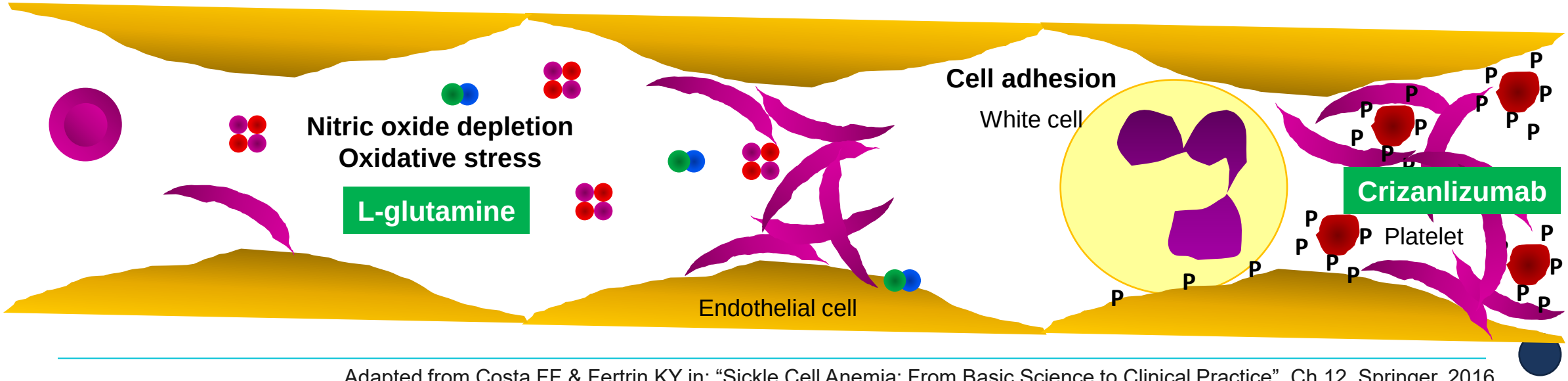
- Acute chest syndrome (ACS) with Hb drop by 1g/dL from baseline
- Hepatic or splenic sequestration, intrahepatic cholestasis
- Symptomatic anemia (usually Hb<6g/dL)
- Preoperative for general anestesia >1h and Hb<9g/dL

Insufficient evidence for:

1. Uncomplicated VOC
2. Priapism
3. Leg ulcers
4. Recurrent splenic sequestration

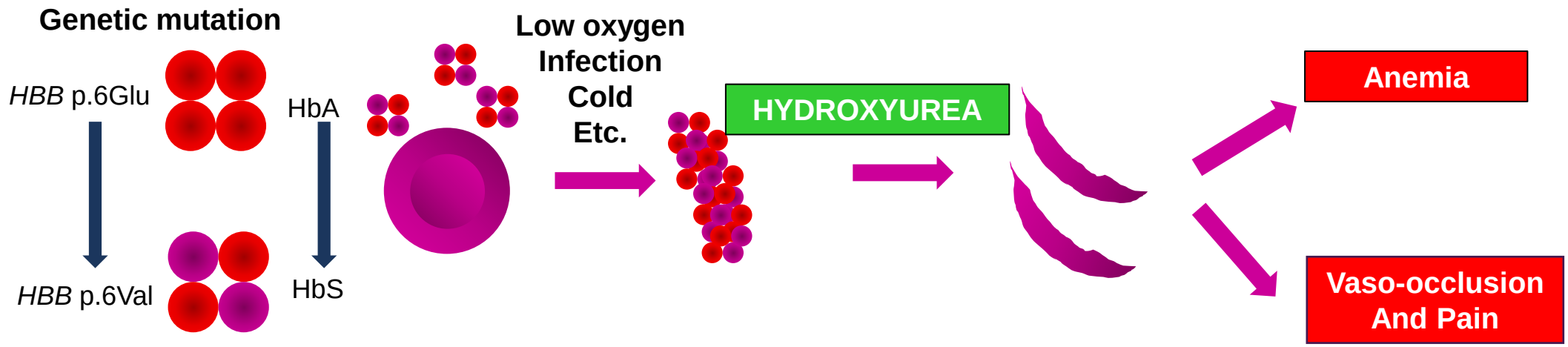
Treatment of sickle cell disease (as of October 2024)

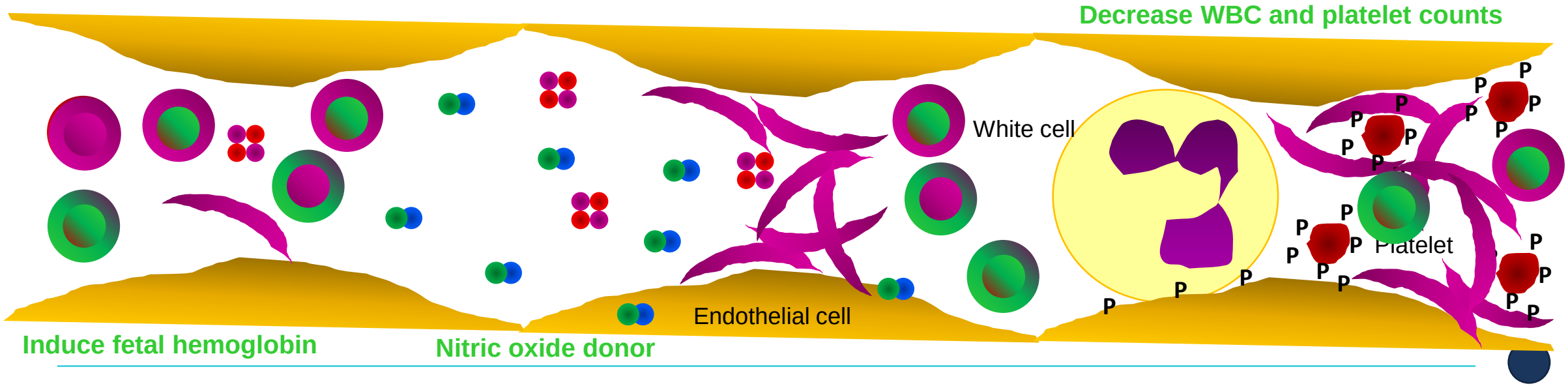




Adapted from Costa FF & Fertrin KY in: "Sickle Cell Anemia: From Basic Science to Clinical Practice", Ch 12, Springer, 2016.

Hydroxyurea is a ribonucleotide reductase inhibitor with multiple effects





Adapted from Costa FF & Fertrin KY in: “Sickle Cell Anemia: From Basic Science to Clinical Practice”, Ch 12, Springe

Typical indications for hydroxyurea in SCD adults

Table 4. Indications for Hydroxyurea in Adult Patients with Sickle Cell Disease

Indication	Strength of Recommendation
SCA with ≥ 3 pain crises per year	Strong
SCA with pain that interferes with ADL and QoL	Strong
History of severe or recurrent ACS	Strong
Chronic kidney disease on epoetin	Weak
HbSβ+ and HbSC with pain that interferes with ADL and QoL; consult sickle cell disease expert	Moderate

ACS = acute chest syndrome; ADL = activities of daily living; QoL = quality of life; SCA = sickle cell anemia.

Vivien A. Sheehan. Hematology-Oncology 12:1, 2-15

Summary: disease-modifying therapies for SCD

	Hydroxyurea	L-glutamine	Crizanlizumab
Route/dose	PO 15-35mg/kg/d	PO 5-15g BID (per weight)	IV 5mg/kg - week 0, 2, then q 4weeks
VOC/year	4.5→2.5 **(44%)**	4.0→3.0 **(25%)**	3.0→ 1.6 **(45%) (not confirmed in Phase 3)**
Time to 1st VOC (mo)	1.5→3.0	1.8→2.8	1.4→ 4.1
Time to 2nd VOC (mo)	4.6→8.8	4.4→7.0	5.1→ 10.3
Increase Hb	**Yes**	No	No
Adverse events	GI, cytopenia, hair loss	GI	GI, arthralgia, infusion reaction (rare)

L-glutamine decreased rate of VOCs/year in SCD

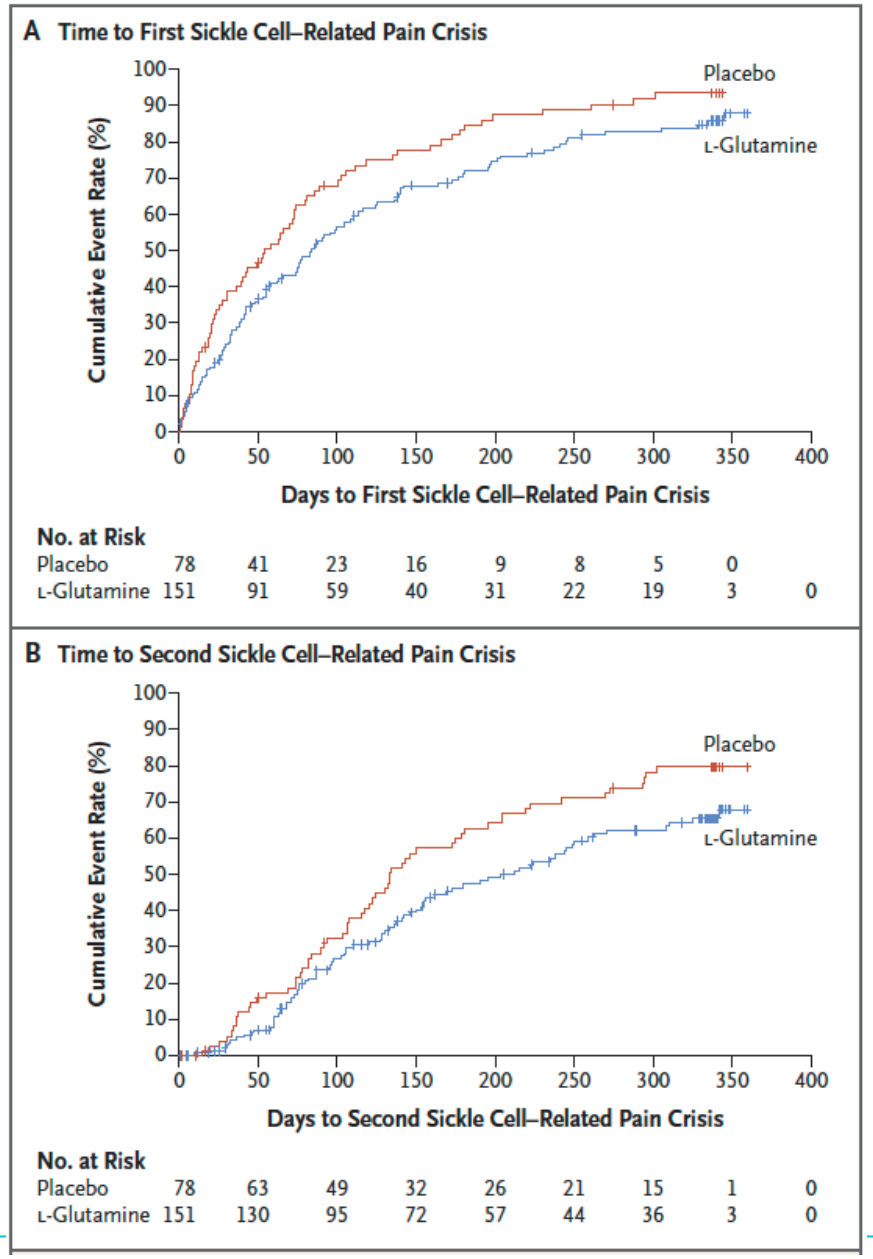
ORIGINAL ARTICLE

A Phase 3 Trial of L-Glutamine in Sickle Cell Disease

N Engl J Med 2018;379:226-35.

48 weeks on L-glutamine BID vs. placebo

- Rate of VOC/year decreased 4.0 vs. 3.0
- Admissions per year decreased 3.0 vs. 2.0
- Time to first VOC: 54 vs. 84 days
- Time to 2nd VOC: 133 → 212 days
- ACS: 23.1% (18/78)→ 8.6% (13/152)



Phase 2 SUSTAIN trial: crizanlizumab reduced frequency of VOC in SCD

Rate of VOC/year decreased by 45% on high dose:

2.98 (placebo), 2.01 (2.5mg/kg), 1.63 (5mg/kg)

Per frequency: 2-4 VOC/y: 2.00→ 1.14;

5-10 VOC/y: 5.32→1.97

Per genotype: HbSS 3.01→1.97;

HbSC/Sbeta: 2.00→0.99

Longer time to first VOC: 1.38→ 4.07 months

Longer time to second VOC: 5.09→ 10.32 months

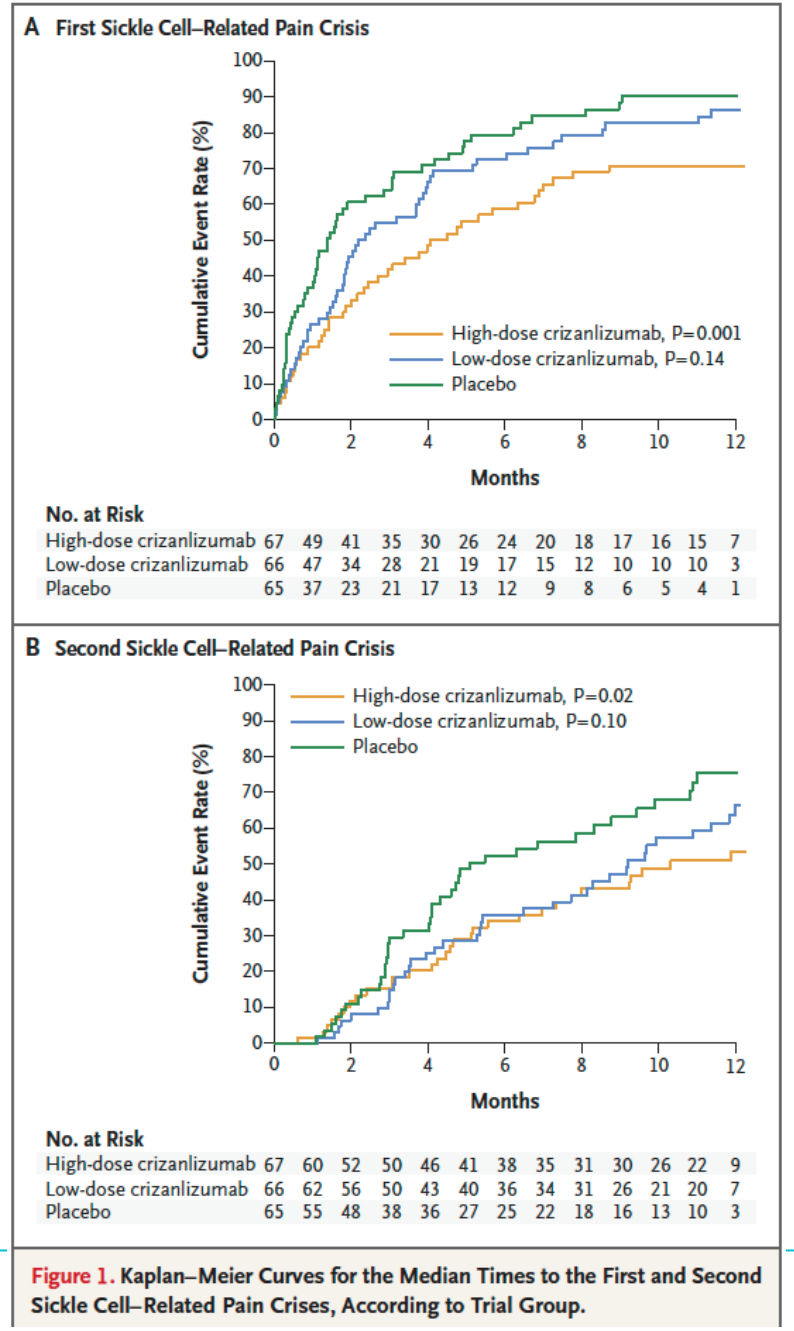


Figure 1. Kaplan–Meier Curves for the Median Times to the First and Second Sickle Cell–Related Pain Crises, According to Trial Group.

Phase 3 STAND trial: crizanlizumab did not achieve primary endpoint

Negative binomial regression treatment comparisons of VOC leading to a healthcare visit (FAS)						
				Between treatment comparison (vs PBO)		
Treatment	n	Adjusted annualized rate of VOC	(95% CI)	Rate ratios	(95% CI)	Adjusted P value
PBO	85	2.30	(1.75, 3.01)			
Crizanlizumab 5 mg/kg	84	2.49	(1.90, 3.26)	1.08	(0.76, 1.55)	>0.999
Crizanlizumab 7.5 mg/kg	83	2.04	(1.56, 2.65)	0.89	(0.62, 1.27)	>0.999

- Annualized rate of VOC did not differ significantly among groups
- Annualized rate of VOCs in all groups was lower than observed at enrollment (PBO 3.8, CRZ5 3.6, CRZ7.5 3.9)

https://ash.confex.com/ash/2023/webprogram/Paper185429.html

Question

An 18-year-old woman with HbSS admitted for VOC, Hb 5.9g/dL with reticulocytes 400,000/µL receives 2 pRBC units and is discharged home after proper pain management and Hb 8.0g/dL. She returns 6 days later with back pain and a Hb 4.5g/dL, MCV 102fL, reticulocytes 150,000/µL. Her electrophoresis shows HbA 10%, HbS 82%, HbF 5%, and HbA_2 3%. LDH level is elevated at 1205 U/L.

What is the most likely diagnosis?

a. Aplastic crisis
b. Acute hemolytic transfusion reaction
c. Hyperhemolysis syndrome
d. Megaloblastic crisis

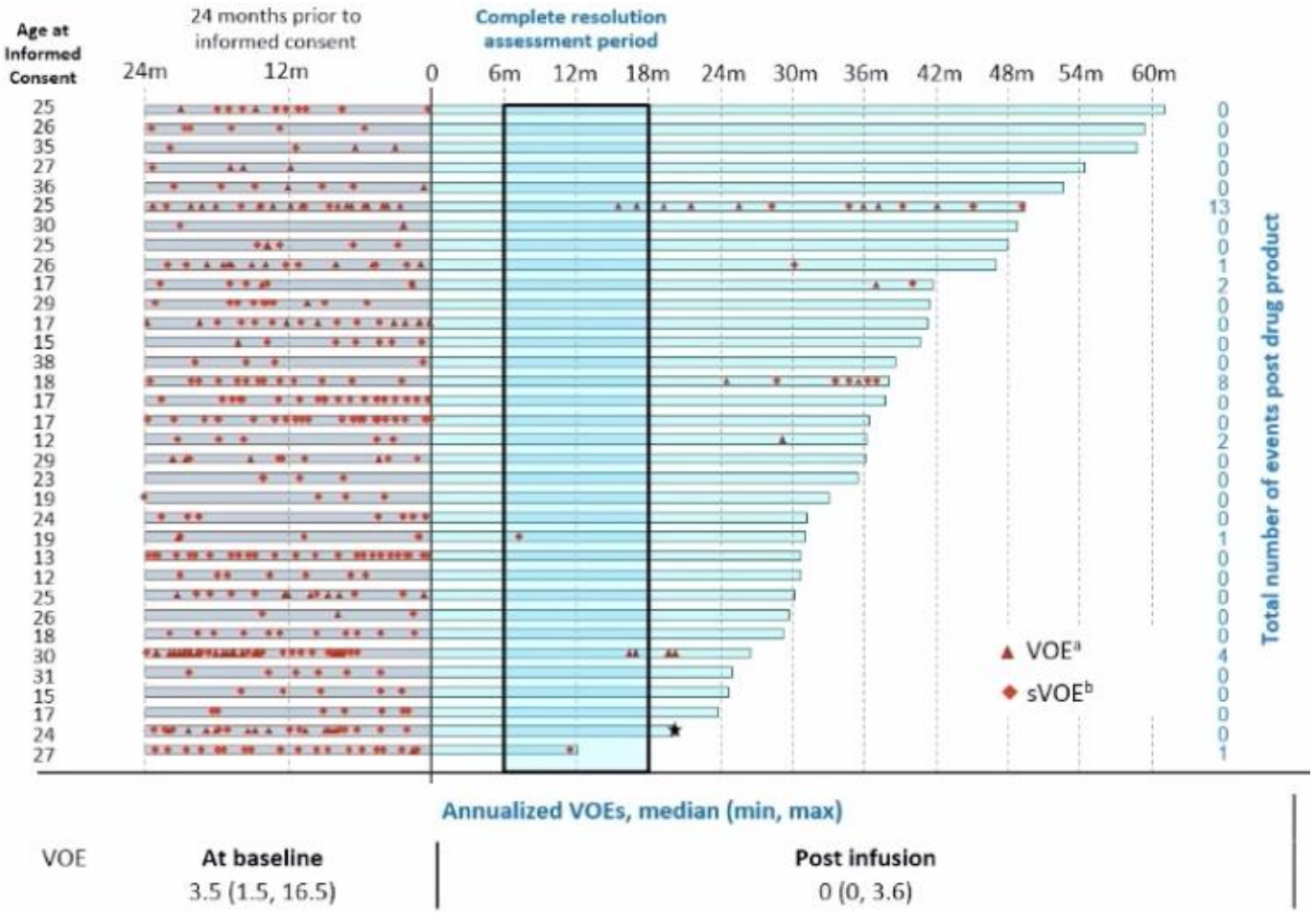
Hyperhemolysis syndrome

- Severe complication of delayed hemolytic transfusion reaction
  - “Bystander hemolysis” of self-RBCs – complement-mediated?
- Most commonly diagnosed in sickle cell disease but can happen in other hemolytic anemias
- **Key findings:**
  - **Significant drop in Hb within 21 days of transfusion; and**
  - **≥1 of the following: increased LDH, new alloantibody, hemoglobinuria, accelerated increase in HbS and drop in HbA, reticulocytosis or reticulocytopenia from baseline**
- Management:
  - Avoid transfusion unless life-threatening anemia
  - **First line: immunosuppression (IVIg and high dose steroids)**
  - Second line: eculizumab
  - Support with EPO +/- IV iron

Allogeneic hematopoietic cell transplant in SCD

- Curative approach for severe SCD
- **NIH criteria:**
  - **Stroke**
  - **TRV>2.6m/s or diagnosed pulmonary hypertension**
  - **2 or more VOCs/year**
  - **Acute chest syndrome while on HU**
  - **Sickle nephropathy**
  - **Sickle hepatopathy**
- Only 17% SCD patients have a matched related donor
  - 47% patients may have a matched unrelated donor
  - >90% may have a haploidentical donor

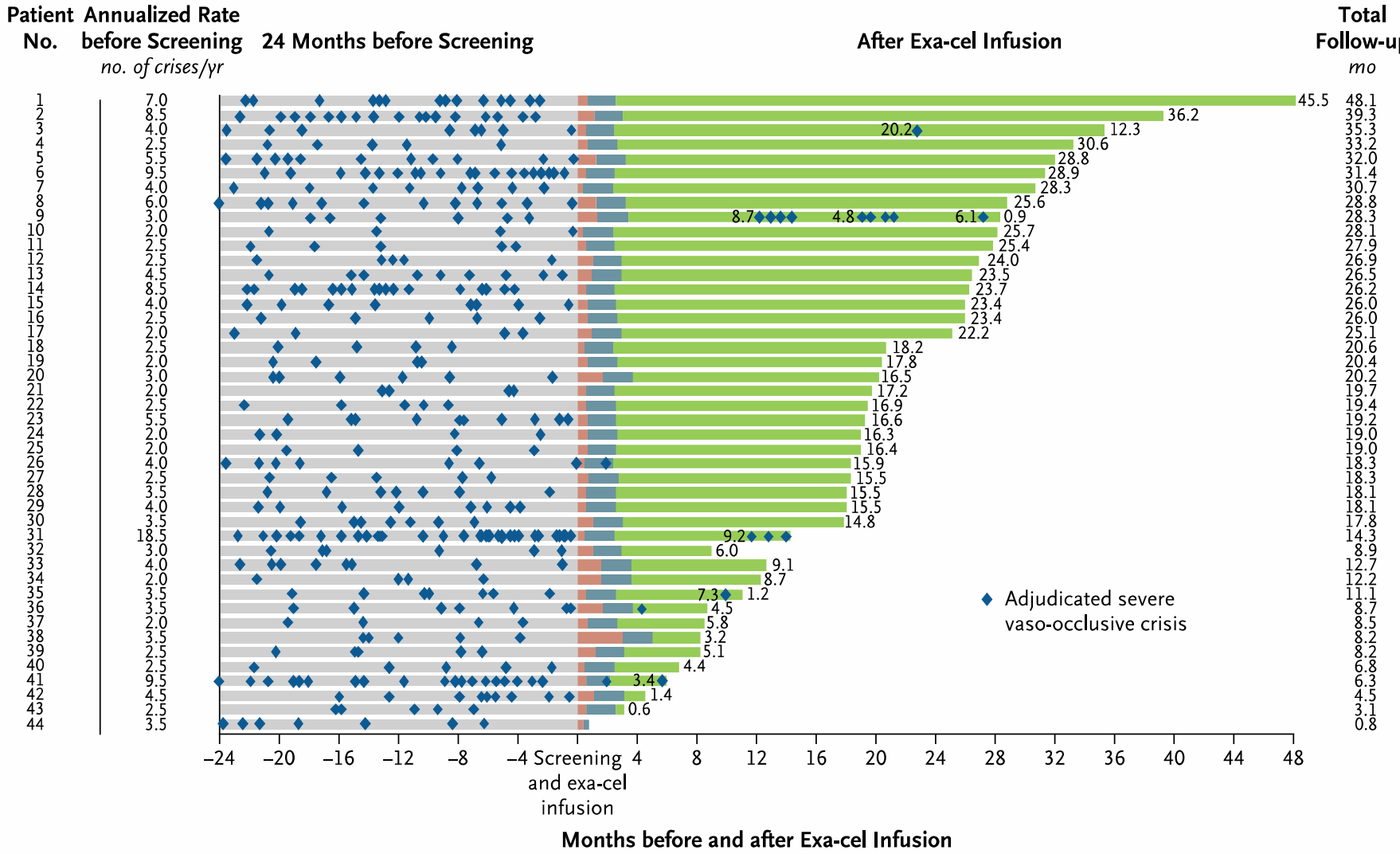
Lovotibeglogene autotemcel (Lovo-cel): lentiviral-based gene therapy for SCD



- 30/34 (88%) of patients achieved complete resolution of all VOEs during 6-18 months assessment period
- Patients who had VOEs post-treatment experienced a reduction of ≥50%
  - Median baseline VOE rate:
    3.5 per year (1.5, 16.5)
  - Median post-treatment:
    0.0 per year (0.0, 3.6)
- 1 case of MDS

https://ash.confex.com/ash/2023/webprogram/Paper174229.html

Exa-cel for sickle cell disease (approved by FDA in December 2023)



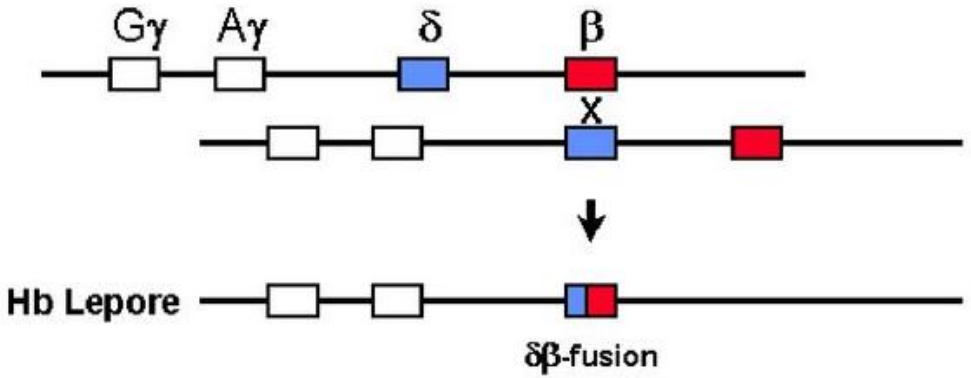
- 29/30 (97%) of patients remained free of VOEs for 12 consecutive months
- 31/32 (97%) remained free of VOE for at least 9 consecutive months

Frangoul et al. N Engl J Med. 2024 May 9

ABIM Hematology exam blueprint

- **Thalassemias**
  - β-thalassemia
  - α-thalassemia
  - Hemoglobin E disorders
- **Sickle cell disorders**
  - Sickle cell trait
  - Sickle cell anemia (hemoglobin SS disease)
  - Hemoglobin SC disease and C hemoglobinopathy
  - Sickle cell-β^0 and sickle cell-β^+ thalassemias
- **Non-sickle hemoglobinopathies**
- **Educational resources**

Hemoglobin Lepore



- **Abnormal fusion** of β and δ globin genes
- Decreased synthesis of β-like globins
- **Homozygote: β-thal major phenotype**
  - 70-92% Hb F
  - 8-30% Hb Lepore
- **Heterozygote: β-thalassemia minor (trait) phenotype**

Hereditary persistence of HbF (HPFH)

- Clinically silent (e.g. found in blood donation; no anemia or erythrocytosis)
- Up-regulation of γ-chain synthesis

- Caused by:
  - Deletional: involves β and δ genes (nearly 100% HbF);
  - Non-deletional: point mutations in γ-chain promoter (variable HbF);
  - decreased expression of *KLF1*, a transcription factor that activates HbF suppressor gene *BCL11A*

- Significantly modifies clinical outcomes when co-inherited with Hb S

Unstable hemoglobin disease

Congenital chronic non-spherocytic anemia

- CBC: variable severity ± low MCV
- Rare, AD mutations (defective heme binding by globin chains)
- Diagnosis:
    - Heinz bodies precipitation in RBCs on isopropanol test
    - There are about 200 “unstable” Hb variants → DNA sequencing
    - Hb Köln (most common, may occur *de novo*): anemia, retics 10-25%, splenomegaly
- Treatment: avoid oxidant drugs, RBC transfusions as needed, splenectomy may be considered in transfusion-dependent cases

Oxidized Hb: Hb M and methemoglobinemias

- **Hemoglobins M**
  - Autosomal dominant, amino acid substitution in heme pocket: Fe^{2+} →Fe^{3+}
  - Asymptomatic cyanosis, slate grey/brownish skin, no dyspnea or hypoxia
  - Cyanosis from birth (alpha globin mutation e.g. Hb M Boston) or during the first year (beta globin mutation, e.g. Hb M Saskatoon or M Milwaukee)
- Diagnosis: low SpO2, Hb electrophoresis/spectra, **metHb < 30%,** DNA sequencing
- No therapy

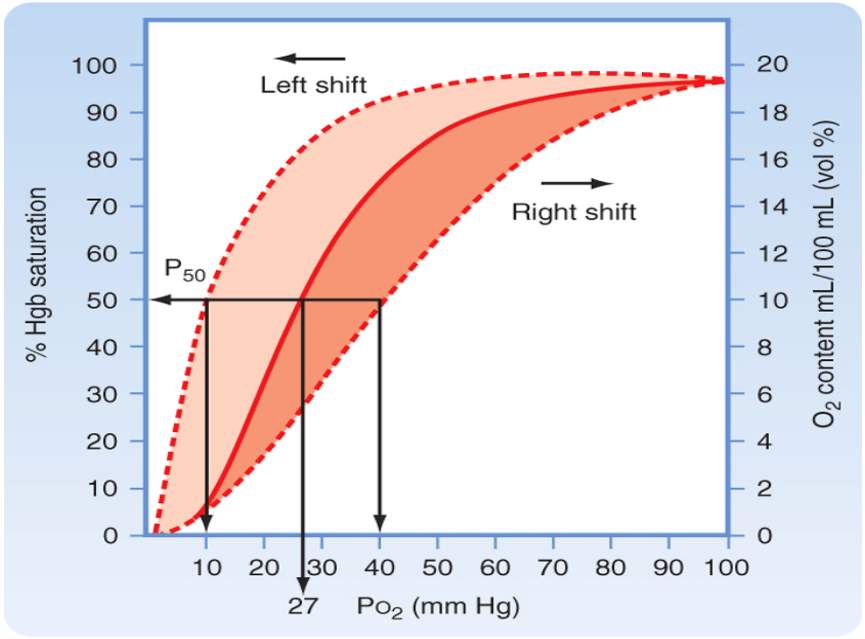
- Other methemoglobinemias (treat with methylene blue)
  - **Toxins/drugs:** nitrites, sulfanilamide, dapsone, primaquine, phenazopyridine, etc.
    - CBC with “bite” cells
    - Symptomatic with **metHb> 30%** (> 50% is lethal!)
  - **Congenital deficiency in cytochrome b5 reductase:**
    - cyanosis improves with methylene blue or vitamin C, avoid oxidizing drugs above

Percy et al. Blood Rev 2005 Mar;19(2):61-8

Hemoglobins with abnormal affinity for oxygen

- **Hb with high O_2 affinity:**
  - AD, familial **erythrocytosis**,
  - α or β-chains can be affected
  - Diagnosis: low P_{50} (left shifted on O_2 dissociation curve), variant Hb in electrophoresis, DNA sequencing
  - No phlebotomy unless Ht>60%
  - Differential dx: polycythemia vera, secondary polycythemias

- **Hb with low O_2 affinity:**
  - Right shift on O_2 dissociation curve (high P_{50} ~ 30-40 mmHg)
  - Cyanosis, but otherwise asymptomatic (depending on degree of right shift)
  - No treatment required



Fred Hutch Cancer Center

UW Medicine

Thank you