Sickle Cell Disease: Past, Present, & Future

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EASTERN MAINE MEDICAL CENTER

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Disclosures

- None

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Objectives

- Brief overview of sickle cell disease
  - Historical perspective
  - Pathophysiology and common complications
- Review current state of SCD and standard(s) of care
  - Treatment strategies and current guidelines
- Discuss future directions in treatment of SCD
  - Emerging therapies and clinical trials

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Sickle Gene Areas of Origin

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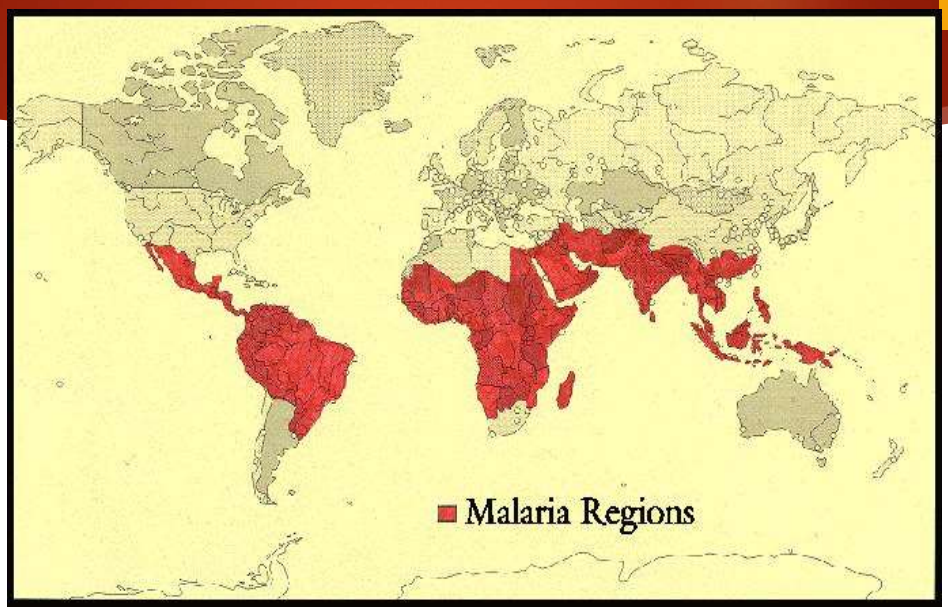

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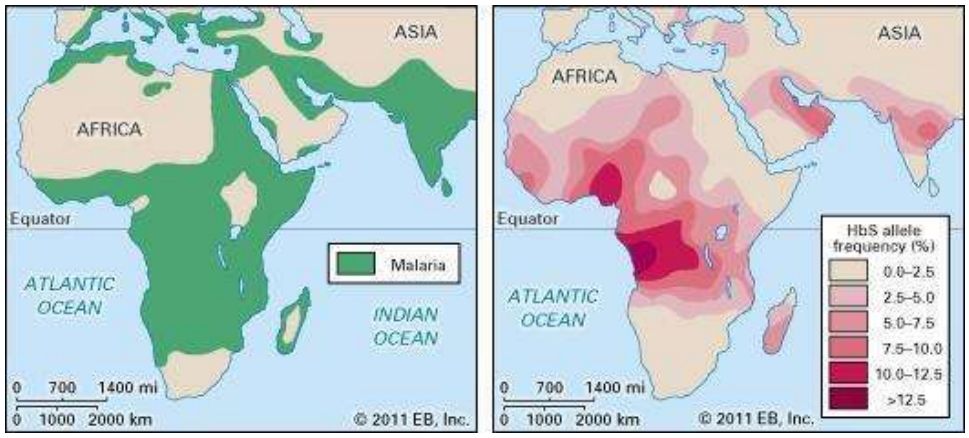
Hemoglobin S and Malaria



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Sickle Cell Disease in Africa

- As many as 20-30% of the population in certain parts of Africa carry the gene for SCD
- As many as 150,000 children are born in Africa each year with sickle cell disease
- Majority die before 5 years of age from infectious complications
- Having sickle cell trait (SCT) confers at least partial resistance to malarial infection

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SCD in North America

- Dr. James Herrick – 1904
- Dental student from Grenada presented to Chicago hospital with muscle pain, headaches, heart palpitations
- Unusual findings on blood smear

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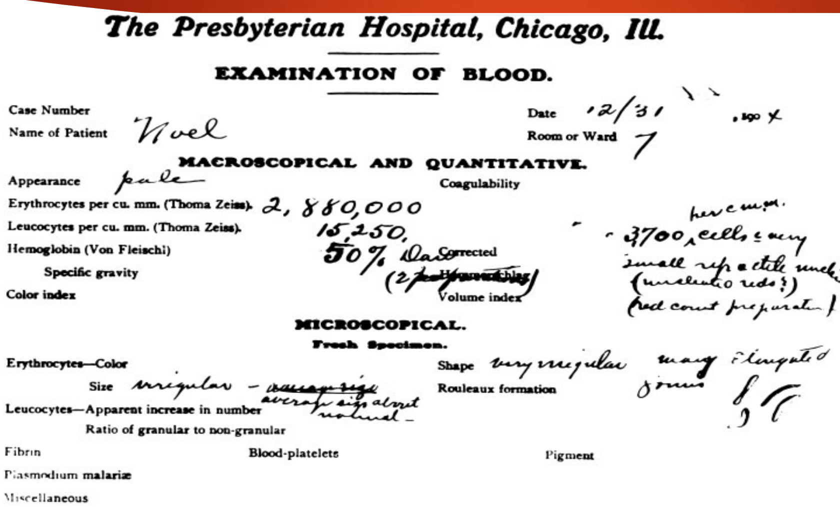
Blood Sample from Walter Noel


The Presbyterian Hospital, Chicago, Ill.

EXAMINATION OF BLOOD.

Case Number
Name of Patient Noel
Date 12/31, 1904
Room or Ward 7

MACROSCOPICAL AND QUANTITATIVE.

Appearance pale
Coagulability
Erythrocytes per cu. mm. (Thoma Zeiss). 2,880,000
Leucocytes per cu. mm. (Thoma Zeiss). 15,250,
Hemoglobin (Von Fleischl) 50%
Corrected
Specific gravity
Color index
Volume index
3700 cells per cu. mm. small refractile nuclei (nucleated reds?) (red count preparation)

MICROSCOPICAL.

Fresh Specimen.

Erythrocytes—Color
Size irregular — average size almost natural —
Shape very irregular many elongated forms
Rouleaux formation
Leucocytes—Apparent increase in number
Ratio of granular to non-granular
Fibrin
Blood-platelets
Pigment
Plasmodium malariæ
Miscellaneous

"Peculiar, elongated and sickle-shaped red blood corpuscles"

12/31/1904

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SCD in North America

- 1949 → Linus Pauling concludes SCD is due to defect in hemoglobin molecule
- 1956 → Hemoglobin S recognized as variant of Hemoglobin A with single amino acid substitution (valine for glutamate)
- 1960 → Structure of human hemoglobin identified
- 1972 → Nixon signs Sickle Cell Anemia Control Act into law
- 2006 → WHO recognized SCD as public health problem

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SCD Treatment Milestones

- 1982 → First known cure of SCD with bone marrow transplantation
- 1986 → PCN prophylaxis shown to greatly reduce incidence of Pneumococcal infections in children with SCD
- 1995 → Hydroxyurea (HU) shown to reduce frequency of painful crises in adults with SCD
- 2006 → Newborn screening for SCD becomes universal in United States (recommended in 1987)

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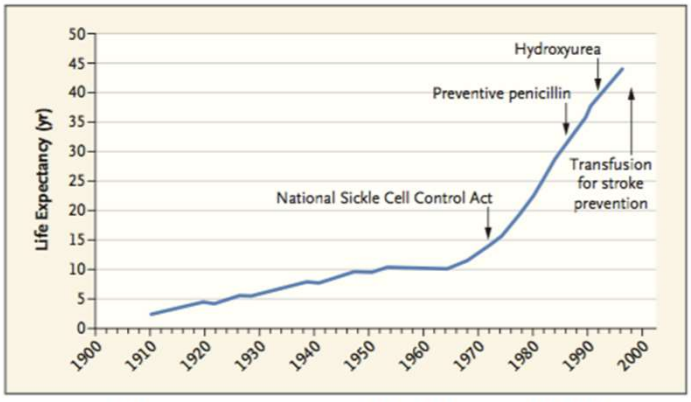
SCD Treatment Milestones



Increases in Life Expectancy in Persons with Sickle Cell Disease, 1910–2000.

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Sickle Cell Disease - Overview

- Inherited life-threatening disorder of red blood cells
- Affects 1 in 400 African American children born each year in U.S.
- ~100,000 people currently living with SCD in U.S.
- Caused by single β-globin gene mutation
  - Valine for glutamate at position 6
- Deoxygenation leads to formation of sickle-shaped RBC's
- HbSS, HbSC, $HbS\beta^+$, $HbS\beta^0$

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Sickle Cell Disease - Overview

- *Painful episodes* are hallmark of disease
- Chronic pain becomes more prevalent throughout life
- More frequent VOE associated with early mortality
- Hospitalizations associated with decreased HRQOL
- Adolescents with SCD prone to social isolation, depression, anxiety
- SCD treatments have improved, however significant morbidity remains

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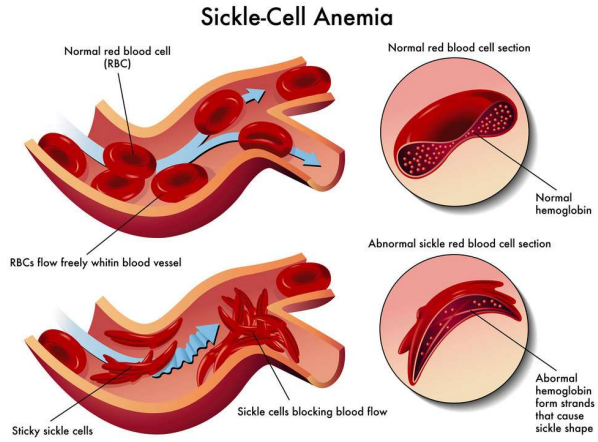
Pathophysiology of SCD



- Complex process involving:
  - Microvascular occlusion
  - Endothelial damage
  - Oxidative stress
  - Cell adhesion
  - Inflammatory mediators

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Sickle Cell Disease - Complications

- Acute painful episodes
- Hemolytic anemia
- Stroke
- Acute chest syndrome
- Fever/Infection
- Splenic sequestration
- Osteonecrosis
- Leg ulcers
- Priapism
- Pulmonary Hypertension
- Nephropathy

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Acute Painful Episodes

- VOC/VOE → Hallmark complication of SCD
- Complicated and poorly understood process
  - *Microvascular occlusion → Tissue ischemia → Tissue damage → Pain perception*
- May be precipitated by exposure to cold, stress, infection, dehydration
- Can be result of "rebound" from incomplete resolution of previous pain episode
- Often can be treated at home with oral pain medications
- Goal is to minimize pain and prevent complications

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Acute Painful Episodes: Management

- Parenteral analgesics
  - Morphine → at least 0.1 mg/kg, titrate to effect
  - Early initiation of patient-controlled analgesia (PCA)
  - Ketorolac → 0.5 – 1 mg/kg every 6 hours
  - *Ask patient what works for them!*
  - *PRN = "patient receives nothing!"*
- IV fluids ~ 1-1.25 x maintenance rate
- Labs → CBC with retic, culture if febrile, CXR if symptoms

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Acute Painful Episodes: Management

- Consideration of RBC transfusion
- Supportive/alternative therapies
  - Massage, yoga, acupuncture, guided imagery, PT
- Bowel regimen
- Incentive spirometry
- Frequent reassessment of pain
- Transition to oral regimen when appropriate

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Sickle Cell Disease: Current Preventative Treatment Strategies

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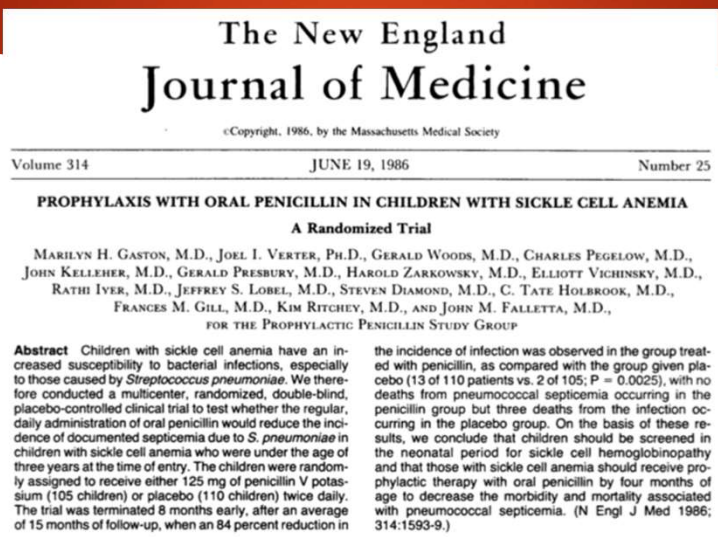
Penicillin Prophylaxis



The New England
Journal of Medicine

Volume 314 JUNE 19, 1986 Number 25

PROPHYLAXIS WITH ORAL PENICILLIN IN CHILDREN WITH SICKLE CELL ANEMIA

A Randomized Trial

MARILYN H. GASTON, M.D., JOEL I. VERTER, PH.D., GERALD WOODS, M.D., CHARLES PEGELOW, M.D., JOHN KELLEHER, M.D., GERALD PRESBURY, M.D., HAROLD ZARKOWSKY, M.D., ELLIOTT VICHINSKY, M.D., RATHI IYER, M.D., JEFFREY S. LOBEL, M.D., STEVEN DIAMOND, M.D., C. TATE HOLBROOK, M.D., FRANCES M. GILL, M.D., KIM RITCHEY, M.D., AND JOHN M. FALLETTA, M.D., FOR THE PROPHYLACTIC PENICILLIN STUDY GROUP

Abstract Children with sickle cell anemia have an increased susceptibility to bacterial infections, especially to those caused by *Streptococcus pneumoniae*. We therefore conducted a multicenter, randomized, double-blind, placebo-controlled clinical trial to test whether the regular, daily administration of oral penicillin would reduce the incidence of documented septicemia due to *S. pneumoniae* in children with sickle cell anemia who were under the age of three years at the time of entry. The children were randomly assigned to receive either 125 mg of penicillin V potassium (105 children) or placebo (110 children) twice daily. The trial was terminated 8 months early, after an average of 15 months of follow-up, when an 84 percent reduction in the incidence of infection was observed in the group treated with penicillin, as compared with the group given placebo (13 of 110 patients vs. 2 of 105; P = 0.0025), with no deaths from pneumococcal septicemia occurring in the penicillin group but three deaths from the infection occurring in the placebo group. On the basis of these results, we conclude that children should be screened in the neonatal period for sickle cell hemoglobinopathy and that those with sickle cell anemia should receive prophylactic therapy with oral penicillin by four months of age to decrease the morbidity and mortality associated with pneumococcal septicemia. (N Engl J Med 1986; 314:1593-9.)

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Penicillin Prophylaxis

- 215 children with SCD under < 3 years of age at study entry
- Randomized to Pen VK 125 mg BID vs placebo
- Primary endpoint *S. pneumo* bacteremia
- 84% reduction in episodes of bacteremia in PCN group led to early study termination (13 in placebo vs 2 in PCN)
- PCN prophylaxis now considered standard of care for children with SCD

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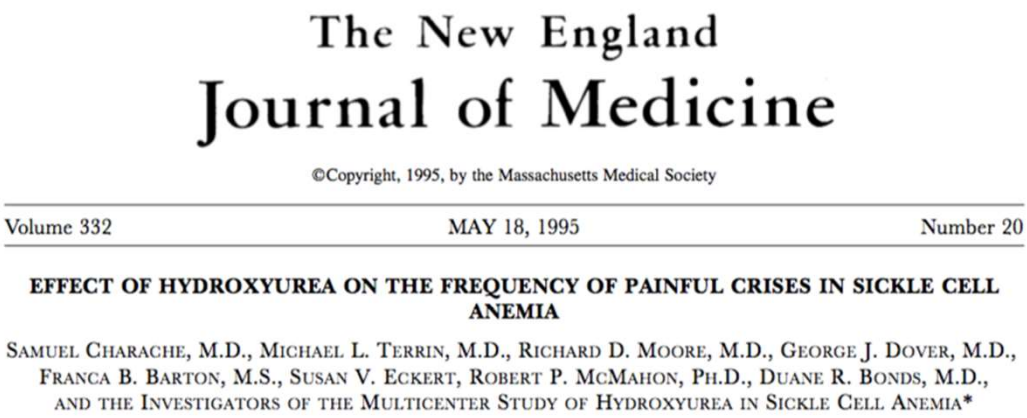
Hydroxyurea



The New England
Journal of Medicine

Volume 332 MAY 18, 1995 Number 20

EFFECT OF HYDROXYUREA ON THE FREQUENCY OF PAINFUL CRISES IN SICKLE CELL ANEMIA

SAMUEL CHARACHE, M.D., MICHAEL L. TERRIN, M.D., RICHARD D. MOORE, M.D., GEORGE J. DOVER, M.D., FRANCA B. BARTON, M.S., SUSAN V. ECKERT, ROBERT P. MCMAHON, PH.D., DUANE R. BONDS, M.D., AND THE INVESTIGATORS OF THE MULTICENTER STUDY OF HYDROXYUREA IN SICKLE CELL ANEMIA*

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Hydroxyurea

- 299 adults with SCD who experienced at least 3 pain crises in previous year
- 152 received HU (starting dose 15 mg/kg/day) vs 147 given placebo
- HU group showed:
  - Fewer crises during study period (2.5 vs 4.5 crises/year)
  - Longer time to first and second crises
  - Fewer episodes of ACS
  - Fewer transfusions
- No significant toxicities reported

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Hydroxyurea

Hydroxycarbamide in very young children with sickle-cell anaemia: a multicentre, randomised, controlled trial (BABY HUG)

Winfred C Wang, Russell E Ware, Scott T Miller, Rathi V Iyer, James F Casella, Caterina P Minniti, Sohail Rana, Courtney D Thornburg, Zora R Rogers, Ram V Kalpatthi, Julio C Barredo, R Clark Brown, Sharada A Sarnaik, Thomas H Howard, Lynn W Wynn, Abdullah Kutlar, F Daniel Armstrong, Beatrice A Files, Jonathan C Goldsmith, Myron A Waclawiw, Xiangke Huang, Bruce W Thompson, for the BABY HUG investigators

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Hydroxyurea

- 193 children 9 – 18 months of age at study entry
- 96 received HU at starting dose of 20 mg/kg/day
- HU group showed:
  - Fewer pain events including dactylitis
  - Fewer episodes of ACS, hospitalization, transfusion
  - Higher hemoglobin
  - Higher fetal hemoglobin
- Led to recommendation of HU for children with SCD starting at 9 months of age

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Red Cell Transfusion

PREVENTION OF A FIRST STROKE BY TRANSFUSIONS IN CHILDREN WITH SICKLE CELL ANEMIA

PREVENTION OF A FIRST STROKE BY TRANSFUSIONS IN CHILDREN WITH SICKLE CELL ANEMIA AND ABNORMAL RESULTS ON TRANSCRANIAL DOPPLER ULTRASONOGRAPHY

ROBERT J. ADAMS, M.D., VIRGIL C. MCKIE, M.D., LEWIS HSU, M.D., PH.D., BEATRICE FILES, M.D., ELLIOTT VICHINSKY, M.D., CHARLES PEGELOW, M.D., MIGUEL ABBOUD, M.D., DIANNE GALLAGHER, M.S., ABDULLAH KUTLAR, M.D., FENWICK T. NICHOLS, M.D., DUANE R. BONDS, M.D., AND DONALD BRAMBILLA, PH.D.

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Red Cell Transfusion

- 130 children with SCD and TCD velocities of 200 cm/s or greater
- 63 randomized to transfusion protocol, 67 to "standard care"
- Primary endpoint was stroke incidence
- 10 strokes + 1 bleed in standard group vs 1 stroke in transfusion group
- 92% reduction in stroke incidence with transfusion protocol

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Red Cell Transfusion

Hydroxycarbamide versus chronic transfusion for maintenance of transcranial doppler flow velocities in children with sickle cell anaemia—TCD With Transfusions Changing to Hydroxyurea (TWiTCH): a multicentre, open-label, phase 3, non-inferiority trial

Russell E Ware, Barry R Davis, William H Schultz, R Clark Brown, Banu Aygun, Sharada Sarnaik, Isaac Odame, Beng Fuh, Alex George, William Owen, Lori Luchtman-Jones, Zora R Rogers, Lee Hilliard, Cynthia Gauger, Connie Piccone, Margaret T Lee, Janet L Kwiatkowski, Sherron Jackson, Scott T Miller, Carla Roberts, Matthew M Heeney, Theodosia A Kalfa , Stephen Nelson, Hamayun Imran, Kerri Nottage, Ofelia Alvarez, Melissa Rhodes, Alexis A Thompson, Jennifer A Rothman, Kathleen J Helton, Donna Roberts, Jamie Coleman, Melanie J Bonner, Abdullah Kutlar, Niren Patel, John Wood, Linda Piller, Peng Wei, Judy Luden, Nicole A Mortier, Susan E Stuber, Naomi L C Luban, Alan R Cohen, Sara Pressel, Robert J Adams

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Red Cell Transfusion

- 121 patients (age 4– 16) with SCD and abnormal TCD (> 200 cm/s) who had received at least 12 months of transfusion therapy
- 61 continued transfusions, 60 began Hydroxyurea therapy
- No new strokes identified in either group during study period
- Conclusion: *patients with SCD and abnormal TCD without history of stroke can be safely transitioned to HU after receiving 1 year of transfusion therapy*

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Red Cell Transfusion

Stroke With Transfusions Changing to Hydroxyurea (SWiTCH)

Russell E. Ware[1] and Ronald W. Helms,[2] for the SWiTCH Investigators

[1]Baylor College of Medicine, Houston, TX; and [2]Rho Inc, Chapel Hill, NC

Stroke is a devastating complication of sickle cell anemia (SCA) with high recurrence if untreated. Chronic transfusions reduce recurrent strokes but have associated morbidities including iron overload. Stroke With Transfusions Changing to Hydroxyurea (SWiTCH) was a multicenter phase 3 randomized trial comparing standard treatment (transfusions/chelation) to alternative treatment (hydroxyurea/phlebotomy) for children with SCA, stroke, and iron overload. SWiTCH was a noninferiority trial with a composite primary end point, allowing an increased stroke risk but requiring superiority for removing iron. Subjects on standard treatment received monthly transfusions plus daily deferasirox iron chelation. Subjects on alternative treatment received hydroxyurea plus overlap transfusions during dose escalation to maximum tolerated dose (MTD), followed by monthly phlebotomy. Subjects on standard treatment (N = 66) maintained 30% sickle hemoglobin (HbS) and tolerated deferasirox at 28.2 ± 6.0 mg/kg/d. Subjects on alternative treatment (N = 67) initiated hydroxyurea and 60 (90%) reached MTD at 26.2 ± 4.9 mg/kg/d with 29.1% ± 6.7% fetal hemoglobin (HbF). Adjudication documented no strokes on transfusions/chelation but 7 (10%) on hydroxyurea/phlebotomy, still within the noninferiority stroke margin. The National Heart, Lung, and Blood Institute closed SWiTCH after interim analysis revealed equivalent liver iron content, indicating futility for the composite primary end point. Transfusions and chelation remain a better way to manage children with SCA, stroke, and iron overload. This clinical trial was registered at ClinicalTrials.gov NCT00122980. (*Blood.* 2012;119(17):3925-3932)

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Red Cell Transfusion

- 133 children with SCD and history of documented stroke on transfusion protocol at least 18 months
- 66 continued transfusions, 67 transitioned to Hydroxyurea
- No recurrent strokes in transfusion group, 7 in HU group
- No differences in liver iron content
- Conclusion: *transfusion therapy remains best option for those who have had documented strokes*

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Other Health Maintenance

- Immunizations - standard childhood vaccines + PCV23
- Transcranial doppler screening
- Retinopathy screening
- Pre-operative transfusion to Hb > 10 g/dL
- Proteinuria screening
- Contraception/reproductive counseling
- Mental health screening
- AVN screening for those with persistent pain
- Cardiac screening for symptomatic patients

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Published Guidelines for SCD


Clinical Review & Education

Special Communication

Management of Sickle Cell Disease
Summary of the 2014 Evidence-Based Report
by Expert Panel Members

Barbara P. Yawn, MD, MSc, MSPH; George R. Buchanan, MD; Araba N. Afenyi-Annan, MD, MPH; Samir K. Ballas, MD; Kathryn L. Hassell, MD; Andra H. James, MD, MPH; Lanetta Jordan, MD, MPH, MSPH; Sophie M. Lanzkron, MD, MHS; Richard Lottenberg, MD; William J. Savage, MD, PhD; Paula J. Tanabe, PhD, RN; Russell E. Ware, MD, PhD; M. Hassan Murad, MD, MPH; Jonathan C. Goldsmith, MD; Eduardo Ortiz, MD, MPH; Robinson Fulwood, PhD, MSPH; Ann Horton, MS; Joylene John-Sowah, MD, MPH

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Emerging Therapies for Sickle Cell Disease

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Strategic Targets

- Vasocclusion
- Inflammation
- HbS Polymerization
- Modifying the genotype

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Strategic Targets

- Vasocclusion
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- Modifying the genotype

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Glutamine

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

Yutaka Niihara, M.D., M.P.H., Scott T. Miller, M.D., Julie Kanter, M.D., Sophie Lanzkron, M.D., M.H.S., Wally R. Smith, M.D., Lewis L. Hsu, M.D., Ph.D., Victor R. Gordeuk, M.D., Kusum Viswanathan, M.D., Sharada Sarnaik, M.D., Ifeyinwa Osunkwo, M.D., Edouard Guillaume, M.D., Swayam Sadanandan, M.D., Lance Sieger, M.D., Joseph L. Lasky, M.D., Eduard H. Panosyan, M.D., Osbourne A. Blake, M.D., Tamara N. New, M.D., Rita Bellevue, M.D., Lan T. Tran, M.P.H., Rafael L. Razon, M.D., Charles W. Stark, Pharm.D., Lynne D. Neumayr, M.D., and Elliott P. Vichinsky, M.D., for the Investigators of the Phase 3 Trial of L-Glutamine in Sickle Cell Disease*

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Glutamine

- Glutamine thought to reduce oxidative stress in sickled erythrocytes by increasing reduced form of nicotinamide adenine dinucleotide (NADH)
- 230 patients (age 5 – 58 years) with HbSS or $HbSB^0$ with 2 or more acute pain episodes in previous year
- Received L-glutamine (0.3 mg/kg/dose BID) vs placebo
- Primary endpoint was reduction in painful episodes

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Glutamine

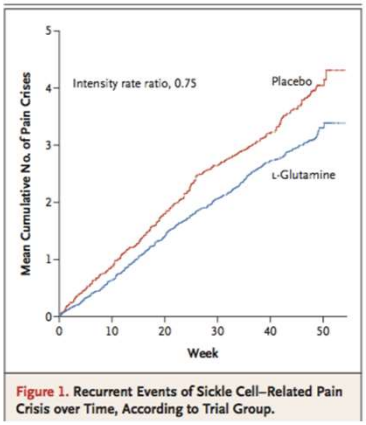
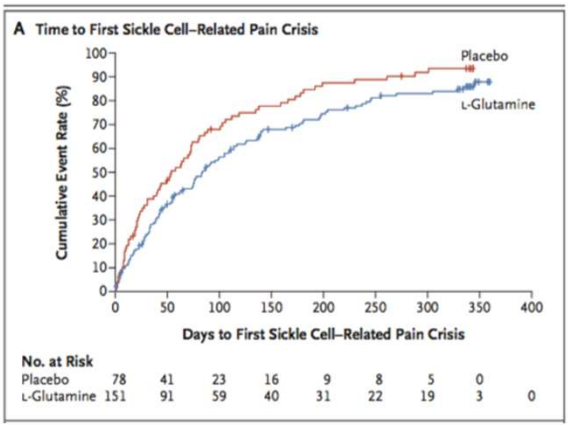


Figure 1. Recurrent Events of Sickle Cell–Related Pain Crisis over Time, According to Trial Group.



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Glutamine

- Those in glutamine group experienced fewer pain episodes (3 vs 4) and hospitalizations (2 vs 3) during 48-week study period
- Also had longer time to first and second painful episodes
- Well-tolerated with generally non-specific side effects
- FDA approval of glutamine for SCD in those 5 years of age or older
- High cost, bad taste, poor compliance

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Crizanlizumab

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease

K.I. Ataga, A. Kutlar, J. Kanter, D. Liles, R. Cancado, J. Friedrisch, T.H. Guthrie, J. Knight-Madden, O.A. Alvarez, V.R. Gordeuk, S. Gualandro, M.P. Colella, W.R. Smith, S.A. Rollins, J.W. Stocker, and R.P. Rother

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Crizanlizumab

- Monoclonal antibody against P-selectin
- Assigned to low dose, high dose, or placebo
- Administered IV 14 times over period of 52 weeks (+/- HU)
- Primary end point was annual rate of SCD-related pain crises
- 198 patients at 60 sites (ages 16 – 63)
- 63% decrease in pain crises in high dose treatment group
- Time to first crisis and hospital days also better in treatment group
- FDA approved in 2019 to reduce frequency of VOC in SCD patients 16 years and older

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Strategic Targets

- Vasocclusion
- Inflammation
- HbS Polymerization
- Modifying the genotype

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Targeting Inflammation in SCD

- Statins
  - Simvastatin found to reduce adhesion of white blood cells and when combined with HU decrease pain crises and markers of inflammation
- N-Acetylcysteine (NAC)
  - Shown to inhibit dense cell formation and restore glutathione levels toward normal; downward trend in decreased RBC sickling
- Anticoagulant/Antiplatelet agents
  - Rivaroxaban
  - Clopidogrel

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Strategic Targets

- Vasocclusion
- Inflammation
- HbS Polymerization
- Modifying the genotype

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Voxelotor

- Small molecule which acts to bind Hb S and stabilize in high oxygen affinity state, thereby inhibiting polymerization
- Reduces RBC sickling and decreased blood viscosity
- Results from Phase 2 studies showed ~ half of patients achieving increase in Hb of > 1 g/dL
- Improved indices of hemolysis, less pain, fewer transfusions
- FDA approved for SCD patients 12 and older in 2019; subsequently approved for ages 4 – 11 in 2022

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Voxelotor

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 8, 2019 VOL. 381 NO. 6

A Phase 3 Randomized Trial of Voxelotor in Sickle Cell Disease

Elliott Vichinsky, M.D., Carolyn C. Hoppe, M.D., Kenneth I. Ataga, M.D., Russell E. Ware, M.D., Ph.D., Videlis Nduba, M.B., Ch.B., M.P.H., Amal El-Beshlawy, M.D., Hoda Hassab, M.D., Maureen M. Achebe, M.D., M.P.H., Salam Alkindi, M.B., B.Ch., R. Clark Brown, M.D., Ph.D., David L. Diuguid, M.D., Paul Telfer, M.D., Dimitris A. Tsitsikas, M.D., Ashraf Elghandour, M.D., Victor R. Gordeuk, M.D., Julie Kanter, M.D., Miguel R. Abboud, M.D., Joshua Lehrer-Graiwer, M.D., Margaret Tonda, Pharm.D., Allison Intondi, Ph.D., Barbara Tong, Ph.D., and Jo Howard, M.D., for the HOPE Trial Investigators*

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Voxelotor

- 274 participants randomized to low-dose, high-dose, or placebo
- Once daily oral medication
- Primary end point was % of patients with hemoglobin response
- 51% in high-dose group had hemoglobin response
- Significant reductions from baseline in bilirubin and reticulocyte count
- Trend toward reduction in pain crises, though data still a bit unclear
- Similar results in pediatric trial leading to FDA approval

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Strategic Targets

- Vasocclusion
- Inflammation
- HbS Polymerization
- Modifying the genotype

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Bone Marrow Transplantation

- Only curative option for SCD currently
- Historically performed in patients with more severe disease course
  - History of stroke, recurrent ACS, > 3 pain crises/year
- Best results with matched sibling donors
  - Only 10 - 15% of patients have this option
- Historically relied on myeloablative conditioning regimens
  - Organ damage, infertility, secondary malignancies

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Bone Marrow Transplantation

- Matched sibling transplants:
  - Largest series reported 93% EFS and 95% OS at 5 years
    - < 16 years = 95%, > 16 years = 81% OS
  - Low graft rejection, acceptable GVHD rates
  - Younger pts with fewer comorbidities fare better
- Matched unrelated donor transplants:
  - 69% EFS and 79% OS at 2 years
  - Chronic GVHD 62% at 1 year
  - 34% experienced PRES

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Bone Marrow Transplantation

- Reduced intensity conditioning (RIC):
  - Allows for mixed chimerism and lower rates of GVHD
  - May ameliorate some toxicities of myeloablative conditioning
  - Higher rates of graft failure
- Haploidentical transplants:
  - Promising option to expand the donor pool in SCD
  - Current graft failure rates of 40 – 50%
  - Only in the context of clinical trials currently

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Gene Therapy for SCD

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Gene Therapy in a Patient with Sickle Cell Disease

Jean-Antoine Ribeil, M.D., Ph.D., Salima Hacein-Bey-Abina, Pharm.D., Ph.D., Emmanuel Payen, Ph.D., Alessandra Magnani, M.D., Ph.D., Michaela Semeraro, M.D., Ph.D., Elisa Magrin, Ph.D., Laure Caccavelli, Ph.D., Benedicte Neven, M.D., Ph.D., Philippe Bourget, Pharm.D., Ph.D., Wassim El Nemer, Ph.D., Pablo Bartolucci, M.D., Ph.D., Leslie Weber, M.Sc., Hervé Puy, M.D., Ph.D., Jean-François Meritet, Ph.D., David Grevent, M.D., Yves Beuzard, M.D., Stany Chrétien, Ph.D., Thibaud Lefebvre, M.D., Robert W. Ross, M.D., Olivier Negre, Ph.D., Gabor Veres, Ph.D., Laura Sandler, M.P.H., Sandeep Soni, M.D., Mariane de Montalembert, M.D., Ph.D., Stéphane Blanche, M.D., Philippe Leboulch, M.D., and Marina Cavazzana, M.D., Ph.D.

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Gene Therapy for SCD

- Harvested bone marrow from patient
- Transduced CD-34+ cells with LentiGlobin BB305 vector
  - Lentivirus encodes for anti-sickling B-globin chain and production of modified adult hemoglobin (HbA T87Q)
- Myeloablative conditioning regimen with expected toxicities
- Autologous BMT
- Monitored for engraftment, HbA, HbS, HbF

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Gene Therapy for SCD

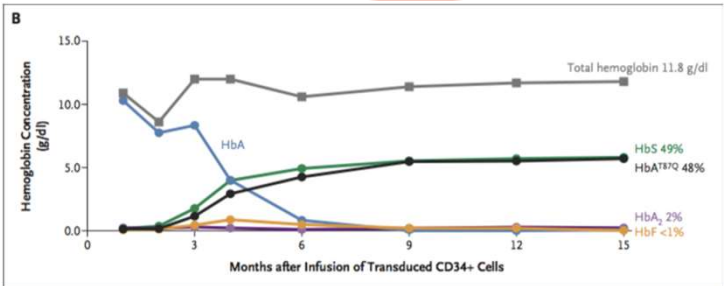

Figure 1. Engraftment with Transduced Cells and Therapeutic Gene Expression in the Patient.

Panel A shows vector copy number values in blood nucleated cells and the short-lived CD15+ (neutrophils) fraction thereof over 15 months after infusion of transduced CD34+ cells. Initial values in transduced cells before the infusion are shown. Panel B shows total hemoglobin levels and calculated levels of each hemoglobin fraction based on high-performance liquid chromatography measurements of globin chains. The percent contribution of hemoglobin fractions at month 15 is also indicated. The hemoglobin A (HbA) levels are derived from the regular red-cell transfusions received by the patient before gene therapy and briefly thereafter (the last red-cell transfusion occurred on day 88). HbA_2 is an alternative adult hemoglobin that is not derived from transfused blood. HbF denotes fetal hemoglobin, and HbS sickle hemoglobin.

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Gene Therapy for SCD

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Biologic and Clinical Efficacy of LentiGlobin for Sickle Cell Disease

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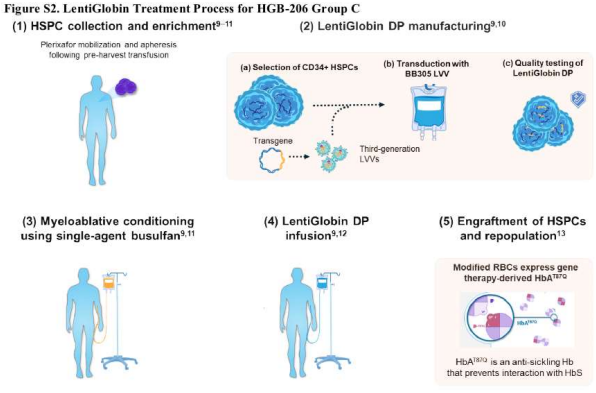
Gene Therapy for SCD

Figure S2. LentiGlobin Treatment Process for HGB-206 Group C



DP, drug product; Hb, hemoglobin; HbA^{T87Q}, Hb with modified β-globin gene ($\beta^{A\text{-}T87Q}$); HbS, sickle Hb; HSPC, hematopoietic stem and progenitor cell; LVV, lentiviral vector; RBC, red blood cell.

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Gene Therapy for SCD

- Optimized treatment process when compared to earlier trials
  - Pre-transplant transfusion protocol
  - Cell mobilization with Plerixafor and collection via apheresis
  - Refined manufacturing process
- 35 patients received Lentiglobin infusion
- Increase in baseline hemoglobin from 8.5 g/dL to > 11 g/dL
- Reduction in markers of hemolysis
- Resolution of severe VOE
- 3+ years of follow up

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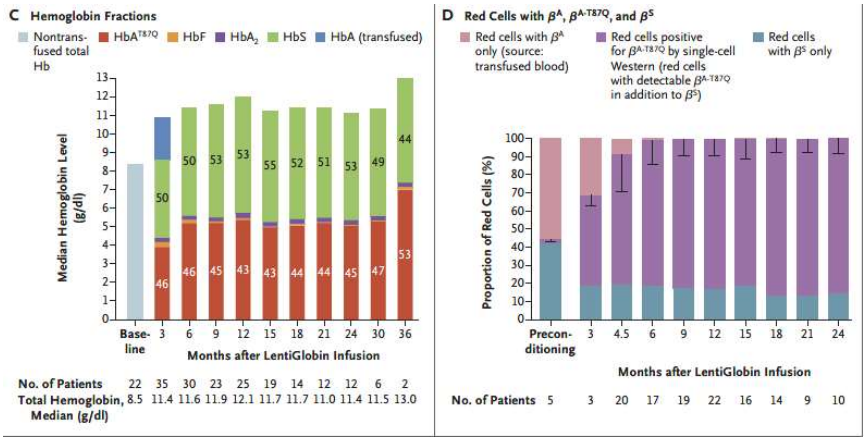
Gene Therapy for SCD



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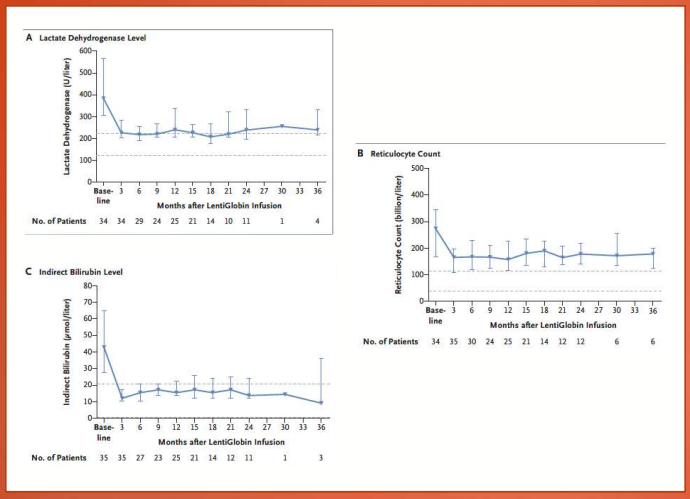

Gene Therapy for SCD

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Summary of Treatment Targets

Table. Treatments Targeting Specific Pathogenetic Mechanisms of Sickle Cell Disease

Pathogenetic Mechanism	Counteragent
P-selectin inhibition	Crizanlizumab
Polymerization	Voxelotor
Upregulation of fetal hemoglobin production	Hydroxyurea Butyrate 5-Azacytidine, Decitabine
Oxidative stress	L-glutamine
Genetic mutation	CRISPR/Cas 9 technology and transplantation
Abnormal rheology	Poloxamer 188

CRISPR/Cas 9, clustered regularly interspaced short palindromic repeats/CRISPR-associated protein 9.

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Questions?

Thank you for your attention!

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