UNIVERSITY of MARYLAND
SCHOOL OF MEDICINE

Sickle Cell Disease Management: In the Era of Definitive Therapy

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February 27, 2026

Outline

- Brief review → pathophysiology of sickle cell disease
- Discuss currently available medical therapies
- Describe curative and transformative therapies
- Impact of definitive therapy on state of sickle cell care

History of Sickle Cell Disease

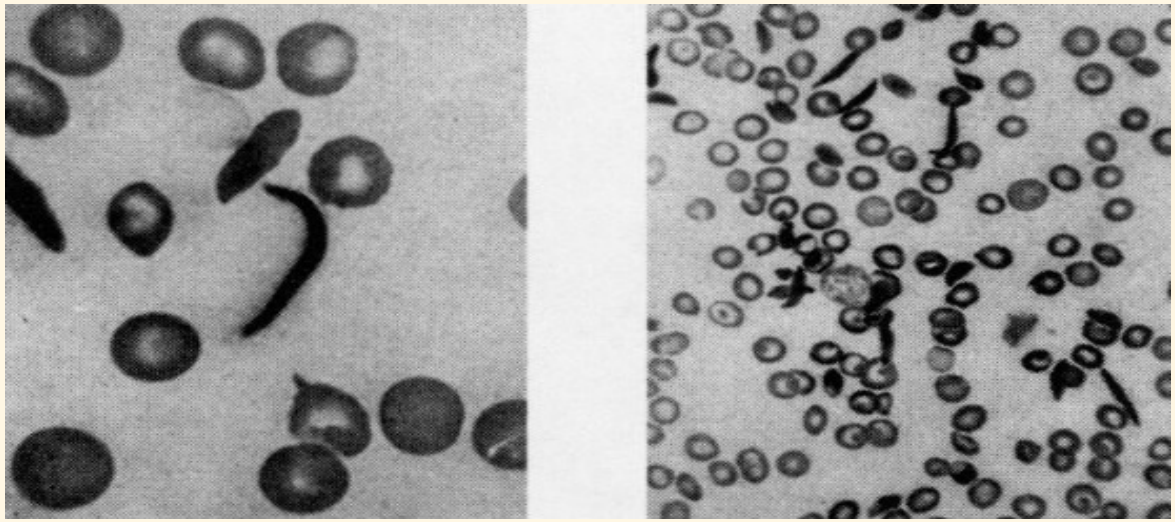
PECULIAR ELONGATED AND SICKLE-SHAPED RED BLOOD CORPUSCLES IN A CASE OF SEVERE ANEMIA

JAMES B. HERRICK, M.D.
CHICAGO

This case is reported because of the unusual blood findings, no duplicate of which I have ever seen described. Whether the blood picture represents merely a freakish poikilocytosis or is dependent on some peculiar physical or chemical condition of the blood, or is characteristic of some particular disease, I cannot at present answer. I report some details that may seem non-essential, thinking that if a similar blood condition is found in some other case a comparison of clinical conditions may help in solving the problem.

History.—The patient was an intelligent negro of 20, who had been in the United States three months, during which time he was a student in one of the professional schools in Chicago. His former residence had been Grenada, West Indies, where he had been born and brought up, one of a family of four children, all living, and all well with the exception of himself. His mother was living and in good health; his father had died of accident. At the age of 10 the patient had had yaws. This was a common disease in the locality where he lived. The lesions, as he described them, had been pustular, with formation of ulcers and scabs. On healing, scars, many of which he pointed out, were left. Some of the ulcers had been as large as a silver quarter of a dollar. The disease lasted about one year and during this time he had felt somewhat weak and indisposed. Most of the ulcers had been on the legs and the patient himself had thought that this location of the lesions might have been due to the bruises and scratches that were frequently produced as he ran about, a barefoot boy, through the streets and the brush. He was sure he had never had ground-itch, though he said it was not uncommon in Grenada. He had attended school up to the age of 17. Since leaving school, that is, for the past three years, he had felt a disinclination to take exercise. For about a year he had noticed some palpitation and shortness of breath which he had attributed to excessive smoking. There had been times when he thought he was bilious and when the whites of the eyes had been tinged with yellow. At such times he had not had any pain, chill or fever. Three years previously he had had a purulent discharge from the right ear lasting six months. He had had no diarrheas and no hemorrhages at any time. He denied syphilis and gonorrhea. There was never any rheumatism or other joint trouble. On landing in New York in September, 1904, he had a sore on one ankle for which he consulted a physician. Tincture of iodin was applied and in a week the sore had healed, leaving a scar similar to the others on the limbs. For the past five weeks he had been coughing. Two days prior to examination he had "taken cold," his cough had grown worse and he had had a slight chill, followed by fever. It was this cough and fever for which he wished treatment at the hospital, and of which he chiefly complained, though he mentioned also that he felt weak and dizzy, had headache and catarrh of the nose.

- First hemoglobin variant discovered
  - 1904 → dental student from Grenada
  - Relocated to Chicago for school
  - Peripheral smear → new technology
- 1920s → illness termed *sickle cell anemia*



Steensma DP, Kyle RA, Shampo MA. *Mayo Clin Proc*. 2010;85:e74-75.

History of Sickle Cell Disease

November 25, 1949, Vol. 110 SCIENCE

Sickle Cell Anemia, a Molecular Disease[1]

Linus Pauling, Harvey A. Itano,[2] S. J. Singer,[2] and Ibert C. Wells[3]

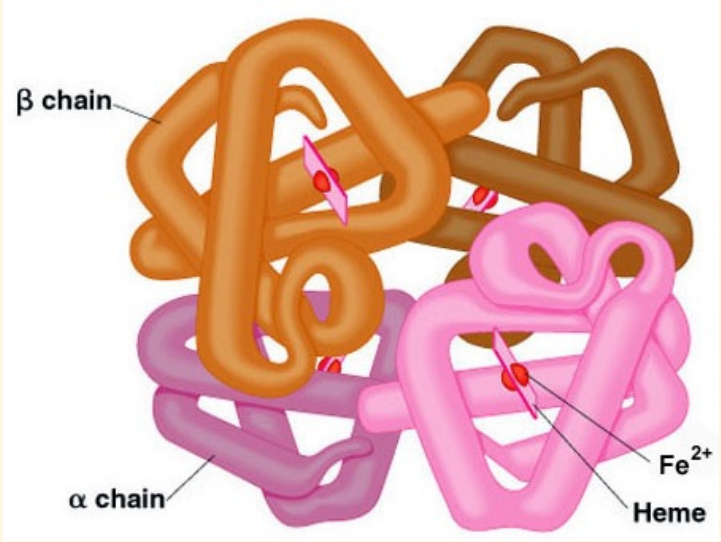
Gates and Crellin Laboratories of Chemistry,
California Institute of Technology, Pasadena, California[4]

- Used electrophoresis → determined that sickle cell hemoglobin was different from normal hemoglobin
  - Sickle cell disease → first disease understood at a molecular level
- Parallel results from Dr. James V. Neel → demonstrated genetic inheritance of sickle cell disease
- 1956 → Dr. Vernon Ingram discovered the single amino acid substitution responsible for sickle cell anemia

Gormley M. *Endeavour*. 2007;31:71-77.

Hemoglobin: Background

- Hemoglobin (Hb) → oxygen carrying protein within red blood cells



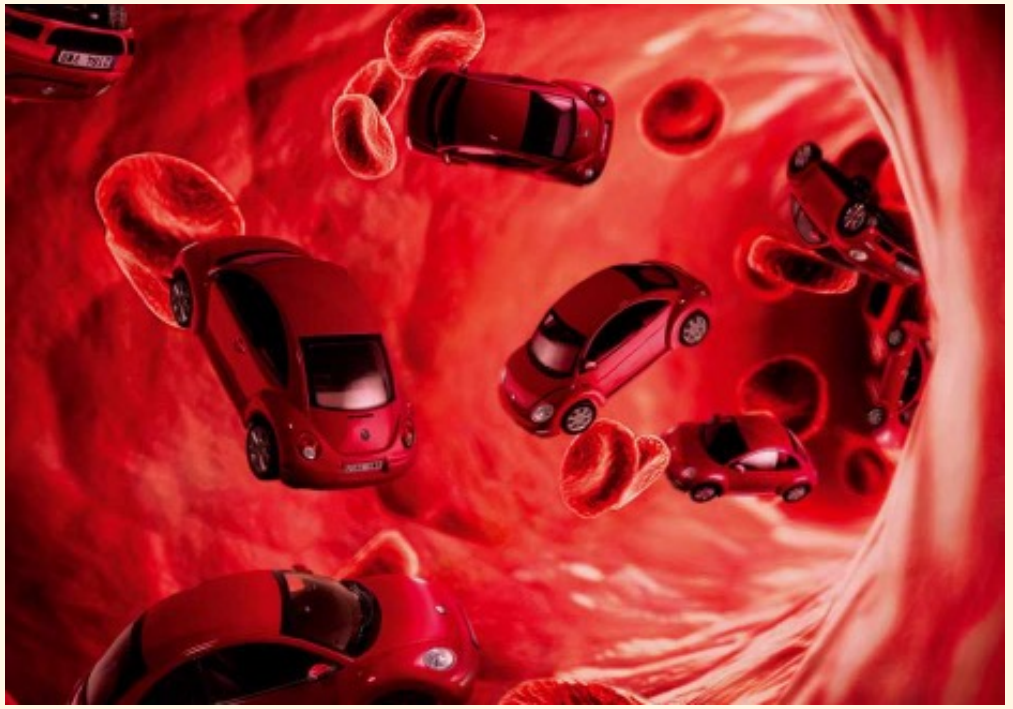
- Two main types of globins
  - α globin → chromosome 16
  - β globin → chromosome 11

- Heme → complex of ferrous iron and protoporphyrin
  - Linked covalently to each globin monomer
  - Can bind reversibly to one oxygen molecule → enables oxygen delivery to tissues

Hemoglobin: Background

- Red blood cell is a car → delivering oxygen to tissues

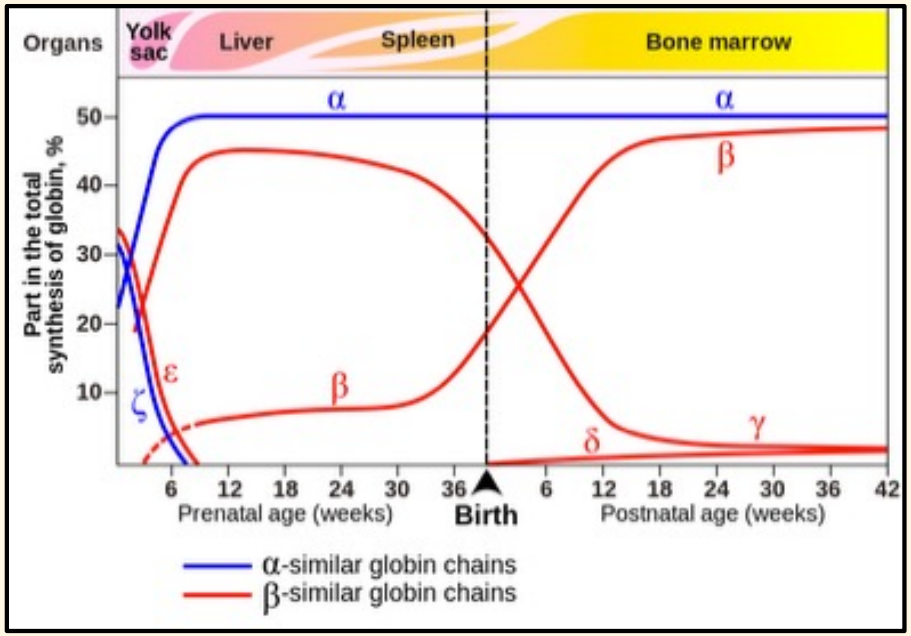
- Hemoglobin → the wheels that help the car get to where it needs to go



Hemoglobin: Background

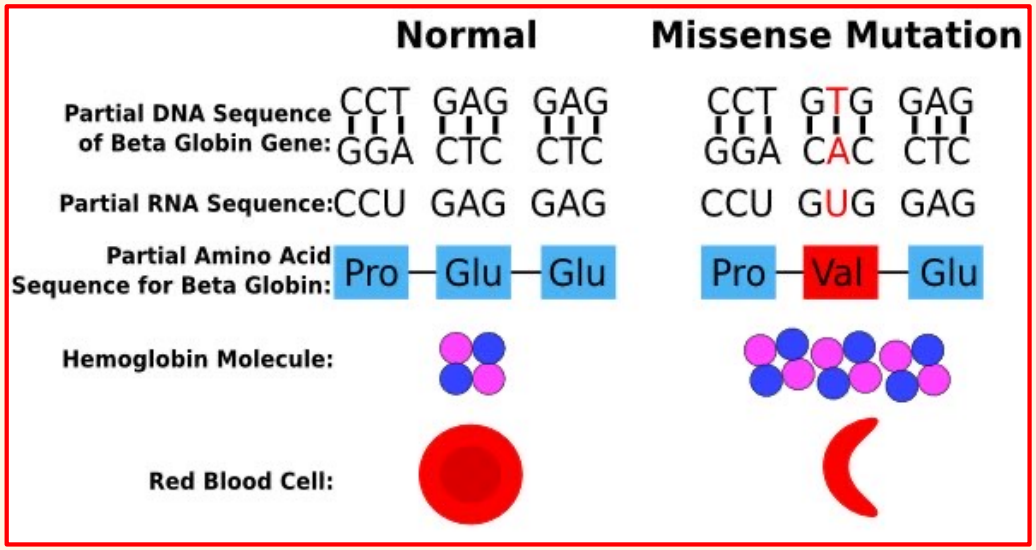
- Normal adult hemoglobin → HbA
  - Consists of two α-globins and two β-globins → $\alpha_2\beta_2$

- Post embryonic hemoglobin
  - Majority is HbA → $\alpha_2\beta_2$
  - Adult variant (HbA_2) → $\alpha_2\delta_2$
  - Fetal Hemoglobin (HbF) → $\alpha_2\gamma_2$



Hemoglobin: Background

- Sickle cell disease → qualitative hemoglobinopathy
  - Decreased solubility of hemoglobin
  - Results from a single amino acid substitution in the gene encoding the β-globin



Defining Sickle Cell Disease

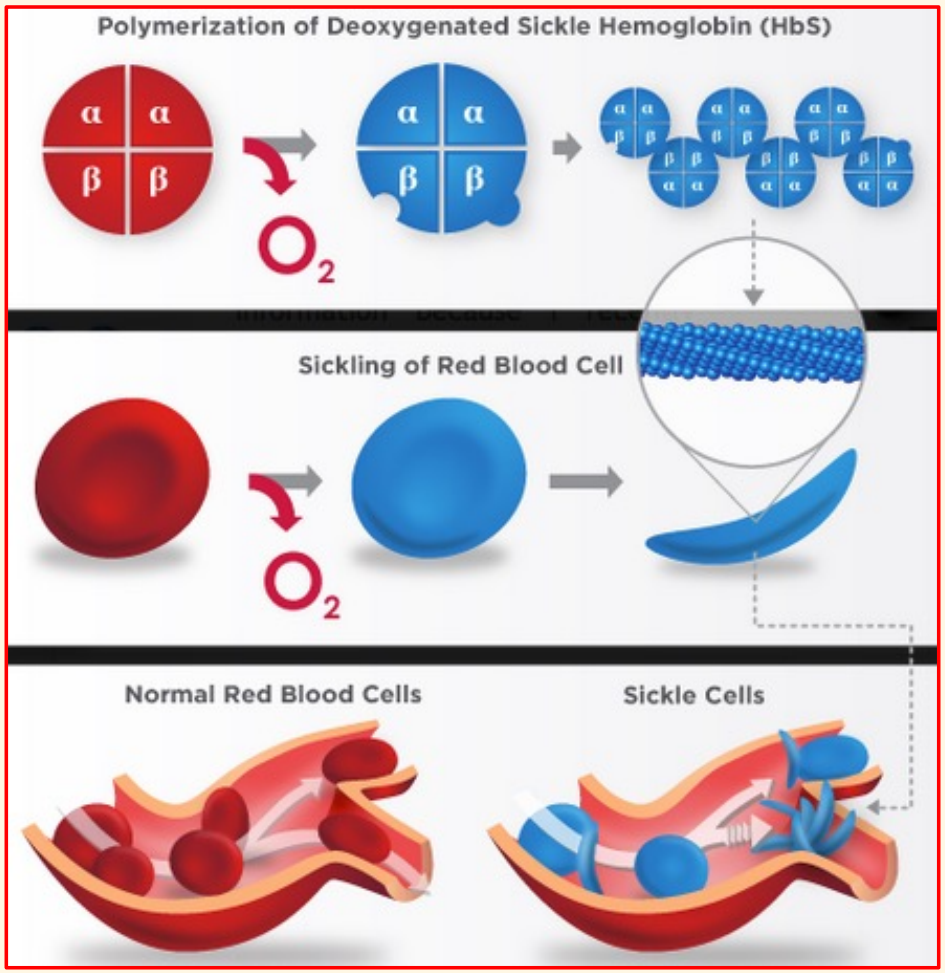
- Four genotypes
  - HbSS
  - HbSβ^0Thalassemia

  } Sickle cell anemia

  - HbSC
  - HbSβ^+Thalassemia

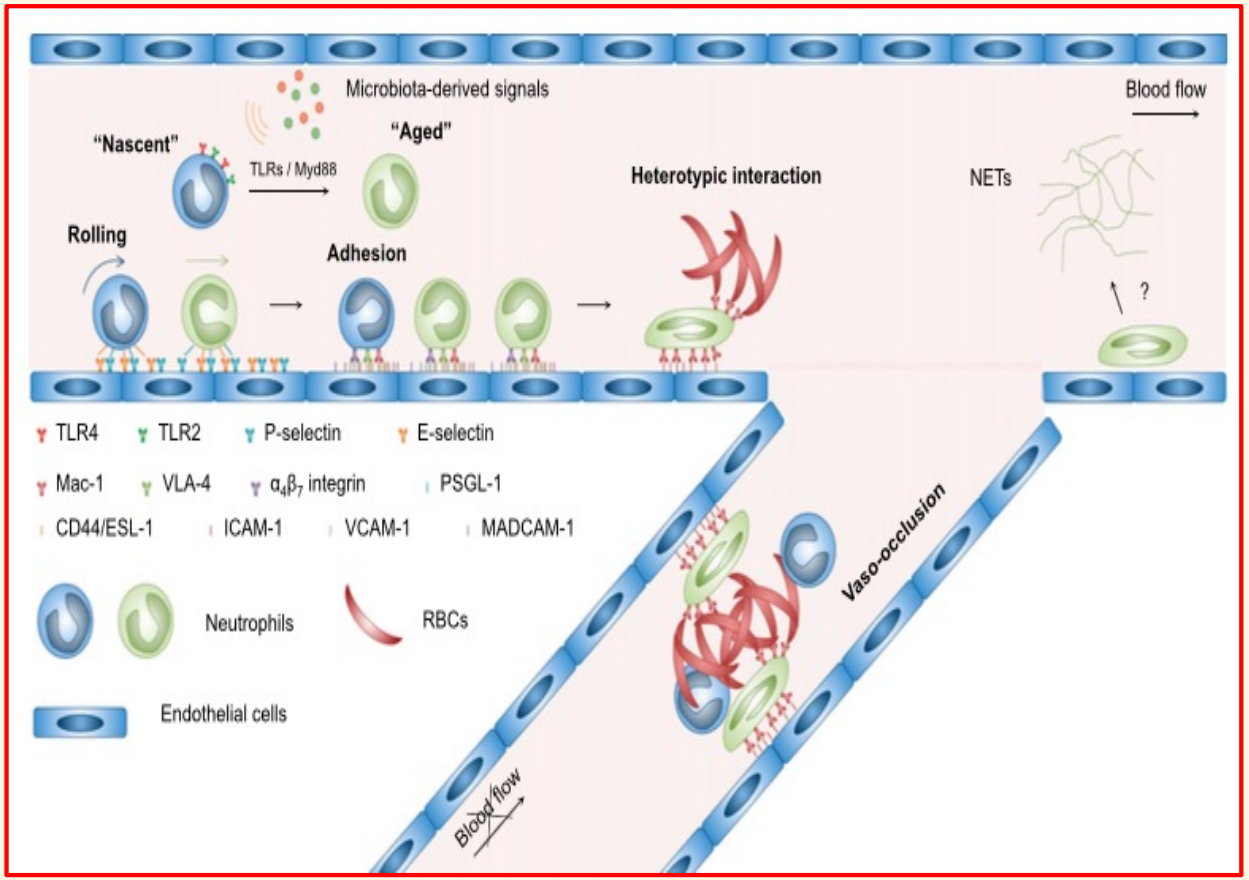
  } Sickle cell disease

Sickle Cell Disease: Pathophysiology



- Stressor → decreased oxygen
  - HbS conformational change
  - Exposes hydrophobic "water hating" valine
- Hydrophobic patches interact with one another → get tangled
- Form long rigid fibers → polymerization
- Affected erythrocytes → sickled shape

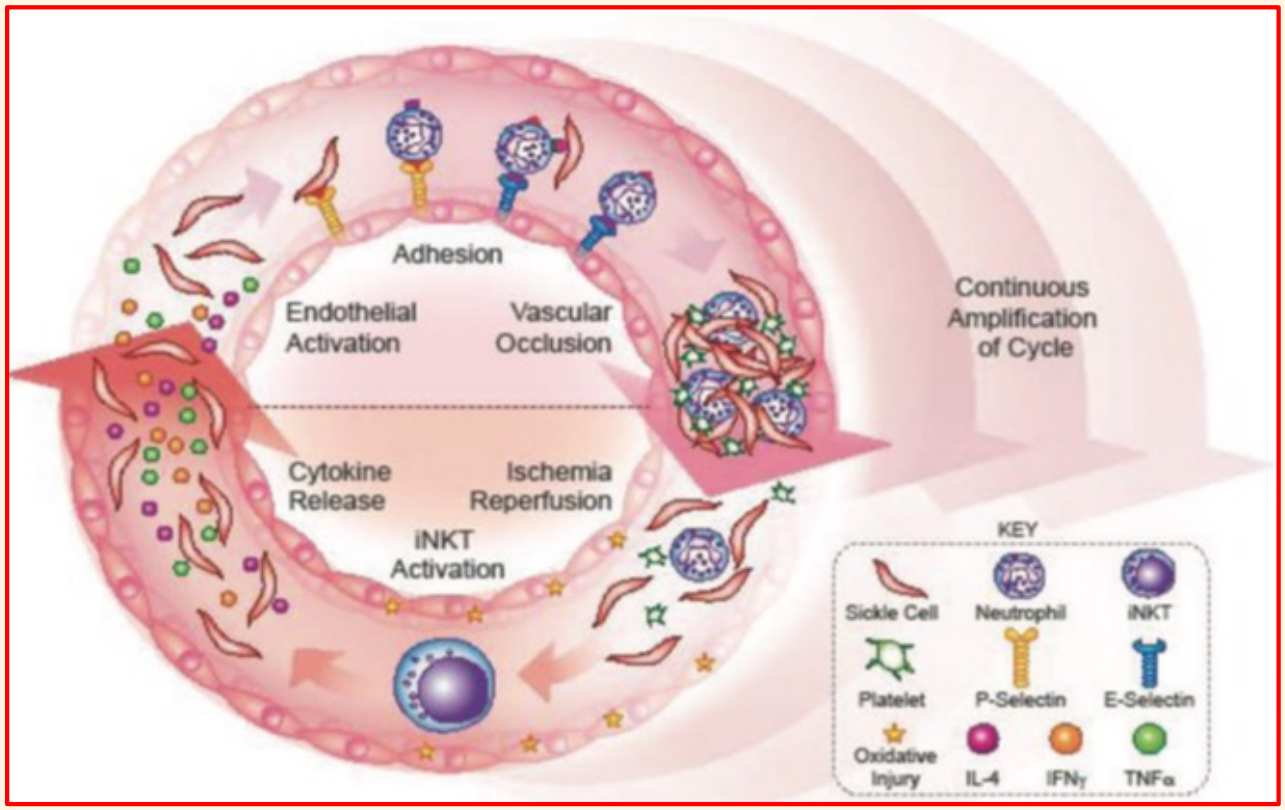
Sickle Cell Disease: Pathophysiology



- Inflammatory stimuli → endothelial cell activation
- Neutrophils → bind to sickled RBCs
- Obstruction of venous blood flow → ischemia and vaso-occlusion

Zhang D, et al. *Blood*. 2016;127:801-809.

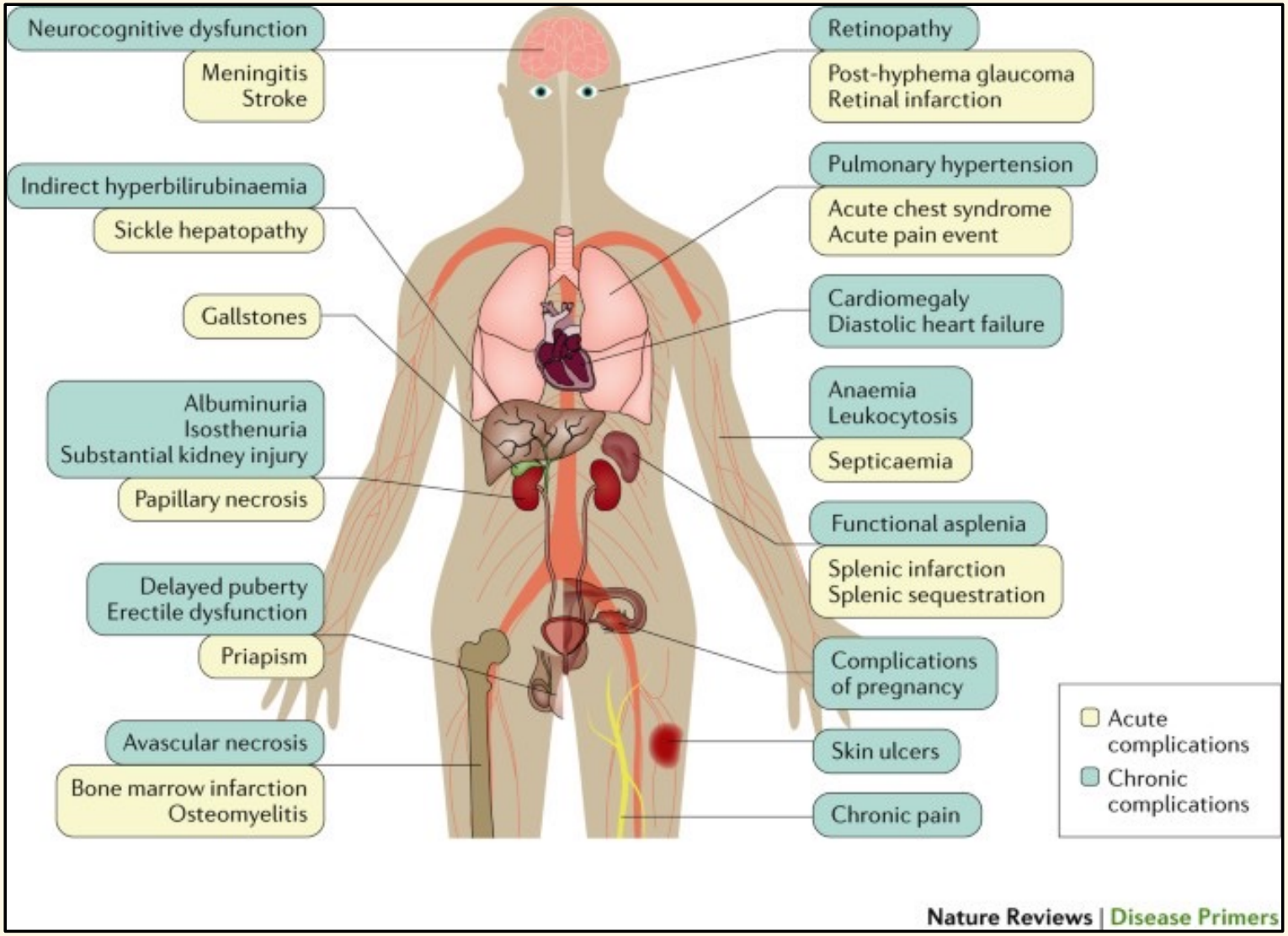
Sickle Cell Disease: Pathophysiology



- Formation of the sickled cell is first step in vaso-occlusion
- Sickled RBCs interact with neutrophils, endothelial cells and platelets → occlusive clot
- Further cellular activation → more vaso-occlusion

Field JJ. *Hematology Am Soc Hematol Educ Program*. 2015;2015:426-432.

Clinical Manifestations of Sickle Cell Disease



Kato GJ PS, et al. *Nat Rev Dis Primers*. 2018;4:18010.

Clinical Manifestations of Sickle Cell Disease

- Vaso-occlusive crisis → hallmark feature of disease
- Primary reason patients come to care
- Even without pain → sickle cell disease causes both:
  - Acute and chronic organ damage
  - Requires expert management

Mortality in Sickle Cell Disease

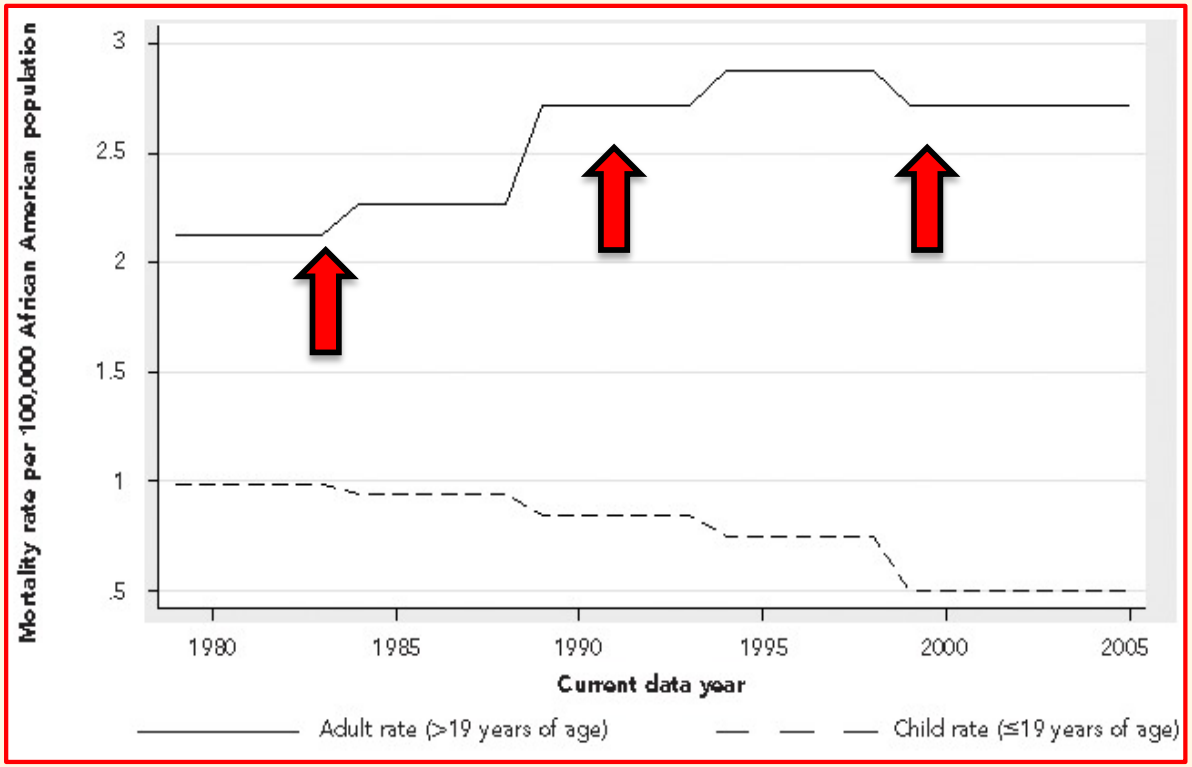
- Platt et al. (1994)
  - Prospective study → 3764 patients

- Median age of death for HbSS patients
  - Men → 42 years
  - Women → 48 years

- Median age of death for HbSC patients
  - Men → 60 years
  - Women → 68 years

Platt OS, et al. *N Engl J Med*. 1994;330:1639-1644.

Mortality in Sickle Cell Disease



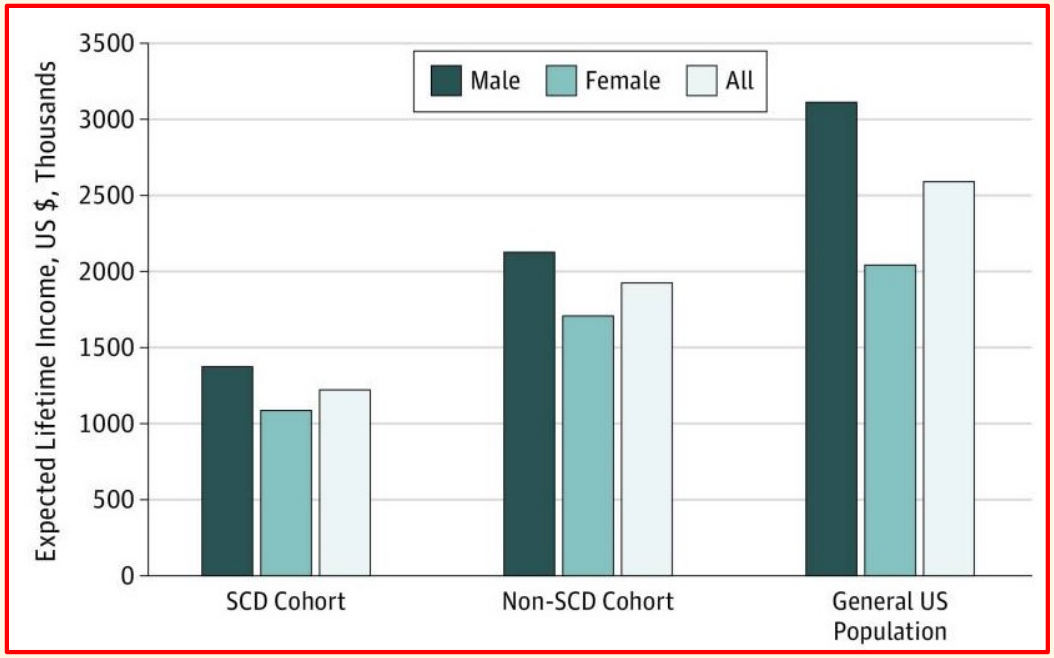
- Lanzkron et al. (2013)
  - Reviewed mortality rates and age at death from 1979-2005
- Striking improvement in outcomes for pediatric population
- Median age of death for affected adults unchanged

Lanzkron S, et al. *Public Health Rep*. 2013;128:110-116.

Mortality in Sickle Cell Disease

- Life expectancy for patients with SCD → 20 years shorter than expected

- Quality-adjusted life years → 30 years shorter

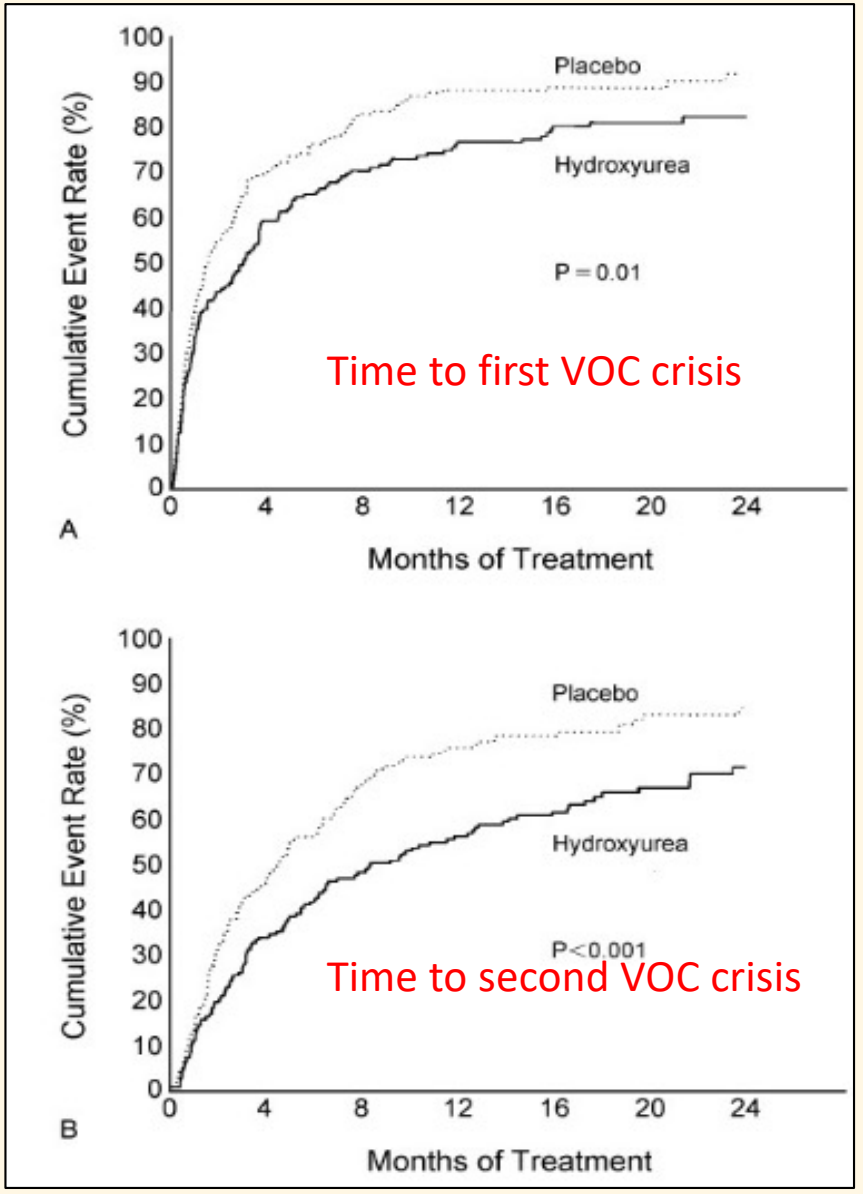


Lubeck D, et al. *JAMA Netw Open*. 2019;2:e1915374.

Current Standard of Care

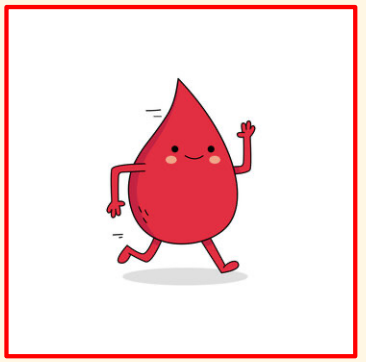
- Options for disease management:

- Hydroxyurea → MSH trial (1995)
  - Induces fetal hemoglobin
  - Interferes with HbS polymerization
  - Enrolled HbSS patients only
  - 50% reduction in VOCs, ACS, and hospitalizations
  - Role in HbSC pts unknown



Carache S, et al. *N Engl J Med.* 1995;332:48-56.

Current Standard of Care



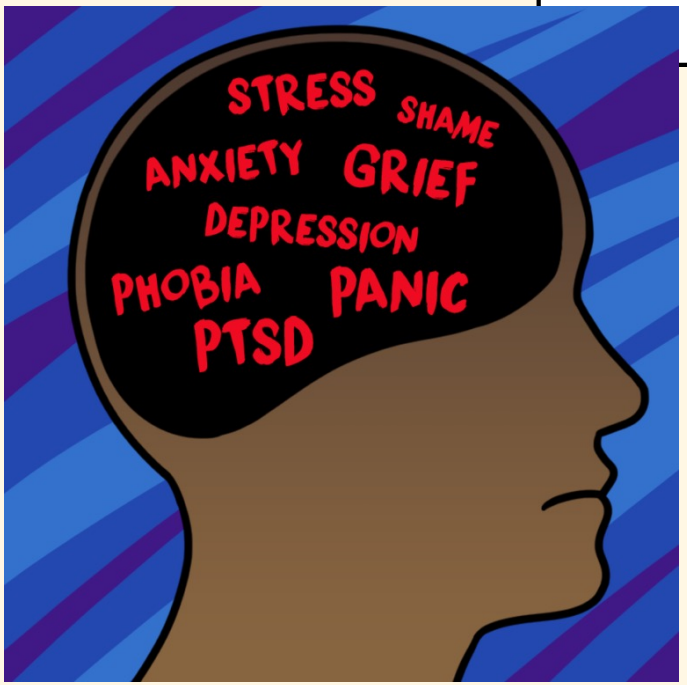
- Chronic transfusion therapy
  - Efficacy in preventing primary or secondary stroke
  - Prevent recurrent acute chest syndrome
  - Partial or full RBC exchange to minimize iron overload

- Other therapies with disease modifying potential
  - Crizanlizumab → p-selectin inhibitor, reduces VOCs
  - L-glutamine → more oxygen to RBC, anti-inflammatory
  - New therapies under investigation

Ataga KI, et al. *N Engl J Med.* 2017;376:429-439.

Current Standard of Care

- Supportive measures
  - Pain management
  - Hydration
  - Mental Health Care



Case Vignette

- 27 year old F with HbSS
  - On maximum tolerated dose Hydroxyurea
  - Prior h/o intubations for recurrent ACS peds/young adult
  - AVN R hip → hip replacement at age 25
- Admission for acute chest x 2 mo → vvECMO
- Comes to clinic → what's next??
  - Can I avoid any more life-threatening complications?
  - Can I be cured?

Definitive Therapy

- Sickle cell disease → multisystem disorder
  - Reduced life expectancy
  - Reduced quality of life
  - Multi-organ dysfunction
- Can we offer a more **definitive** therapy for patients?

Allogenic Stem Cell Transplant

- First transplanted patient → 1984
  - 8-year-old girl with HbSS and AML
  - Transferred to St. Jude for matched sib alloSCT
  - Cured both AML and sickle cell disease
  - Started the idea…

- Walters et al. (1996)
  - 22 children < 16 years of age → HbSS, HbSC, HbS-beta thal
  - HLA identical siblings
  - 20/22 patients survived

Walters MC, et al. *N Engl J Med.* 1996;335:369-376.

Allogeneic Stem Cell Transplant

- Early challenges in adoption of alloSCT:
- Limited donor availability
  - 14% chance of having available donor
  - Underrepresentation in donor registries
  - Diversity of HLA system → uncommon HLA types

- Myeloablative conditioning
  - Too toxic for individuals with end-organ disease
  - Non-relapse mortality ~ 10%
  - Graft loss with recurrent SCD ~ 10%

Hoppe CC, et al. *Curr Opin Oncol*. 2001;13:85-90.

Allogeneic Stem Cell Transplant

- Barriers:
  - Limited donor pool
  - Treatment related toxicities

- Two strategies developed to overcome:
  - Reduced intensity conditioning (RIC) haploSCT with posttransplant cyclophosphamide (PTCy)
  - Gene therapy

Jones RJ, et al. *Blood*. 2025;9:877-883.

Allogeneic Stem Cell Transplant

- Hsieh et al. (2014)
  - Matched sibling alloSCT with RIC
  - Reversed sickle cell phenotype → 26/30 patients
  - HLA-matched sibling donors found < 10% individuals
- Only one death due to relapsed SCD
- 87% patients → long-term stable donor engraftment
  - No acute or chronic GVHD

Hsieh M, et al. *JAMA*. 2014;312:48-56.

Allogeneic Stem Cell Transplant

- Hematologic malignancies → use of PTCy with haplo donor
  - Outcomes similar to those seen with matched related donors
  - FluCy + TBI + ATG
  - GVHD prophylaxis PTCy, CellCept, tacrolimus or sirolimus

- Initial studies in patients with SCD → high rate of graft failure (43%)
  - JHH group → increased dose of TBI
  - Improved outcomes → 1/12 with graft failure

Bolaños-Meade J, et al. *Blood*. 2012;120:4285-4291.

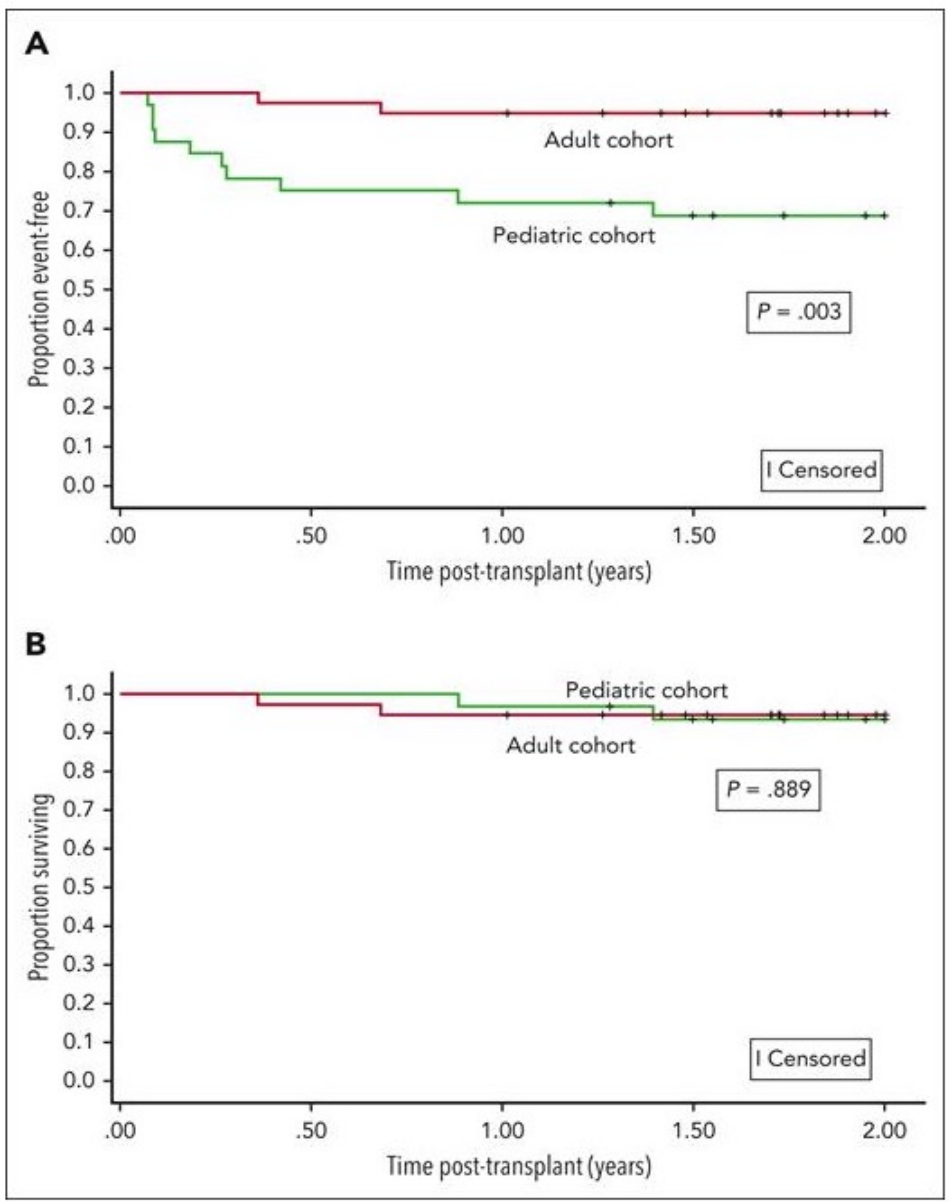
Allogeneic Stem Cell Transplant

- International multicenter phase 2 study
  - Nonmyeloablative haploSCT with PTCy

- 70 patients
  - Graft failure only in 8/70 patients and only in patients < 18 years
  - Severe GVHD rate → 10%
  - 5 patients died from infectious complications
  - Readily available curative therapy for most adults

Kassim AA, et al. *Blood*. 2024;143:2654-2665.

Allogeneic Stem Cell Transplant



Event free survival for adults → 94.7%

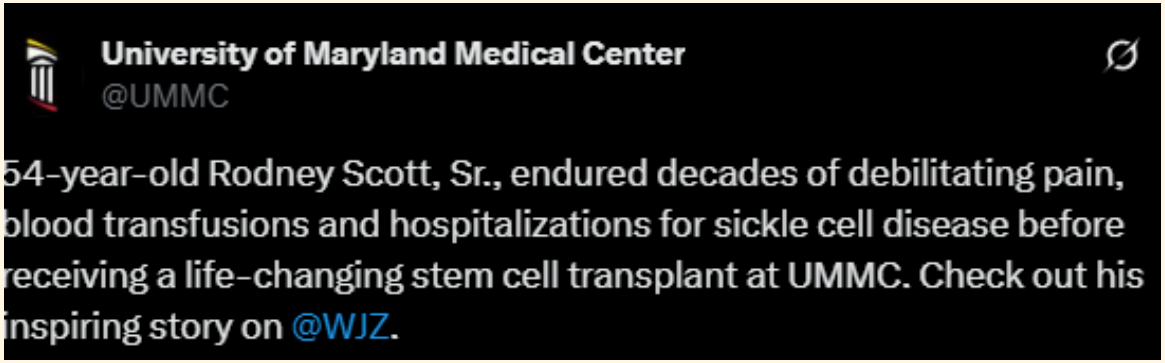
Overall survival for adults → 94.7%

Kassim AA, et al. *Blood*. 2024;143:2654-2665.

Allogeneic Stem Cell Transplantation

7/14/2017 1604	7/14/2017 1604	2/25/2020 1347	2/25/2020 1439
10.0			13.0
8.6			15.2
25.3			43.5
316			263
Present			
Abnormal			
			7.10
55			54.6
			4.2
37			32.5
			1.4
8			11.0
			0.1
			0.4
			0.2
			1.2
3	0.3		0.0
2.8			0.0
32.5			31.8
34.0			34.9
95.5			91.0
9.0			8.9
2.65			4.78
27.1			14.0
100			
Abnormal			
1+			
Slight			
1+			
Present			

- "I never knew I could feel this good"
- "The crises and pain that once ruled my life, couldn't hurt me anymore"



Allogeneic Stem Cell Transplantation

- “Transplant gave me my life back”

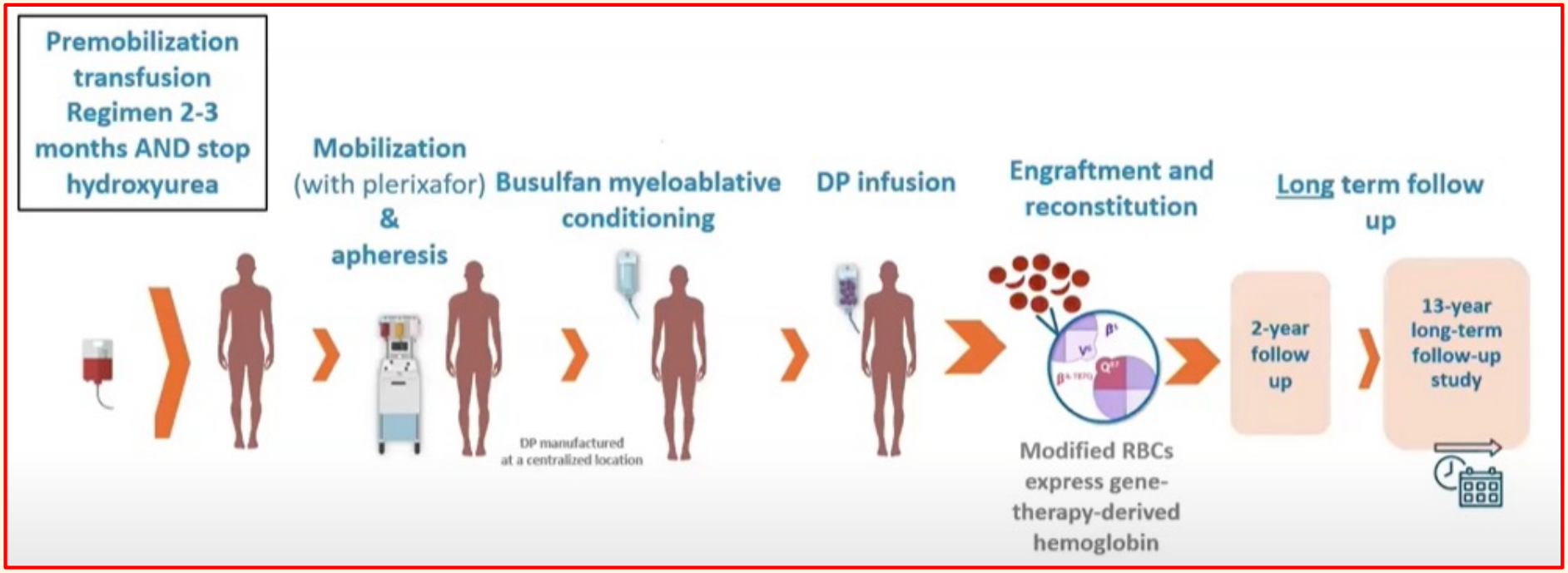
Gene Therapy

- Developed as an option to circumvent lack of available donors
  - Uses autologous CD34+ cells
- Prototype disease to showcase the promise of gene therapy
  - Point mutation in 1 gene
  - Expressed in just 1 cell type → RBCs

Ribeil JA, et al. *N Engl J Med*. 2017;376:848-855.

Gene Therapy: Timeline

- Time to therapy is LONG → much of the work is before cells are given
- Estimate at least 1 year lead up to therapy



Gene Therapy: Timeline

- Start on RBC exchange to lower HbS < 30%
- Discontinue disease modifying therapy (HU) at least 60 days prior to collection
  - Stop iron chelator 7 days prior to collection
- Fertility Preservation
- Recommend at least 2 cycles of exchange a month apart prior to mobilization
  - RBC exchange within 4 days of mobilization
  - Should continue to the preparative regimen

Gene Therapy

- Two approved gene therapies for sickle cell disease (2023)
  - Lovo-cel → Lyfgenia
  - Exa-cel → Casgevy

Gene Therapy: Lovo-cel

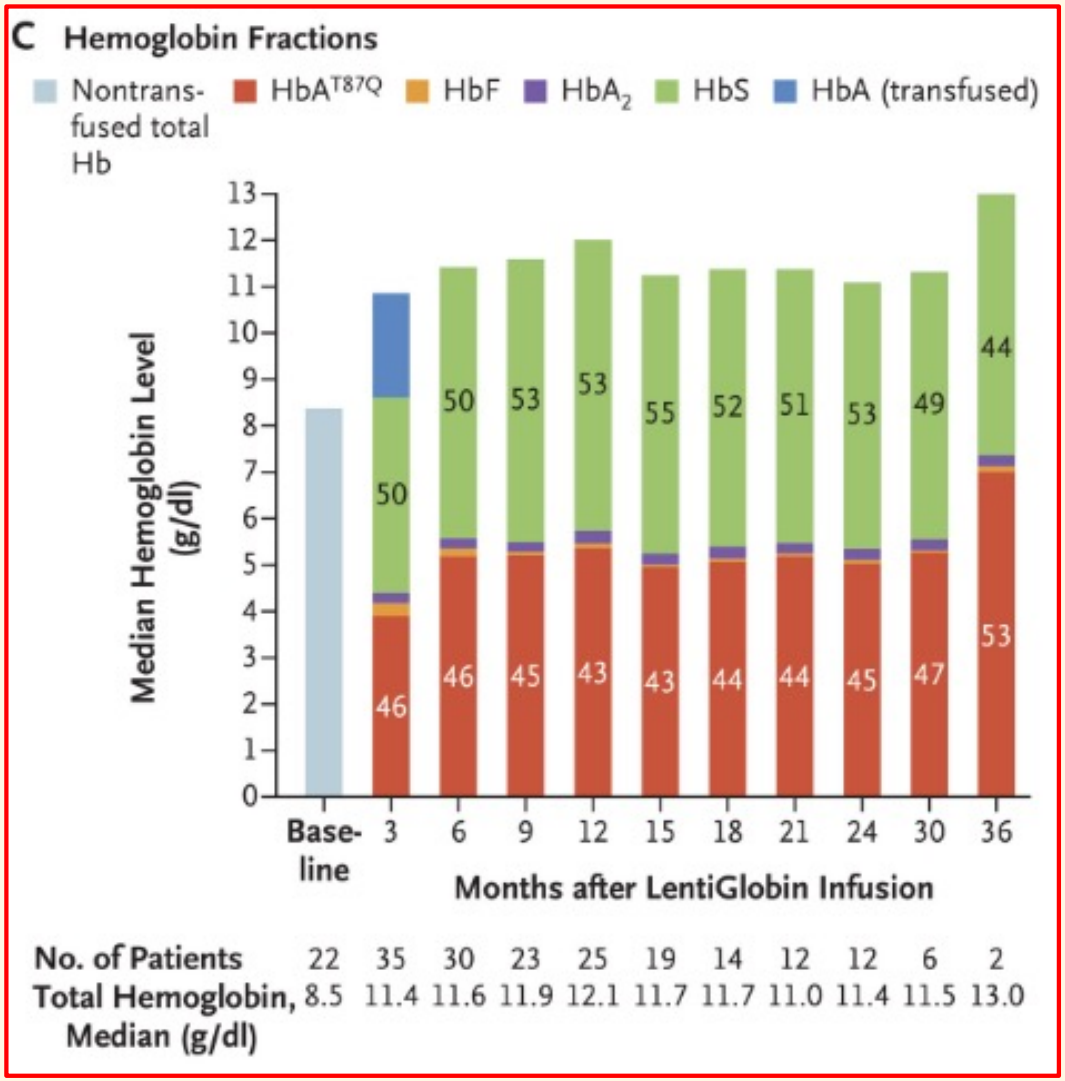
- Lovo-cel → one time cell-based gene therapy
- Uses an inactive HIV viral vector → to introduce a new gene into the stem cells
  - Does not cause HIV infection
  - Results in production of a new anti-sickling hemoglobin variant → HbA^{T87Q}
- Does not remove or change any of the existing genes

Gene Therapy: Lovo-cel

- Phase 1-2 study→ 3 cohorts
- 35 patients in final cohort
  - 12-50 years of age → median age 24 years
  - HbSC excluded
  - No option for matched HLA identical donor
  - No history of stroke with associated vasculopathy
- Plerixafor mobilization + apheresis
- Pts had a median of 3 VOEs per year

Kanter J, et al. *N Engl J Med*. 2022;386:617-628.

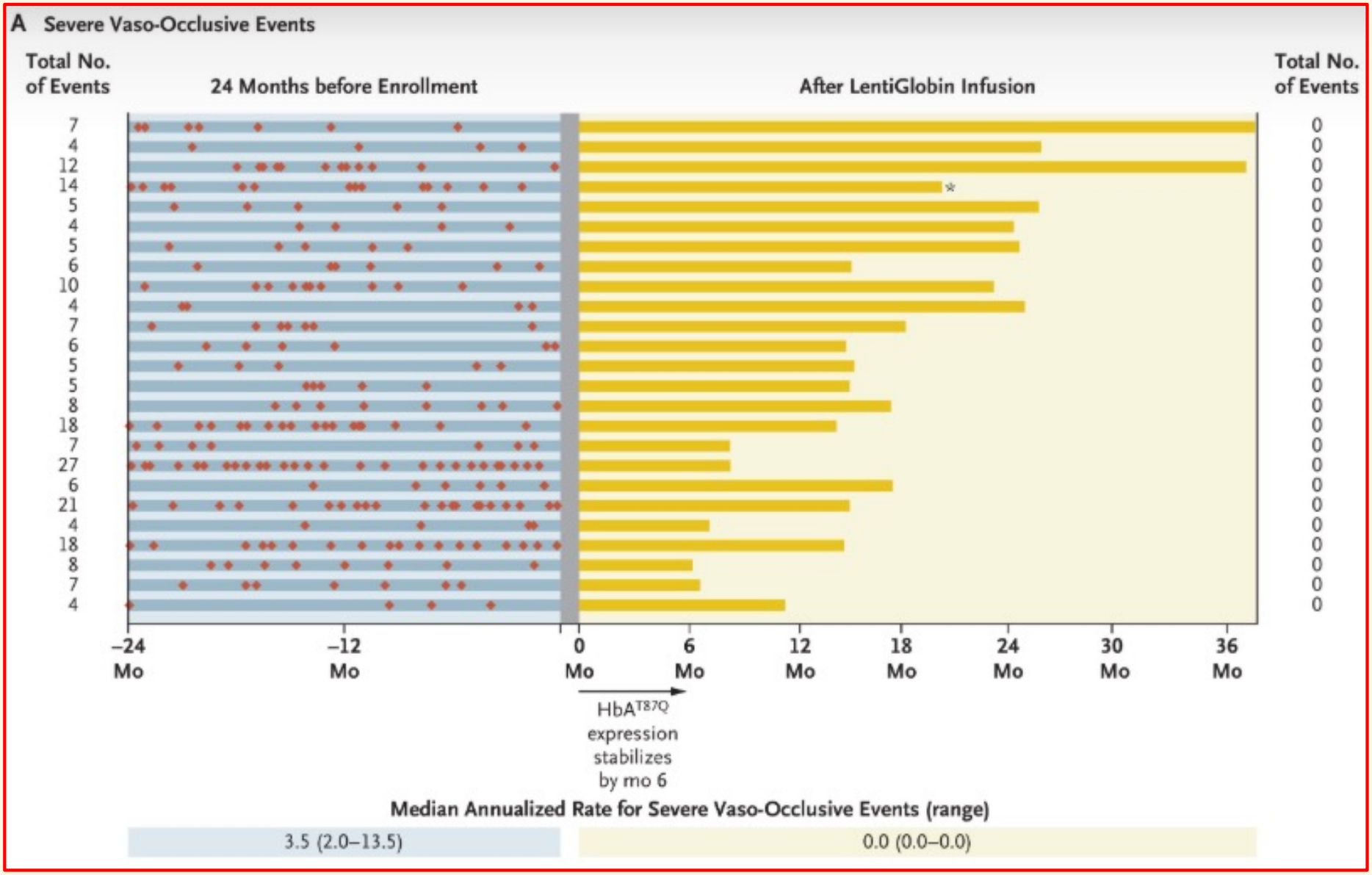
Gene Therapy: Lovo-cel



- Median Hgb 8.5 g/dL
- 6 mo post infusion → 11 g/dL
- Sickle hemoglobin ~ 50% at 6 mo → sustained at 36 mo

Kanter J, et al. *N Engl J Med*. 2022;386:617-628.

Gene Therapy: Lovo-cel



Kanter J, et al. *N Engl J Med*. 2022;386:617-628.

Gene Therapy: Lovo-cel

- Adverse events related to busulfan exposure
  - Nausea/vomiting, mucositis, febrile neutropenia
- 95% reduction in severe VOE
- Appears durable → early cohort now followed ~ 8 years
- Early cohort → 2 patients developed AML
  - No evidence of insertional oncogenesis found
  - Manufacturing process refined in later group
- Lovo-cel approved but with Black Box warning re AML

Goyal S. *N Engl J Med*. 2022;386:138-147.

Gene Therapy: Not quite “cured”

- **Transformative** therapy
  - Increase total hemoglobin
  - Increases non-sickled hemogloblin
  - Nearly normalize hemolysis markers
  - Decrease or eliminate painful crises
  - Improve fatigue and quality of life

- But sickled cells are still present…
  - Many unknowns
  - Does not repair damage that has occurred already

Gene Editing: Exa-cel

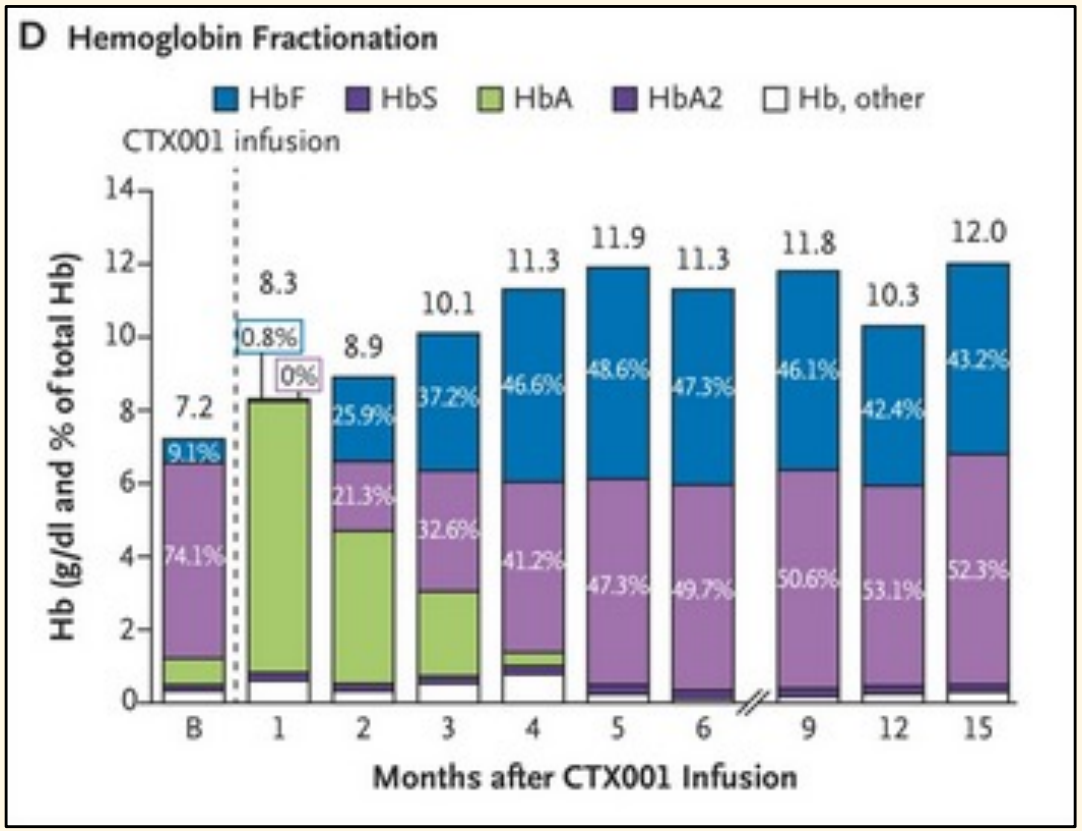
- CRISPR
  - Technology used to edit genes
  - Can turn genes “on” and “off”

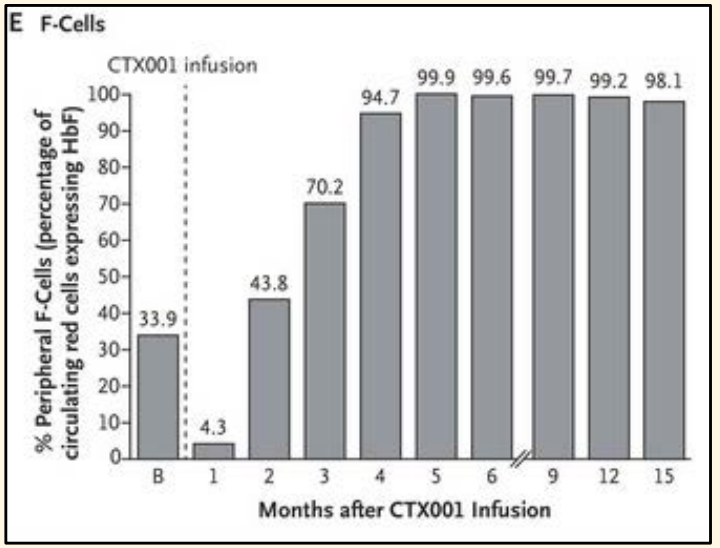
- Uses CRISPR to “turn off” BCL11A expression on chromosome 2
  - Turns back on production of fetal hemoglobin

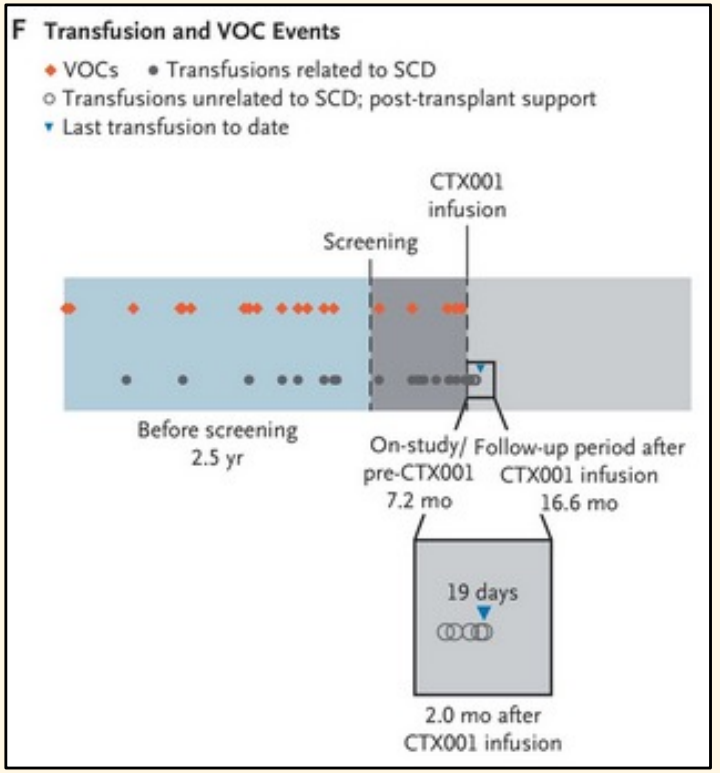
- Relies on patient’s own CD34+ stem cells
  - Receive some chemotherapy to “make room” for edited cells

Frangoul H, et al. *N Engl J Med*. 2021;384:252-260.

Gene Editing: Exa-cel







Frangoul H, et al. *N Engl J Med*. 2021;384:252-260.

Gene Editing: Exa-cel

- Durable increases in fetal hemoglobin to ~ 40%
- Improvements in measures of hemolysis and quality of life
- Less individuals far out from infusion
  - Time of FDA approval → only 3 patients two years out
- 93% of patients without VOCs post infusion
- Patients aged 12-35 enrolled, HbSC patients again excluded

Kanter J, et al. *N Engl J Med*. 2022;386:617-628.

Lovo-cel versus Exa-cel

	Lovo-cel	Exa-cel
Population	12-50 years old, no HbSC	12-35 years old, no HbSC
Mechanism	Gene addition using lentiviral vector → insert gene encoding for HbA^{T87Q}	*CRISPR/Cas 9* editing to turn off *BCL11A* expression → increase HbF
Inclusion/Exclusion	• ≥ 4 VOEs in 24 mo • No MRD • HU failure or intolerance • Excluded severe vasculopathy	• ≥ 2 severe VOEs in 24 mo • No MRD • HU failure or intolerance • Excluded severe vasculopathy • Patients > 10 unplanned hospitalizations or ED visit related to SCD (chronic pain)

Gene Therapy: Not quite “cured”

- **Transformative** therapy
  - Increase total hemoglobin
  - Increases non-sickled hemogloblin
  - Nearly normalize hemolysis markers
  - Decrease or eliminate painful crises
  - Improve fatigue and quality of life

- But sickled cells are still present…

Gene Therapy: Not quite “cured”

- Unknowns
  - Does this protect against stroke?
  - Does this protect against kidney damage
    - Individuals with sickle cell trait → can have inc risk of kidney issues
  - Ophthalmologic complications?
    - How to screen post infusion?

- Does not repair damage which has occurred prior to infusion

Gene Therapy: Challenges

- Administration is logistically challenging and complex
  - Not just an “autoSCT”
- Risk of infertility due to myeloablative conditioning
- High cost → $2-3 million just for the cells
- Questions regarding long term risk of malignancy
- Potential for other stem cell changes

Gene Therapy: Challenges

- Cost infective therapy per conventional standards
- More cost-effective when considering equitable health care + reduction in disparities
- Very limited numbers of patients will be able to access these therapies
  - Just 1 patient in 2024 received commercial product!

NYTimes 9/17/24

Goshua G, et al. *Ann Intern Med.* 2023;176:779-787.

AlloSCT versus Gene Therapy

	AlloSCT	Gene Therapy
Outcome + Durability	Curative + Lifelong	Transformative + ?
Eligible	All genotypes	Excludes HbSC
Cost	~$300-500K	$2-3 million
Time to therapy	~2-3 months	~1 year

Jones RJ, et al. *Blood*. 2025;9:877-883.

Who Should be Referred?

American Society of Hematology 2021 guidelines for sickle cell disease: stem cell transplantation

- Gene therapy → experienced at least 3 VOEs in the 24 months prior to assessment:
  - Vaso-occlusive pain crisis
  - Priapism episode lasting > 2 hours, may require medical care
  - Acute chest syndrome
  - Acute hepatic or splenic sequestration
  - History of acute stroke
- Experiencing VOEs despite disease modifying therapy
- Pattern of engagement with care
- Exclude → HbSC, α-/α-, HIV positive, cerebral vasculopathy

Kanter J, et al. *Blood Adv*. 2021;5:3668-3689.

Does Definitive Therapy Help Sickle Cell Care Overall?

- More patients are being referred to see a sickle cell specialist
- Most will end up not wanting transformative therapy BUT will hear about disease-modifying therapy to improve outcomes
- Sickle cell centers will be better staffed
- Increased interest in wanting to learn about and care for individuals with sickle cell disease

Does Definitive Therapy Help Sickle Cell Care Overall?

- Personnel needed to help deliver definitive therapy can also be used to care for other patients with sickle cell disease

Hematologist	**Infectious Disease**	**SCD Navigator**
Stem Cell Transplant	**Ophthalmologist**	**Fertility Specialist**
Transfusion Medicine	**Pharmacist**	**Transplant Coordinator**
Pulmonologist	**Psychologist**	**Psychiatrist**
Cardiologist	**SCD Social Worker**	**Nephrologist**

Conclusions

- Access to specialized sickle cell care essential for management of this complex disease

- Recognize that options for definitive management of sickle cell disease exists

- Broader access and uptake for definitive therapy is a reason to **HOPE** for all our patients

We Want to Help!

- Connect patient to specialized sickle cell care
  - Telemedicine available
  - Transportation assistance available

- New patient referral → umgcccreferrals@umm.edu

- Email → jennielaw@umm.edu

- Office → 410-328-6373