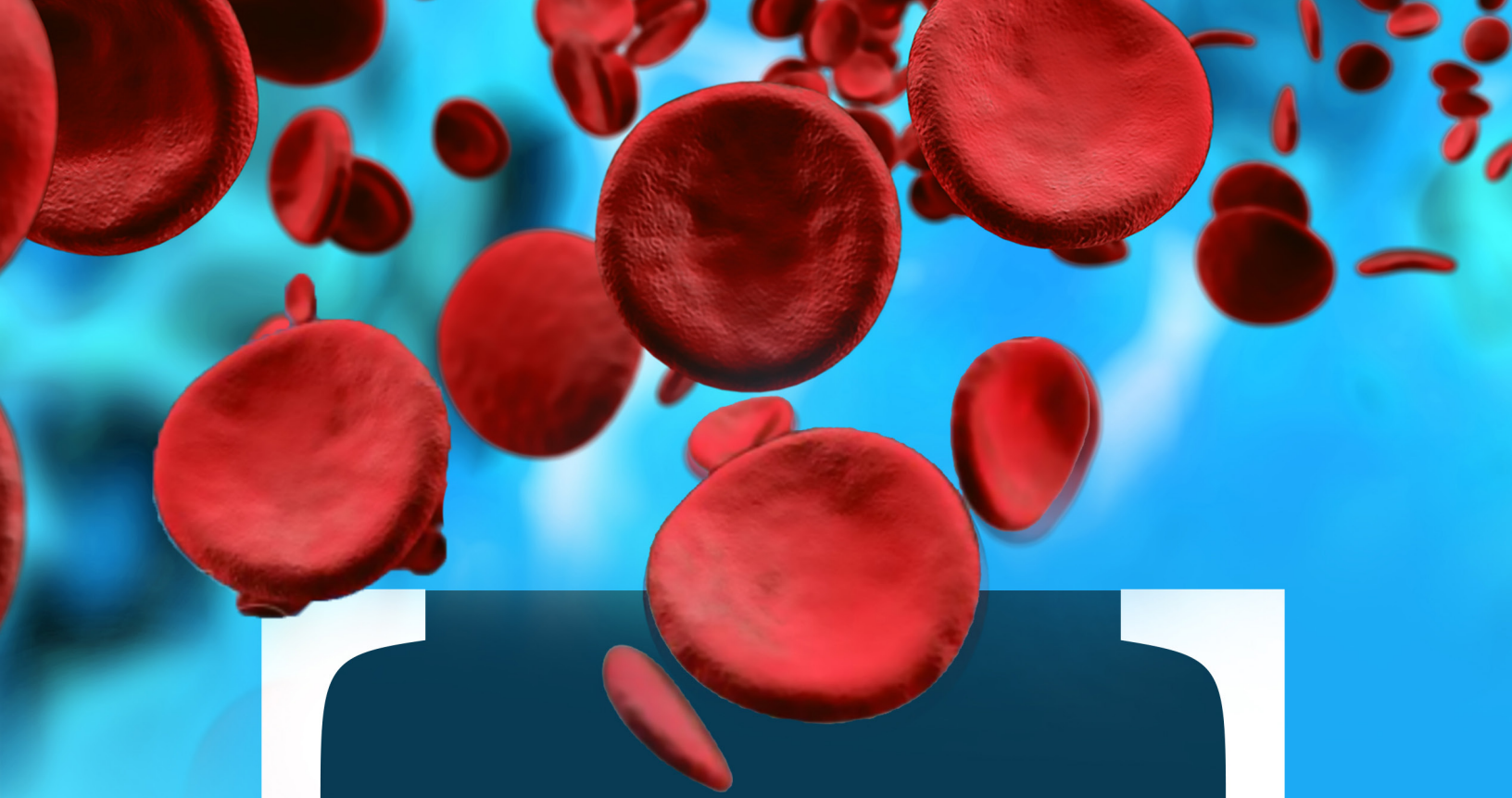

Advances in the Therapeutic Management of Patients with CHRONIC HEMATOLOGICAL CONDITIONS

THURSDAY, FEBRUARY 3, 2022

This activity is provided by Med Learning Group.
This activity is co-provided by Ultimate Medical Academy/Complete Conference Management (CCM).
This activity is supported by an educational grant from Novo Nordisk.

AGENDA

1. Hemophilia: An Overview
    a. Epidemiology
    b. Pathophysiology
    c. Clinical, social, and economic burdens
2. Challenges in Diagnosis and Management of Patients with Hemophilia
    a. Screening and diagnostic methods
    b. Acute care management of patients with hemophilia and SCD in emergency care settings and the important role of emergency medicine physicians
    c. Personalizing treatment
3. Review of MOAs and Clinical Trial-derived Efficacy and Safety Data in Hemophilia
    a. Standard of care therapies and associated unmet needs
    b. Approved agents
    c. Emerging agents
4. Sickle Cell Disease: An Overview
    a. Epidemiology
    b. Pathophysiology
    c. Clinical, social, and economic burdens
5. Challenges in Diagnosis and Management of Patients with Sickle Cell Disease
    a. Screening and diagnostic methods
    b. Acute care management of patients with hemophilia and SCD in emergency care settings and the important role of emergency medicine physicians
    c. Personalizing treatment
6. Review of MOAs and Clinical Trial-derived Efficacy and Safety Data in Sickle Cell Disease
    a. Standard of care therapies and associated unmet needs
    b. Approved agents
    c. Emerging agents
7. Multidisciplinary Team-based Patient-Centered Shared Decision Making (SDM) Approaches to the Management of Chronic Hematological Conditions
    a. Benefits of multidisciplinary team-based approaches to the management of patients with chronic hematological conditions
    b. Team members and their respective roles
    c. Benefits of SDM approaches in general
    d. SDM approaches specific to patients with chronic hematological conditions
8. Case Studies

Advances in the Therapeutic Management of Patients with Chronic Hematological Conditions – A Whiteboard Preceptorship

FACULTY PRESENTERS

Martin H. Steinberg, MD
Professor of Medicine, Pediatrics, Pathology and Laboratory Medicine
Division of Hematology/Oncology
Boston University School of Medicine
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Children's Healthcare of Atlanta
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Atlanta, GA

PROGRAM OVERVIEW

Recent advances in treatment strategies promise to improve the lives of patients with sickle cell disease or hemophilia. In this program, experts in both fields will assist clinicians in developing individualized management plans using state-of-the-art and emerging therapies, and highlight opportunities to implement multidisciplinary, patient-centered approaches to care. Case studies and interactive question and answers will provide learners practice in applying patient-specific factors to treatment decisions. This activity will feature whiteboard animations that will reinforce learning and help participants gain a higher level of understanding.

TARGET AUDIENCE

This activity is designed to meet the educational needs of hematologists, emergency medicine physicians and other healthcare practitioners who treat patients with hemophilia A or B and SCD.

LEARNING OBJECTIVES

Upon the completion of this program, attendees should be able to:

- Evaluate evidence from clinical trials assessing available and emerging therapies for the treatment of patients with chronic hematologic conditions including hemophilia and SCD
- Evaluate patient-specific characteristics when developing individualized management plans for those with chronic hematologic conditions including hemophilia and SCD
- Facilitate a multidisciplinary patient-centered SDM approach to the management of those with chronic hematologic conditions including hemophilia and SCD

ACCREDITATION STATEMENT

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CREDIT DESIGNATION STATEMENT

Med Learning Group designates this live activity for a maximum of 1.5 *AMA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the live activity.

NURSING CREDIT INFORMATION

Purpose: This program would be beneficial for nurses involved in the care of patients with chronic hematologic conditions including hemophilia and SCD.

CNE Credits: 1.5 ANCC Contact Hour.

CNE ACCREDITATION STATEMENT

Ultimate Medical Academy/CCM is accredited as a provider of nursing continuing professional education development by the American Nurses Credentialing Center's Commission on Accreditation.

Awarded 1.5 contact hour of continuing nursing education of RNs and APNs.

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DISCLOSURE OF CONFLICTS OF INTEREST

Faculty Member	Disclosures
Martin H. Steinberg, MD	Dr. Steinberg is a consultant for Vertex Pharmaceuticals, Alexion, Astellas/Mitobridge, and Fulcrum Therapeutics. He is also a member of the Data Monitoring Committee for Imara.
Michael White, MD, MSC	Dr. White has received a research fellowship award from the National Hemophilia Foundation – Takeda.

CME Content Review

The content of this activity was independently peer reviewed.
The reviewer of this activity has nothing to disclose.

CNE Content Review

The content of this activity was peer reviewed by a nurse reviewer.

Douglas Cox, MSN, MHA, RN
Ultimate Medical Academy/CCM – Lead Nurse Planner

The reviewer of this activity has nothing to disclose

Staff Planners and Managers

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METHOD OF PARTICIPATION

There are no fees for participating and receiving CME credit for this live activity. To receive CME/CNE credit participants must:

1. Read the CME/CNE information and faculty disclosures.
2. Participate in the live activity.
3. Submit the evaluation form to Med Learning Group.

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For CME questions, please contact Med Learning Group at info@medlearninggroup.com

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Advances in the Therapeutic Management of Patients with Chronic Hematological Conditions— A Whiteboard Preceptorship

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Disclosures

- Dr. White has received a research fellowship award from the National Hemophilia Foundation – Takeda.
- Dr. Steinberg is a consultant for Vertex Pharmaceuticals, Alexion, Astellas/Mitobridge, and Fulcrum Therapeutics. He is also a member of the data monitoring committee for Imara.

This activity is supported by an educational grant from Novo Nordisk.

Educational Objectives

- Evaluate evidence from clinical trials assessing available and emerging therapies for the treatment of patients with chronic hematologic conditions, including hemophilia and sickle cell disease (SCD)
- Evaluate patient-specific characteristics when developing individualized management plans for those patients with chronic hematologic conditions, including hemophilia and SCD
- Facilitate a multidisciplinary patient-centered shared decision-making approach to the management of those patients with chronic hematologic conditions, including hemophilia and SCD

Sickle Cell Disease

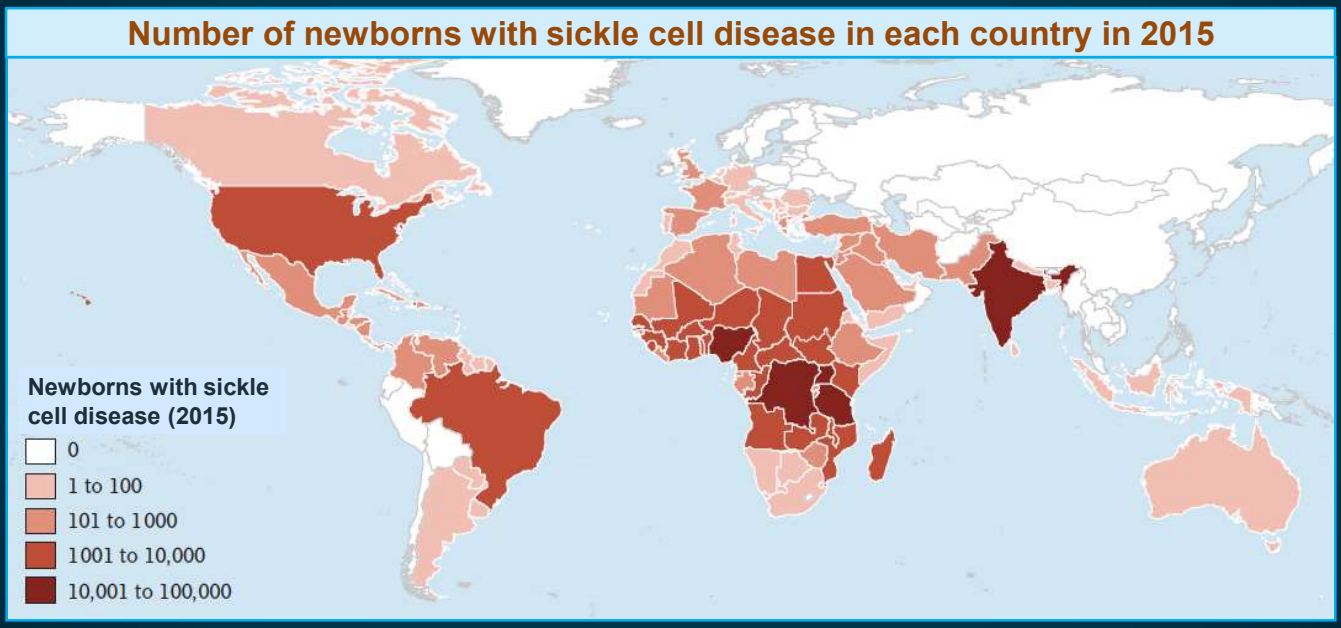
Martin H. Steinberg, MD

Origin and Spread of HbS

HbS = sickle hemoglobin.

Shriner D, Rotimi CN. *Am J Hum Genet.* 2018;102:547-556. (www.ncbi.nlm.nih.gov/pmc/articles/PMC5985360/pdf/main.pdf)

Global Distribution of Sickle Cell Disease



Piel FB, et al. *N Engl J Med.* 2017;376:1561-1573.

Sickle Cell Trait

- ~8% of African Americans
- Normal hematology; HbA ~60%, HbS~40%
- Normal lifespan
- Splenic infarction at altitude
- Hyposthenuria, hematuria, CKD
- VTE risk increased 2–4 times
- Death from exertional heat illness increased
- Counseling for reproductive risks and sports participation

HbA = normal hemoglobin; CKD = chronic kidney disease; VTE = venous thromboembolism.

Steinberg MH, et al (eds). *Disorders of Hemoglobin: Genetics, Pathophysiology, Clinical Management.* 2nd edition. Cambridge University Press, 2009.

Case 1

- A 38-year-old woman, while visiting relatives in Boston, presented to the ED complaining of widespread severe pain due to sickle cell disease. Pain was unrelieved by her oral opioids, and she demanded intravenous hydromorphone. She recounted multiple ED visits and hospitalizations for acute back and chest pain due to sickle cell disease. A cholecystectomy for stones was done in the past. As outpatient pain treatment she was given oral opioids but had run out of medication. She had never been transfused.
- Vital signs were normal except for a pulse of 100. Examination of the chest, abdomen and extremities was normal.
- Laboratory studies showed a PCV of 42, MCV of 89 fL, leukocyte count of 6,000 with a normal differential, reticulocytes of 0.7% and platelets 250,000. Hemoglobin fractionation by HPLC, returned after her discharge, showed 57.5% HbA, 39% HbS, 1% HbF and 2.5% HbA_2.
-
- Hemoglobin fractionation was diagnostic of sickle cell trait. The normal hematology results that are immediately available in the ED were normal and inconsistent with any genotype of sickle cell disease. With rare exceptions, sickle cell trait is not associated with acute vaso-occlusive pain episodes. This is an example of Munchausen syndrome in an individual with sickle cell trait. HbS-β^+ thalassemia, which should not be confused with sickle cell trait, usually has mild microcytic anemia and on HPLC has 20 and 30% HbA with >3.5% HbA_2.

ED = emergency department; PCV = packed cell volume; MCV = mean cell volume; HPLC = high-performance liquid chromatography; HbF = fetal hemoglobin.

Common Genotypes of Sickle Cell Disease

- Sickle cell anemia: 1/600 (homozygosity for HbS gene)
- HbSC disease: 1/800 (compound heterozygosity for HbS and HbC genes)
- HbS-β thalassemia: 1/1600 (compound heterozygosity for HbS and β thalassemia genes)
- HbSE: uncommon
- HbSD: rare; many other genotypes even rarer

HbSC = HbS inherited from one parent and HbC from the other; HbS-β thalassemia = HbS inherited from one parent and β-thalassemia trait from the other; HbSE = HbS inherited from one parent and abnormal HbE from the other; HbSD = HbS inherited from one parent and abnormal HbD from the other.

Steinberg MH, et al (eds). *Disorders of Hemoglobin: Genetics, Pathophysiology, Clinical Management.* 2nd edition. Cambridge University Press, 2009.

HbSC Disease

- Some unique pathophysiologic features
- Hemoglobin level ~8–12 g/dL
- About half the rate of complications as HbSS
- Possibly more prone to multiorgan failure
- High PCV often requires RBC exchange treatment
- Hydroxyurea might or might not help

HbSS = HbS inherited from both parents; RBC = red blood cell.

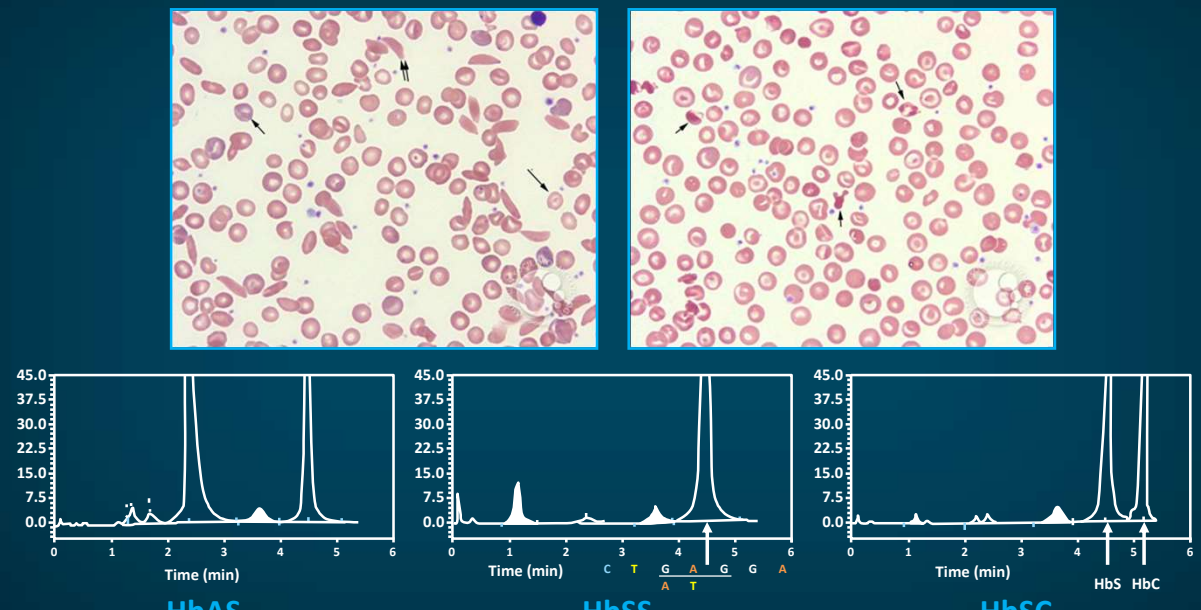
Steinberg MH.

Case 2

- A 60-year-old man with HbSC disease was seen in the ED with the acute onset of dyspnea, fever, the most severe back and chest pain he has ever experienced, cough and disorientation. Acute painful episodes occurred every few years causing hospitalization for 1 to 3 days. His only regular medication was amlodipine.
- Temperature was 101, BP 110/80, pulse 125, respirations 25, O_2 saturation 80% on room air, increasing to 95% after nasal O_2. A chest X-ray showed bilateral pulmonary infiltrates. PCV was 32%, leukocytes 28,000/cu mm, platelets 60,000/cu mm, LDH 1250, creatine kinase 1000 and serum creatinine, 2.5 mg/dL. The blood film showed numerous nucleated red cells.
- Severe pain, hypoxia, leukocytosis, thrombocytopenia, pulmonary infiltrates and multiorgan failure suggest pulmonary embolism with necrotic fatty marrow causing acute chest syndrome. In addition to supportive measures and antibiotics direct admission to the ICU should be recommended and exchange transfusion planned.
-
- HbSC disease is often a "milder" genotype of sickle cell disease but prone to the development of bone marrow necrosis with fat embolization and multiorgan failure. Exchange transfusion is the best option for treating acute chest syndrome with multiorgan failure. If this is not possible, simple transfusions can be used with care to avoid hyperviscosity.

BP = blood pressure; LDH = lactate dehydrogenase; ICU = intensive care unit.

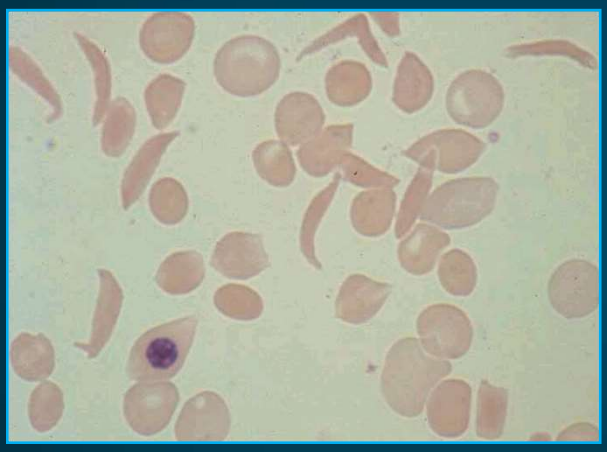
Diagnosis of Sickle Cell Disease (SCD)

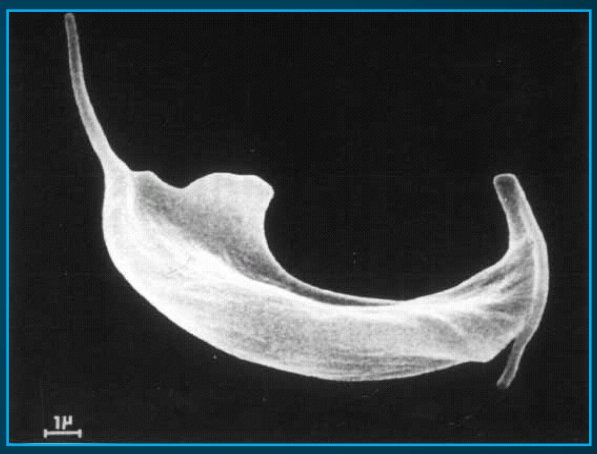


min = minute(s).

Steinberg MH.

Irreversibly Sickled Cells Are Always Present and Do Not Indicate Acute Sickle Cell Events



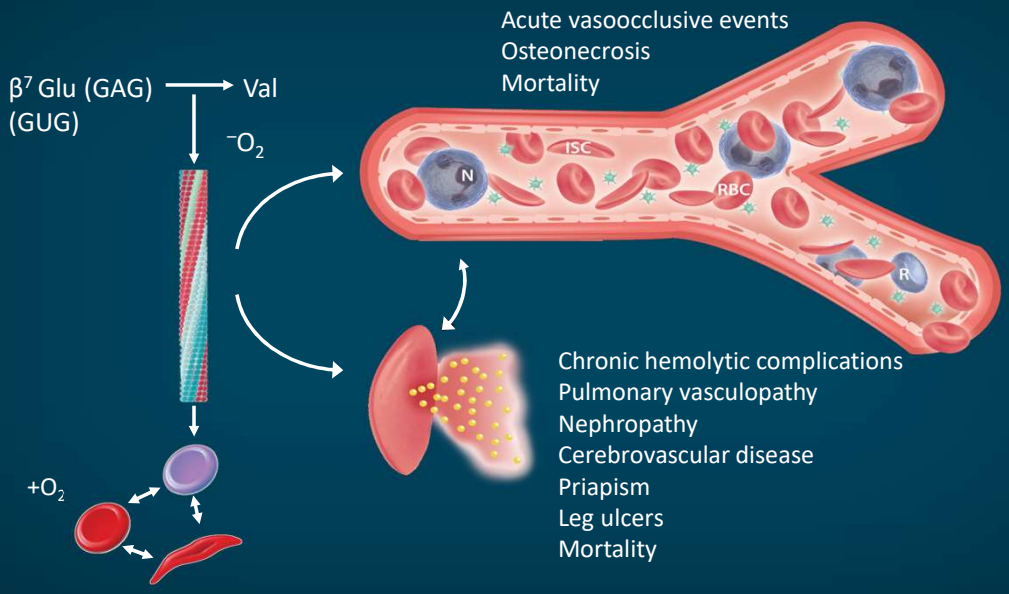


Steinberg MH.

Whiteboard Animation
Sickle Cell Pathophysiology

14

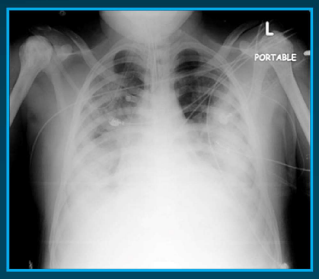
Pathophysiology of Sickle Cell Disease (SCD)



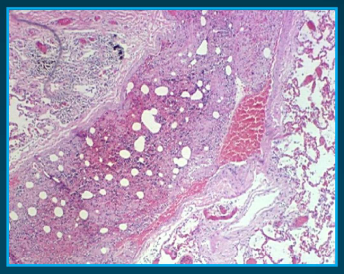
Glu = glutamine; GAG = glutamic acid codon; Val = valine; GUG = valine codon; ISC = irreversibly sickle cell; N = neutrophil; R = reticulocyte; RBC = red blood cell.

Modified from Steinberg MH. *Blood.* 2019;133:1797-1798.

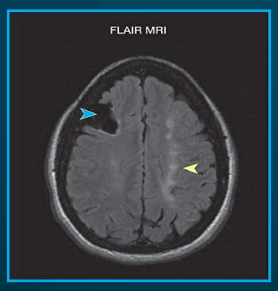
Common Severe Complications of SCD



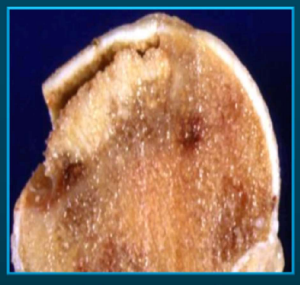
Acute chest syndrome



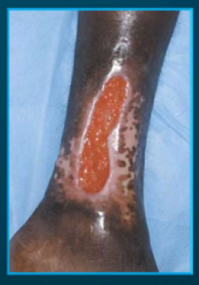
Bone-marrow emboli



Stroke



Osteonecrosis



Leg ulcers

Pain in Sickle Cell Disease

- **Acute**
  - acute painful episode—most frequent
  - acute chest syndrome—often presents as acute pain
- **Chronic**
  - osteonecrosis
  - leg ulcers
- **Acute on chronic**
- **Neuropathic**
  - opioid-induced, secondary to acute pain

Steinberg MH.

Pain Management in SCD

- Know and believe the patient; have individual ED and inpatient care plans
- Understand pathophysiologic and socioeconomic basis of SCD pain
- Know the pharmacology of some analgesics
- Consider nonpharmacological treatment
- Prudent use of IV fluids
- Educate providers and patients

ED = emergency department; IV = intravenous.

Steinberg MH.

American Society of Hematology (ASH) 2020 Guidelines for Sickle Cell Disease: Management of Acute Pain

Use of a standardized protocol to treat acute SCD pain in acute-care setting

- Rapid (within 1 hour of ED arrival) assessment and administration of analgesia with frequent reassessments (every 30–60 minutes) to optimize pain control
- Non-IV routes of administration (eg, subcutaneous and intranasal) can facilitate rapid analgesic treatment
- Tailored opioid dosing based on consideration of baseline opioid therapy and prior effective therapy

Brandow AM, et al. *Blood Advances.* 2020;4:2656-2701.

ASH 2020 Guidelines for Sickle Cell Disease: Management of Acute Pain (continued)

Nonopioid pharmacological therapies for acute SCD pain

- Short course (5 to 7 days) of NSAIDs in addition to opioids for acute pain management
- Avoid corticosteroids for acute pain management
- Subanesthetic (analgesic) ketamine infusion as adjunctive treatment of pain that is refractory or not effectively treated with opioids alone
- Regional anesthesia treatment approaches for localized pain that is refractory or not effectively treated with opioids alone

NSAID = nonsteroidal anti-inflammatory disease.

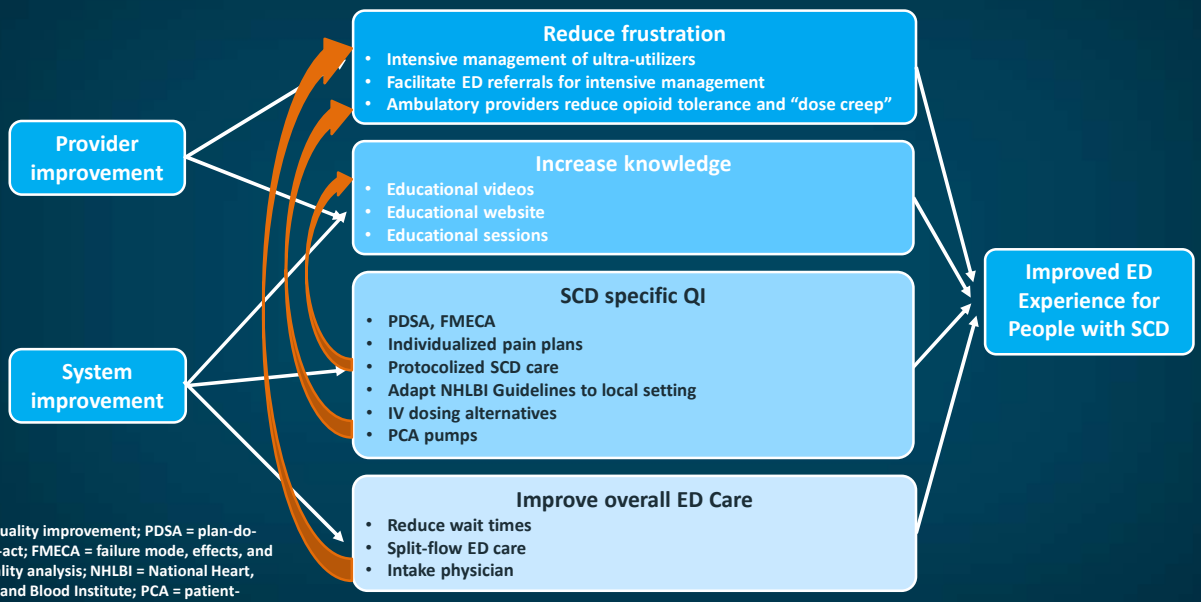
Brandow AM, et al. *Blood Advances.* 2020;4:2656-2701.

Improving Emergency Department-Based Care of Acute Painful Episodes

- SCD pain is a diagnosis of exclusion
- Pulse oximetry and cardiac monitoring during the initial analgesic phase
- Hydration does not cure painful episodes

Glassberg JA. *Hematology Am Soc Hematol Educ Program.* 2017;2017:412-417.

Implementing Guideline-Adherent Emergency Sickle Cell Care



QI = quality improvement; PDSA = plan-do-study-act; FMECA = failure mode, effects, and criticality analysis; NHLBI = National Heart, Lung, and Blood Institute; PCA = patient-controlled analgesia.

Glassberg JA. *Hematology Am Soc Hematol Educ Program.* 2017;2017:412-417.

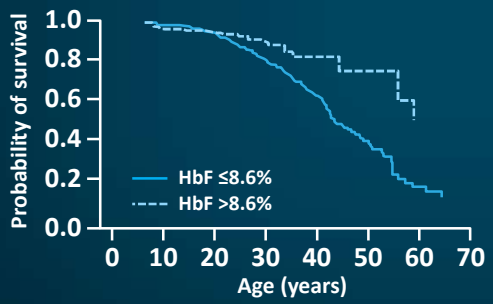
General Management Principles

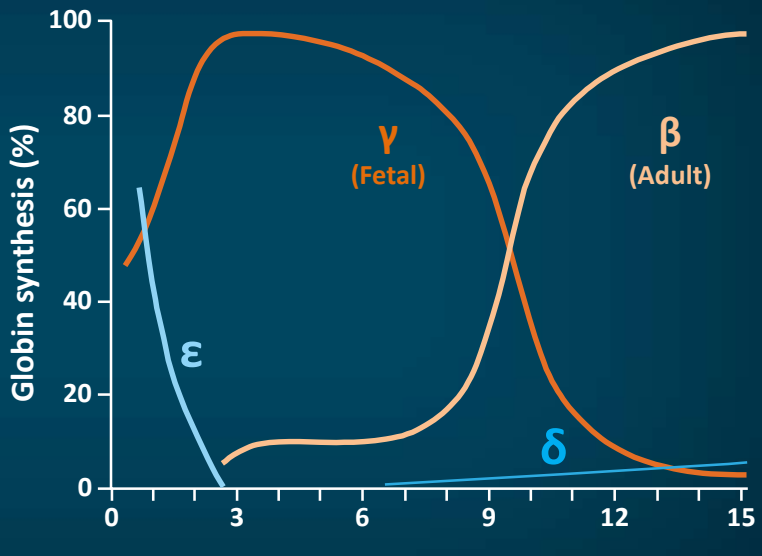
- In the ED…
  1. Pain treatment with IV opioids, individualized care plans
  2. Exclude acute chest syndrome
- In the clinic…
  1. Multidisciplinary teams lead by hematology
  2. Develop outpatient, ED, and inpatient care plans for EHR
  3. Outpatient infusion center
- In the hospital…
  1. Telemetry unit for 1st 48–72 hours
  2. Consider direct ICU admission for moderate-severe ACS

EHR = electronic health record; ICU = intensive care unit; ACS = acute coronary syndrome.

Steinberg MH.

HbF in Sickle Cell Disease





HbF = fetal hemoglobin.

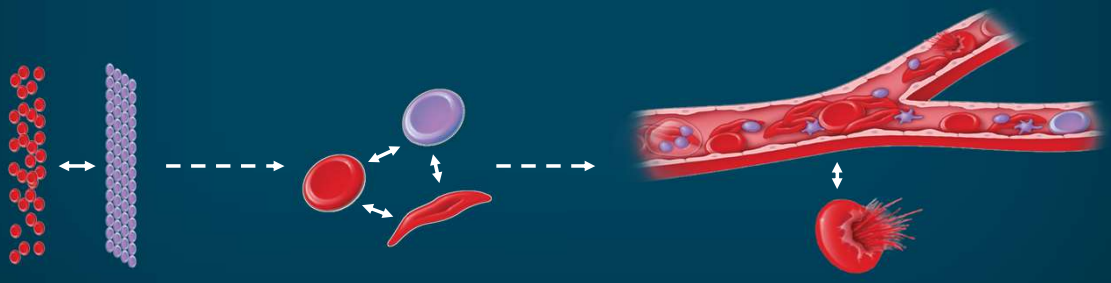
Watson J. *Am J Med Sci.* 1948;215:419-423. Platt OS, et al. *N Engl J Med.* 1994;330:1639-1644.

HbF Thwarts HbS Polymerization and Polymer-Induced Pathophysiology

Step 1: prevents HbS polymerization

Step 2: prevents RBC damage

Step 3: prevents vaso-occlusion and hemolysis



Steinberg MH.

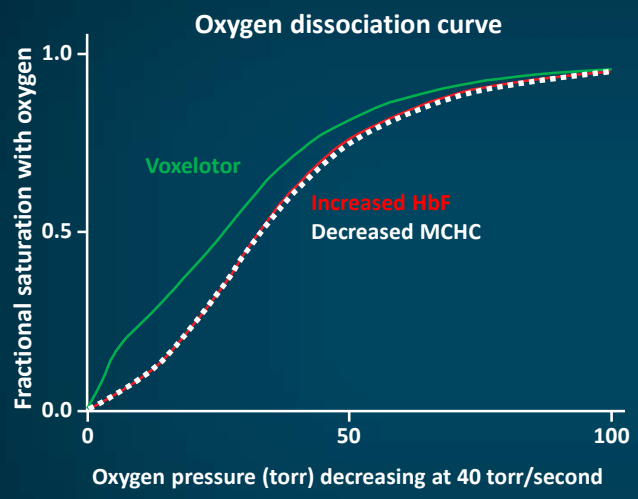
Pharmacologic Induction of HbF: Hydroxyurea

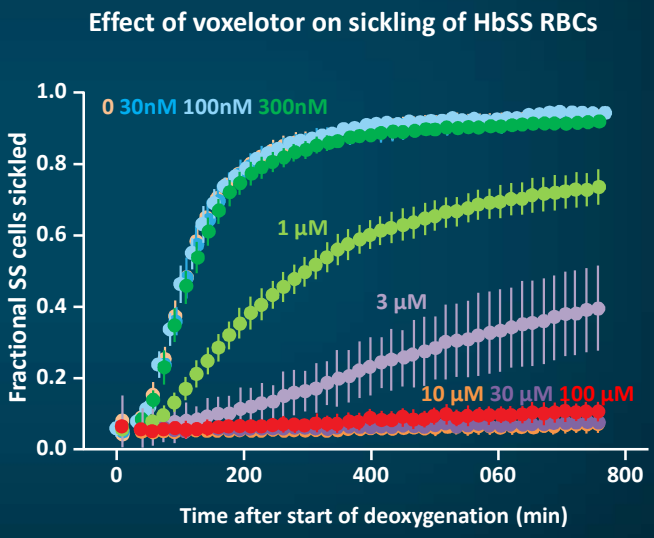
- Standard of care starting at 6-12 months
- Titration to MTD for optimal effects usually takes 6–12 months
  1. HbF = 33%
  2. Hemoglobin = 10 g/dL
- ↓vaso-occlusion, hemolysis, mortality
- CBC and HbF level followed for toxicity and efficacy

MTD = maximum tolerated dose.

McGann PT, et al. *Am J Hematol.* 2019;94:871-879.

Effects of Voxelotor on P_{50} and Sickling





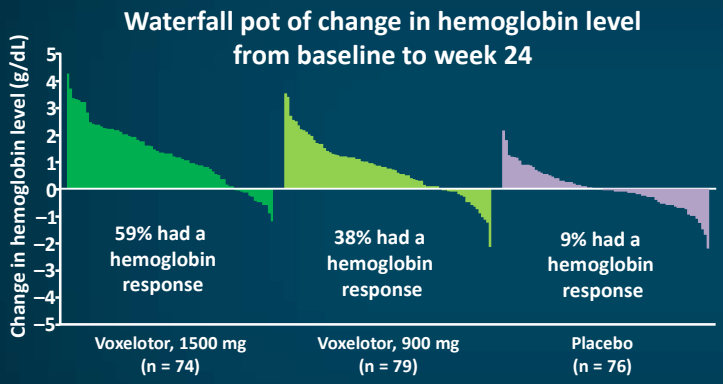
P_{50} = partial oxygen pressure at which hemoglobin is 50% saturated with oxygen; torr = unit of pressure defined as 1/760 of an atmosphere; MCHC = mean corpuscular hemoglobin concentration.

Henry ER, et al. *Blood.* 2021;138:1172-1181.

Phase 3 HOPE Trial and Real-World Results

Voxelotor Increases Hemoglobin in Sickle Cell Disease

Clinical trial results



- Bilirubin ↓ 29.1%
- Reticulocytes ↓ 19.9%
- LDH ↓ 4.5%
- Results sustained over 48–72 weeks

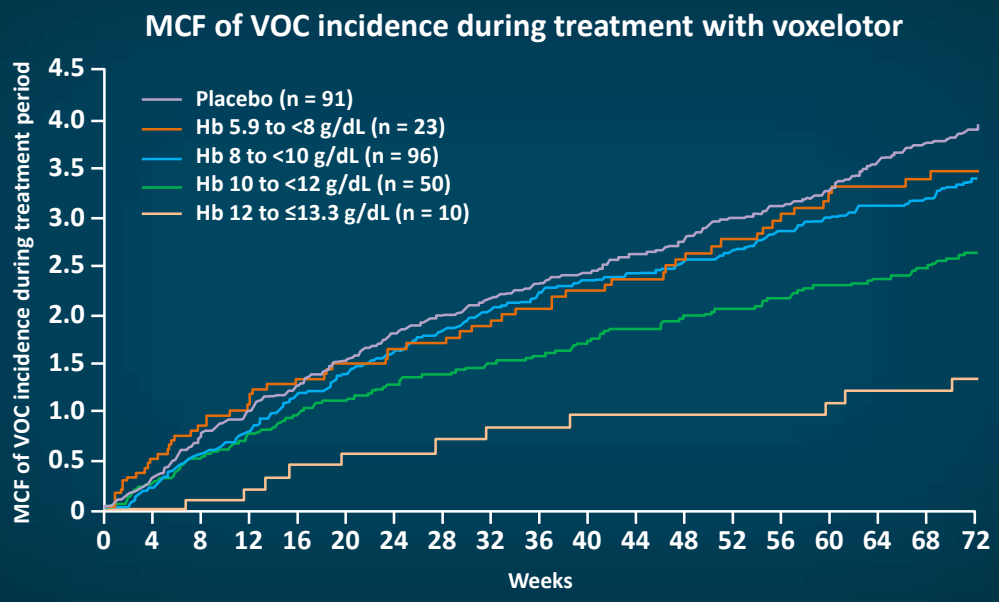
"Real-world" results

Values before and after voxelotor treatment		
	Before	After
Hemoglobin, g/dL, over 1 year	7.9	8.9
Transfusions, PPY	3.2	1.8
VOC, ≥1 in 3 mos	10.9	8.5
Hospitalizations, all cause, in 3 mos	7.5	4.8

PPY = per patient year; mo(s) = month(s); VOC = vaso-occlusive crisis.

Vichinsky E, et al. *N Engl J Med.* 2019;381:509-519. Shah N, et al. ASH, 2021, abstract 2052 (https://ash.confex.com/ash/2021/webprogram/Paper153138.html). Achebe M, et al. ASH, 2021, abstract 3224. (https://ash.confex.com/ash/2021/webprogram/Paper153582.html). Accessed 12/7/2021.

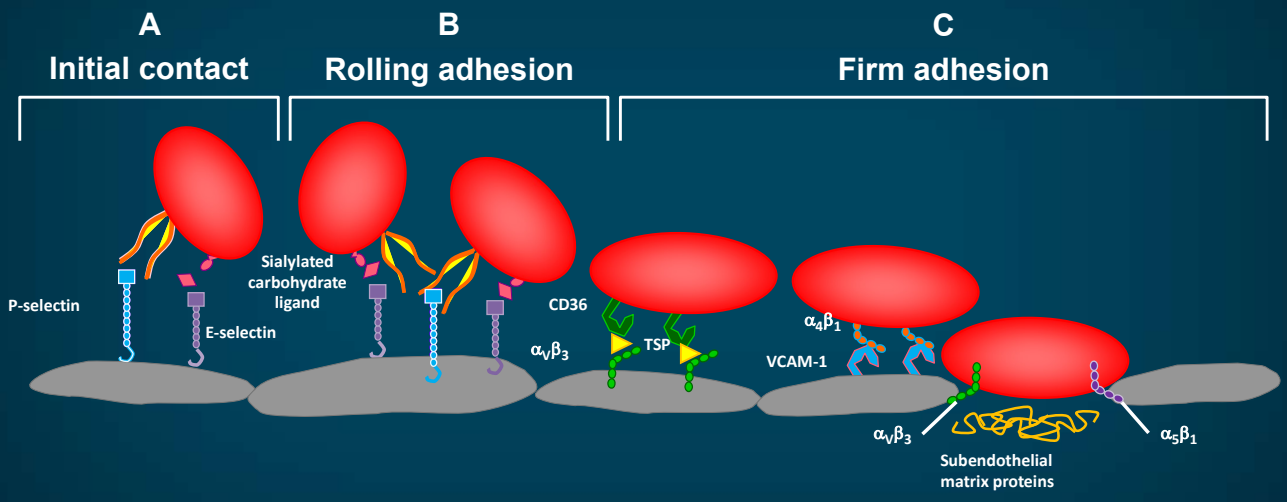
Vaso-occlusion and Hemoglobin Levels in Voxelotor-Treated SCD



MCF = mean cumulative function; VOC = vaso-occlusive crisis; Hb = hemoglobin.

Vichinsky E, et al. *Blood.* 2020;136(suppl 1): 31-32.

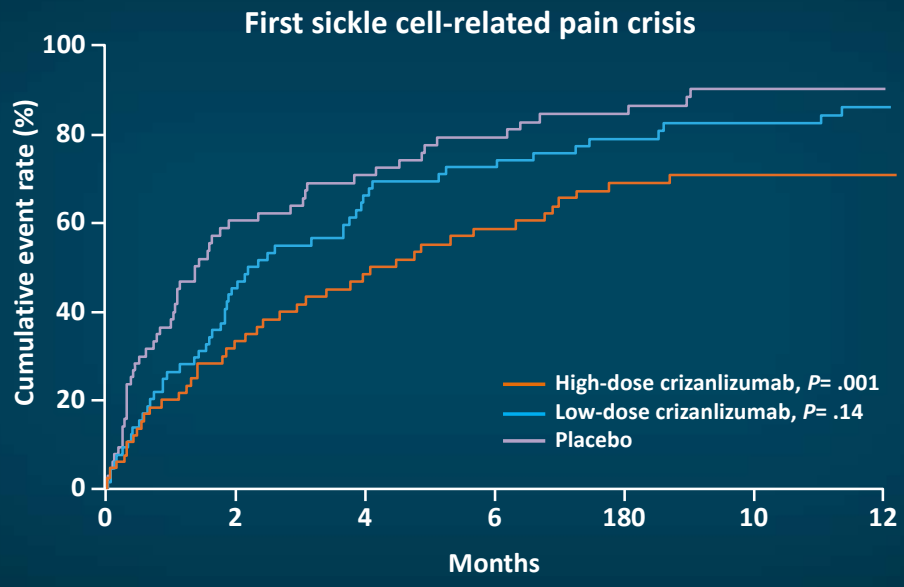
P Selectin and Sickle Cell Adhesivity



CD = cluster of differentiation; VCAM = vascular cell adhesion molecule-1.

Matsui NM, et al. *Blood.* 2001;98:1955-1962. Kutlar A, et al. *Am J Hematol.* 2012;87:536-539.

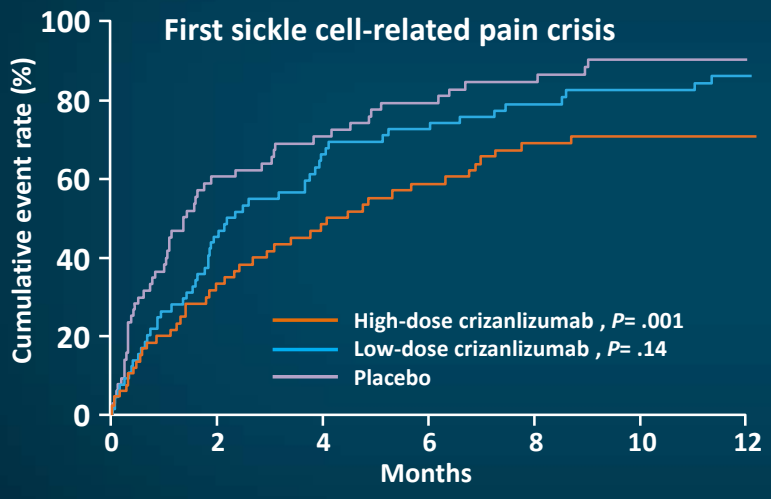
Crizanlizumab Decreases SCD-Related Vaso-occlusion and Pain Crises



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

Crizanlizumab Decreases Sickle Vaso-occlusion

Clinical trial results



"Real-world" results

- 11 NASCC-type center
- 5481 patients
- 297 prescriptions
- 238 patients dosed
- 32% discontinued

NASCC = National Alliance for Sickle Cell Centers.

Ataga K, et al. *N Engl J Med.* 2017;376:429-439. Kanter J, et al. ASH, 2021 (https://ash.confex.com/ash/2021/webprogram/Paper153136.html). Accessed 12/7/2021

Transfusion

- **Usually**
  - Severe symptomatic anemia (*simple transfusion*)
  - Treatment and prevention of CVA (*exchange transfusion*)
  - Preoperative (*simple transfusion*)
  - Severe ACS (*simple/exchange transfusion)*
- **Sometimes**
  - Pregnancy (*simple transfusion*)
  - Renal failure (*simple transfusion*)
- **Avoid**
  - Acute pain, chronic asymptomatic anemia

CVA = cerebrovascular accident.

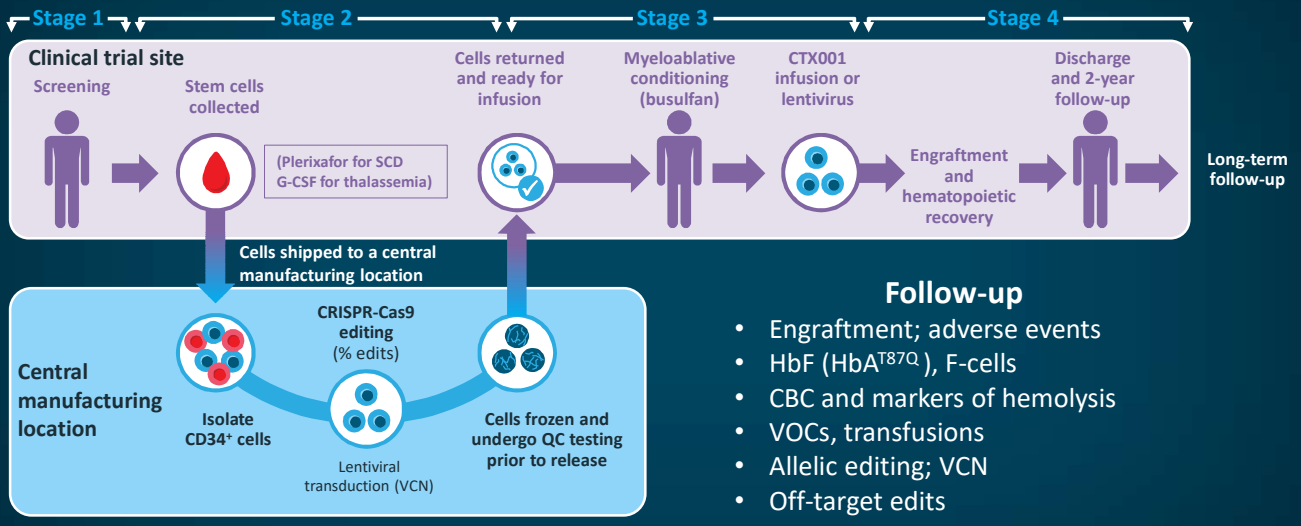
Chou ST, et al. *Blood Adv.* 2020;4:327-355.

Hematopoietic Stem-Cell Transplantation

- Offer to patients with HLA identical matches
- Matches available for ~15% of cases
- Event-free survival 95–100%
- Haploidentical transplants less successful
- Conditioning regiments are genotoxic
- Immunosuppression required

Steinberg MH, et al (eds). *Disorders of Hemoglobin: Genetics, Pathophysiology, Clinical Management*. 2nd edition. Cambridge University Press, 2009.

Approaches to Gene Therapy Using CD34+ HSPCs



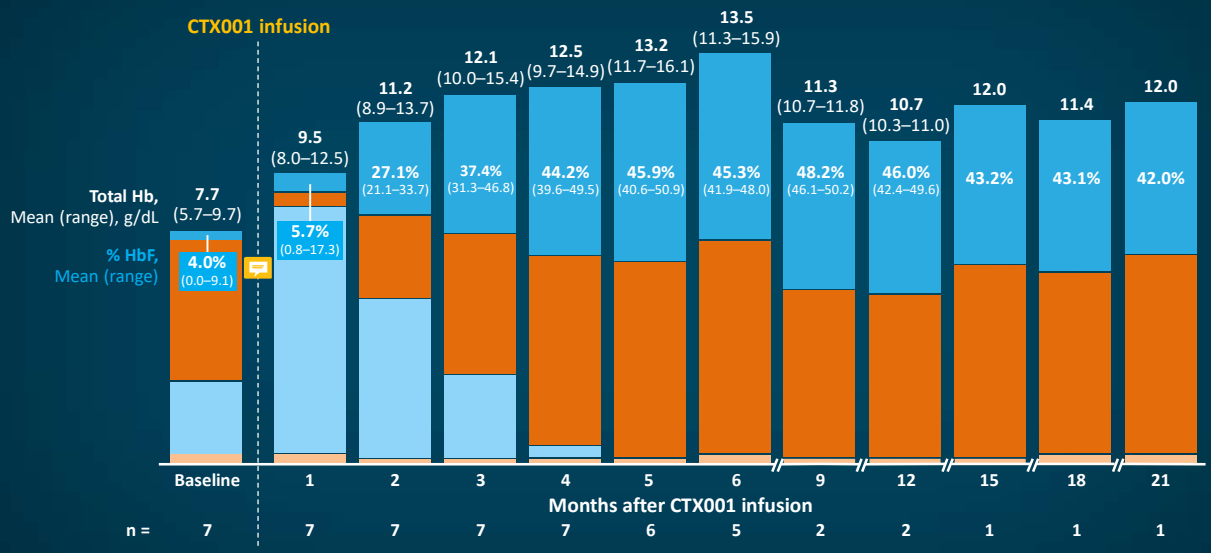
Follow-up

- Engraftment; adverse events
- HbF (HbA^{T87Q}), F-cells
- CBC and markers of hemolysis
- VOCs, transfusions
- Allelic editing; VCN
- Off-target edits

HSPC = hematopoietic stem and progenitor cell; G-CSF = granulocyte colony stimulating factor; VCN = vector copy number.

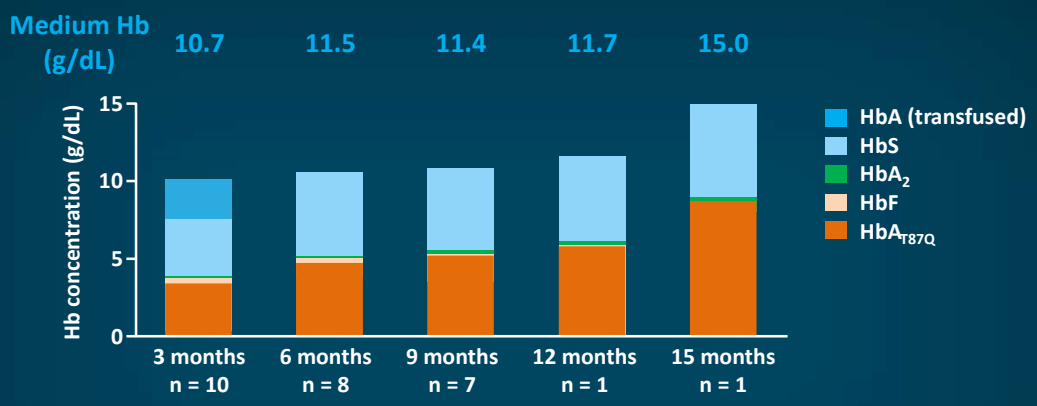
Modified from Frangoul H, et al. *N Engl J Med.* 2021;384:252-260 and supplement. Frangoul H, et al. *Blood.* 2020;136(suppl 1): 3-4.

Hemoglobin Fractions After BCL11A-Enhancer Editing In Sickle HPSCs



Grupp S, et al. European Hematology Associaton (EHA) virtual congress, 2021 (https://library.ehaweb.org/eha/2021/eha2021-virtual-congress/325494/stephan.grupp.ctx001.for.sickle.cell.disease.safety.and.efficacy.results.from.html). Accessed 11/18/2021.

Lentivirus-Mediated (βT87Q) Gene Therapy for SCD



- LDH 225.0 (130.0–337.0) U/L; reticulocytes 150.0 (42.1–283.0) 109/L; bilirubin 1.3 (0.2–2.0) mg/dL
- No VOC or ACS
- MDS and AML reported 2/16/21

MDS = myelodysplastic syndrome; AML = acute myeloid leukemia.

Kanter J, et al. ASH, 2019: abstract 991 (https://ashpublications.org/blood/article/134/Supplement_1/991/427127/Crizanlizumab-5-0-Mg-Kg-Exhibits-a-Favorable). bluebird bio press release. 2/16/2021 (https://investor.bluebirdbio.com/news-releases/news-release-details/bluebird-bio-announces-temporary-suspension-phase-12-and-phase-3). URLs accessed 12/7/2021.

Pharmacologic and Cell-Based Algorithm

*Includes pain medication, transfusion, and L-glutamine.

Steinberg MH. *Am J Hematol.* 2020;95:338-342.

SCD Complications and Specialists Needed

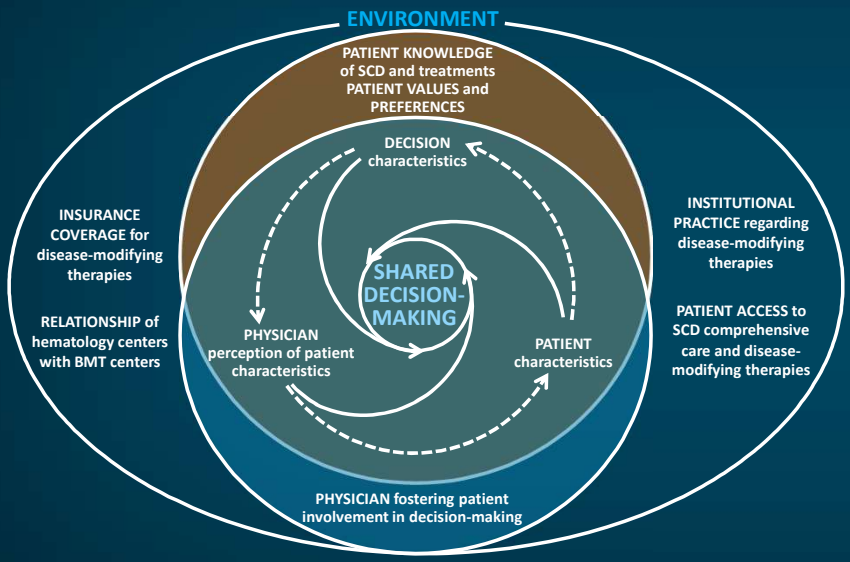
Complication	Specialists	ES or P
Retinopathy	Retinal specialist	ES
Leg ulcer	Wound care	ES
Restrictive lung disease	Pulmonary	ES
Pulmonary hypertension	Cardiology (or pulmonary)*	ES
Renal disease	Nephrology	ES
AVN	Orthopedics	ES
Gallstones/hypersplenism	General surgeon	ES
Mood disorders	Psychiatry/psychology	ES
Neurovascular disease	Neurosurgeon	ES
Priapism	Urology	ES
Transfusion-related complications	Blood-bank specialist	ES
Pregnancy-related complications	Maternal-fetal medicine/high-risk OBGYN	ES
Iron overload (assessment)	Radiologic specialists	P
Chronic pain	Pain specialist	P

*Prefer (not essential) a specialist with specific training for SCD.

ES = essential; P = preferred; AVN = avascular necrosis; OBGYN = obstetrics and gynecology (specialist).

Kanter J, et al. *Blood Adv*. 2020;4:3804-3813.

Factors Influencing Decision-Making Regarding Disease-Modifying Therapies in SCD



Patient characteristics
- Severity of SCD
- Level of risk acceptable
- Perceived burden of treatment for self and family
- Impact of SCD on QoL
- Availability of donor
- Expectations from treatment
- Trust
- Adherence

Decision characteristics
- Risks and benefits
- Reversibility of treatment
- Response to current/past treatment
- Practice variability
- Urgency of decision
- Physician philosophy and experience

Physician perception of patient characteristics
- Psycho-social patient characteristics
- Burden of caregiving
- Patient/caregiver motivation and commitment

BMT = bone marrow transplantation; QoL = quality of life.

Bakshi N, et al. *PLoS One*. 2017;12:e0178413.

Required and Suggested Components of SCD Center

Elements of an adult sickle cell center

- **Essential elements** represent the minimal components necessary for a functional and effective comprehensive adult sickle cell center
- **Optimal elements** reflect valuable resources that may be included as part of an adult sickle cell center, although they are not essential
- **Adjunct elements** serve as a supplement to the required and optimal elements and are considered preferred but not strictly necessary

GYN = gynecologist.

Kanter J, et al. *Blood Adv*. 2020;4:3804-3813.

Summary

- Hydroxyurea should be given at maximally effective doses to all patients
- New drugs that could modify disease are available
- Integration of these new drugs into practice is challenging
- Acute and chronic pain are the most difficult management issues
- Transfusions have a major therapeutic role but should be carefully targeted

Summary (continued)

- Stem-cell transplantation can be “curative”; however, ~15% have identical sibling donors
- HbF is the most important modifier of sickle cell disease phenotypes
- Cell-based approaches to increasing HbF are efficacious
- Small-molecule HbF-inducing agents will be more effective

Questions?

Hemophilia

Michael H. White, MD, MSc

Overview of Hemophilia

Clinically manifests as the body's inability to maintain hemostasis due to a deficiency in clotting factor [factor VIII (FVIII) for hemophilia A or factor IX (FIX) for hemophilia B]

Congenital disorder inherited as X-linked recessive pattern

Estimated to affect ~33,000 males in United States, occurring in approximately 1 of every 5000 male births.

Hemophilia A is approximately 4 times as common as hemophilia B.

Clinical Manifestations of Hemophilia A and B

Type	Factor VIII or IX level	Clinical phenotype
Severe	<1%	• Deep soft tissue and joint bleeding (spontaneous) • Recurrent mucocutaneous bleed • Post-surgical or post-circumcision bleeding
Moderate	1–5%	• Bleeding following trauma or surgery • Occasional joint bleeding but uncommon • Spontaneous bleeding uncommon
Mild	6–49%	• May be silent in absence of hemostatic challenge • Bleeding with major trauma or surgery • Joint bleeds uncommon

US Centers for Disease Control and Prevention (CDC). Hemophilia facts (cdc.gov/ncbddd/hemophilia/facts.html). CDC. Hemophilia data and statistics (cdc.gov/ncbddd/hemophilia/data.html). NHF. What is hemophilia A? (www.hemophilia.org/bleeding-disorders-a-z/types/hemophilia-a). NHF. What is hemophilia B? (www.hemophilia.org/bleeding-disorders-a-z/types/hemophilia-b). Accessed 11/17/2021.

Hemophilia Timeline

- **2nd century AD**
  - It was taught: If she circumcised her first son and he died, and her second son and he too died, she should not circumcise her third son, so taught Rebbi. (Yevamot 64:)
- **1803**
  - American Physician John Conrad Otto characterized an unknown bleeding disorder mostly affecting men. The term hemophilia was first coined.
- **1837–1901**
  - Queen Victoria ruled England. She was verified to be a hemophilia B carrier. Her youngest son Leopold had hemophilia and died as an adult after a fall.
- **1940s**
  - Average life expectancy is 20 years.
- **1965**
  - Judith Pool discovers fractionated plasma offering first effective therapy


Hemophilia Federation of America (HFA). Bleeding disorders historical timeline (www.hemophiliafed.org/updated-historical-timeline/). Yevamot 64 (www.talmudology.com/jeremybrownmdgmailcom/2014/11/27/circumcision-death-and-hemophilia-a). Accessed 11/18/2021.

Hemophilia

- X-linked recessive bleeding disorder
- >30% of cases are spontaneous
  - No family history
- **Hemophilia A**
  - Deficiency of factor VIII (8)
  - Incidence of 1:~5600 males
- **Hemophilia B**
  - Deficiency of factor IX (9)
  - Incidence 1:~25,000 males
- Females may be affected
  - Symptomatic carriers (normal levels with bleeding)
  - Clinical disease in certain circumstances (ie, extreme lyonization, homozygosity, or chromosomal abnormality ie, Turner syndrome)
  - ~30% of carriers have factor levels <50%

Mayo Clinic. Hemophilia, 10/7/2021 (www.mayoclinic.org/diseases-conditions/hemophilia/symptoms-causes/syc-20373327). National Hemophilia Foundation (NHF). What is hemophilia A? (www.hemophilia.org/bleeding-disorders-a-z/types/hemophilia-a). NHF. What is hemophilia B? (www.hemophilia.org/bleeding-disorders-a-z/types/hemophilia-b). Centers for Disease Control and Prevention (CDC). Hemophilia facts (cdc.gov/ncbddd/hemophilia/facts.html). URLs accessed 11/18/2021.

Clinical Manifestations

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Blanchette V et al. *SickKids Handbook of Pediatric Thrombosis and Hemostasis*, 2013. CDC hemophilia data and statistics (cdc.gov/ncbddd/hemophilia/data.html). NHF. What is hemophilia A? (www.hemophilia.org/bleeding-disorders-a-z/types/hemophilia-a). NHF. What is hemophilia B? (www.hemophilia.org/bleeding-disorders-a-z/types/hemophilia-b). URLs accessed 11/17/2021.

Approach to the Bleeding Patient (ED setting)

- Bleeding disorders can be inherited or acquired
- Evaluation of a child presenting with bleeding should include:
  - Comprehensive medical and bleeding history
  - Family history
  - Detailed exam
  - Targeted laboratory studies
- When should one consider a bleeding disorder in a child?
  - In cases of an excessive bleeding response to a common challenge
  - If there is a high clinical index of suspicion or a concerning family history

History Should Include…

- Age and gender of the patient
- Birth history
  - Maternal history, delivery, instrumentation, vitamin K administration
  - Need for blood products or other interventions
- Past medical and surgical history
- Medications (ie, NSAIDs, anticoagulants, herbal supplements)
- Family history
  - Consanguinity, mindful of inheritance pattern
  - Special populations, for example, factor XI deficiency in Jews of Ashkenazi decent

Bleeding History Should Include…

- **Epistaxis**
  - **>10 minutes, >5 per year**
  - Unilateral/bilateral
  - Seasonal
  - Spontaneous or traumatic
- **Skin**
  - Bruises larger than 5 cm
  - In **unusual locations** where trauma is unlikely (ie, head, back, chest/abdomen, axilla)
  - More than 5 in any location
  - Petechiae?
  - Non traumatic? After vaccinations? Venipuncture?
- **Bleeding from minor wounds**
  - >5 minutes, >5 times a year
- **Hematuria**
- **Gastrointestinal (GI) bleeding**
  - Hematemesis
  - Melena
  - Hematochezia
  - Presence of underlying GI disorder
- **Intracranial bleeding**
- **Oral bleeding**
  - With brushing and/or flossing
  - **With tooth eruption/extraction**
  - With dental or other surgery
- **Surgical bleeding/bleeding with trauma**
- **Deep-muscle hematoma or hemarthrosis**
- **Menstrual bleeding**
  - Bleeding for >7 days
  - Flooding or gushing of blood that limits daily activities (school, sports, work, social)
  - Passing clots that are bigger than a quarter
  - Changing pad/tampon > every 2 hours
- **Other bleeding**
  - Umbilical stump bleeding, cephalohematoma
  - **Post-circumcision**
  - Post-venipuncture
- **Delayed wound healing**
- **Treatment/Interventions**
  - Prior diagnosis of or treatment for anemia?
  - Transfusions (ie, blood, platelets, plasma)?
  - Surgical intervention/correction?

Pediatric Bleeding Questionnaire

Symptom	Score					
	–1	0	1	2	3	4
Epistaxis	—	No or trivial (≤5 per year)	>5 per year OR >10 minutes duration	Consultation only	Packing or cauterization or antifibrinolytic	Blood transfusion, replacement therapy, or desmopressin
Cutaneous	—	No or trivial (≤1cm)	>1 cm AND no trauma	Consultation only	—	—
Minor wounds	—	No or trivial (≤5 per year)	>5 per year OR >5 minutes duration		Surgical hemostasis or antifibrinolytic	Blood transfusion, replacement therapy, or desmopressin
Oral cavity	—	No	Reported at least once	Consultation only	Surgical hemostasis or antifibrinolytic	Blood transfusion, replacement therapy, or desmopressin
GI tract	—	No	Identified cause	Consultation only or Steri-strips	Surgical hemostasis, antifibrinolytic	Blood transfusion, replacement therapy, or desmopressin
Tooth extraction	No bleeding in at least 2 extractions	None done or no bleeding in 1 extraction	Reported, no consultation	Consultation only	Resuturing, repacking, or antifibrinolytic	Blood transfusion, replacement therapy, or desmopressin
Surgery	No bleeding in at least 2 surgeries	None done or no bleeding in 1	Reported, no consultation	Consultation only	Surgical hemostasis or antifibrinolytic	Blood transfusion, replacement therapy, or desmopressin
Menorrhagia	—	No	Reported or consultation only	Antifibrinolytic or contraceptive pill	D&C or iron therapy	Blood transfusion, replacement therapy, desmopressin, or hysterectomy
Postpartum	No bleeding in at least 2 deliveries	No deliveries or no bleeding in 1 delivery	Reported or consultation only	D&C, iron therapy or antifibrinolytic	Blood transfusion, replacement therapy, or desmopressin	—
Muscle hematoma	—	Never	Post-trauma, no therapy	Spontaneous, no therapy	Spontaneous or traumatic, requiring replacement therapy or desmopressin	Spontaneous or traumatic, requiring surgical intervention of blood transfusion
Hemarthrosis	—	Never	Post-trauma, no therapy	Spontaneous, no therapy	Spontaneous or traumatic, requiring replacement therapy or desmopressin	Spontaneous or traumatic, requiring surgical intervention or blood transfusion
CNS	—	Never	—	—	Subdural, any intervention	Intracerebral, any intervention
Other *	—	No	Reported	Consultation only	Surgical hemostasis, antifibrinolytic or iron therapy	Blood transfusion, replacement therapy, or desmopressin

Other bleeding includes umbilical stump, cephalohematoma, post-circumcision, post-venipuncture, and macroscopic hematuria; scores ≥2 are abnormal.

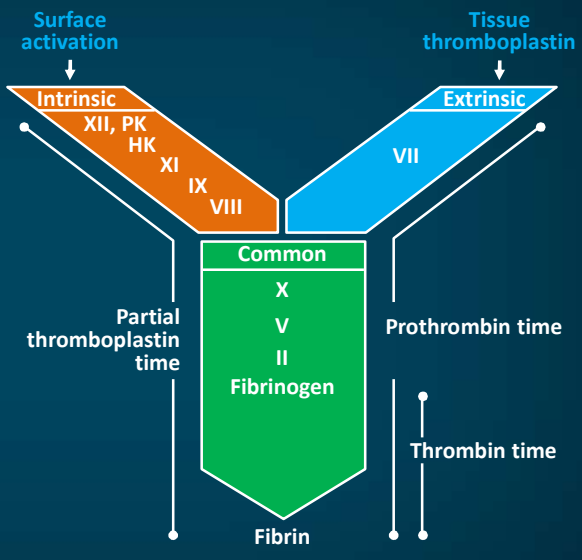
CNS = central nervous system; D&C = dilation and curettage.

Modified from International Society on Thrombosis and Haemostasis/Scientific and Standardization Committee (ISTH/SSC) Bleeding assessment tool (https://bleedingscore.certe.nl/). Accessed 11/18/2021.

Evaluation Laboratory Tests for the ED

- **Initial screen**
  - CBC with differential
  - PT/INR and aPTT
  - Fibrinogen activity
  - Thrombin time
  - PFA-100

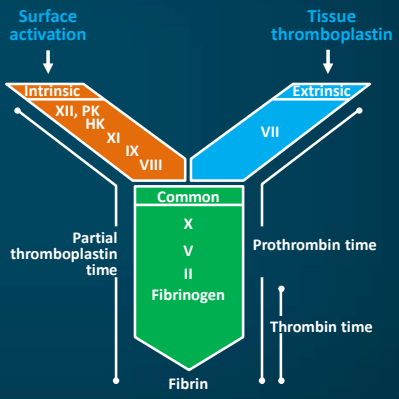
  } Bleeding screen profile
- **von Willebrand disease profile**
  - VWF ristocetin cofactor activity (VWF:RCo)
  - VWF antigen (VWF:Ag)
  - Factor 8 activity assay (FVIII:C)
  - VWF: GPIbM (send out)
  - Saved specimen for additional testing
- Specific factor assays



CBC = complete blood count; PFA = Platelet Function Analyzer; VWF = von Willebrand factor; GPIbM = glycoprotein Ib without ristocetin; PK = prekallikrein; HK = high molecular weight kininogen.

Lab Evaluation—"2nd Tier"

- **Specific factor assays**
  - ***Normal PT/aPTT does not rule out mild factor deficiencies → test specific factor levels if suspicious***
  - Prolonged aPTT — Factors XII, XI, IX, VIII (12, 11, 9, 8)
  - Prolonged PT — Factor VII (7)
  - Prolonged aPTT and PT — Factors X, V, II (10, 5, 2), and fibrinogen
  - **Normal PT/aPTT** — Consider factor 13
  - ***Coagulation labs → blue top tube (plasma with citrate)***



- **Platelet aggregation study**
  - Additional testing based on results includes:
    1) Platelet electron microscopy
    2) Platelet flow cytometry for GPIIb/IIIa and GPIb-IX-V deficiencies

Hemophilia Management

- **Primary treatment = factor replacement**
- Aminocaproic acid (Amicar®) for mucosal bleeding
- Desmopressin acetate (DDAVP®, Stimate®) in patients with mild hemophilia A (factor 8 deficiency) if DDAVP responsive. (*Stimate® likely not available until 2022*)
- **Blood products such as FFP and/or cryoprecipitate are no longer recommended**
  - **Eliminates patients from clinical trials and limited effectiveness**
  - **Often occurs in ED setting; need good communication with bleeding-disorder team**
- **If concern for bleed or active bleeding on exam → treat!**
- If head trauma, always treat with 100% factor correction first and then do head CT scan
- Avoid use of medications that affect platelet function (eg, NSAIDs)

DDAVP = 1-deamino-8-D-arginine vasopressin; CT = computed tomography.

Srivastava A, et al. *Haemophilia.* 2020;26(suppl 6): 10158.

Hemophilia Management
(continued)

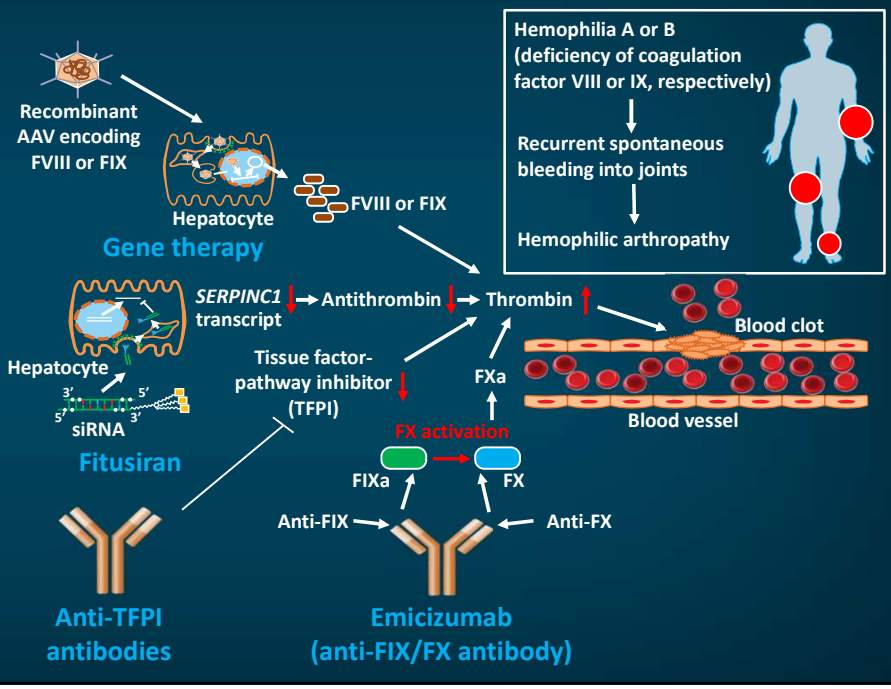
- **Hemophilia A (FVIII deficiency)**
  - 1 U/kg of recombinant FVIII raises FVIII levels by 2%
    - Products: pdFVIII, rFVIII, and EHL FVIII
    - $t_{1/2}$ = 8–12 hours (less in young children)
  - 25 U/kg dose → 50% correction
  - 50 U/kg dose → 100% correction
- **Hemophilia B (FIX deficiency)**
  - 1 U/kg recombinant FIX raises FIX levels by 0.7–0.8%
    - Products: SHL rFIX and EHL FIX
    - $t_{1/2}$ = 18–24 hours (less in young children)
  - 60–70 U/kg dose → 50% correction
  - 120–140 U/kg dose → 100% correction

pdFVIII = plasma-derived factor 8.

Srivastava A, et al. *Haemophilia.* 2020;26(suppl 6): 10158.

Hemophilia Treatment Strategies

- Emicizumab
- Fitusiran (not FDA approved)
- Anti-TFPI mab agent (not FDA approved)



FDA = US Food and Drug Administration; mab = monoclonal antibody; AAV = adeno-associated virus; RNA = ribonucleic acid; siRNA = small interfering RNA; FIX = (coagulation) factor 9; FX = (coagulation) factor 10.

Modified from Butterfield JSS, et al. *Mol Ther.* 2020;28:997-1015.

Whiteboard Animation: Non-factor Replacement Therapies

How Do We Choose Which Product to Use?

- Shared decision-making
  - Early discussion
  - Avoiding decision at time of first bleed
- This information is relevant to ED provider since first dose of factor treatment is often given in ED setting during an acute bleed
- General framework
  - Previously untreated patients (PUPs)
  - Previously treated patients (PTPs)
  - Factor versus non-factor treatment

Hemophilia A

PUPs
Plasma-derived FVIII
Human cell line FVIII
Emicizumab

PTPs
Plasma-derived FVIII
Recombinant FVIII
EHL recombinant FVIII
Emicizumab

Product type	Mean Adult Half-Life, hours	
	Factor VIII	Factor IX
Plasma-derived	14.8–17.9	21.0–25.3
Recombinant	10.8–17.1	18.1–25.7
EHL	14.2–19.7	83.0–104
Emicizumab	~4 weeks	—

EHL = extended half-life (products); hr(s) = hour(s).

Marchesini E, et al. *Biologics*. 2021;15:221-235.

Hemophilia B

PUPs
SHL FIX
EHL FIX

PTPs
Plasma-derived FIX
Recombinant FIX
EHL recombinant FIX

Product type	Mean Adult Half-Life, hours	
	Factor VIII	Factor IX
Plasma-derived	14.8–17.9	21.0–25.3
Recombinant	10.8–17.1	18.1–25.7
EHL	14.2–19.7	83.0–104
Emicizumab	~4 weeks	—

SHL = standard half-life.

Marchesini E, et al. *Biologics*. 2021;15:221-235.

Standard of Care: Prevention

Avoid risky behaviors

Category	Definition	Sports
1 (low risk)	Most individuals with hemophilia can participate safely	Stationary bicycling, tai chi, fishing, hiking, swimming
2 (moderate risk)	The physical, social, and psychological benefits often outweigh the risks of these sports	Baseball, bowling, mountain biking, running, tennis, track and field, volleyball, weight-lifting
3 (high risk)	Risks outweigh the benefits; dangerous for those even without hemophilia	Boxing, wrestling, lacrosse, football, rugby, rock climbing, karate

NHF. Playing It Safe (https://stepsforliving.hemophilia.org/sites/default/files/playing-it-safe.pdf). Accessed 11/18/2021.

Prophylaxis Improves Outcomes

Regular infusions of FVIII or FIX prior to age 3 is the standard of care
Personalization of dosing is critical in this current era

1960

2021

FVIII = coagulation factor 8; FIX = coagulation factor 9.

Srivastava A, et al. *Haemophilia*. 2020;26(suppl 6): 10158. Modified from World Federation of Hemophilia. Hemophilia in pictures (www1.wfh.org/publications/files/pdf-1311.pdf). Accessed 11/17/2021.

SHARE

- **S**eek patient participation
- **H**elp patients explore and compare treatment options
- **A**ssess patient's values and preferences
- **R**each a decision with patient on treatment
- **E**valuate patient's decision

Agency for Healthcare Research and Quality (AHRQ). The SHARE approach (www.ahrq.gov/professionals/education/curriculum-tools/shareddecisionmaking/index.html). Accessed 11/17/2021.

Hemophilia and Inhibitors

- Some patients develop inhibitors, or alloantibodies, to replacement clotting factors, rendering the treatment ineffective and requiring an alternate treatment strategy
  - Estimated 25–30% of patients with severe hemophilia A and 1–5% of patients with severe hemophilia B develop inhibitors
- Diagnosed with a blood test that measures an inhibitor titer
- Inhibitor development has clinical implications and poses an economic burden including:
  - Impaired quality of life
  - Impaired orthopedic functioning
  - Increases in hemorrhages
  - Increased absenteeism

CDC. Hemophilia facts, 2020 (cdc.gov/ncbddd/hemophilia/facts.html). CDC. Inhibitors and hemophilia, 2020 (cdc.gov/ncbddd/hemophilia/inhibitors.html). URLs accessed 11/18/2021. Gomez K, et al. *Blood Transfus.* 2014;12(suppl 1):s319-s329. Brown TM, et al. *Haemophilia.* 2009;15:911-917. Darby SC, et al. *J Thromb Haemost.* 2004;2:1047-1054. Di Minno MND, et al. *Haemophilia.* 2010;16:e190-e201.

Risk Factors for Hemophilia A Inhibitors

Genetic risk factors → **Inhibitors** ← **Treatment-related risk factors**

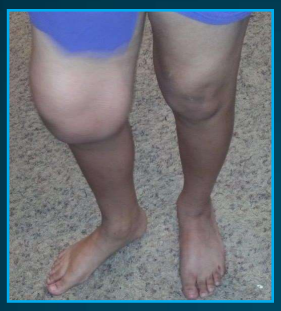
- F8 mutation type
- Ethnicity
- Human leucocyte antigen (HLA) type
- F8 polymorphisms

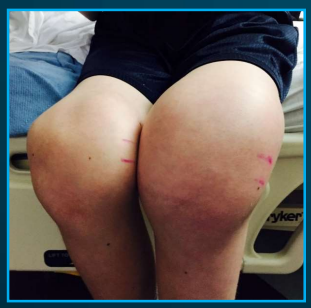
- Intensity of FVIII treatment
- FVIII product type
- Trauma/surgery
- Timing of prophylaxis
- Young age at first treatment

Why this matters:
Severe bleeding events typically are managed in ED, and choice of factor is made acutely

Chambost H. *Haemophilia*. 2010;16(suppl 2):10-15. Gomez K, et al. *Blood Transfus*. 2014;12(suppl 1):s319-s329. Witmer C, Young G. *Ther Adv Hematol*. 2013;4:59-72.

Clinical Impact of Inhibitors





- Normal FVIII treatment fails
- Difficult to control or prevent bleeding
- Decreased ability to safely perform surgery
- More severe joint abnormalities
- Increased risk of life/limb-threatening bleed
- Risk of anaphylactic reaction for patients with hemophilia B

Treatment of Patients with Inhibitors

- **Bypassing agents (rFVIIa vs aPCC)**
  - Hemostatic efficacy ~70%
  - ~30% of patients responded to one and not the other
  - Response can change over time
    - **aPCC (FEIBA®) 85 units/kg/dose every 12 hrs (do not exceed 200U/kg/day)***
    - **FVIIa (NovoSeven RT®) 90 mcg/kg/dose every 2–12 hrs (rarely dose higher)**
- **High-dose FVIII**
  - Low-titer inhibitor (<5 BU/mL) patients, although some high-titer patients respond
    - Based on FVIII level; 15–30 minutes after dose for FVIII
  - **Variable ability to utilize high-dose FVIII (ask your friendly hemophilia doc)**

*This dosing is for patients not on emicizumab.

Choices of Bypassing Agent (BPA) for Inhibitor Management

	Typical regimen to treat bleeds	Advantages	Special considerations
aPCC (FEIBA®)[1,2]	50–100 IU/kg every 6–12 hrs (max 200 IU/kg/day)	• Lasts longer vs rFVIIa • Can be given every 6–12 hrs	• Plasma derived • Large volume • 30–45 minutes to administer • Not to be given with tranexamic acid • Contains some FVIII • Has a higher rate of thrombosis if given concomitantly at high doses for >1 day in patients on emicizumab
Factor VIIa (recombinant) (NovoSeven RT®) [1,3]	90 mcg/kg Q2H until controlled; repeat every 3–6 hrs after hemostasis for severe bleeds	• Recombinant • Small volume • Can be given over 2–5 minutes • Can be given with tranexamic acid • Appears to be safer when given in combination with emicizumab	• Does not last very long (shorter half-life) • Needs to be given more frequently
Factor VIIa (recombinant)-jncw (Sevenfact®)[4]	75 mcg/kg Q3H until controlled or single dose of 225 mcg/kg + 75 mcg/kg 6–9 hrs later if not controlled	• Approved for adolescents and adults with hemophilia A and B with inhibitors	• Data coming on combination with emicizumab; MASAC recommending lower dose in the interim • Emerging data on higher-dose regimen

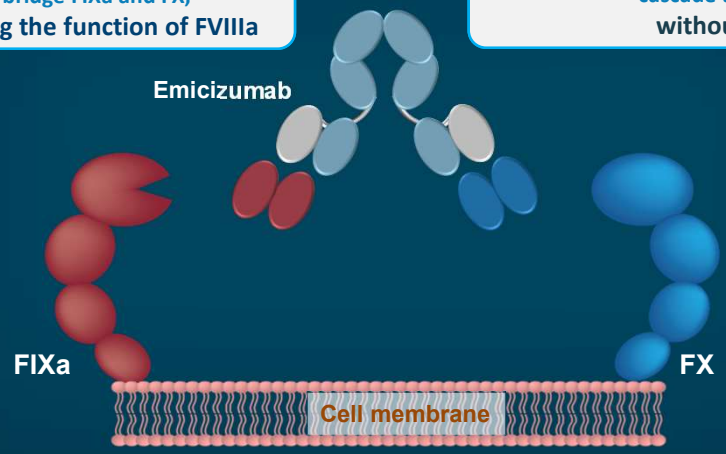
IU = international unit; Q2H = every 2 hours; Q3H = every 3 hours; MASAC = Medical and Scientific Advisory Council (for NHF).

1. Carcao M, Goudemand J. *Treatment of Hemophilia.* 2018;7:1-19 (www1.wfh.org/publication/files/pdf-1122.pdf). 2. aPCC (FEIBA®). Prescribing information (PI), 2020 (https://dailymed-us-east-1.awsprod.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=752604e5-4ea2-44f4-83ed-1569373f6412&type=display). 3. rFVIIa (NovoSeven® RT) PI , 2020 (www.novo-pi.com/novosevenrt.pdf). 4. rFVIIa-jncw (Sevenfact®) PI, 2020 (https://sevenfact.com/Sevenfact_PI.pdf). URLs accessed 11/18/2021.

Emicizumab Mechanism of Action

Emicizumab is a therapeutic bispecific antibody designed to bridge FIXa and FX, **thereby replacing the function of FVIIIa**

This allows the coagulation cascade to continue **without FVIIIa**



FX = (coagulation) factor 10.

Kitazawa T, et al. *Nat Med.* 2012;18:1570-1574. Sampei Z, et al. *PLoS One.* 2013;8:e57479.

Compatibility of Assays and Emicizumab

- If a FVIII activity (one-stage) is obtained, FVIII will be falsely elevated to >200–300%
- **PTT will be short (20–35s), and FVIII will be elevated!**

Results affected by emicizumab	Results unaffected by emicizumab
aPTT will be normal for 4–6 months after stopping emicizumab	Bethesda assay using bovine chromogenic reagents
Standard Bethesda assay	Thrombin time
One-stage aPTT single factor assays	One-stage PT-based factor assays
aPTT-based activated protein S resistance assay	Chromogenic single factor assay other than FVIII
Activated clotting time	Genetic thrombophilia DNA tests (PT gene mutation, FVL, etc.)
	Chromogenic FVIII assay using bovine reagents

DNA = deoxyribonucleic acid; FVL = factor V Leiden.

Sang Medicine. Clotting concentrates and non-clotting factor therapies: assays (https://practical-haemostasis.com/Factor%20Assays/EHL_products_novel_agents.html). Accessed 12/03/2021.

Bleeding Treatment in Patients on Emicizumab

- **Most bleeds can be observed first** (if non-life threatening)
  - For minor head trauma and no clinical evidence of a head bleed, may consider obtaining head CT first, prior to treatment
- **If emergent or life-threatening bleed:**
  - **Consider rFVIIa at 90 mcg/kg x 1**
  - Additional doses only to be given after discussion with the HTC
  - **aPCCs** (ie, FEIBA®) **should be avoided as first-line therapy**
    - Doses of FEIBA >100 U/kg/24 hr are associated with thrombosis and thrombotic microangiopathy (vague abdominal pain, increased bleeding, ill-appearing, nausea, anemia, thrombocytopenia with normal ADAMTS13)
  - Antifibrinolytics can be used with FVIII or BPA → discuss with the HTC
  - Discuss treatment plan with HTC if bleeding is persistent, refractory, or non-responsive to rFVIIa

HTC = Hemophilia treatment center; ADAMTS13 = a disintegrin and metalloprotease with thrombospondin type I motif, member 13.

HAVEN Clinical Trials of Emicizumab in Hemophilia A

HAVEN trials represent the largest clinical trial program of hemophilia A patients with and without FVIII inhibitors

HAVEN 1 (N = 109) (with inhibitors)	HAVEN 2 (N = 63) (with inhibitors)	HAVEN 3 (N = 152) (w/o inhibitors)	HAVEN 4 (N = 41) (with or w/o inhibitors)
• Adult and adolescent males ≥12 years and ≥40 kg • Emicizumab 1.5 mg/kg QW maintenance	• Children <12 years, or 12–17 years and <40 kg • Emicizumab 1.5 mg/kg QW maintenance	• Adult and adolescent males ≥12 years and ≥40 kg • Emicizumab 1.5 mg/kg QW maintenance	• Adult and adolescent males ≥12 years and ≥40 kg • Emicizumab 6 mg/kg Q4W maintenance

- Demonstrated superiority of emicizumab over FVIII and is the standard of care for inhibitor patients
- Control of bleeds was excellent and can anticipate ABRs <3
- Majority were traumatic bleeds and there were no participants who gave prophylactic doses of FVIII or BPA prior to physical activity
- There is no evidence of a pattern of bleeds following reported physical activity

w/o = without; ABR = annualized bleed rate.

Callaghan MU, et al. *Blood.* 2021;137:2231-2242. Emicizumab-kxwh (Hemlibra®) PI, 2021 (www.gene.com/download/pdf/hemlibra_prescribing.pdf). Accessed 11/18/2021.

Warnings and Precautions in the ED

Thrombotic microangiopathy (TMA) and thromboembolism

- **In clinical trials, TMA was reported in 0.8% of patients (3/391) and thrombotic events were reported in 0.5% of patients (2/391). In patients who received at least one dose of aPCC, TMA was reported in 8.1% of patients (3/37) and thrombotic events were reported in 5.4% of patients (2/37).**
- Patients with TMA presented with thrombocytopenia, microangiopathic hemolytic anemia, and acute kidney injury, without severe deficiencies in ADAMTS13.
- Consider the benefits and risks if aPCC must be used in a patient receiving emicizumab prophylaxis. Monitor for development of TMA and/or thromboembolism when administering aPCC. Immediately discontinue aPCC and interrupt emicizumab prophylaxis if clinical symptoms, imaging, or laboratory findings consistent with TMA and/or thromboembolism occur and manage as clinically indicated.

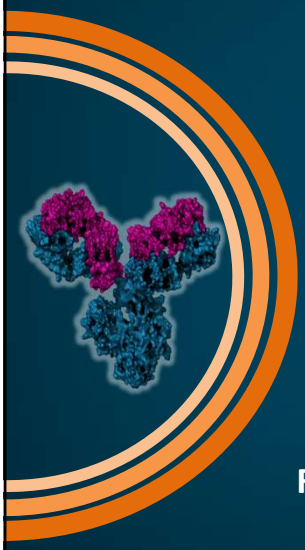
Emicizumab-kxwh (Hemlibra®) PI, 2021 (www.gene.com/download/pdf/hemlibra_prescribing.pdf). Accessed 11/18/2021.

ITI Is Still Only Strategy for Inhibitor Eradication

- Immune tolerance induction (ITI) in the form of high-dose FVIII exposure is the only clinically proven strategy for eradication of inhibitors
- Known factors associated with increased risk of ITI failure include:
  - Time since inhibitor diagnosis to start of ITI
  - Historical peak inhibitor titre
  - Inhibitor titre at start of ITI
  - Peak inhibitor titre while on ITI
  - Monthly bleeding rate during ITI
- Unclear whether rFVIII or pdFVIII has impact on achieving tolerance

Carcao M, et al. *Haemophilia.* 2019;25:676-684. Gringeri A, et al. *Haemophilia.* 2007;13:373-379. Kreuz W, et al. *Haemophilia.* 2016;22:87-95.

Immune Tolerance Induction (ITI) for Eradication of Inhibitors
(Pre-2019 Standard)



Intensive treatment with intravenous route

Typical dosing regimens require daily high-dose/volume FVIII

May need 24–36 months; can require several rounds

Success rate ≈70% in hemophilia A

Immunosuppresive therapy occasionally required (rituximab, cyclophosphamide)

Extremely expensive

Relapse rate as high as 30%

Witmer C, Young G. *Ther Adv Hematol*. 2013;4:59-72.

Immune Tolerance Induction

Standard ITI strategies

- Bonn protocol: high-dose regimen (FVIII 100–150 IU/kg every 12 hrs until <1 BU, then FVIII 150 IU/kg)
- Malmo protocol: high-dose regimen (FVIII continuous infusion targeting plasma levels >30 IU/dL until negative titer, then 60–90 IU/kg weekly + cyclophosphamide + IV immunoglobulin)
- Dutch protocol: low-dose regimen (neutralizing, then tolerizing dose)

ITI combined with prophylactic emicizumab

- LD protocol (25–50 IU FVIII/kg 3 x week) + emicizumab weekly
- **Atlanta protocol** (100 IU FVIII/kg 3 x week) + emicizumab weekly
- Bonn protocol (100–200 IU FVIII/kg 1 x day) + emicizumab weekly

ITI in pediatric patients with hemophilia A and inhibitors receiving emicizumab prophylaxis

Atlanta protocol

Emicizumab prophylaxis

Loading dose
- 3 mg/kg SC weekly × 4 weeks

Maintenance dose
- 1.5 mg/kg SC weekly OR
- 3 mg/kg SC every 2 weeks
- 6 mg/kg SC every 4 weeks

Immune tolerance induction

Recombinant or plasma-derived FVIII
- 100 IU/kg IV 3 times per week *starting ≥4 weeks after emicizumab initiation*

SC = subcutaneous; LD = low dose.

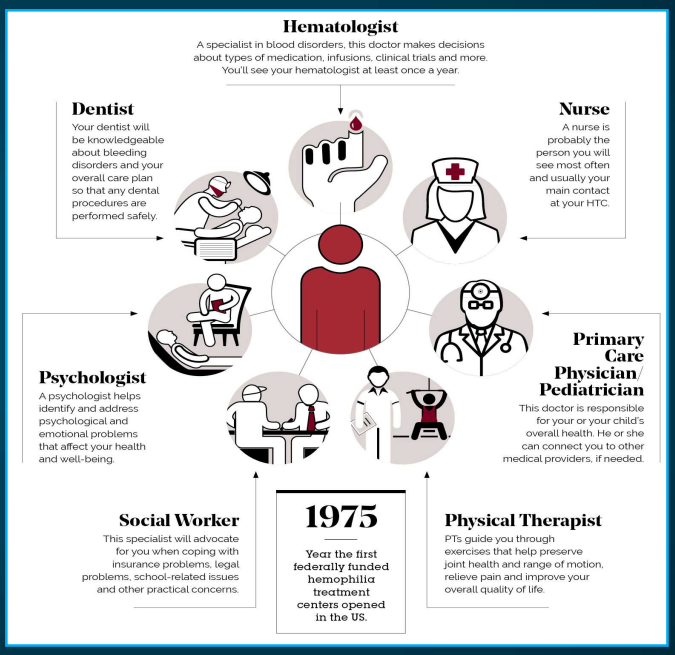
Franchini M, Lippi G. *J Thromb Thrombolysis*. 2011;32:439-447. Modified from Batsuli G, et al. *Haemophilia*. 2019;25:789-796.

HTCs…

Comprehensive care team at your HTC

Physician typically leads team of the following professionals:

1) MD/DO
2) APP
3) Nurse
4) Physical therapist
5) Social worker
6) Orthopedic surgeon



MD = doctor of medicine; DO = doctor of osteopathic medicine; APP = advanced-practice provider.

Hemaware.org (https://hemaware.org/bleeding-disorders-z/hemophilia-treatment-centers-101). Accessed 11/18/2021.

Teamwork Rules….

- ~30,000 males/females with hemophilia in the US
- Estimated yearly cost is $150,000 to $900,000 per patient
- Life expectancy is ~70 years
  - Reduced only if patient has an inhibitor or comorbidities
  - Majority age 45 and older have HIV and HCV
- Comprehensive care model seeks to:
  - Deliver family centered comprehensive care
  - Provide optimal care
  - Incorporate the role of family in planning and providing care

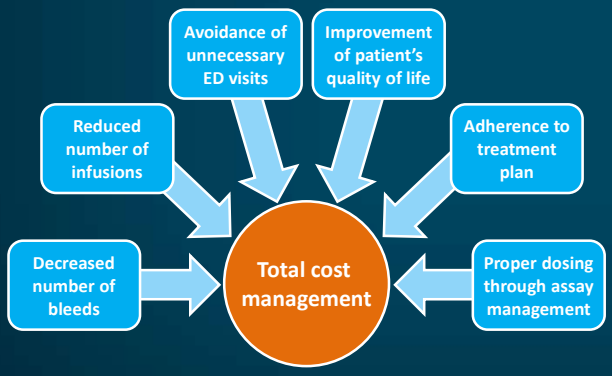
US = United States; HIV = human immunodeficiency virus; HCV = hepatitis C virus.

CDC. Comprehensive Hemophilia Management, 2019.

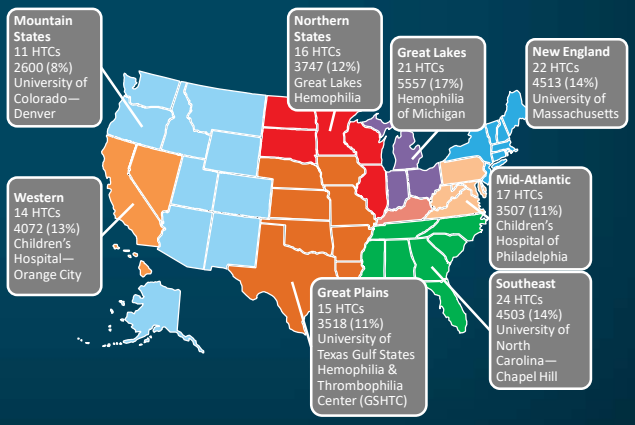
Let's Keep Them Out of the ED/Hospital...

A hemophilia treatment center

- Federally recognized comprehensive care team whose staff spend the majority of their time caring for these patients
- Accountability maintained by MCHB



US is divided into 8 regions of HTC under MCHB grant



MCHB = Maternal Child and Health Bureau.

CDC. Comprehensive Hemophilia Management, 2019.

Self-Reliance Is Taught, if Possible...

- Goal is to recognize bleeding events at home and start treatment immediately
- Patients may bring their own factor products to the ED
- Many patients with hemophilia know how to self-infuse

Carlson M. Independence days (https://hemaware.org/life/independence-days). Accessed 11/18/2021.

What About Hemophilia B Inhibitors?

- <5% of patients with hemophilia B exposed to factor IX develop inhibitory antibodies
- Inhibitors develop at a similar time compared with hemophilia A, occurring at a median of 11 exposure days to FIX replacement therapy
  - Mainly IgG4 with high affinity and preceding transient IgG1 response
  - 58% (51/88) of patients with inhibitors in the International FIX Inhibitor Registry of ISTH-SSC reported allergic manifestation
  - Usually within first 20 exposures
    - Mast-cell activation and an IgE-mediated hypersensitivity response by the smaller mass (55,000 kd) with extracellular distribution
- **You may see a patient like this with mild-to-severe hypersensitivity reaction in ED setting**

DiMichele D. *Br J Haematology*. 2007;138:305-315.

Hemophilia B and Inhibitors

BPA choice in hemophilia B with low- or high-titer inhibitors

LTI with allergic response	LTI w/o allergic response	HTI regardless of allergic response
rFVIIa	• high-dose rFIX • rVIIa • Can consider aPCC	rFVIIa

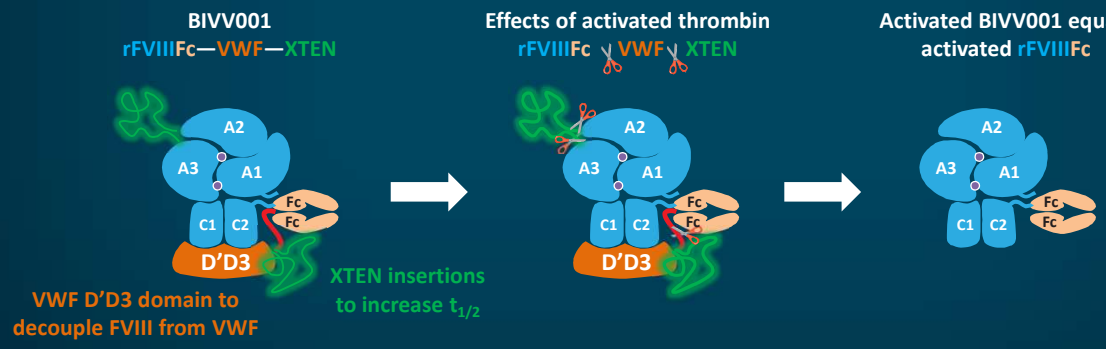
	Typical regimen to treat bleeds	Advantages
Factor VIIa (recombinant) (NovoSeven® RT)	90 mcg/kg Q2H until controlled; repeat every 3–6 hours after hemostasis for severe bleeds	• Recombinant • Small volume • Can be given over 2–5 minutes • Can be given with tranexamic acid • Appears to be safer when given in combination with emicizumab
Factor VIIa (recombinant)-jncw (Sevenfact®)	75 mcg/kg Q3H until controlled or single dose of 225 mcg/kg + 75 mcg/kg 6–9 hours later if not controlled	• Approved for adolescents and adults with hemophilia A and B with inhibitors

LTI = low-titer inhibitor.

Dioun AF, et al. *J Allergy Clin Immunol*. 1998;102:113-117. Bon A, et al. *Ital J Pediatr*. 2015;41:12. Meeks SL, Batsuli G. *Hematology Am Soc Hematol Educ Program*. 2016;2016:657-662. rFVIIa (NovoSeven® RT) PI , 2020 (www.novo-pi.com/novosevenrt.pdf). rFVIIa-jncw (Sevenfact®) PI, 2020 (https://sevenfact.com/Sevenfact_PI.pdf). URLs accessed 11/18/2021.

Efanesoctocog Alfa (BIVV001): New Class of FVIII Replacement Therapy

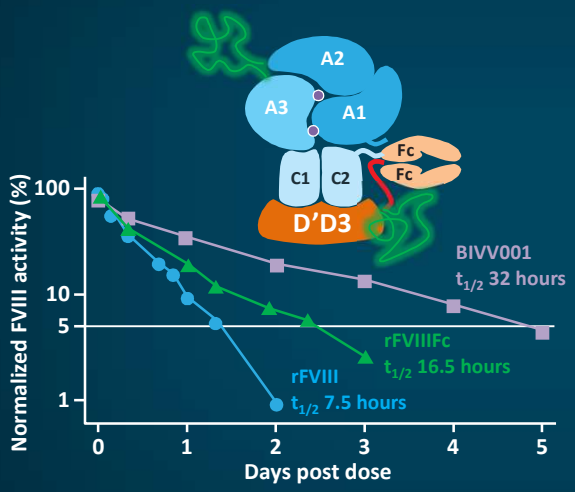
- Single chain FVIII-Fc
- D'D3 domain of VWF: stabilizes FVIII, no binding to endogenous VWF
- 2 XTEN linkers: reduces rate of clearance and degradation and improves bioavailability with subcutaneous injection

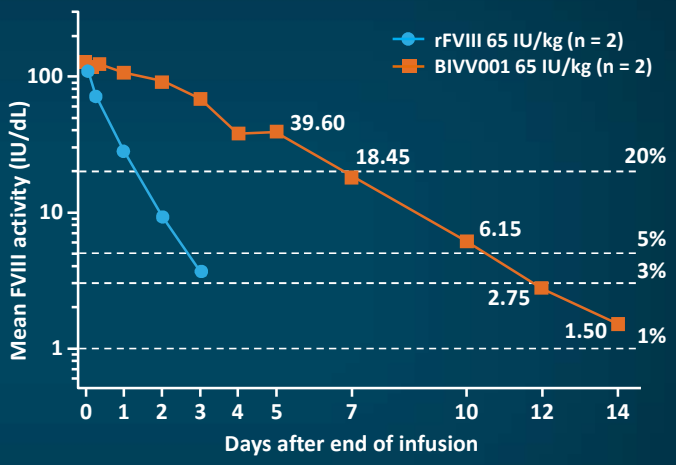


XTEN = unstructured hydrophilic polypeptide.

Modified from Konkle BA, et al. *N Engl J Med.* 2020;383:1018-1027 and supplement.

Efanesoctocog Alfa (BIVV001): Activity Post Infusion





Average post-infusion FVIII activity at 4 and 7 days was 17% and 5%, respectively, in lower-dose group and 51% and 17%, respectively, in higher-dose group

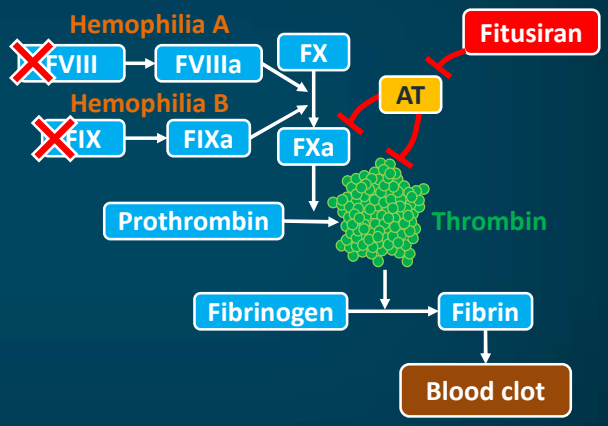
Modified from Konkle BA, et al. *N Engl J Med.* 2020;383:1018-1027.

Fitusiran

Therapeutic hypothesis of antithrombin (AT) lowering

- Hemophilia A and B are caused by an imbalance in hemostasis due to FVIII and FIX deficiency, respectively, resulting in insufficient thrombin generation (TG)[2]
- Fitusiran is designed to lower AT levels, with the goal of rebalancing hemostasis and promoting sufficient TG[2,3]
- Milder bleeding phenotypes are observed in people with hemophilia who have co-inherited thrombophilic markers, such as AT deficiency[4–8]
- Preclinical data[7] and clinical studies[8–10] provide support for this hypothesis

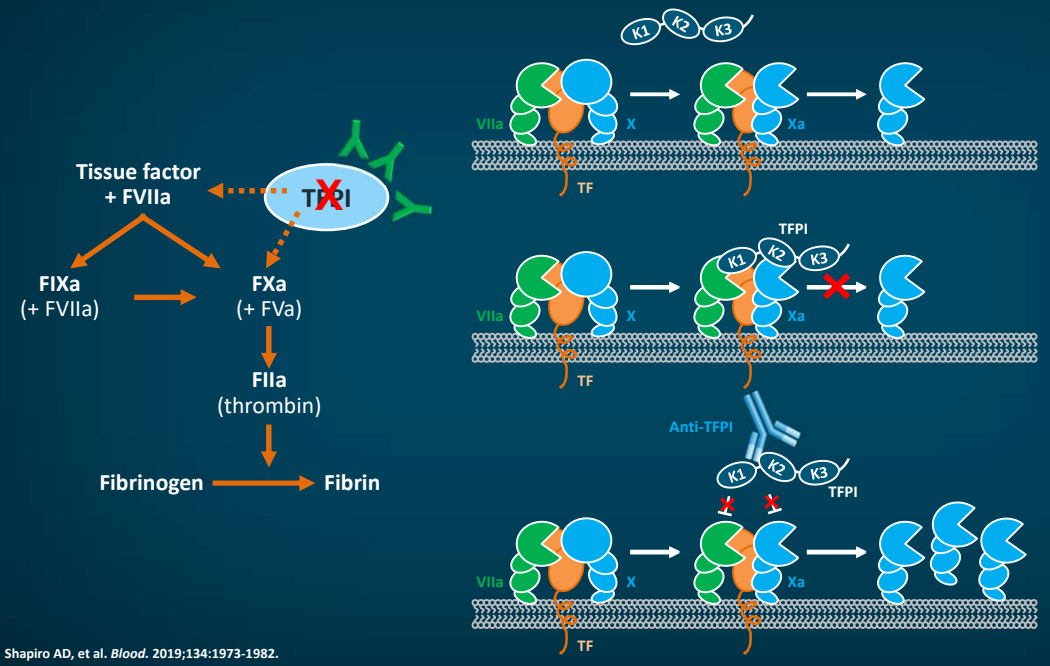
Site of action of fitusiran in the coagulation cascade[1–11]



"a" indicates the activated form of a factor.

1. Machin N, Ragni MV. *J Blood Med.* 2018:9:135-140. 2. Modified from Negrier C et al. *Blood.* 2017;130(suppl 1): 2366 (www.alnylam.de/wp-content/uploads/2017/12/ASH-2017_Negrier_ FINAL.pdf). Accessed 11/18/2021. 3. Sanofi Genzymne. ALN-AT3SC-002 Clinical Study Protcol. May 31, 2018. 4. Kurnik K, et al. *Haematologica.* 2007;92:982-985. 5. Ettingshausen CE, et al. *Thromb Haemost.* 2001;85:218-220. 6. Shetty S, et al. *Br J Haematol.* 2007;138:541-544. 7. Sehgal A, et al. *Nat Med.* 2015;21:492-497. 8. Pasi KJ, et al. *Blood* 2016;128:1397. 9. Ragni MV, et al. *Blood.* 2016;128: 2572. 10. Pasi KJ, et al. *N Engl J Med.* 2017;377:819-828. 11. Alnylam Pharmaceuticals. Investigator's Brochure: Fitusiran (ALN-AT3SC) 5th ed. 2017

Tissue Factor Pathway Inhibitor (TFPI)



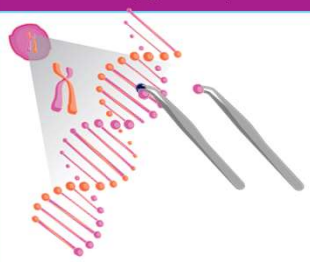
Anti-TFPI antibody against K2 domain
Concizumab and PF-06741086 from Pfizer

Anti-TFPI antibody against K1 and K2 domains
BAY-1093884 from Bayer

Shapiro AD, et al. *Blood.* 2019;134:1973-1982.

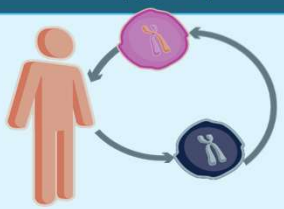
The Ultimate Goal Is Cure…

GENE EDITING (eg, CRISPR)



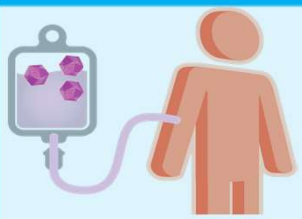
Repairing or replacing a mutated gene[1]

CELL THERAPY (eg, CAR-T)



Introducing a functional (working) gene into cells that are then delivered into the body[2,3]

GENE TRANSFER (eg, vector-based delivery)



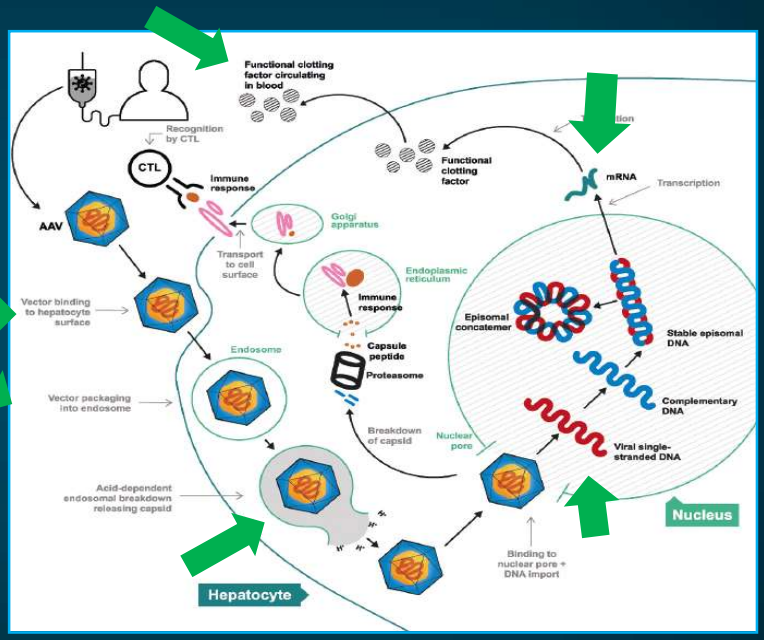
Introducing COPIES of the working, or functional, gene into the body[2,4]

CAR-T = chimeric antigen receptor T-cell therapy; CRISPR = clustered regularly interspaced short palindromic repeats.

1. Dunbar CE, et al. *Science*. 2018;359:eaan4672. 2. Collins M, Thrasher A. *Proc Biol Sci*. 2015;282:20143003. 3. American Society of Gene and Cell Therapy. (www.asgct.org/education/more-resources/glossary). 4. US National Institutes of Health (NIH) (https://ghr.nlm.nih.gov/primer/therapy/genetherapy). Graphic from hemdifferently.com

Gene Transfer…

- Viral vector binds to the target cell
- It is internalized via endocytosis
- Transgene is released and capsid degraded
- Transgene forms a concatemer
- This allows sustained transgene expression in this non-dividing cell without damaging the host cell



What happens to the package upon delivery?

The contents of the package are kept inside the liver cells, and the packing materials are recycled

Sometimes, the immune system can recognize packing materials as unnatural, and can stop subsequent packages from being successfully delivered

AAV = adeno-associated virus; CTL = cytotoxic T lymphocyte; mRNA = messenger RNA.

Current Phase 3 Gene Therapy Trials

Anticipate potentially 2 approved gene therapy products by 2023….

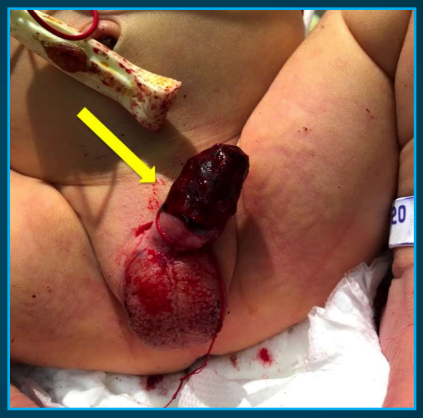
Name	Clinical Target	AAV Serotype (transgene)	NCT Number (sponsor)	Phase 1/2 Study References
Valoctocogene roxaparvovec (BMN270)	Hemophilia A	AAV5 (BDD-FVIII)	NCT03370913 (Biomarin)	Pasi et al
(SPK-8011)	Hemophilia A	Bioengineered capsid (BDD-FVIII)	NCT03432520 (Spark Therapeutics)	High et al
Etranacogene dezaparvovec (AMT-061)	Hemophilia B	AAVS (FIX Padua)	NCT03569891 (uniQure)	Von Drygalski et al
Fidanacogene elaparvovec (PF-06838435)	Hemophilia B	Bioengineered capsid (FIX Padua)	NCT03861273 (Pfizer)	George et al

BDD = B domain deleted.

Pipe SW.. *Haemophilia* 2021;27(suppl 3): 114-121. Studies in the table: Pasi KJ, et al. *N Engl J Med.* 2020:382:29-40. High KA, et al. *Blood.* 2018;132(suppl 1): 487. Von Drygalski A, et al. *Blood Adv.* 2019;3:3241-3247. George LA, et al. *N Engl J Med.* 2017;377:2215-2227.

Case 1—Presentation and History

- 12-day old male presents to ED with persistent oozing from circumcision site x 3 days
  - s/p silver nitrate x 1 at PHP office
  - Urology evaluation on 1st ED visit → application of surgiseal
- NBH/PSH—FT at 39 weeks, NSVD, no instrumentation use. Circumcision at DOL 2.
- Family hx—Mom is adopted but noted heavy menstrual bleeding, easy bruising, and nosebleeds. No bleeding history on father's side.
- DDx?

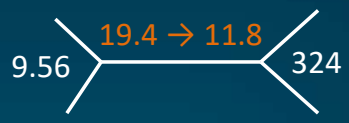


s/p = status post; PHP = primary healthcare provider; NBH/PSH = newborn history/past surgical history; FT = full term; NSVD = normal spontaneous vaginal delivery; DOL = day of life; hx = history; DDx = differential diagnosis.

Mense L, et al. *Cureus.* 2018;10:e3324.

Case 1—Evaluation

- **Pertinent exam findings**
  - Vital signs stable
  - Well appearing male
  - AFOSF, hematoma at occiput
  - No hematoma at sites of IM injections
  - Soaked gauze over penis
- **Labs**



  - PT = 13.3, INR = 1, **aPTT = 98s**
  - Fibrinogen = 180
  - Given vitamin K
  - FFP ordered but…
  - **Factor 8 = <1%**
  - Factor 9 = 30%

- **Diagnosis—Severe hemophilia A** (factor 8 deficiency)

AFOSF = anterior fontanelle open soft and flat; IM = intramuscular; PT = prothrombin time; INR = international normalized ratio; aPTT = activated partial thromboplastin time; FFP = fresh frozen plasma.

Case 1—Treatment Course

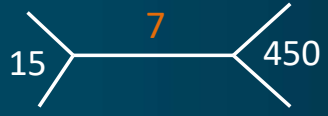
- Admitted to Heme/Onc service
- Received rFVIII infusion (factor 8 replacement) on HD #1
- Additional rFVIII infusion given on HD #2 due to mild oozing noted
- Resolution of circumcision bleeding and hematoma with factor infusions prior to discharge
- Negative head U/S for bleed
- Discharged home on ferrous sulfate with follow-up in our clinic

Heme/Onc = hematology/oncology; rFVIII = recombinant (coagulation) factor 8; HD = hospital day; U/S = ultrasound.

Case 1—Continuation at 9 Months

- Now 9 months of age, the patient is diagnosed with severe hemophilia A (FVIII <1%)
- He presents with "fussiness" and poor feeding
- ***He received 5 previous doses of rFVIII***
- Pertinent ED exam findings
  - Hypertensive
  - Ill-appearing male infant
  - Pale, poorly responsive

- Labs
  - –PT = 13.3; **aPTT = 98s**
  - **–Factor 8 = <1%**



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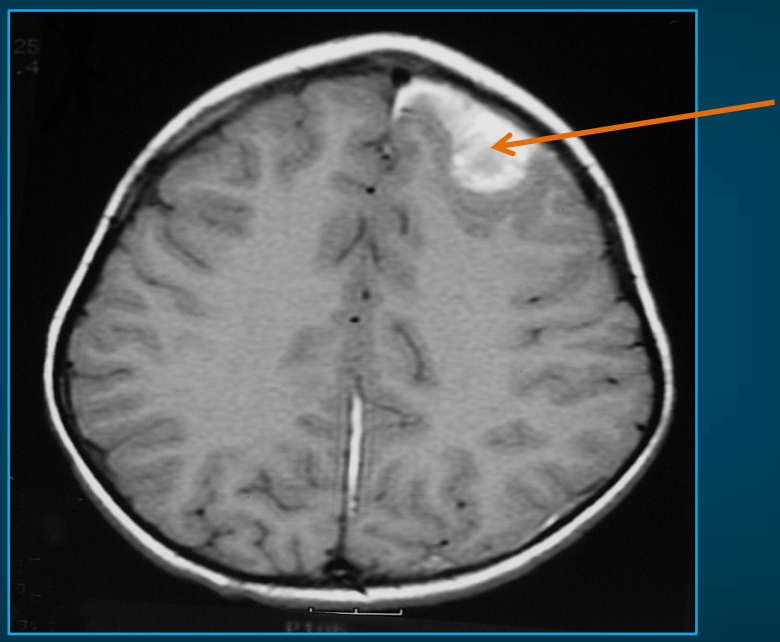
Subdural Hemorrhage



Case 1—Treatment at 9 Months

- 9-month-old male with severe hemophilia A with newly diagnosed inhibitor
  - 15 BU/mL
- **Treatment**
  - Admitted from ED
  - rFVIIa 90 mcg/kg/dose Q2H initially, then slowly transitioned to daily after 7 days to complete 2-week course
  - Place CVAD
  - Subsequently placed on emicizumab

CVAD = central venous access device.

Questions?

Thank you!

Advances in the Therapeutic Management of Patients with Chronic Hematological Conditions – A Whiteboard Preceptorship

Pathophysiology of Sickle Cell Disease

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