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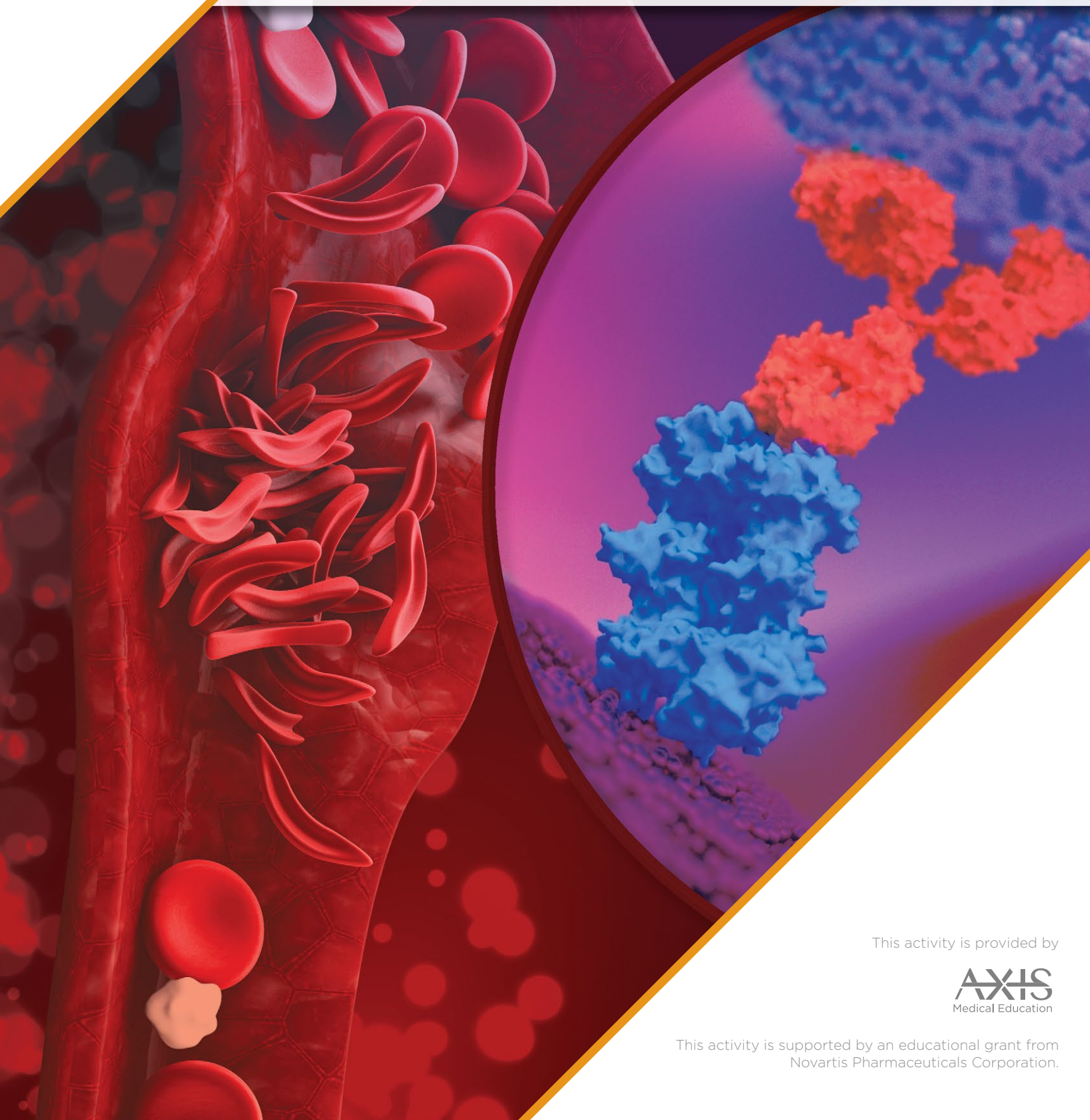
Improving Interprofessional Management of Sickle Cell Disease (SCD) with Disease-Directed Therapies

This transcript has been edited for style and clarity and includes all slides from the presentation.



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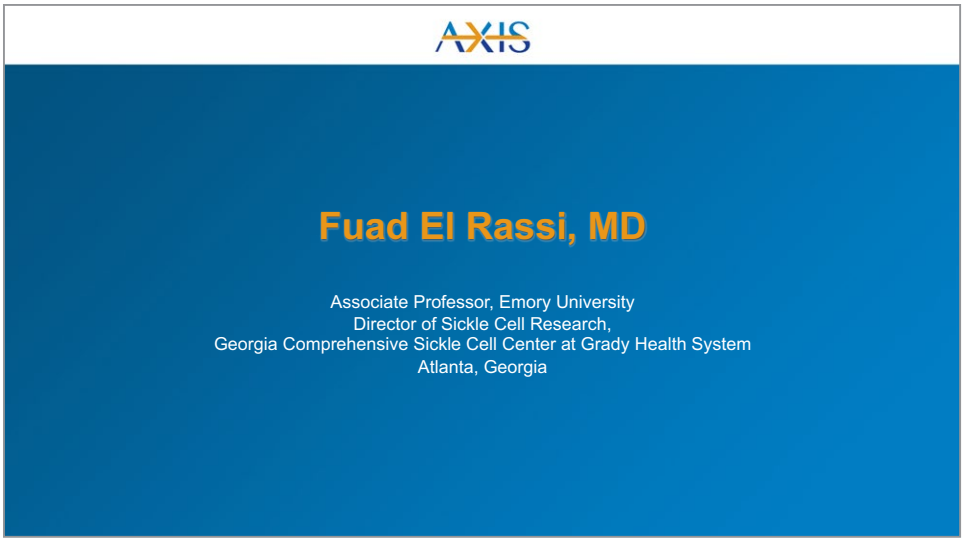
This activity is supported by an educational grant from Novartis Pharmaceuticals Corporation.

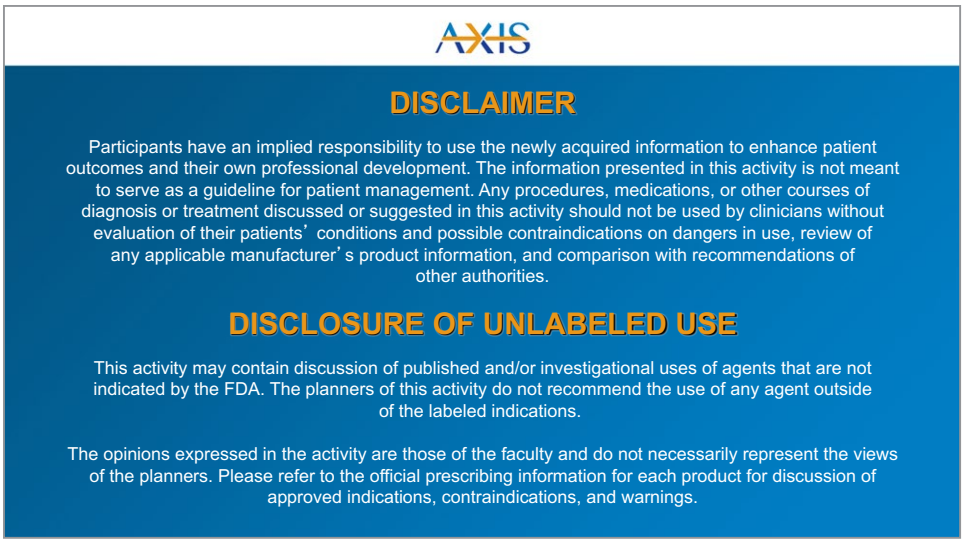
Improving Interprofessional Management of Sickle Cell Disease (SCD) with Disease-Directed Therapies

Fuad El Rassi, MD

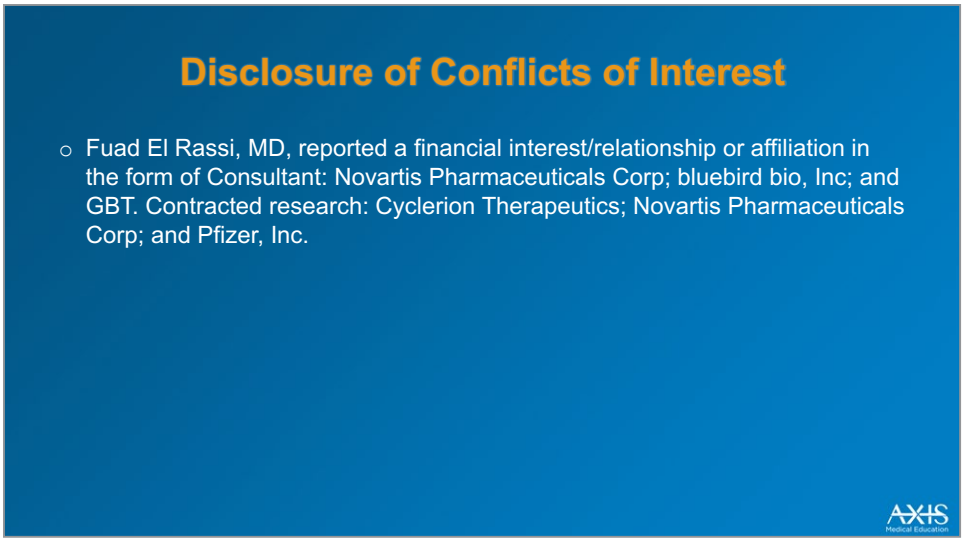
Fuad El Rassi, MD:
Hello and welcome to this educational activity entitled "Improving Interprofessional Management of Sickle Cell Disease with Disease-Directed Therapies."



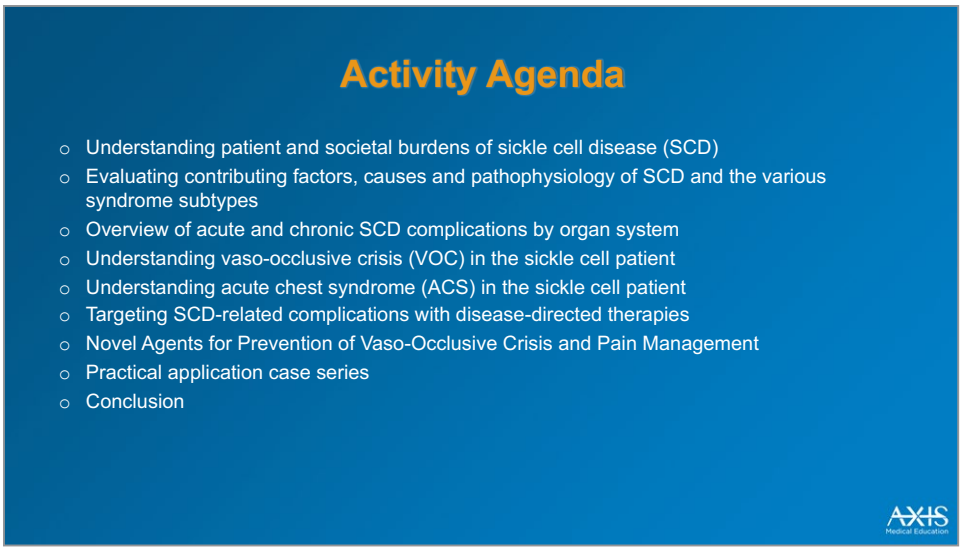
I am Dr. Fuad El Rassi, Associate Professor of Hematology and Medical Oncology at Emory University and Director of the Sickle Cell Research Center at the Georgia Comprehensive Sickle Cell Center at Grady Health System in Atlanta, Georgia.



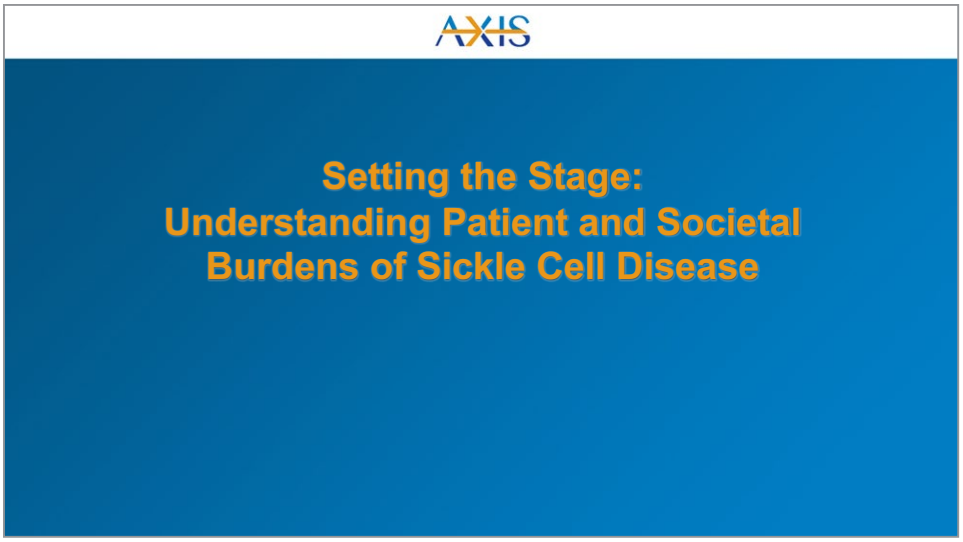
- First, a disclaimer and disclosure indicating that we may be discussing off-label use of approved agents or agents that are in development.



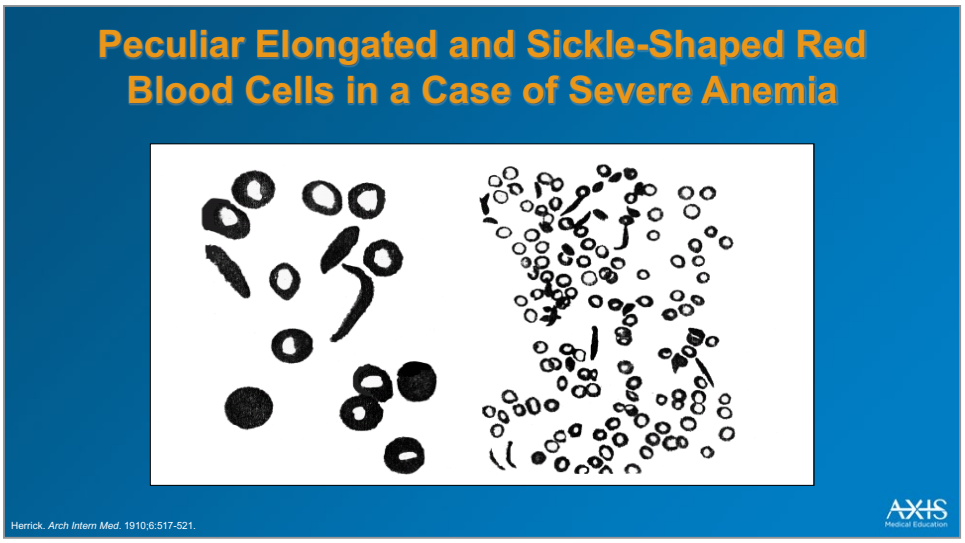
- And then my financial disclosure information.



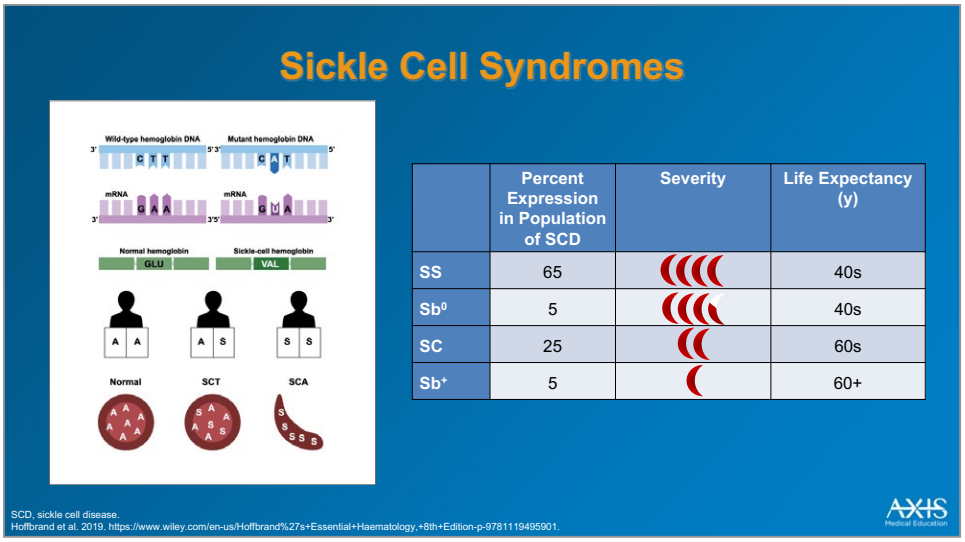
- During this activity, we will look at the burden of sickle cell disease and the latest safety and efficacy data for novel SCD therapies. We will also review how to use these options to manage the symptoms of sickle cell disease and prevent and treat its complications including vasoocclusive pain episodes and acute chest syndrome.



- Setting the Stage: Understanding Patient and Societal Burdens of Sickle Cell Disease.



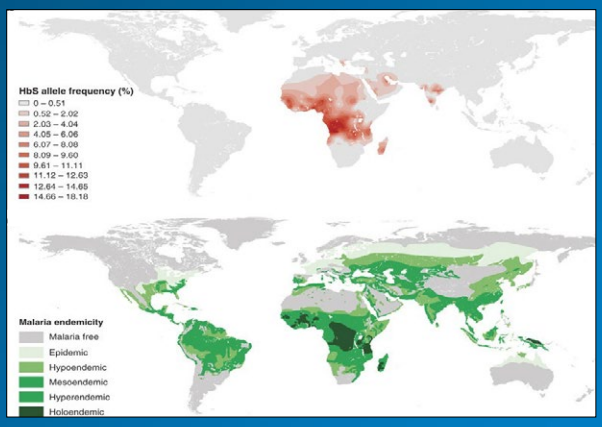
- Sickle cell disease was first coined in 1910. And it was noted on a blood smear obtained from a patient who was a medical student at the University of Chicago. The red blood cells were described as peculiar, elongated, and sickle-shaped with severe anemia. Since then, there has been much more understanding about sickle cell disease.



	Percent Expression in Population of SCD	Severity	Life Expectancy (y)
SS	65		40s
Sb^0	5		40s
SC	25		60s
Sb^+	5		60+

- We know that a single point mutation at the sixth codon of the beta globin chain replacing glutamate with valine leads to the inheritance of the sickle gene and in individuals who have the gene, they need to have two expressions of this gene to have sickle cell disease as we know it. A single expression of one gene from one of the parents will give you sickle cell trait. Compared to the population of different genotypes of sickle cell disease, the percent expression of SS disease is about 65% of the population, the SC disease population is 25%, and then the Sß0 thalassemia and Sß+ thalassemia are both at 5%. And these populations correlate with the severity of the disease as we know, right now, with SS disease being the most severe and Sß+ thalassemia being the least severe. Life expectancy is accordingly correlated with the severity of the disease.

Global Distribution of the Sickle Cell Gene



Piel et al. *Nat Commun*. 2010;1:104.

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- The global distribution of the sickle cell gene is seen in this graph. We notice than in sub-Saharan Africa and in the Indian peninsula and in Arabia, we see a lot of the sickle gene, and this goes along with the malaria endemicity map shown here that correlates with malaria transmission.

United States Sickle Cell Disease Population

Calculation based on birth prevalence and census data, correcting for early mortality:

- Total: ~100,000 individuals
  - 60% adults (at least)
  - 90% Black
  - 10% Hispanic
- Genotype distribution in the United States
  - At birth: HbSS 60%; HbSC 30%; HbSβ-thalassemia 10%
  - In adulthood:
    - At age 30: HbSS 50%
    - At age 60: HbSS 25%

HbSS, sickle cell anemia; HbSC, sickle cell with hemoglobin C disease; HbSβ, hemoglobin S-beta.
Hassell et al. *Am J Prev Med*. 2010;38:S512; Brousseau et al. *Am J Hematol*. 2010;85:77.

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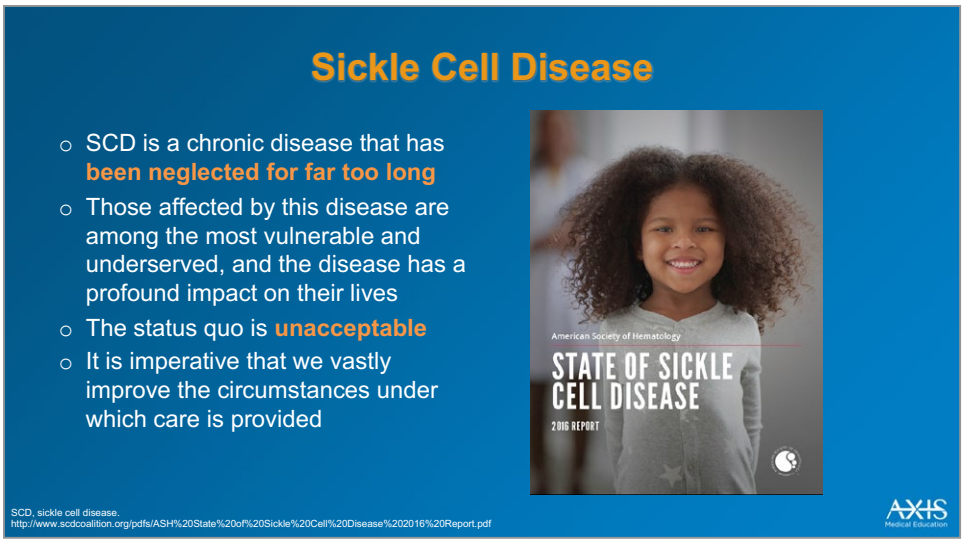
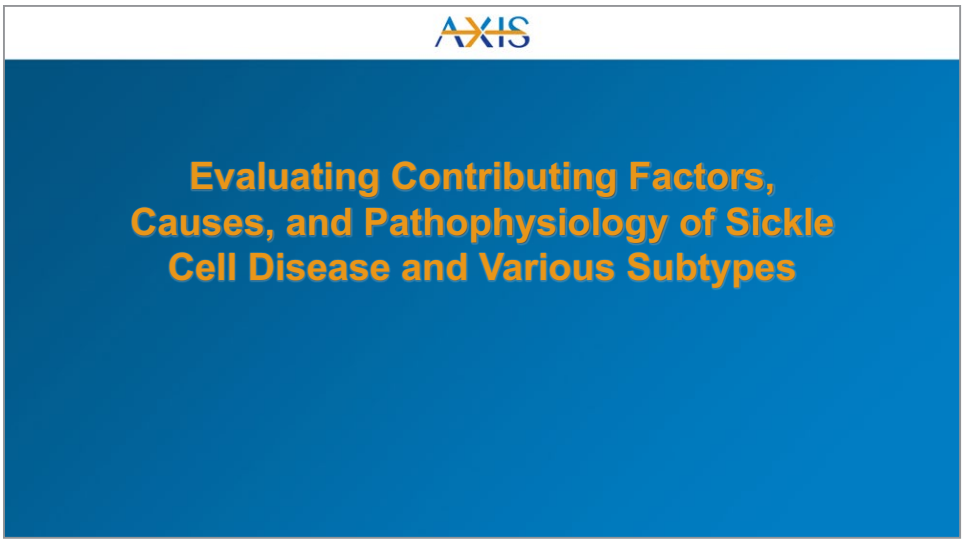
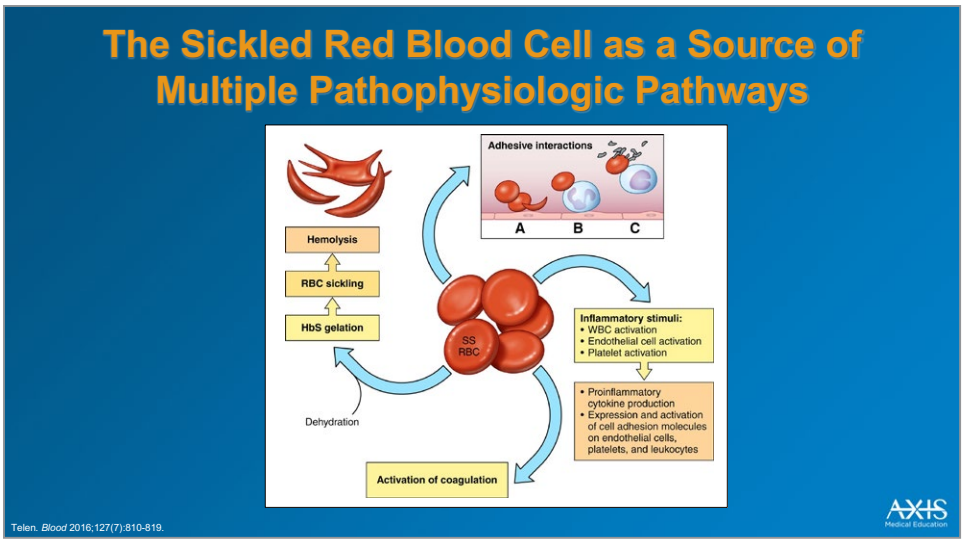
- In the United States, the sickle cell disease population is estimated at around 100,000 individuals, 60% adults, 90% black, and 10% Hispanic. The genotype distribution in the United States at birth shows that 60% of patients have SS disease, 30% have SC disease, and 10% have Sß thalassemia; in adulthood at age 30, 50% of the patients have SS and at age 60, 25% of the patients have SS disease.



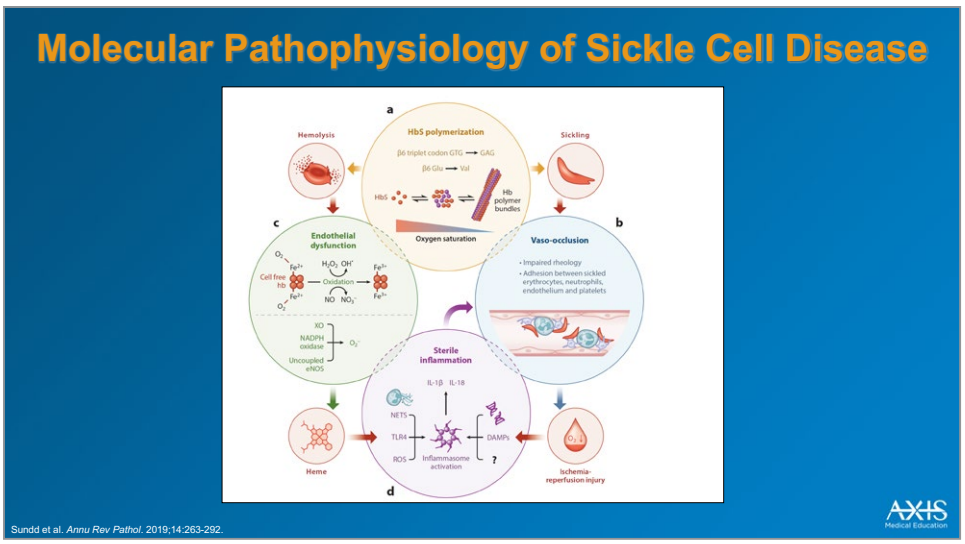
- Sickle cell disease is a chronic disease that has been neglected for far too long. Those affected by the disease are among the most vulnerable and underserved populations, and the disease has a profound impact on their lives. The status quo is unacceptable. It is imperative that we vastly improve the circumstances under which care is provided for patients with sickle cell disease; this was all based on the 2016 report on the state of sickle cell disease from the American Society of Hematology.



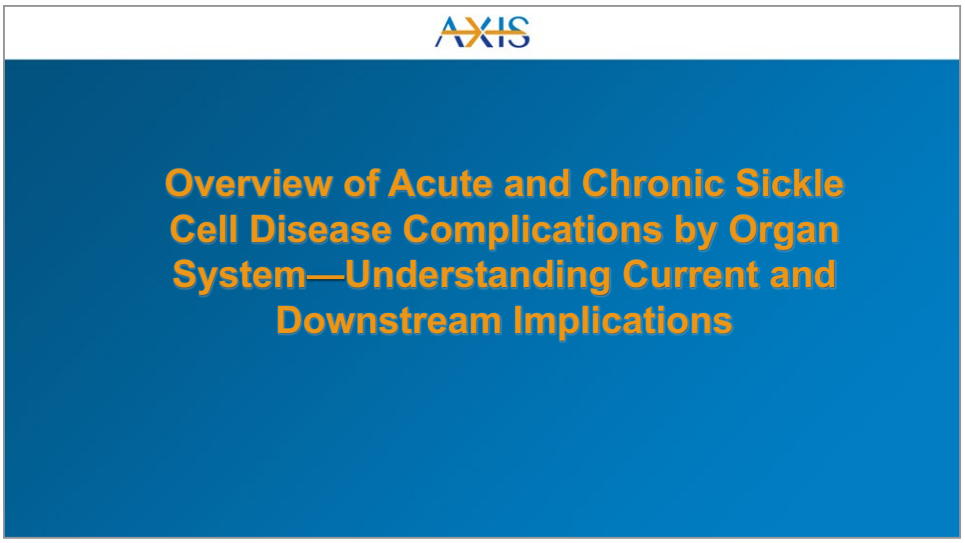
- Evaluating Contributing Factors and Causes and the Pathophysiology of the Sickle Cell Disease in Various Subtypes.



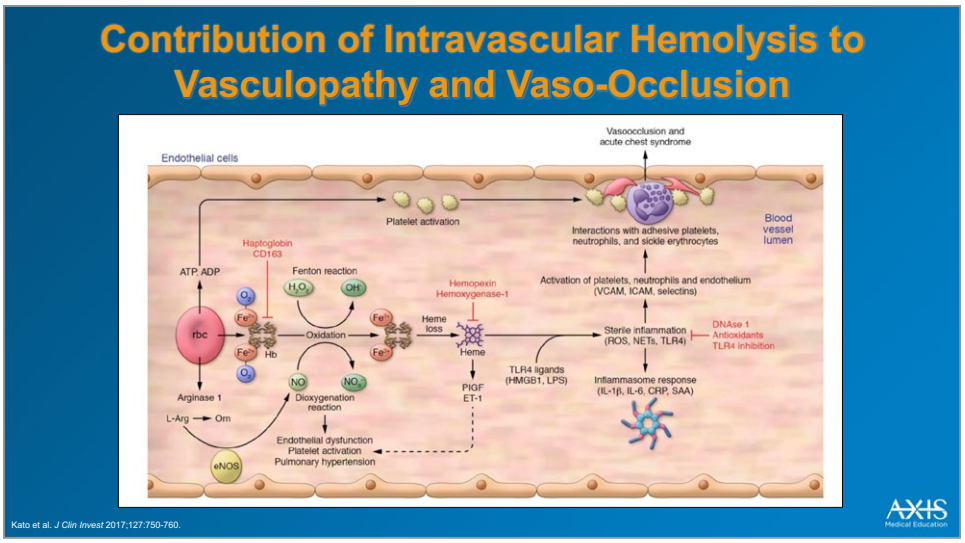
- Looking at sickle cell disease, there are multiple pathophysiologic pathways that are involved. This graph shows a vicious cycle of hemolysis that's caused by the destruction of the red cells because of their shortened lifespan. This leads to the activation of adhesive interactions between the red cells, the platelets, and the endothelium that propagates and drives the inflammatory stimulus that leads to further activation of endothelial cells, platelets, and white blood cell activation, leading to more inflammation, activation of coagulation, and adding more to this vicious cycle of hemolysis and activation of the cells.



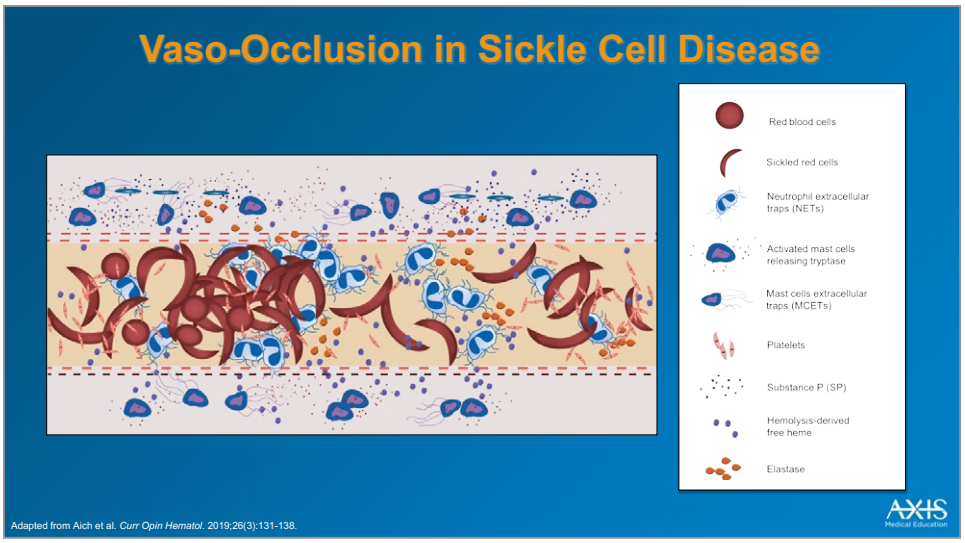
- However, the molecular pathophysiologic outline of sickle cell disease is even much more complicated. We know that hemoglobin S polymerization is at the root cause of sickle cell disease. And in fact, it drives the two other hand-in-hand mechanisms that are involved: hemolysis and sickling. Hemolysis leads to endothelial dysfunction by leading to a state of nitric oxide consumption and reduction and leads to free heme, which is causing the sterile inflammation in the circulation. And sickling itself also leads to the vasoocclusion and the impaired rheology or blood flow of the sickled red blood cells, leading to further adhesion interaction with the white cells, platelets, and the endothelium, leading to more ischemia re-perfusion injury, all leading back to the sterile inflammation. More information about the molecular pathophysiology of sickle cell disease is being deciphered.



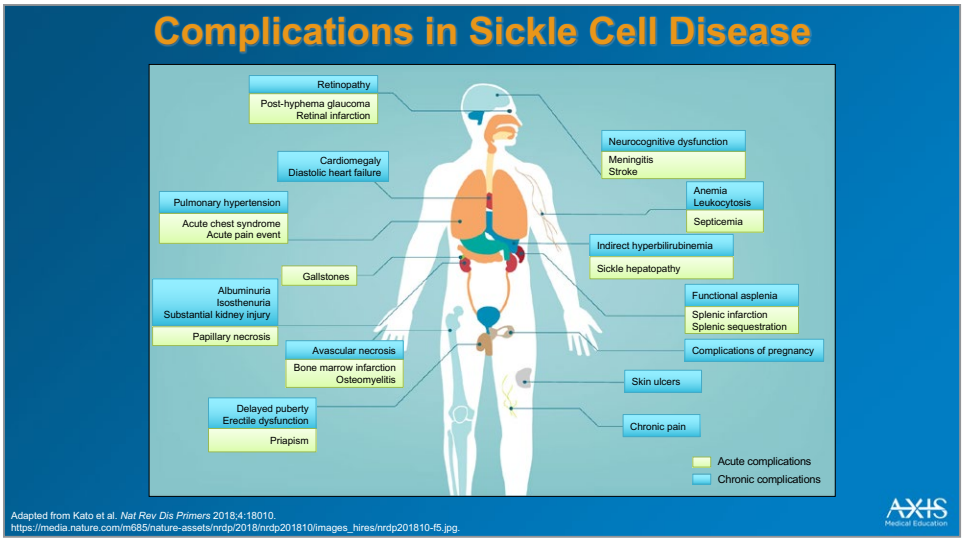
- Overview of Acute and Chronic Sickle Cell Disease Complications by Organ System: Understanding Current and Downstream Implications.



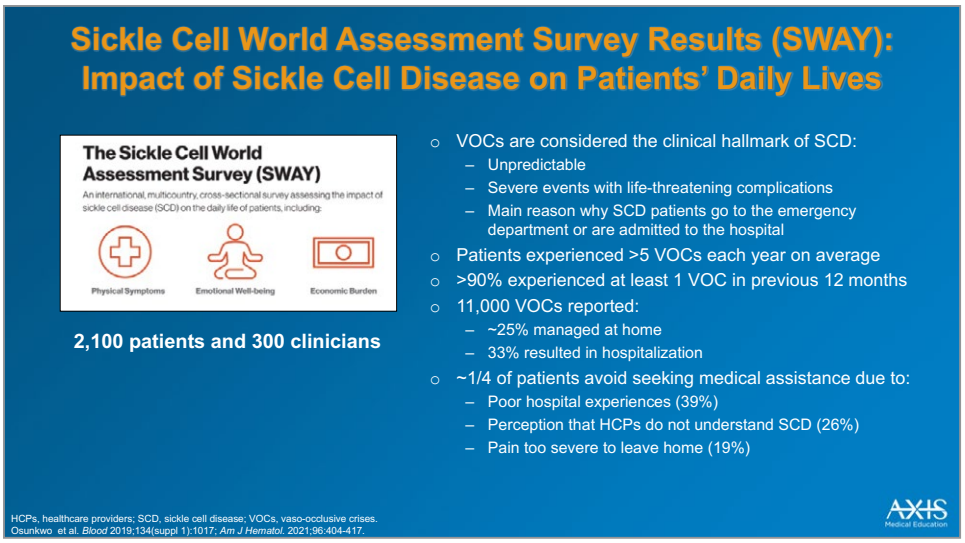
- When you look at the contribution of intravascular hemolysis to vasculopathy and vasoocclusion, the molecular pathway is so detailed that many different factors are involved and there are so many different targets that can be affected by hemolysis from having haptoglobin as a target or hemopexin as a target or even the different antioxidants related to be a target to help reduce hemolysis and the cycle of sickle cell disease.



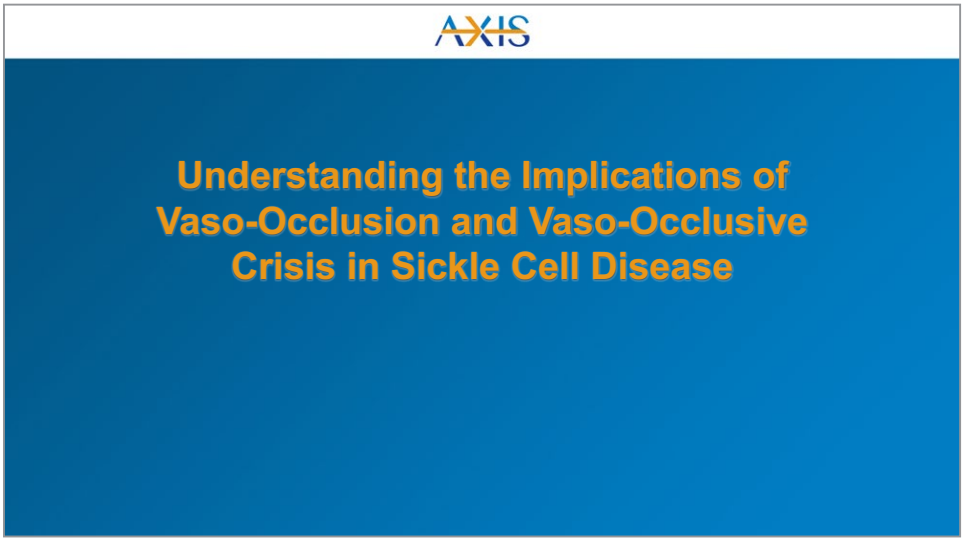
- In addition, vasoocclusion is a key aspect in the activation of the sickle cell painful events. Vasoocclusion is summarized in this graphic showing the red blood cells interacting with the sickled red blood cells, the neutrophils, the platelets, and the endothelium, all going hand-in-hand with what we call activation of the selectin pathway to lead to further propagation of vasoocclusion in sickle cell disease.



- Both mechanisms of hemolysis and vasoocclusion lead to a combined multitude of complications in sickle cell disease, as seen here, where you can have acute and chronic complications that can happen in the patients with sickle cell disease. These complications can vary from retinopathy, cardiomegaly, and diastolic heart failure to pulmonary hypertension, albuminuria, avascular necrosis, chronic pain, functional asplenia, anemia, and neurocognitive dysfunction in the chronic sense, to acute events such as acute stroke, sickle cell hepatopathy, chest syndrome in acute painful events, bone marrow infarction, priapism, and splenic sequestration in the acute events that can happen.



- The combination of these complications that arise in sickle cell disease leave the patient with sickle cell disease suffering a lot. The Sickle Cell World Assessment Survey results showed the impact of sickle cell disease on the patient's daily lives. Vasoocclusive crises (VOCs), which are considered the hallmark of sickle cell disease, are quite unpredictable. They lead to severe events with life-threatening complications and they're the main reason why sickle cell disease patients go to the emergency department or are admitted to the hospital. On average, patients experience more than five VOCs each year, and more than 90% experience at least one VOC in the previous 12 months. In this survey of 2,100 patients and 300 clinicians, there were 11,000 VOCs reported and 25% of those were managed at home, 33% resulted in a hospitalization, and a quarter of the patients avoid seeking medical assistance due to poor hospital experiences or poor perception by healthcare professionals or the pain being too severe for them to leave home.



- Understanding the Implications of Vasoocclusion and Vasoocclusive Crisis in Sickle Cell Disease.

Pain: The Hallmark of SCD

- Primary reason people seek care
- Secondary to vaso-occlusion
- Present throughout life

NOT ALL PAIN IS VOC PAIN

NOT ALL PAIN IS SCD PAIN

SCD, sickle cell disease; VOC, vaso-occlusive crisis.
Artwork used with permission Hertz Nazire.

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- Pain is the hallmark of sickle cell disease. It is the primary reason people seek care and it is because of vasoocclusion and it is present throughout the life of the patient with sickle cell disease. This drawing depicts how patients really experience the pain in sickle cell disease and how it affects and has a huge impact on their lives. However, what we have to remember is that not all pain is VOC pain and not all pain is sickle cell disease–related pain.

VOCs – What Are They, and Why Do They Occur?

- Normal RBCs are doughnut-shaped and flexible, rolling through the vasculature supplying oxygen and nutrients to the body[1]
- RBCs with sickle cell hemoglobin have different properties and are more likely to stick to the cells (endothelium) on the inside of the blood vessel
- WBCs and activated endothelial cells can also trigger adhesive interactions with sickled RBCs, other WBCs, and platelets due to chronic vascular damage[3]
- Blockage of small blood vessels results in vaso-occlusion
- VOCs: Recurrent episodes of vaso-occlusion can lead to severe unpredictable acute pain that may require hospitalization[2-5]

RBCs, red blood cellsVOCs, vaso-occlusive crises; ; WBC, white blood cells.
1. CDC. https://www.cdc.gov/dotw/sickle-cell-disease/. 2. Rees et al. *Lancet* 2010;376(9757):2018-2031. 3. Piel et al. *N Engl J Med*. 2017;376:1561-1573.
4. Zhang et al. *Blood* 2016;127(7):801-809. 5. Habara and Steinberg. *Exp Biol Med*. 2016;241(7):689-696.

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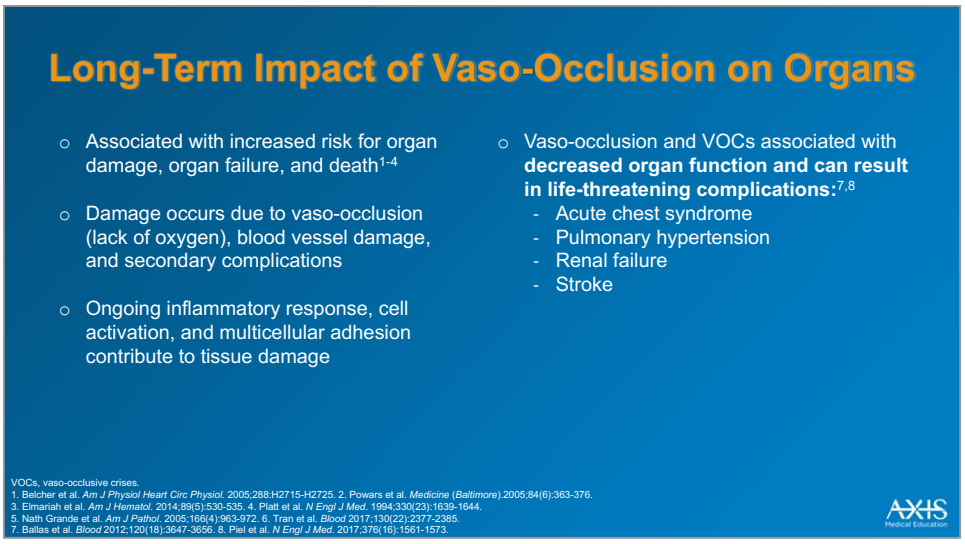
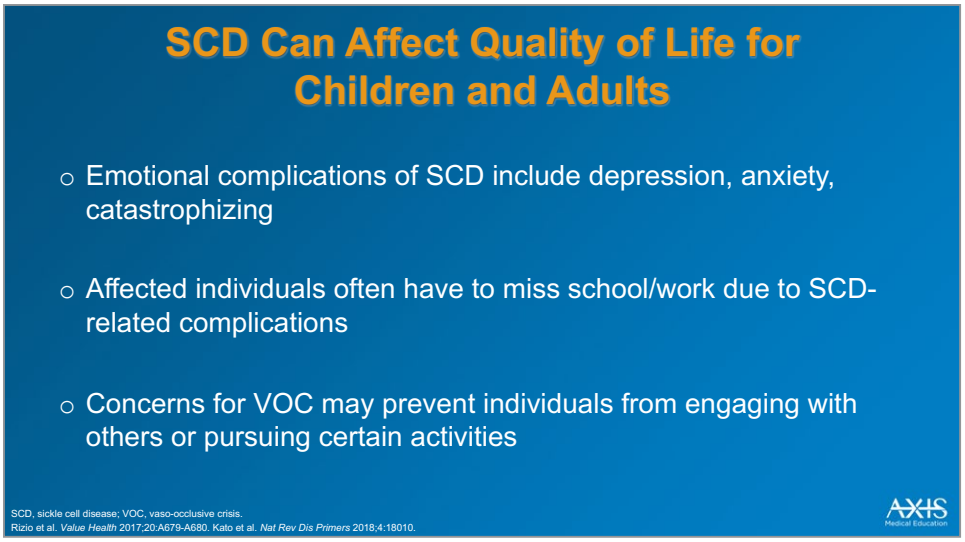
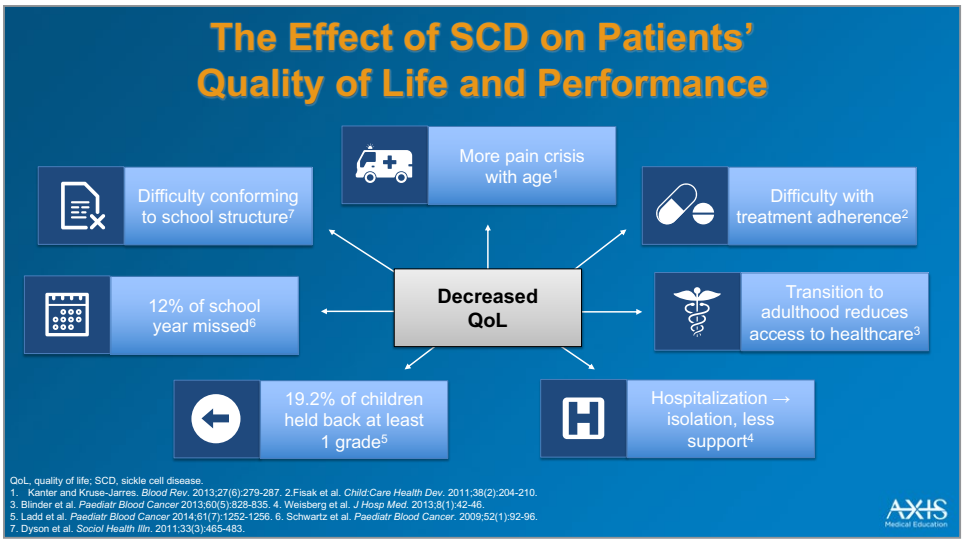
- So, VOCs, what are they? What do they do? Why do they occur? Normal red blood cells are donut-shaped red blood cells; they're flexible, they roll through the vasculature and the supply oxygen and nutrients to the body. The red blood cells with sickled hemoglobin have different properties; they're more sticky, they can interact with the endothelium and lead to activation of the different vasoocclusive events by interacting with the blood vessels. The white blood cells and activated endothelial cells can also trigger adhesive interactions with sickled red blood cells, other white blood cells, and platelets due to chronic vascular damage. Blocking the small blood vessels results in vasoocclusion and VOCs are the recurrent episodes of vasoocclusion that can lead to severe, unpredictable, acute pain that may require hospitalization.



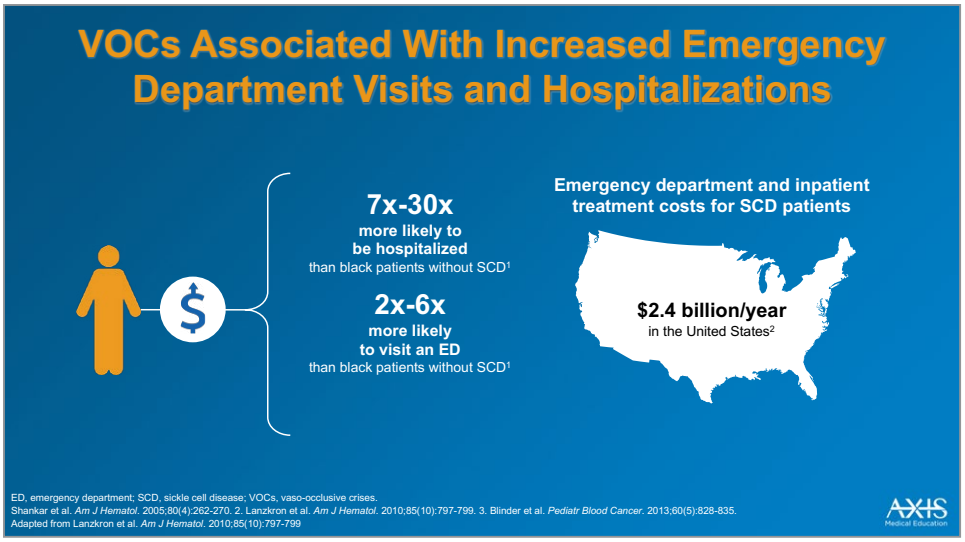
- The long-term impact of vasoocclusion on organs is huge. Ongoing vasoocclusion and VOCs are associated with an increased risk for organ damage, organ failure, and death. Damage occurs due to vasoocclusion, leading to lack of oxygen, blood vessel damage, and secondary complications. Ongoing inflammatory response, cell activation, and multi-cellular adhesion contribute to the tissue damage. Vasoocclusion and VOCs are associated with decreased organ function and can result in life-ending complications, such as acute chest syndrome, pulmonary hypertension, renal failure, and stroke.



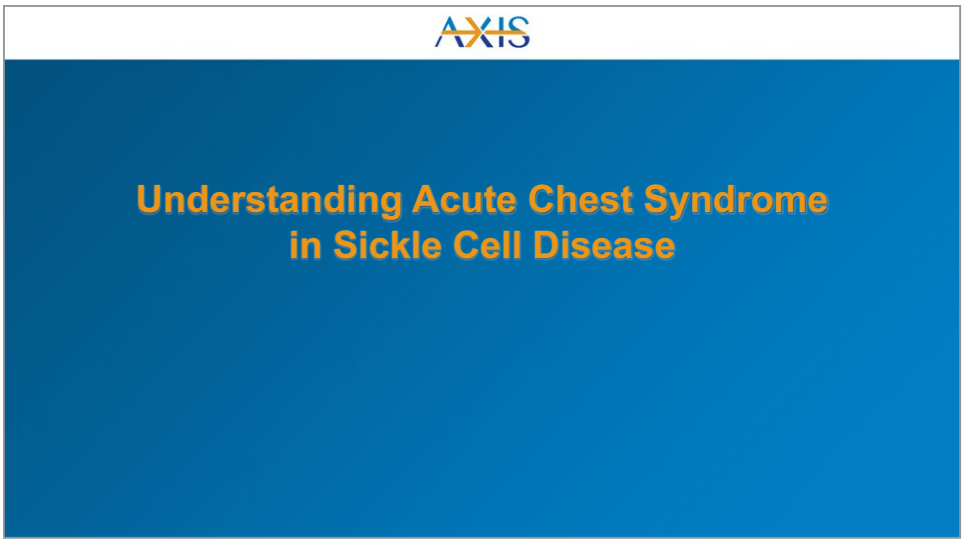
- Sickle cell disease can affect the quality of life of children and adults. Emotional complications of sickle cell disease include depression, anxiety, and catastrophizing. Affected individuals often have to miss school or work due to sickle cell disease–related complications. And the concern for VOC may prevent individuals from engaging with others or pursuing certain activities.



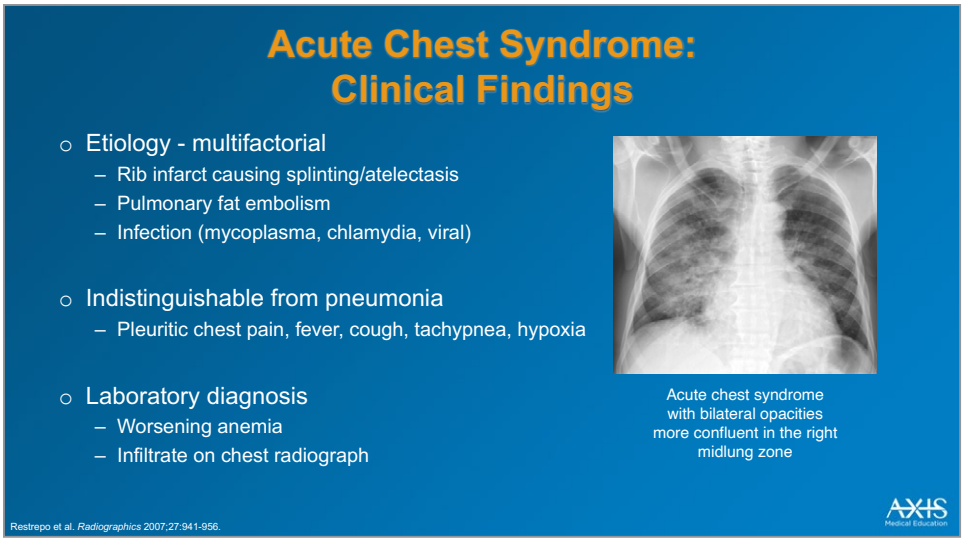
- The effect of the sickle cell disease on the patients' quality of life and performance is shown here. At the center of this graphic, we see decreased quality of life for the patients, which leads to more pain, more pain crises as they age, difficulty with treatment adherence, difficulty to transition to adulthood due to lack of access to healthcare, more hospitalization, more isolation, and less support. More missed time at school and in fact, 12% of the school year could be missed in children with sickle cell disease, and 19.2% of children are held back by at least one grade because of this disease.



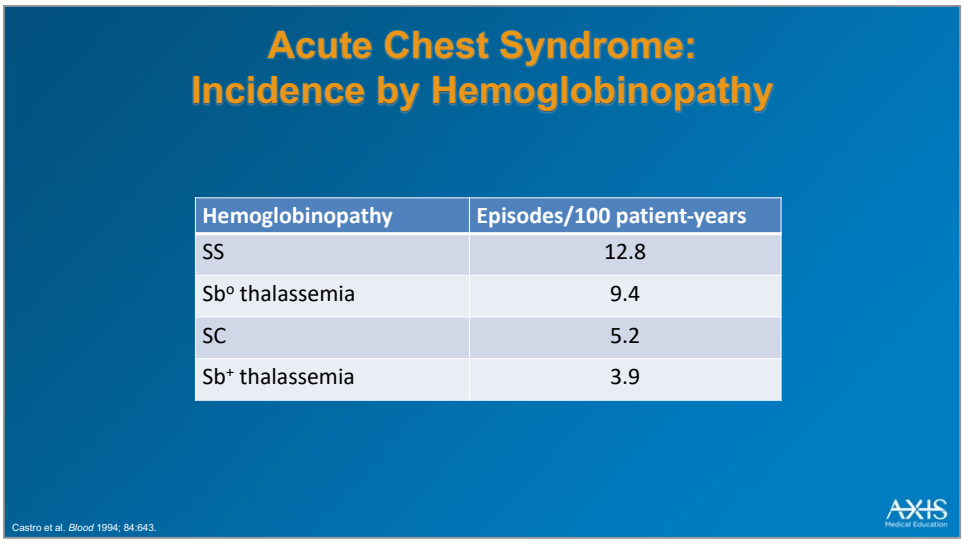
- In the United States, VOCs are associated with an increase in emergency department visits and hospitalizations. In fact, patients with sickle cell disease are seven to thirty times more likely to be hospitalized than patients without sickle cell disease and two to six times more likely to visit an emergency department than comparable patients without sickle cell disease. And emergency department and inpatient treatment cost for sickle cell disease is estimated to be 2.4 billion dollars a year in the United States.



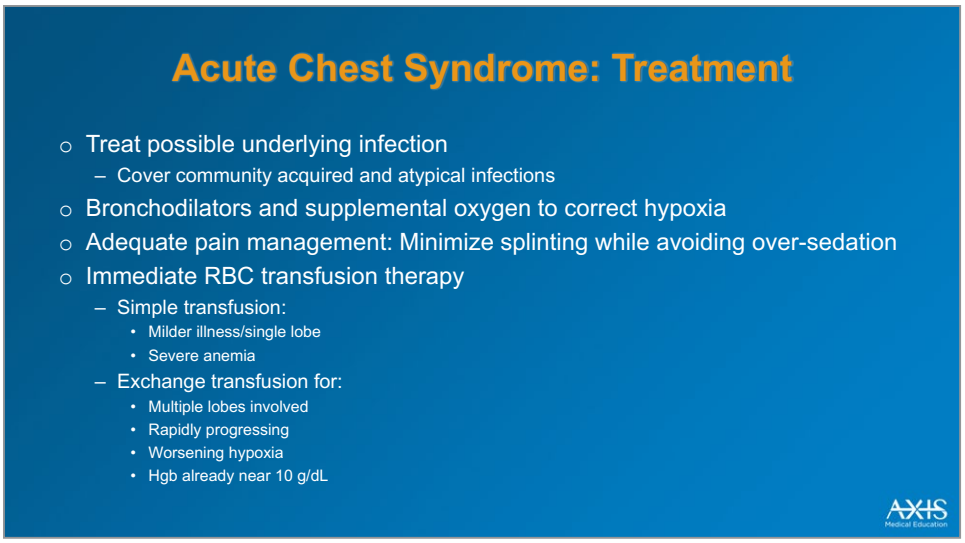
- Understanding Acute Chest Syndrome in Sickle Cell Disease.



- Acute chest syndrome is one of the most feared complications that can be tackled in the setting of an acute painful event in a patient with sickle cell disease. Clinical findings are typical of a pneumonia picture. You'll see an infiltrate on a chest radiograph, you'll have a fever, and hypoxia, as well, and the etiology is typically multi-factorial. Could be because of a rib infarct causing splinting and atelectasis in a patient with sickle cell disease. Could be due to pulmonary fat embolism happening in the setting of a multi-organ failure, or could be due to infection because of mycoplasma and chlamydia, viral, or whatnot. It's definitely indistinguishable from pneumonia because the clinical symptoms that are experienced, pleuritic chest pain, fever, cough, tachypnea, hypoxia, are identical. Laboratory diagnosis reveals a worsening anemia and an infiltrate on chest radiograph.

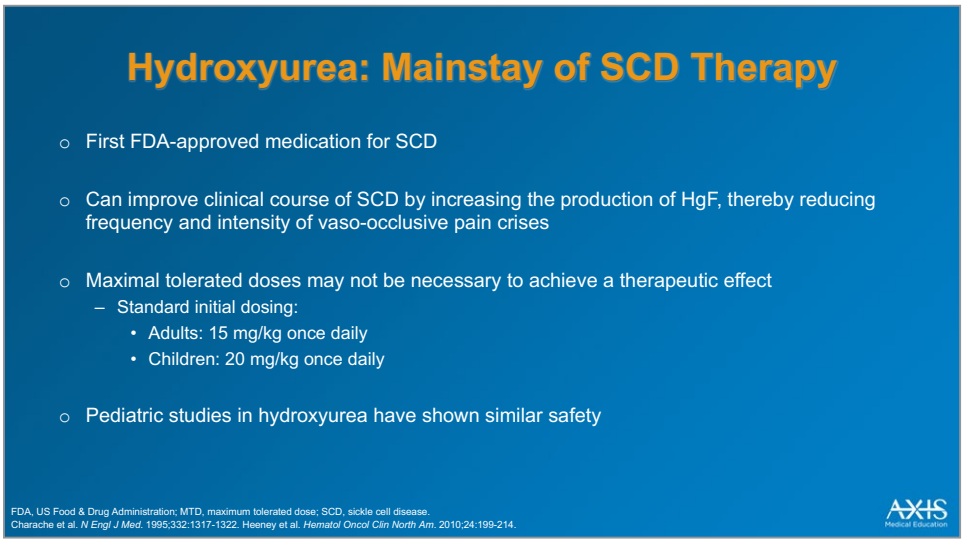


- Acute chest syndrome incidence varies according to the different genotypes. SS disease, which is the most severe genotype is reported at about 12.8 episodes per 100 patient years. Sß0 is less as 9.4, SC 5.2, and the Sß+ thalassemia population experiences it about 3.9 episodes per 100 patient years.



- For the treatment of acute chest syndrome, we start with treating a possible underlying infection. We cover community-acquired pneumonias and atypical infections. You can use bronchodilators and supplemental oxygen to correct the hypoxia. You can also use adequate pain management to minimize splinting while avoiding oversedation. Immediate RBC transfusion therapy is definitely recommended and that can come in two different forms. In the milder, single-lobe, milder illness of acute chest, you can consider a simple transfusion especially if the clinical setting shows a severe anemia where a simple transfusion is possible. But in the more complicated, multi-lobe involvement with acute chest especially if the patient is rapidly progressing with a worsening hypoxia and a hemoglobin already concentrated between 9 and 10 g/dL, an exchange transfusion is crucial and should happen immediately to prevent high mortality in that situation.

- Targeting SCD-Related Complications with Disease Directed Therapies.



- Hydroxyurea remains the mainstay of sickle cell disease therapy. It was the first FDA-approved medication for sickle cell disease and it works by improving the clinical course of the disease by increasing the production of fetal hemoglobin, thereby reducing frequency and intensity of the vasoocclusion and vasoocclusive pain crisis. Maximal tolerated dose of hydroxyurea may not be necessary to achieve a therapeutic effect. Standard initial dosing starts for adults at 15 mg/kg once a day and for children it starts at 20 mg/kg once a day. The dose may be increased by 5 mg/kg per day every 8 to 12 weeks until a maximum tolerated dose of 35 mg/kg daily is reached or the blood counts start to show a drop in the white count, platelet, or reticulocyte count and remaining at an acceptable range. Pediatric studies in hydroxyurea have shown similar safety to adult studies in terms of dose titration and although it's very effective, hydroxyurea is not universally accepted among patients and providers.

Multicenter Hydroxyurea Trial

Group	Hydroxyurea	Placebo	*P*
Pain Episodes	2.5/y	4.5/year	<.001
Pain Admits	1.0/y	2.4/year	<.001
Acute Chest	25 episodes	51 episodes	<.001
Transfused	48	73	<.001
Total Units	336	586	.004

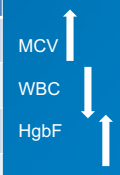
Charache et al. *N Engl J Med*. 1995;322:1317.

- The multi-center hydroxyurea trial from 1995 reveals patients on hydroxyurea had significantly fewer pain episodes per year compared to placebo, fewer admissions to the hospital per year as compared to placebo, fewer acute chest episodes, fewer transfusions, and fewer total number of transfused blood units.

Hydroxyurea

Laboratory Effects of Hydroxyurea Treatment

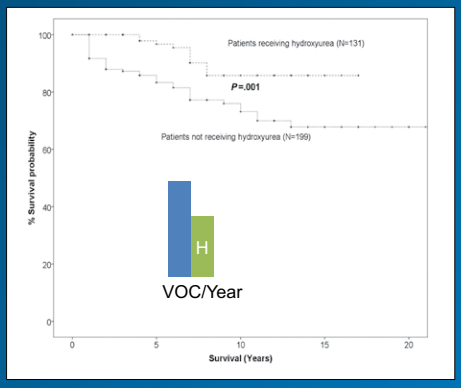
Variable	Change from Month 0 to Month 12 (95% CI)
Hemoglobin (g/dL	+1.0 (0.8-1.0)
Mean corpuscular volume (fl)	+13 (12-13)
Fetal hemoglobin (g/dL)	+12.5 (11.8-13.1)
White cells per mm^3	-6,300 (-6,900 to -5,600)
Absolute neutrophil count per mm^3	-2,500 (-2,700 to -2,200)
Platelets per mm^3	-67,600 (-82,000 to -52,000)



HgbF, fetal hemoglobin; MCV, mean corpuscular volume; WBC, white blood cell.
Tshilolo et al. *Blood* 2019;380:121-131.

- When looking for laboratory effects of hydroxyurea treatment, we noticed that hemoglobin will increase in time, meaning corpuscular volume increases in time, and fetal hemoglobin increases in time with reduction in the white cell count, the absolute neutrophil count, and the platelet count.

Hydroxyurea



- Probability of 10-year overall survival in patients with sickle cell disease with and without hydroxyurea:
  - Hydroxyurea: 86%
  - Conventionally treated: 65%
  - *P* = .001

Voskaridou et al. *Blood* 2010;115:2354-2363.

- The probability of a 10-year overall survival in patients with sickle cell disease with and without hydroxyurea is vast and significantly in favor of hydroxyurea at 86% versus conventional treatment at 65%.

What Is the Issue With Hydroxyurea?

- Minimal side effects
- Disproportionate perceptions of carcinogenicity, teratogenicity, and reduced fertility
- Widely underutilized in the Western world
  - Pharmacy data: filling 1 or more hydroxyurea prescriptions during the 3, 6, or 12 months after a third pain crisis = 22.7%
- Access to hydroxyurea in areas of high disease burden needs to improve

Stettler et al. *JAMA* 2015;313:1671-1672; Voskaridou et al. *Blood* 2010;115:2354-2363.

- What is the issue with hydroxyurea? Despite the minimal side effects seen for patients on hydroxyurea, there is disproportionate perception of carcinogenicity, teratogenicity, and reduced fertility. It remains wildly under-utilized in the western word. Pharmacy data show filling one or more of the hydroxyurea prescriptions to be at 22% at different intervals. And access to hydroxyurea in areas of high disease burden needs to improve, such as Africa.

Transfusion Therapies: Three Therapeutic Modalities

- Blood transfusion is a disease-modifying therapy for the treatment and prevention of acute and chronic complications of SCD[1]
- Blood may be administered by:
  - Simple transfusion[1]
  - Manual exchange
  - Automated red blood cell exchange
- Main complications of transfusion[1,2]:
  - Alloimmunization
  - Iron overload
  - Hyper-hemolytic transfusion reactions
  - Transfusion-associated circulatory overload

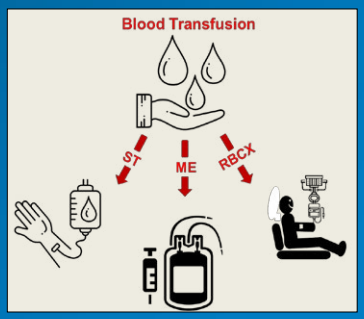


Image courtesy of Fuad El Rassi, MD.
ME, manual exchange; RBCX, red blood cell exchange; SCD, sickle cell disease; ST, simple transfusion
1. Howard. *ISBT Science Series* 2013;8:225-228; 2. Agnihotri and Agnihotri. *Indian J Crit Care Med*. 2014;18(6):396-398.

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- Transfusion therapies remain to be utilized but they're not the mainstay therapy in sickle cell disease for several issues. We have three therapeutic modalities that can be used in transfusion therapy. Blood transfusion can be administered as a simple transfusion, as a manual exchange, or an automated red blood cell exchange. However, the main complications of transfusion therapy are linked to alloimmunization, iron overload, hyperhemolytic transfusion reactions due to the transfusion itself, or transfusion-associated circulatory overload.

Primary Use of Transfusion Therapy in SCD

Chronic RBC Transfusion Therapy

- Primary stroke prevention (abnormal blood vessels)
- Secondary stroke prevention (previous stroke)
- Recurrent acute chest syndrome

Acute RBC Transfusion Therapy

- Severe symptomatic anemia
- Acute chest syndrome
- Acute stroke or neurologic compromise
- Inability to make RBCs (aplastic anemia)

Transfusions are not indicated for typical sickle cell vaso-occlusive pain management.

RBC, red blood cell; SCD, sickle cell disease.
Howard. *ISBT Science Series* 2013;8:225-228. Agnihotri and Agnihotri. *Indian J Crit Care Med*. 2014;18(6):396-398.

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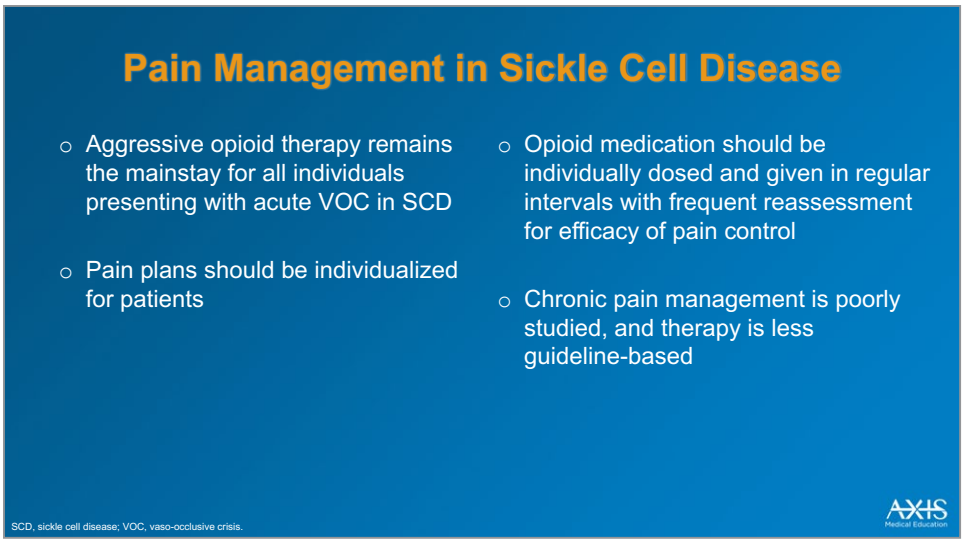
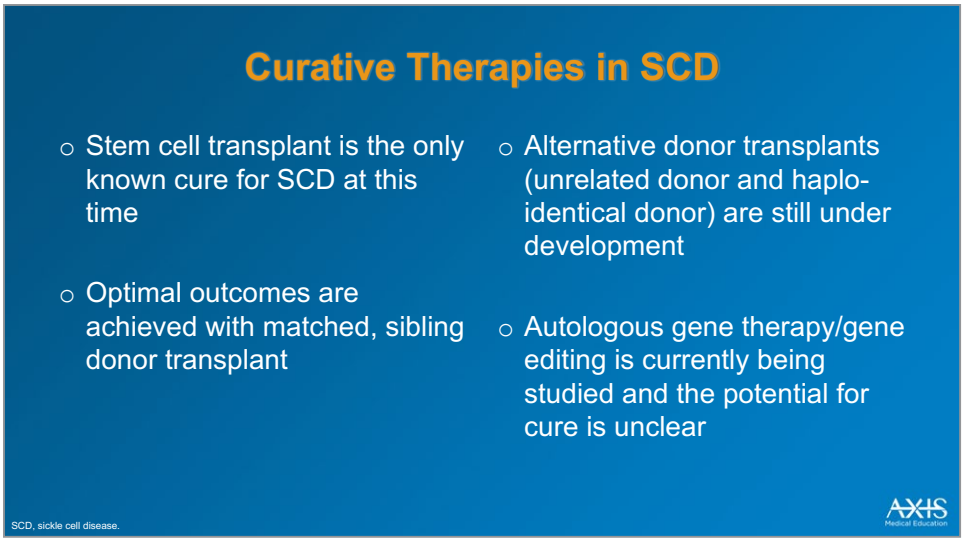
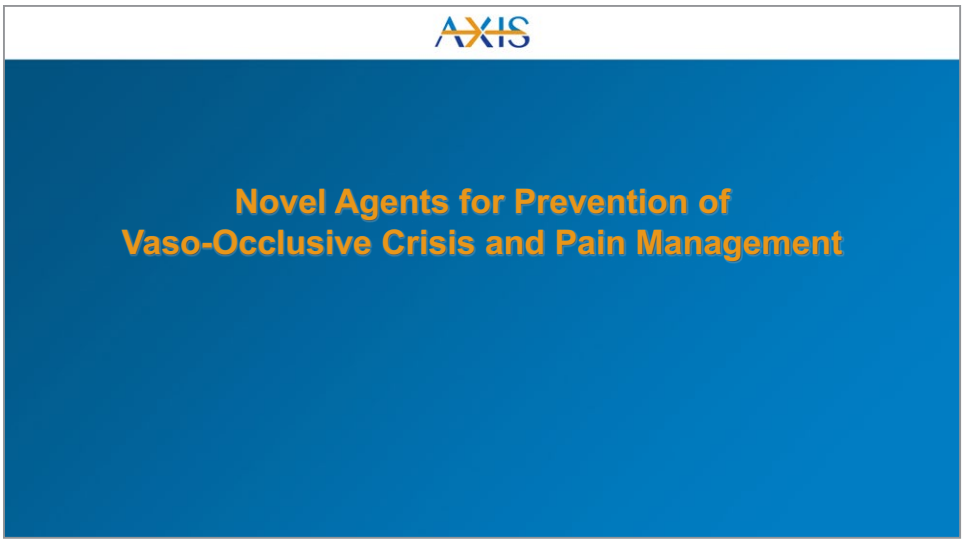
- Primary use of transfusion therapy in sickle cell disease remains restricted to specific situations. Chronic RBC transfusion therapy is employed in primary stroke prevention or secondary stroke prevention or recurrent acute chest syndrome and acute RBC transfusion therapy is employed in severe symptomatic anemia patients, acute chest syndrome, acute stroke or neurologic complications, or inability to make red blood cells, such as an aplastic anemia. One thing to know is transfusions are not indicated for typical sickle cell vasoocclusive pain management.



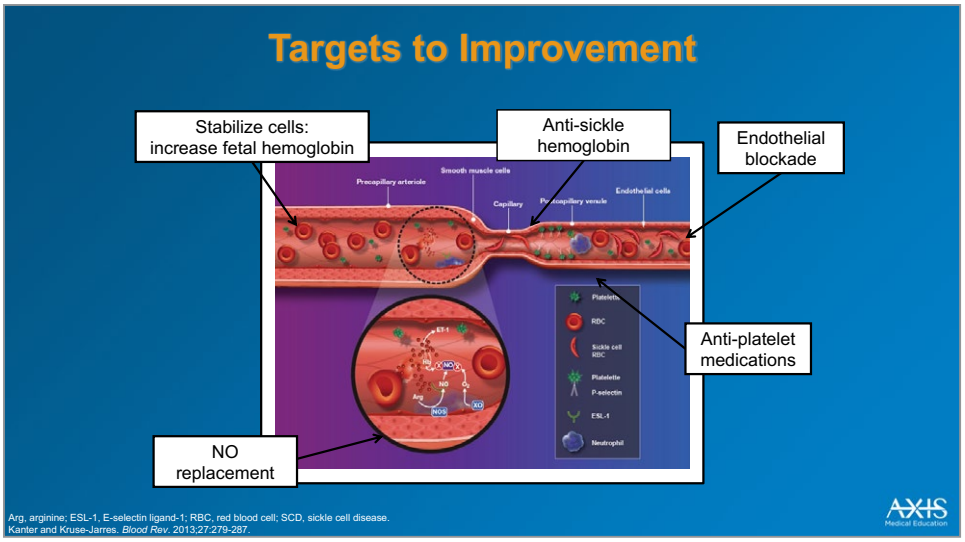
- Pain management in sickle cell disease remains key in the setting of an acute pain crisis. Aggressive opioid therapy is the mainstay of therapy. Pain plans should be individualized for patients and the scope of this presentation does not involve going into the nitty and gritty details of the pain plan. Opioid medication should be individually dosed and given at regular intervals with frequent reassessment for efficacy of pain control. Chronic pain management is poorly studied and therapy is less guideline-based and is being more understood currently.



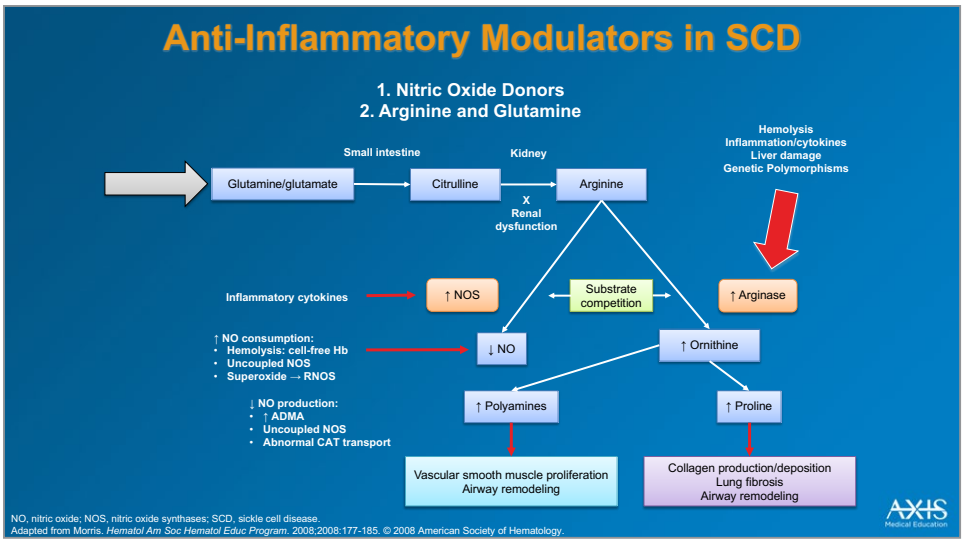
- Stem cell therapy is the only known cure for sickle cell disease at this time. Optimal outcomes are achieved with matched sibling donor transplants. Alternative donor transplants, such as unrelated donor and haploid identical donor are still under development. Autologous gene therapy or gene editing is currently being studied, as well, and the potential for cure remains to be determined.



- Novel Agents for Prevention of Vasoocclusive Crisis and Pain Management.



- Targets to improve or control sickle cell disease vary based on the molecular pathophysiology of sickle cell disease. You can attempt to stabilize the sickled red blood cells by increasing fetal hemoglobin. You can work on an anti-sickle hemoglobin effect. You can work on an endothelial blockade effect. You can have an anti-platelet medication effect. And you can work on nitric oxide replacement. We will look at the latest therapies and the way they target sickle cell disease.



- When we look at anti-inflammatory modulators in sickle cell disease, nitric oxide donors, such as arginine and glutamine, are first that come to mind. In the cascade of nitric oxide, glutamine and arginine are direct precursors of nitric oxide and supplementation of both arginine and glutamine may be a pathway that can help increase nitric oxide levels and reduce complications from sickle cell disease. Alternatively, increasing the downstream signal from nitric oxide can also lead to the similar outcomes as noted from increasing glutamine and arginine.

L-glutamine: FDA Approval

Date	July 7, 2017
Indication	to reduce the acute complications of sickle cell disease in adult and pediatric patients 5 years of age and older
Recommended Dose	• 5 grams to 15 grams orally, twice daily based on body weight • Each dose should be mixed in 8 oz. (240 mL) of cold or room temperature beverage or 4 oz. to 6 oz. of food before ingestion
Administration	Oral powder
Trial	Phase 3, NCT01179217

Reduction in the number of sickle cell crises through Week 48 and prior to the start of tapering	• Median number of sickle cell crises
	  • L-glutamine: 3
	  • Placebo: 4
	• Median number of hospitalizations for sickle cell pain:
	  • L-glutamine: 2
	  • Placebo: 3

Most common adverse reactions (>10%)	Constipation, nausea, headache, abdominal pain, cough, pain in extremity, back pain, and chest pain

US Food & Drug Administration. July 7, 2017.

- This lead to the approval of L-glutamine in July 2017. The indication is to reduce the acute complications of sickle cell disease in adult and pediatric patients, 5 years of age and older. The recommended dose is 5 g to 15 g orally, twice daily based on body weight. Each dose should be mixed in 8 ounces of cold or room temperature beverage. The administration is an oral powder. And the main effect of this medication was the reduction in the median number of sickle cell crises from four on the placebo arm to three on the L-glutamine arm. And reduction in the median number of hospitalizations for sickle cell pain from three on the placebo arm to two on the L-glutamine arm. The most common adverse reactions reported were constipation, nausea, headache, abdominal pain, cough, pain in the extremity, back pain, and chest pain.

Voxelotor

- Oral, once-daily, direct-acting hemoglobin modifier
- HbS polymerization inhibitor
- Prevents sickling of RBCs: increases hemoglobin's affinity for oxygen, delays polymerization of HbS, restores normal RBC function in preclinical SCD models
- Phase 2/3 trial of GBT440 in SCD started in December 2016

HbS, hemoglobin S; RBCs, red blood cells; SCD, sickle cell disease.
Dufu et al. *Blood* 2014;124:217.
NCT02285088.

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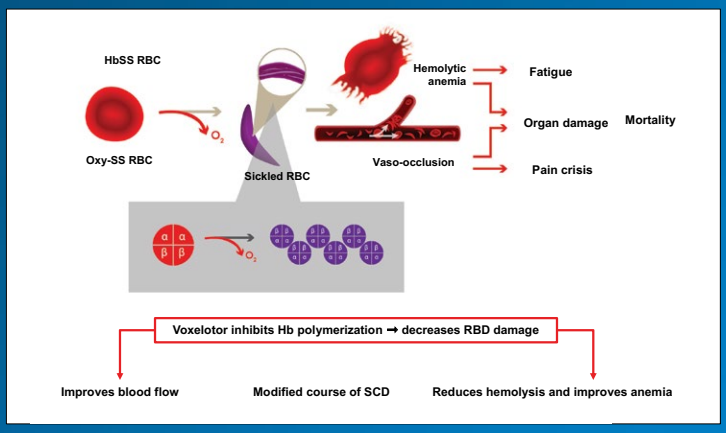
- The next agent I would like to discuss is voxelotor, which is an oral, once daily, and direct-acting hemoglobin modifier.

Voxelotor Trials



eoxy, deoxygenated; Hb, hemoglobin, HbS, sickle hemoglobin; O_2, oxygen; oxy, oxygenated; RBC, red blood cell; SCD, sickle cell disease; SS, sickle cell anemia.
dapted from Lehrer-Graiwer et al. *Haematologica* 2016;101:125.
ttps://clinicaltrials.gov/ct2/show/NCT03036813. https://clinicaltrials.gov/ct2/show/NCT02850406.

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- It prevents sickling of red blood cells by increasing hemoglobin's affinity for oxygen, delaying polymerization of sickle hemoglobin, and restoring normal red blood cell function in pre-clinical sickle cell disease models. The study that was done for voxelotor was a phase 2/3 trial that was started in December 2016.

HOPE Trial: Voxelotor

- **Study Population:** SCD patients randomly assigned in a 1:1:1 ratio to receive a once-daily oral dose of 1,500 mg of voxelotor, 900 mg of voxelotor, or placebo
- **Results**: Voxelotor significantly increased hemoglobin levels and reduced markers of hemolysis
  - Participants who had a Hb response (>1 g/dL increase in Hb from baseline to Week 24):
    - 51% in the 1,500 mg voxelotor group
    - 7% in the placebo group
- **Adverse Reactions:**
  - Grade 3/4 adverse events:
    - 26% in the 1,500 mg voxelotor group
    - 23% in the 900 mg voxelotor group
    - 26% in the placebo group
  - Most common adverse reactions: headache, diarrhea, abdominal pain, nausea, rash, and pyrexia

HbS, sickle hemoglobin; Hb, hemoglobin; SCD, sickle cell disease.
Vichinsky et al. *N Engl J Med*. 2019; 381:509-519; Oxbryta prescribing information, 2021.

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- The HOPE trial had looked at patients with sickle cell disease and randomized and assigned patients in a one-to-one ratio between a placebo arm, a 900 mg arm, and a 1,500 mg arm of voxelotor. The results showed that voxelotor significantly increased the hemoglobin level and reduced markers of hemolysis. Participants who had a hemoglobin response increased by >1 g/dL at 24 weeks of the study were seen in 51% of the patients on the 1,500 mg arm, as compared to the 7% of the patients in the placebo group. The adverse reactions were grade 3 and grade 4 events occurred in 26% of the participants in the 1,500 mg voxelotor group versus 23% in the 900 mg voxelotor group and 26% in the placebo group; the most common adverse reactions were headache, diarrhea, abdominal pain, nausea, rash, and pyrexia.

HOPE Kids Trial: Voxelotor

- **Study Population:** Pediatric patients with SCD aged 4 to 11 years received once-daily voxelotor 1500 mg or 1500 mg weight-based-equivalent dosing for up to 48 weeks
- **Results**: Voxelotor increased Hb and decreased markers of hemolysis
  - Participants who had a Hb response (>1 g/dL increase in Hb from baseline to Week 24): 36%
- **Adverse Reactions:**
  - Most common treatment-related AEs: diarrhea (11%), vomiting (11%), and rash (11%)
  - Most common adverse reactions: pyrexia, vomiting, rash, abdominal pain, diarrhea, and headache

HbS, sickle hemoglobin; Hb, hemoglobin; SCD, sickle cell disease.
Estepp et al. EHA2021. Abstract: S260; Oxbryta prescribing information, 2021.

AXIS Medical Education

- This study was followed by the HOPE-KIDS trial looking again at voxelotor in children aged 4 to 11 who received a one-a-daily dose of voxelotor 1,500 mg or 1,500 mg weight-based equivalent dosing for up to 48 weeks. Results of this study also showed a similar response with an increase in hemoglobin by >1 g/dL from baseline to 24 weeks in 36% of the participants with a very similar profile of adverse reactions in pediatric patients aged 4 to 11.

Voxelotor: FDA Approvals

	Age ≥12	Ages 4-11
Date	November 2019	December 2021
Indication	accelerated approval for the treatment of SCD in adults and pediatric patients 12 years of age or older	accelerated approval to treat SCD in pediatric patients 4-11 years of age
Recommended Dose	1,500 mg once daily	Based on body weight: • 40 kg or greater: 1,500 mg once daily • 20 kg to <40 kg: 900 mg once daily • 10 kg to <20 kg: 600 mg once daily
Administration	Oral	Oral (tablets or tablets for oral suspension)
Trial	Phase 3 HOPE	Phase 2 HOPE-KIDS 1 (Phase 3 HOPE-KIDS 2 ongoing, NCT04218084)
Hb response rate (Hb increase of >1 g/dL from baseline to week 24)	51.1% vs 6.5% (placebo)	36%
Most common adverse reactions (>10%)	Headache, diarrhea, abdominal pain, nausea, rash, fatigue, and pyrexia	Pyrexia, vomiting, rash, abdominal pain, diarrhea, and headache
Warnings	Hypersensitivity reactions Potential laboratory test interference	

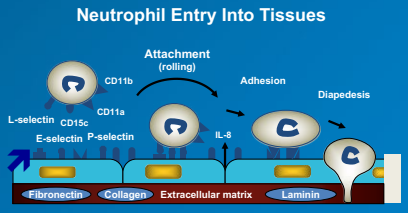
SCD, sickle cell disease .
US Food & Drug Administration. 2019. 2021. Oxbryta prescribing information, 2021.

AXIS Medical Education

- This led to the FDA approval of voxelotor in November 2019 for adults and for children ages 12 and above and then in December 2021 for children ages 4 to 11. The recommended dose is 1,500 mg once daily for ages 12 and above, and for ages 4 to 11, it's based on body weight as you can see in this table. The administration is oral. And the hemoglobin response is increasing the hemoglobin by >1 g/dL at 24 weeks of the study with reduction in markers of hemolysis.

Selectins Mediate WBC Adhesion, Rolling

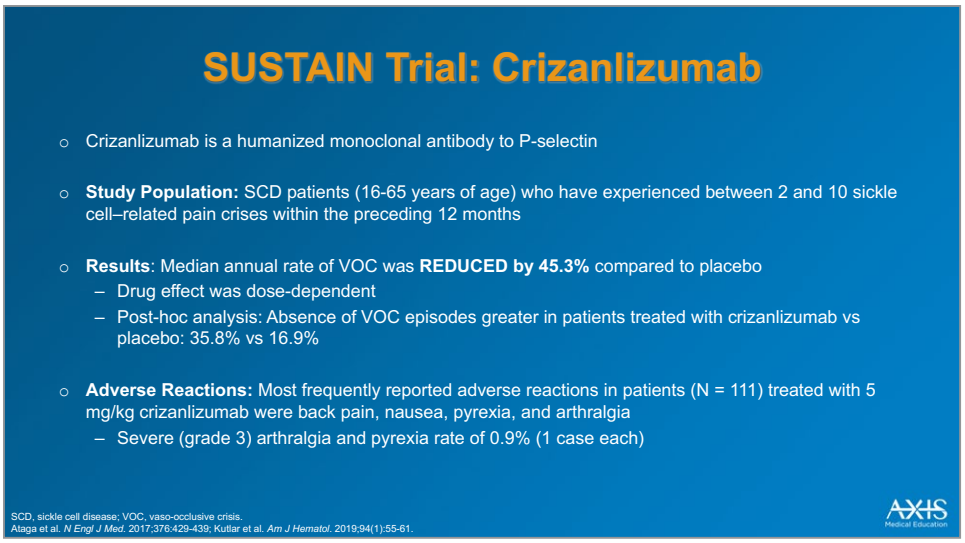
- Selectins are expressed on endothelial cells, platelets, and leukocytes, as well as other cell types[1]
- P-selectin and E-selectin mediate rolling and tethering of blood cells to the endothelium[2]
  - May initiate vaso-occlusion in the post-capillary venules[2]
- SCD cellular and animal models: interruption of selectin-mediated cellular adhesion decreases erythrocyte and leukocyte adhesion and improves blood flow[3-7]



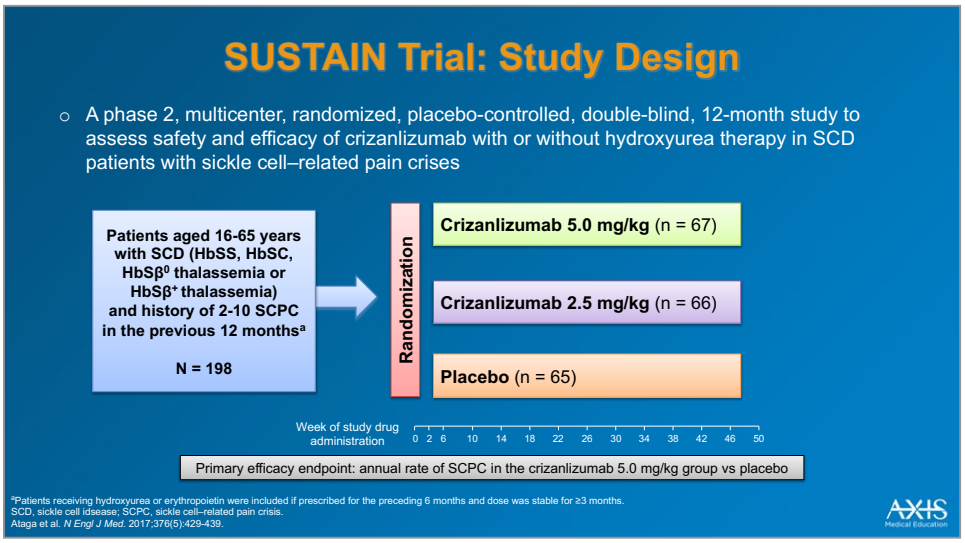
SCD, sickle cell idsase; WBC, white blood cell.
1. Tedder et al. *FASEB J*. 1995;9:866-873. 2. Ley et al. *Nat Rev Immunol*. 2007;7:678-689. 3. Chang et al. *Blood* 2010;116:1779-1786. 4. Matsui et al. *Blood* 2001;98:1955-1962. 5. Matsui et al. *Blood* 2002;100:3790-3796. 6. Embury et al. *Blood* 2004;104:3378-3385. 7. Kutlar et al. *Am J Hematol*. 2012;87:536-539.
Figure adapted from *Nat Rev Immunol*. 2007;7:678-689.

AXIS Medical Education

- The selectin family or the selectin-mediated pathway is the next target that was evaluated in a clinical trial. And selectins are the family of proteins involved in white blood cell adhesion and rolling at the endothelium after interaction with the sickled red blood cells. P-selectins and E-selectins are proteins that are involved in this process and they are linked to vasoocclusion in sickle cell disease.



- SUSTAIN was a clinical trial of crizanlizumab, this monoclonal antibody developed against P-selectin. The study was a phase 2, multi-center, randomized, placebo-controlled, double-blind, 12-month study to assess the safety and efficacy of crizanlizumab in patients with or without hydroxyurea with sickle cell disease. The population of patients ranged from 16 to 65 years of age and it was patients who experienced between two and ten sickle cell–related pain events within the preceding 12 months. The results from this study showed a median annual rate of VOC reduction by 45% compared to placebo with a drug effect that was dose-dependent with a post-hoc analysis that showing the absence of VOC episodes in 35% of patients treated with crizanlizumab as compared to 17% of patients on placebo. The adverse reactions most frequently reported were related to pain, nausea, pyrexia, and arthralgia and severe grade 3 arthralgia and pyrexia were seen in one case.



- The study had analyzed two different arms and based on the results of the clinical trial, the 5 mg/kg arm was more effective in reducing the rate of painful events.

SUSTAIN Trial Summary

Endpoint	High-Dose Crizanlizumab, 5 mg/kg (N = 67)	Low-Dose Crizanlizumab, 2.5 mg/kg (N = 66)	Placebo (N = 65)
Annual rate of crises, ITT			
Median rate of crises/year	1.63	2.01	2.98
Difference from placebo (%)	**-45.3**	-32.6	-
P	.01	.18	-
No (%) of pts with crisis rate of 0 at end of trial	24 (36) >2-fold increase vs placebo	12 (18)	11 (17)
Median annual rate of days hospitalized/year	4.00	6.87	6.87
Difference from placebo (%)	**-41.8**	0.0	-
P	.45	.84	-
Median time to 1st sickle cell–related pain crisis (months)	4.07 3-fold longer vs placebo	2.20	1.38
P	.001	.14	-
Median time to 2nd sickle cell–related pain crisis (months)	10.32	9.20	5.09
P	.02	.10	-

ITT, intention to treat.
Ataga et al. *N Engl J Med.* 2017;376:429-439.

AXIS Medical Education

- The difference as shown here in this table is reduction of VOCs with the high dose crizanlizumab arm—45% reduction in the median annual rate of VOCs versus placebo.

Crizanlizumab-tmca: FDA Approval

Date	November 2019
Indication	to reduce the frequency of VOCs in adults and pediatric patients aged 16 years and older with sickle cell disease
Recommended Dose	5 mg/kg
Administration	Intravenously over a period of 30 minutes on weeks 0, 2, and every 4 weeks thereafter
Trial	Phase 2 SUSTAIN
Annual rate of VOCs leading to a healthcare visit, defined as an acute episode of pain with no cause other than a VOC event requiring a medical facility visit and oral or parenteral opioids, or parenteral NSAIDs	Significant 45% reduction in the median annual rate of VOCs vs. placebo: • Voxelotor: 1.63 median annual rate of VOC • Placebo: 2.98 median annual rate of VOC • *P* = .010
Most common adverse reactions (>10%)	Nausea, arthralgia, back pain, abdominal pain, and pyrexia
Warnings	Infusion-related reactions, interference with automated platelet counts (platelet clumping)

NSAIDs, nonsteroidal anti-inflammatory drugs; VOCs, vaso-occlusive crises.
US Food & Drug Administration. November 15, 2019.

AXIS Medical Education

- This led to the FDA approval of crizanlizumab-tmca in November 2019 to reduce the frequency of VOCs in adults and pediatric patients age 16 years and older with sickle cell disease. The recommended dose is 5 mg/kg. The administration is intravenous over a period of 30 minutes on weeks 0, 2, and then every 4 weeks thereafter, and the most common adverse reactions were nausea, arthralgia, back pain, abdominal pain, and pyrexia. There is a warning related to infusion-related reactions as this drug is a monoclonal antibody and has been reported to cause infusion reactions.

Ongoing Clinical Trials Summary

Drug	Trial	Phase	Treatment Setting	Status
Crizanlizumab	STAND NCT03814746	3	2 different doses of crizanlizumab (5.0 mg/kg and 7.5 mg/kg) vs. placebo, with or without hydroxyurea/hydroxycarbamide, in adolescent and adult SCD patients with VOC, age ≥12 years	Recruiting
	SPARTAN NCT03938454	2	SCD patients with priapism	Recruiting
	STEADFAST NCT04053764	2	SCD patients ≥ 16 years with chronic kidney disease due to sickle cell nephropathy	Active, not recruiting
	SOLACE-kids NCT03474965	2	Dose and safety of crizanlizumab with or without hydroxyurea/hydroxycarbamide in pediatric SCD patients with VOC, ages 6 months to 17 years	Temporarily halted recruitment until dose in Group 2 is confirmed
	SOLACE-adults NCT03264989	2	PK/PD of crizanlizumab with or without hydroxyurea/hydroxycarbamide in SCD patients with VOC, ages 16 to 70 years	Active, not recruiting
Voxelotor	HOPE Kids NCT02850406	2	Pediatric SCD patients, ages 6 months to 17 years (in 4 parts)	Recruiting
	HOPE Kids 2 NCT04218084	3	Pediatric SCD patients, aged ≥ 2 to < 15 years old, vs. placebo	Recruiting

PK, pharmacokinetics; PD, pharmacodynamics.

AXIS Medical Education

- When it comes to ongoing clinical trials, there are several clinical trials going on right now with both crizanlizumab and voxelotor, as you can see in this table. But there are even more therapeutics around the corner targeting both mechanisms of hemolysis and vasoocclusion in sickle cell disease.

L-Glutamine

- L-Glutamine: NO pathway
- 5-15 grams twice daily based on body weight, approved by FDA in 2017
- Oral powder dissolved in fluids, increase NO level
- Safe side effect profile
- Effect
  - ↓ Vaso-occlusive events by 25% compared to placebo

NO, nitric oxide.
Niihara et al. *N Engl J Med.* 2018;379:226-235.

AXIS Medical Education

- In summary, for the therapeutics, L-glutamine is a medication that's available. It works on the nitric oxide pathway and its main effect is reduction in vasoocclusive events by 25% compared to placebo. It is a powder that has to be dissolved.

Voxelotor

- Voxelotor: hemoglobin affinity inducer- reduction of hemolysis, approved by FDA in late 2019 (≥12 years) and 2021 (ages 4-11)
- 1,500 mg orally; if GI side effects, can titrate down to 1,000 mg then uptitrate
- Weigh-based dosing for ages 4-11
- Increases binding of oxygen to red blood cells, with left shift of oxygen dissociation curve
- Effects
  - ↑ Hgb by 1 g/dL
  - ↓ Reticulocytes, bilirubin

FDA, US Food & Drug Administration; GI, gastrointestinal; Hgb, hemoglobin.
Vichinsky et al. *N Engl J Med*. 2019; 381:509-519.

AXIS Medical Education

- Voxelotor is a hemoglobin affinity inducer that works on reduction of hemolysis. Its main effect is increase in hemoglobin by 1 g/dL and reduction of hemolysis marker such as reticulocytes and bilirubin. It is an oral agent.

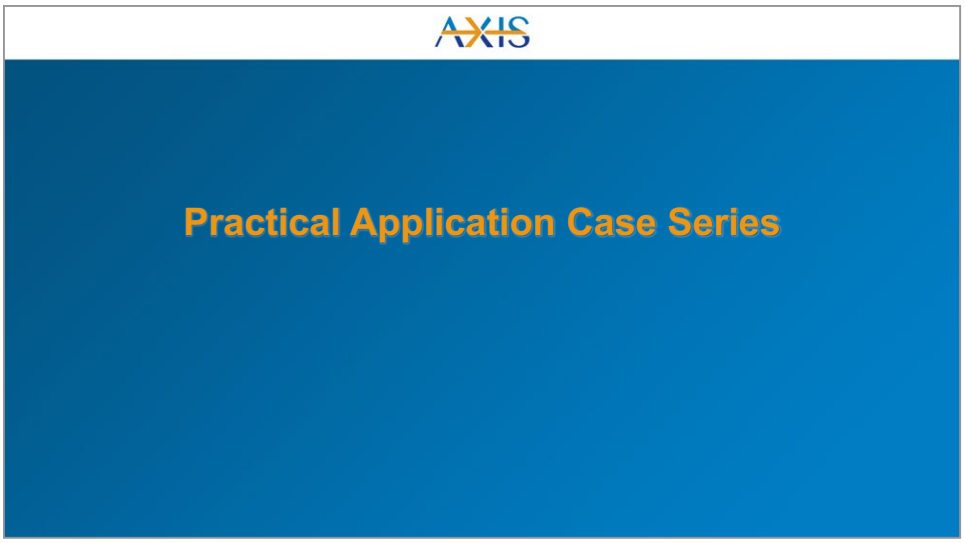
Crizanlizumab

- Crizanlizumab: monoclonal inhibitor of P-selectin adhesion pathway
- Dosing 5 mg/kg, approved by FDA in late 2019
- IV infusion monthly- first infusion prophylactic agent in sickle cell
- Well tolerated with minimal side effect profile
- Effect
  - ↓ VOC events by 45% compared to placebo, and prolongs time to next event

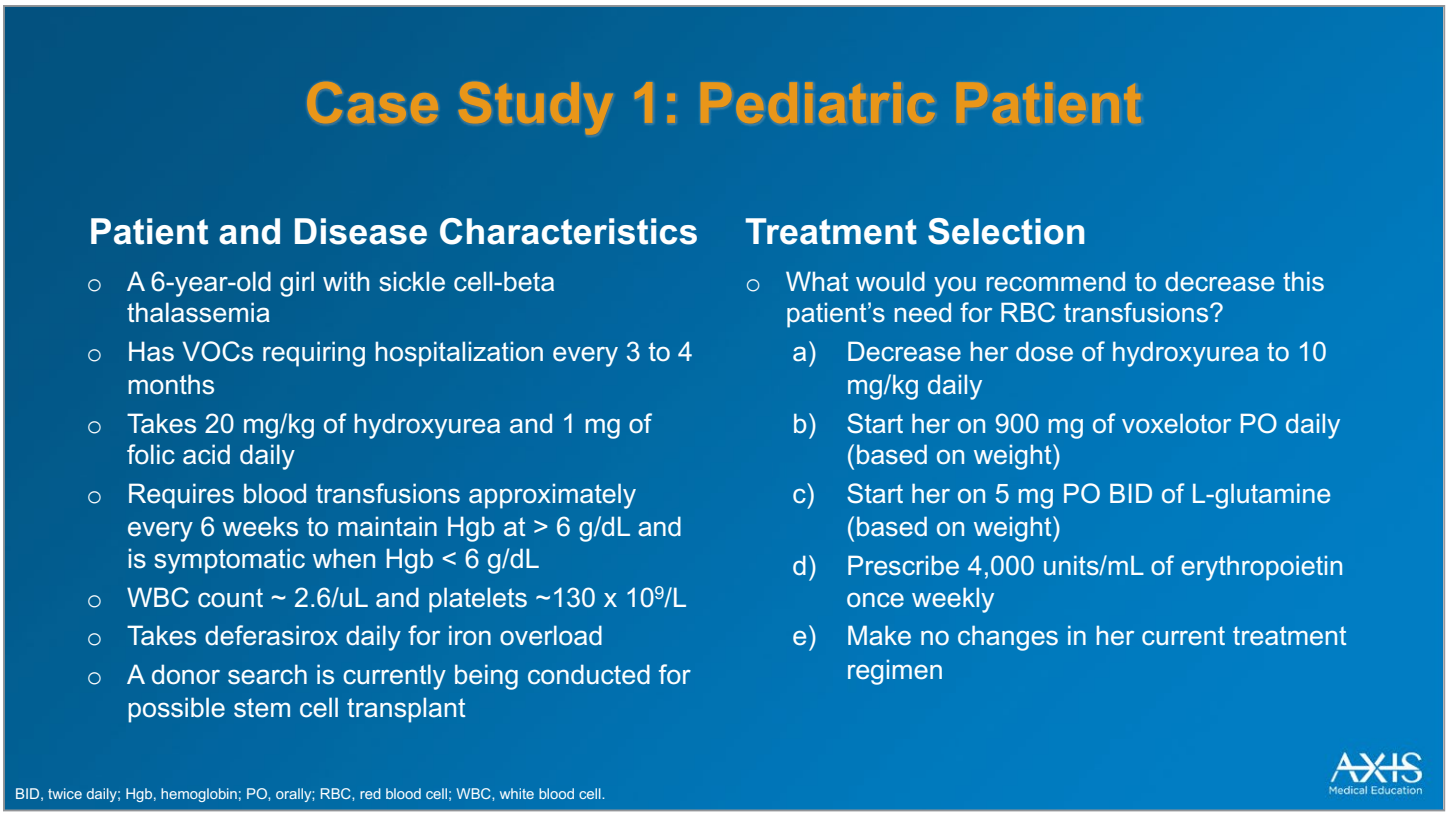
FDA, Us Food & Drug Administration.
Ataga et al. *N Engl J Med*. 2017;376:429-439.

AXIS Medical Education

- And crizanlizumab is a monoclonal antibody inhibitor of P-selectin. It is an IV agent that's infused once a month and its main effect is reduction of VOC by 45% compared to placebo and prolonging the time to the next painful event.



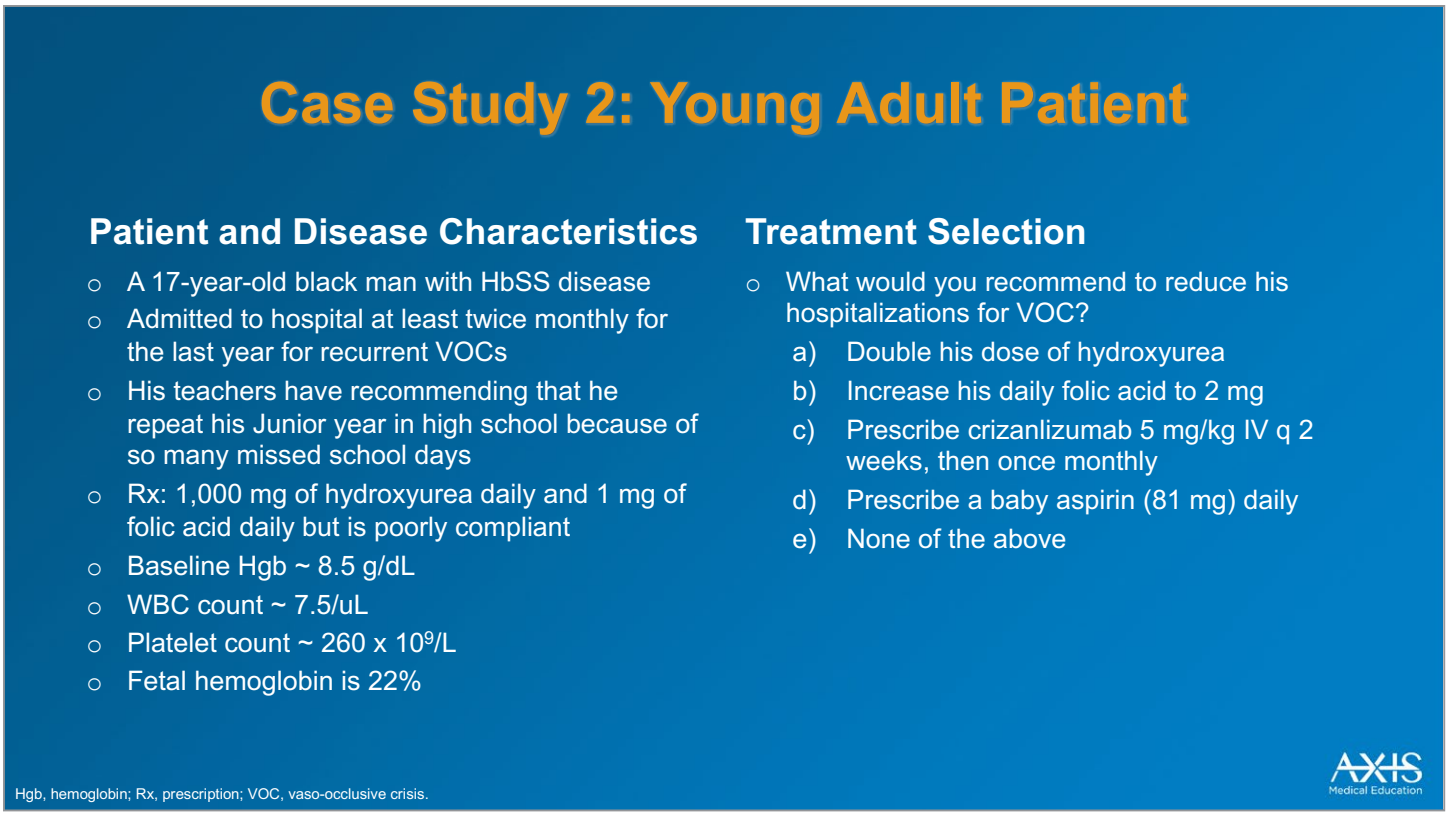
- Now we switch to some practical application case series.



- Case study number 1, a pediatric patient.

  This is a 6-year-old girl with sickle cell ß thalassemia, has VOCs requiring hospitalization every 3 to 4 months, takes 20 mg/kg of hydroxyurea and 1 mg of folic acid daily. Requires blood transfusions approximately every 6 weeks to maintain a hemoglobin at 6 g/dL and is symptomatic when hemoglobin is less than 6 g/dL. The white count is 2.6 thousand and the platelet count is 130,000. She takes deferasirox daily for iron overload and a donor search is currently being conducted for possible stem cell transplant. The question: What would you recommend to decrease this patient's need for red blood cell transfusions? A. Decrease her dose of hydroxyurea to 10 mg/kg daily. B. Start the patient on 900 mg of voxelotor p.o. daily based on weight. C. Start her on 5 mg p.o. twice a day of L-glutamine based on weight. D. Prescribe 4,000 units of erythropoietin once weekly, or E. Make no changes in her current treatment regimen?

  And the answer to this question is B, start her on 900 mg of voxelotor based on weight daily because her main problem is the degree of anemia that she suffers from and it requires a transfusion and definitely decreasing the hydroxyurea dose is not the answer that should be entertained. In fact, one thought would be to increase the dose of hydroxyurea for this patient, however, the white count is already at a restricted range at 2.6 thousand and if you increase the hydroxyurea dose here, the white count would drop further and you'll get into potentially leukopenia and neutropenia and we don't want that. L-glutamineolization is not known to help improve hemoglobin as discussed in this case. We do not know the status of the kidney function for this patient, but if there was some element of kidney disease, considerations for using of erythropoietin is possible but it's not an option given the lack of the knowledge of that in this case.



- Case study 2, a young adult patient.

  This is a 17-year-old black man with hemoglobin SS disease admitted to the hospital at least twice monthly for the last year for recurrent VOCs. His teachers have recommended that he repeat his junior year in high school because of so many missed school days, again showing the quality of life impact of sickle cell disease. His prescriptions include hydroxyurea at 1,000 mg daily and 1 mg of folic acid, but he's poorly adherent and compliant. His baseline hemoglobin is 8.5 g/dL, his white count is 7.5 thousand. His platelets were 260,000 and his fetal hemoglobin is 22%, which is quite good. The question: What would you recommend to reduce his hospitalization for VOC? A. Double his dose of hydroxyurea, which he already does not take as much? B. Increase his daily folic acid dose to 2 mg? C. Prescribe crizanlizumab 5 mg/kg IV every 2 weeks, then once monthly? D. Prescribe a baby aspirin daily? E. Or none of the above?

  The obvious answer here is C, prescribe crizanlizumab 5 mg/kg IV q 2 weeks then once a month afterward because this patient mainly suffers from recurrent painful events that keep him from continuing his studies and affect his daily life and this makes the most sense. Doubling his dose of hydroxyurea would work if the patient has been taking the medication, even at a dose of, a gram of hydroxyurea daily if he is adherent to the medicine, then he would have less painful events. And then increasing the folic acid or prescribing aspirin has no role at all in reducing the painful events.

Case Study 3: Adult Patient

Patient and Disease Characteristics

- A 34-year-old black man with HbSS
- Moved to your city and is seeing you for the first time
- Takes 1,000 mg of hydroxyurea daily
- Takes 1 mg of folic acid daily
- Takes 20 grams daily of L-glutamine
- Current Hgb is 9.7 g/dL
- WBC count is 11.4/uL and platelets 360 x 10^9/L
- Total bilirubin is 2.6 g/dL
- Peripheral blood smear with rare sickle cells and occasional target cells
- Has had exchange transfusions for acute chest syndrome and priapism previously
- Has recently been admitted to hospital 3 times in the past 6 weeks for recurrent episodes of pain in the arms and legs
- Currently taking hydrocodone/acetaminophen for pain every 6 hours and 2 mg of hydromorphone PO q 3 hr prn for breakthrough pain
- He rates his current pain at 8/10

Treatment Selection

- What would you recommend to address this patient's pain events?
  a) Imaging of the hips for AVN
  b) Starting on a long-acting narcotic
  c) Add crizanlizumab to reduce the incidence of VOCs
  d) Set up a pain contract because you suspect that he is over utilizing narcotics
  e) Add voxelotor at 1,500 mg daily

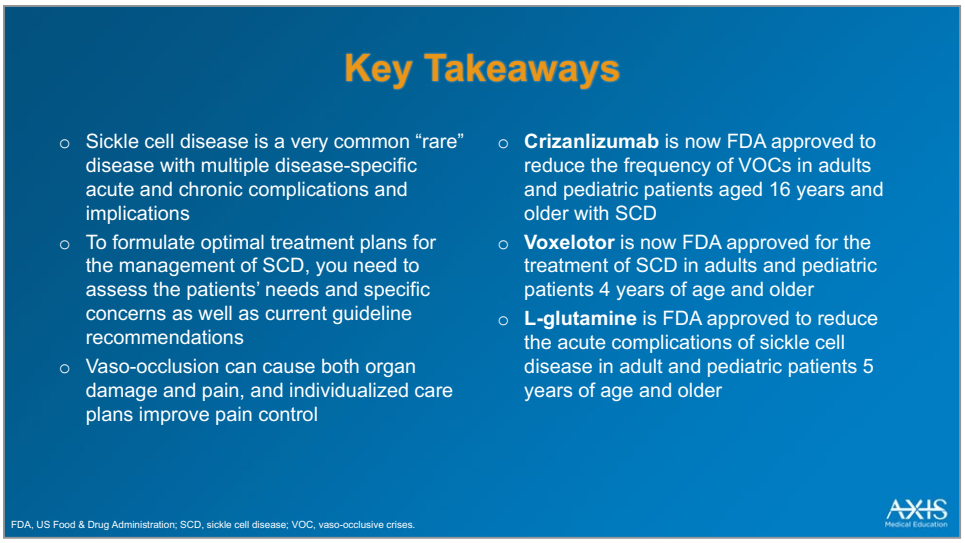
AVN, avascular necrosis; Hgb, hemoglobin; PO, orally; prn, as needed; VOCs, vaso-occlusive crises; WBC, white blood cell.

AXIS Medical Education

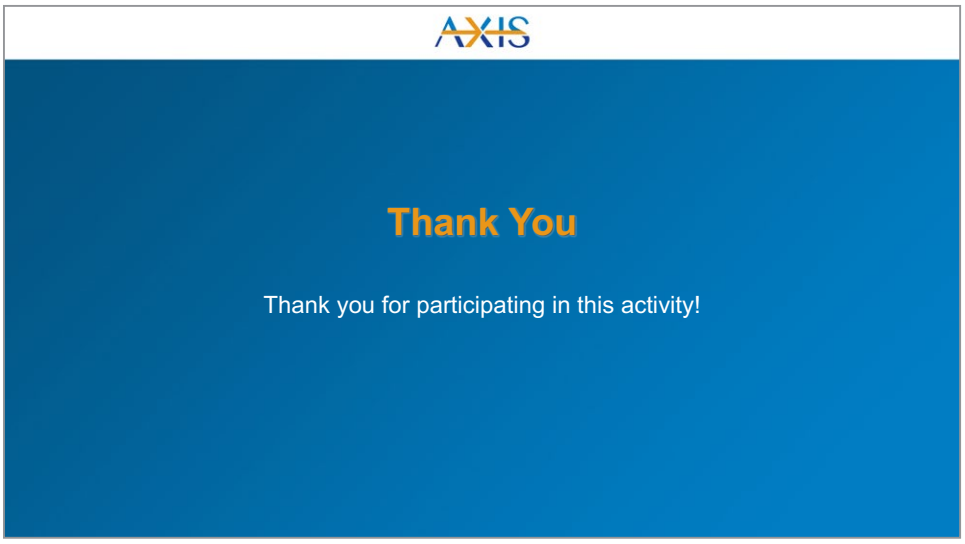
▶ Case study number 3, an adult patient.

This is a 34-year-old black man with hemoglobin SS, moved to the city and seeing us for the first time. Takes 1 g of hydroxyurea, 1 mg of folic acid daily, 20 g daily of L-glutamine with a current hemoglobin of 9.7 g/dL. The white count is 11.4 thousand and the platelets are 360,000. Total bilirubin is 2.6 g/dL. Blood smear show sickle cells. He has had an exchange transfusion for acute chest and priapism. He has recently been admitted to the hospital three times in the past 6 weeks for recurrent pain episodes in the arms and legs. Currently taking hydrocodone, acetaminophen for pain every 6 hours and 2 mg of hydromorphone orally every 3 hours for breakthrough pain. He rates his pain currently at 8/10. The question: What would you recommend to address this patient's pain events? A. Imaging of the hips for AVN (avascular necrosis)? B. Starting on a long-acting narcotic? C. Adding crizanlizumab to reduce the incidence of VOCs? D. Setting up a pain contract because you suspect that he is overutilizing narcotics? E. Or adding voxelotor 1,500 mg daily?

Reviewing the case of this patient, he is on hydroxyurea, L-glutamine, and still is experiencing frequent pain. He has been hospitalized more frequently in the last few weeks with recurrent episodes of pain in the arms and the legs. It doesn't look like he really has a localized pain to consider AVN of the hip, but at one point in time, given his age, it will be suggested to image the hips for AVN evaluation if there is localized pain there. It doesn't look like he is experiencing daily pain, so considering a long-acting narcotic at the current time may not be the best choice. Adding crizanlizumab to reduce the incidence of VOCs makes the most sense here because it looks like since his move, he has been hospitalized more often. It looks like an event happening acutely more than chronically so option C makes most sense. Setting up a pain contract because you suspect that he is over-utilizing is not the case but it's not a bad idea to consider this in the future if you notice more utilization and more days of being in pain than not. And then option E, which is adding voxelotor does not help with reducing or controlling pain.



- Finally, the key take-aways. Sickle cell disease is a very common disease with multi-disease specific acute and chronic complications and implications. To formulate optimal treatment plans for the management of sickle cell disease, you need to assess the patients' needs and specific concerns, as well as current guideline recommendations. Vasoocclusion can cause both organ damage and pain, and individualized pain plans help improve and get better pain control. Crizanlizumab is now FDA-approved to reduce the frequency of VOCs in adults and pediatric patients age 16 years and older. Voxelotor is now FDA-approved for the treatment of sickle cell disease and adults and pediatric patients age 4 years and older. And L-glutamine is FDA-approved to reduce the acute complications of sickle cell disease in adult and pediatric patients age 5 years and older.



- Thank you. And thank you for participating in this activity.

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