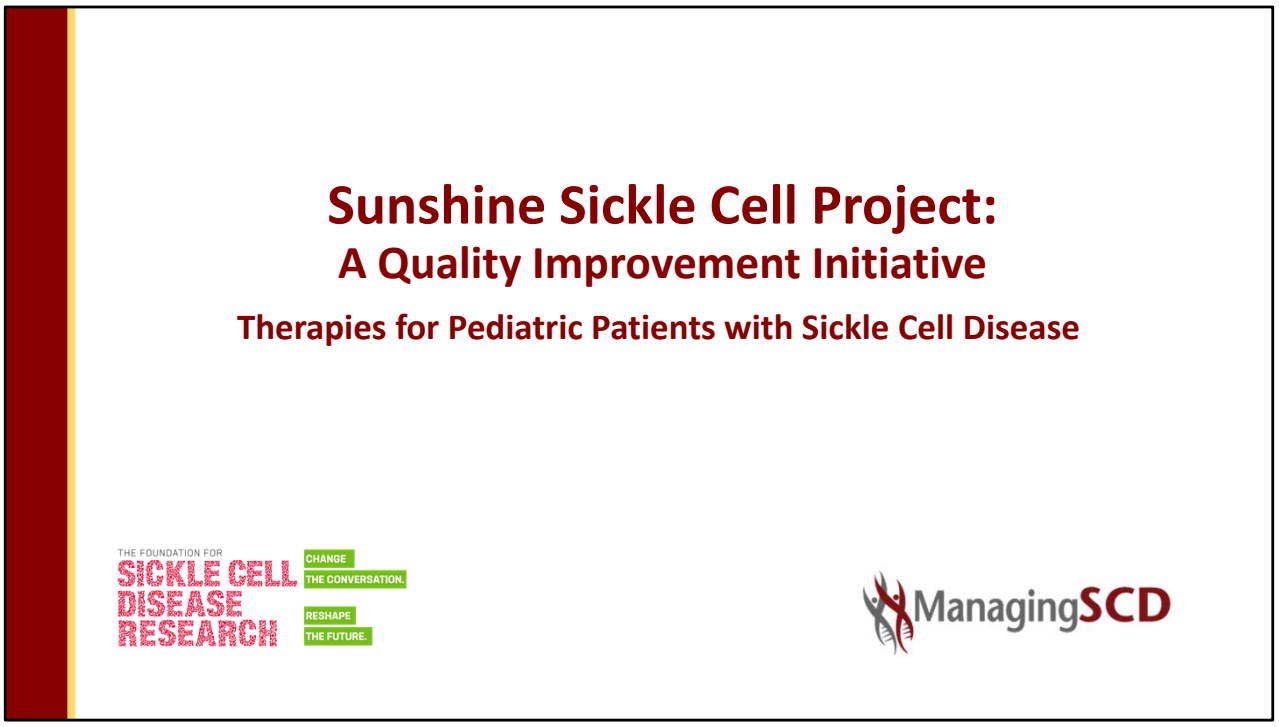


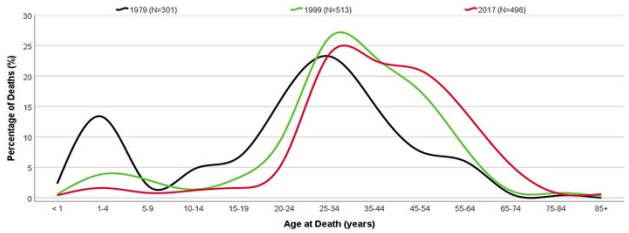
Dr. Lanetta Bronté-Hall: Good afternoon. Thank you for joining us. We are here for the Sunshine Sickle Cell Project, which is a quality improvement initiative. I am Dr. Lanetta Bronté-Hall, the President and Chief Executive Officer of the Foundation for Sickle Cell Disease Research. Today we will discuss *Therapies for Pediatric Patients with Sickle Cell Disease* by Dr. Andrew Campbell of Children's National. Dr. Campbell.

Dr. Andrew Campbell: Thank you so much, Dr. Bronté-Hall. Allow me to speak on this very important initiative. What we're going to talk about today is updated information on *Therapies for Pediatric Patients with Sickle Cell Disease* .

Survival in SCD

- Newborn screening for hemoglobinopathies mandated in all states in 2006[1]
- Prior to universal screening and intervention, infection was the most common cause of death in children with SCD[1]
- Penicillin prophylaxis and pneumococcal vaccines have reduced the rate of invasive pneumococcal disease by up to 90%[1]
- >98% of children with SCD now live to become adults[2]

Proportion of deaths among individuals with SCD by age group[3]



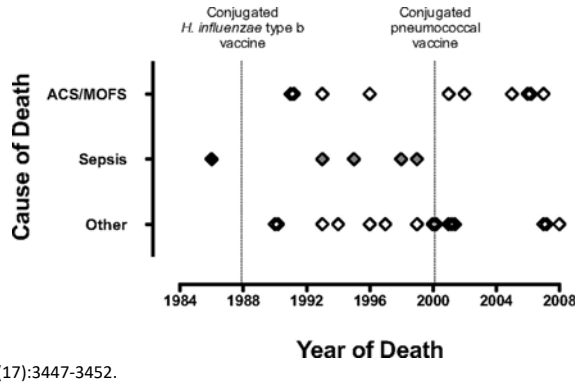
1. Meier ER, Rampersad A. *Pediatr Res.* 2017;81(1-2):249-258. 2. Quinn CT, et al. *Blood*. 2010;115(17):3447-3452. 3. Saulsberry A, et al. *Hematology Am Soc Hematol Educ Program*. 2019;2019(1):496-504.

As many of us know, sickle cell disease over time has made drastic improvements in terms of survival. We know that newborn screening started in approximately 1987 and was mandated in all states by 2006.

Prior to universal screening, infection was the most common cause of death in children with sickle cell disease. The study of penicillin prophylaxis that happened in the '80s and also the emergence of pneumococcal vaccines have reduced the rate of invasive pneumococcal disease by up to 90%. In fact, greater than 98% of children with sickle cell disease now live to become adults living with sickle cell disease.

Causes of Death in Children with SCD: Then and Now

- Deaths due to acute chest syndrome (ACS) and multiorgan failure syndrome (MOFS) are now more common than fatal sepsis



Quinn CT, et al. *Blood*. 2010;115(17):3447-3452.

Causes of death in children with sickle cell disease then and now. This is a figure just really looking at what were the causes early on in sickle cell disease history in terms of therapeutics and morbidity mortality versus later on. You can see these little diamond squares and the deaths due to acute chest syndrome and multiorgan failure are now more common than fatal sepsis. You can see that in 1984, 1988, the conjugated influenza type B vaccine here once that was instituted and also conjugated pneumococcal vaccine.

You can see that sepsis here was very common in this time period but after the 2000s, there is really very little causes of death from infections but still, end-organ damage from acute chest syndrome, multiorgan failure are the most common causes of death and also other causes.

Sickle Cell Genetics

- SCD occurs when one gene for production of Hgb S is inherited from each parent
- SCD is inherited in an autosomal recessive pattern
  - Parents are typically unaffected, carry one normal gene and one abnormal gene
  - Each pregnancy confers a:
    - 25% chance of producing a child with two copies of the abnormal gene
    - 50% chance of producing an unaffected gene carrier
    - 25% chance of producing an unaffected non-carrier
- Genetic counseling services are recommended for both those with SCD and those who carry the abnormal traits

http://www.idph.state.il.us/HealthWellness/fs/sickle.htm

Athletes and SCD

- Sickle red cell accumulation and exertional sickling can occur during intense or excessive exertion
  - Severe hypoxemia, metabolic acidosis, hyperthermia in muscles, and red-cell dehydration all contribute to exertional sickling
  - Can lead to collapse from ischemic rhabdomyolysis
  - Heat, dehydration, altitude, and asthma can increase risk and/or worsen sickling
  - Exertional sickling is a medical emergency and can be fatal
- Diagnostic features of sickling collapse (vs cardiac collapse or heat collapse)
  - Symptoms present within first half-hour of exercise, when core temperatures are not greatly elevated
  - No prodrome of muscle twinges
  - Cramps are less painful vs heat cramping; patients lie still with normal muscle look and feel
  - Presents as sudden muscle weakness and slumping (vs halting with 'locked up' muscles)

https://www.nata.org/sites/default/files/SickleCellTraitAndTheAthlete.pdf

Athletes and SCD (Cont'd)

- Prevention
  - Build training up slowly and allow for longer periods of rest and recovery
  - Encourage sport-specific strength and conditioning
  - Allow exclusion from performance tests such as mile runs, serial sprints, etc.
  - Halt activity with onset of symptoms (muscle 'cramping,' pain, swelling, weakness, tenderness, inability to catch breath, fatigue)
- Treatment
  - Exertional rhabdomyolysis is a medical emergency
    - Breakdown of skeletal-muscle tissue
    - Systemic manifestations, including myoglobinuria
  - Provide aggressive IV fluid resuscitation to decrease CK levels and resolve myoglobinuria

https://www.nata.org/sites/default/files/SickleCellTraitAndTheAthlete.pdf

Nelson DA, et al. *N Engl J Med*. 2016;375(5):435-442.; Manspeaker S, et al. *JBI Database Syst Rev Implement Rep*. 2016;14(6):117-147.

Treatment Evolution for Children with SCD

- Pediatric SCD patients have lacked FDA-approved drug therapies for almost 100 years
- Blood transfusion and supportive therapies (penicillin, folic acid) have the primary treatments for pediatric SCD patients[1]
- The first two FDA-approved drugs in SCD were in 2017 with L-glutamine (July)[2] and hydroxyurea in 1998 for adults and now in pediatric patients from 2 years of age and older (December)[3]
- Two more drugs were approved in November 2019 for adolescents with SCD with voxelotor[4] in patients aged 12 years and older and crizanlizumab[5] in patients 16 years and older

1. NHLBI Publications and Resources. Evidence-based management of sickle cell disease: Expert panel report, 2014. 2. US Food and Drug Administration. FDA approved L-glutamine powder for the treatment of sickle cell disease [press release]. July 2, 2017. 3. US Food and Drug Administration. FDA approves hydroxyurea for treatment of pediatric patients with sickle cell anemia [press release]. December 21, 2017. 4. US Food and Drug Administration. FDA approves novel treatment to target abnormality in sickle cell disease [press release]. November 25, 2019. 5. US Food and Drug Administration. FDA approves crizanlizumab-tcma for sickle cell disease. [press release]. November 19, 2019.

The treatment of sickle cell disease in children have evolved. We know there's not been, believe it or not, an FDA-approved drug for sickle cell disease in children for over 100 years.

It was not until 2017 that children with sickle cell disease had an FDA-approved drug with L-glutamine, also called Endari in July 2017, followed by December 2017, that they formally approved it for hydroxyurea in children two years and older. Therefore, prior to that, blood transfusions and supportive therapies, such as penicillin, folic acid, has been the primary treatment for pediatric sickle cell patients prior to 2017. What's great now is we have two more drugs that were approved for some pediatric patients and adolescent patients with sickle cell disease. That includes in 2019 in November, voxelotor was approved in adolescents 12 and older, and crizanlizumab was approved for sickle cell patients 16 years older.

Case

- 4 y/o male with Hgb SS sickle cell disease who is maintained on hydroxyurea @ 30 mg/kg/day
- Hgb 8.0 and fetal hemoglobin (Hgb F) of 22% (MCV 100)
- Patient just experienced increase painful crises with 3 ER visits in the past 2 months

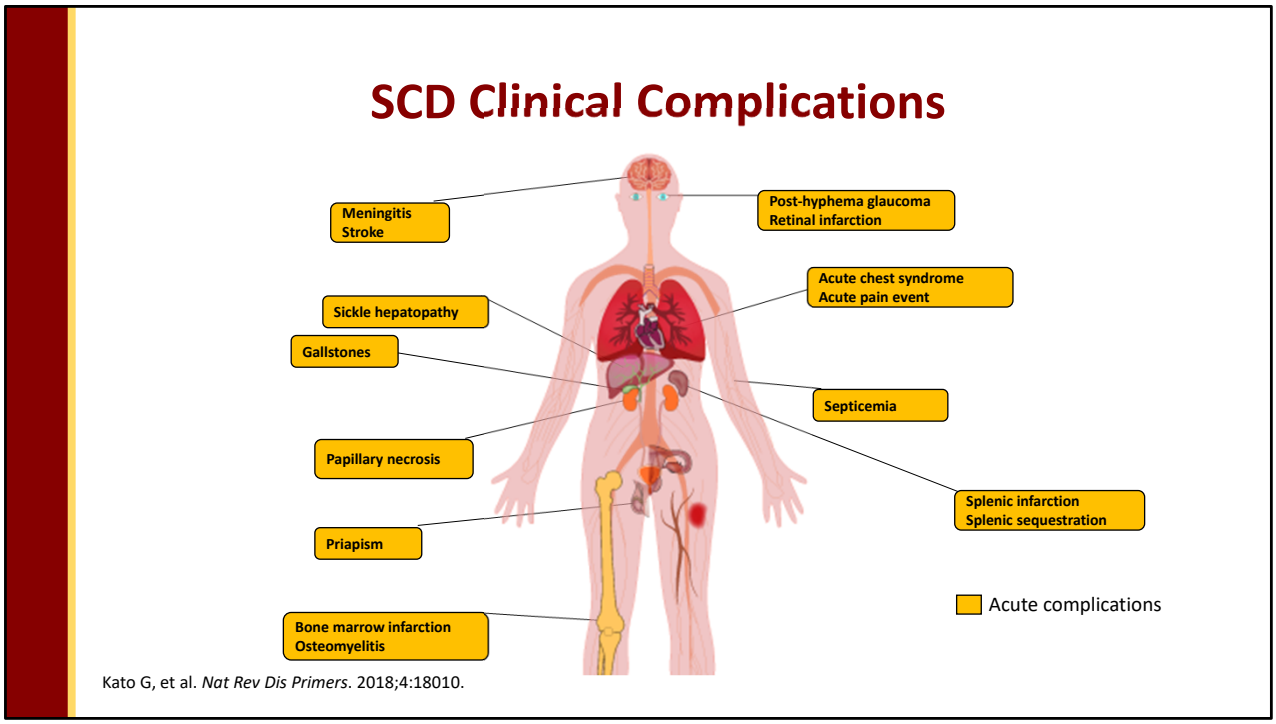
Let's talk about a case. We have this four-year-old male with sickle cell SS disease who's maintained on hydroxyurea at the maximum dose, 30 mg/kg. Now the hemoglobin level was 8.0, which is about average but it's not as high as we want it to be in a hydroxyurea, with a fetal hemoglobin of greater than 20%. That's an invisible market if you will. We'd like to shoot for a hemoglobin F of greater than 20% in our patients taking hydroxyurea.

This MCV of 100 is really shown that this patient is compliant. However, the hemoglobin is still just 8. Patient experience increased painful episodes with three ER visits in the past two months.

How Would You Treat This Patient?

- What should we do to optimize his sickle cell care?
- What are his treatment options?

What should we do for this child? What can we offer this child? What should we do to optimize his care? What are the treatment options?

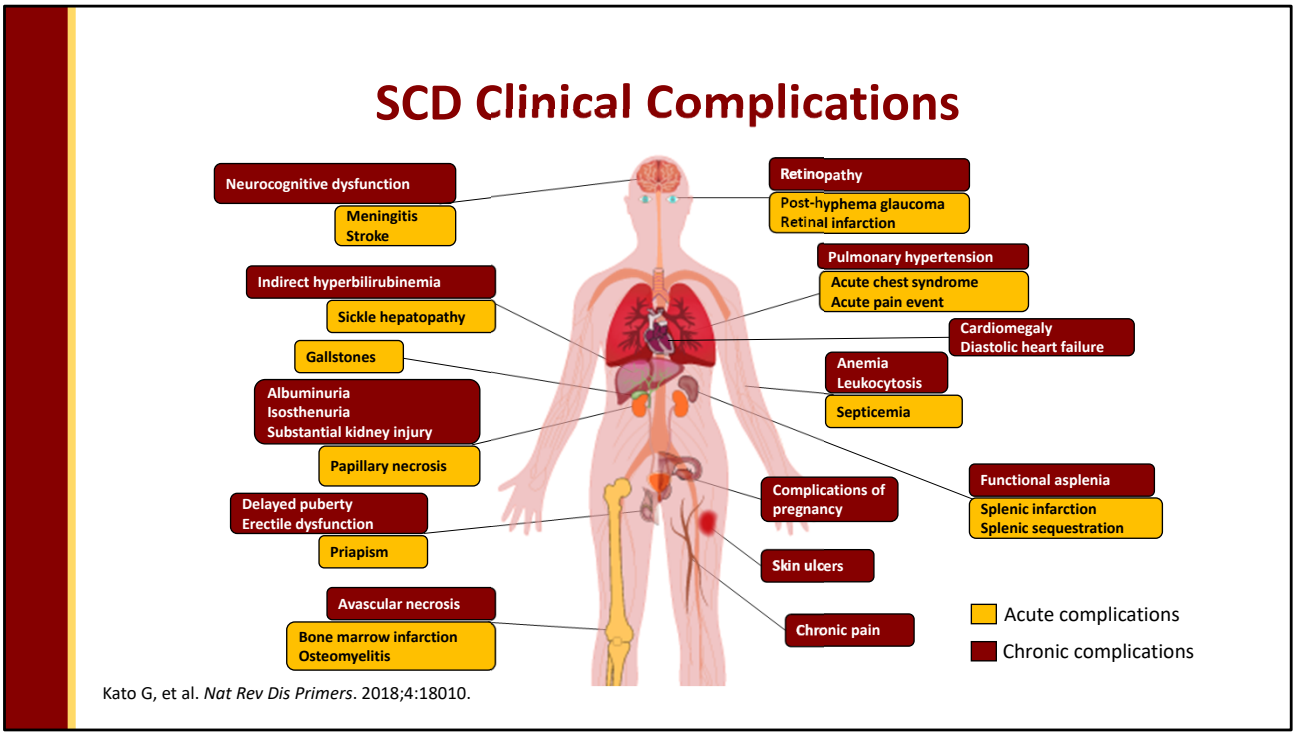


When we talk about treatment options, we've got to think about sickle cell complications. We know that sickle cell disease overall is a multiorgan damaging disease. Essentially, it affects every organ. We know that it affects the organs in pediatrics versus adults differently.

What do we know? We know the acute complications right now, which is in yellow, you can get post-hyphema glaucoma, retinal infarctions. That usually happens in adults, but in adolescents that can happen. Acute chest syndrome, which is sickling in the lungs, pneumonia, acute pain events, septicemia due to damaged spleen. That can happen in children, but also festinate splenectomize adolescent patients, meaning that they got the spleen removed. We know that splenic sequestration, splenic infarcts can happen of course. The splenic sequestration, the spleen gets trapped with blood. Blood goes into the spleen but doesn't go out. The sickle cells block the blockage of blood from coming out of the spleen, so it gets enlarged, gets bigger and smaller. We see that a lot in pediatric patients. We're seeing more of it because of the use of hydroxyurea and we don't get that autoinfarction that we generally see in SS patients because we're making the sickle cell milder now. The splenic sequestration can actually go on for beyond age 5 years of age and go on 7, 8, 9, 10 years of age.

Meningitis and stroke. Meningitis less likely with the advent of introduction of now meningitis vaccines and penicillin prophylaxis. Stroke, about 5% to 10% of children will have a stroke. We screen for stroke risks with transcranial Doppler ultrasounds between the ages of 2 and 16 years of age. Liver disease can happen. Gallstones can happen acutely. The sickle cell hepatopathy is basically sickling in the liver. Gallstones from increased turnover of red blood cells causing bilirubin gallstones. That can cause an acute what we call cystitis inflammation of the gallbladder.

Papillary necrosis in the kidneys. This is chronic damage of the kidneys. Essentially what can happen is you can have an acute injury to the kidneys and you can get what's called hematuria, where blood goes into the urine. Priapism, acute sickling in the arterial tree of the penis. That can cause significant pain in the penis, sometimes needing local irrigation by a urologist. Then bone marrow infarction. Acute pain crisis. Severe bone marrow infarctions from severe pain crisis. We can see infarcts on X-rays, sometimes even MRI, showing that severe infarction can happen in any bones where commonly in the long bones. Osteomyelitis, you see most commonly from Salmonella. You handling reptiles and around the reptilians pets and/or just having it. That is something that we see acutely and that can cause acute cholecystitis and osteomyelitis, most commonly osteomyelitis.



I'll just quickly just say chronically, all of these things could also happen. Retinopathy of the eye, pulmonary hypertension can be screened by getting an ultrasound, measuring TR jet velocity. Cardiomegaly could happen over time. The heart can be stressed, anemia, leukocytosis. High white count, very common in sickle cell disease. Asplenia, we talked about. Complications of pregnancy in women, very well known. That is something that sometimes you need transfusions during pregnancy because you can get more anemic. Skin ulcers can happen in adolescence through adulthood in very anemic sickle cell patients. Chronic pain happens over time in adolescent and young adult patients with repeated bouts of pain crisis. Neurocog dysfunction, we've seen in pediatric patients from just a chronic anemia and silent infarcts that can happen in about 30% of pediatric patients with sickle cell disease. Proteinuria in the kidneys is very, very common. We see about a third of patients by the age of 20 will have kidney disease, proteinuria.

Delayed purity, we see that. And growth, we see two years behind their peers. As patients are going through adolescence, two years behind their peers in growth and also pupal development. We always tell our families not to worry too much, it will happen. In the studies, that's happened to large studies in the past. It happens about 1.5 and 2 years later. Avascular necrosis, very common, especially in SC disease where a higher percentage of patients have that. Avas associated with dead bone in the femoral heads, in the hip bones. Second place is the shoulders and the humeral bones but can happen anywhere. In the knee, the ankles, the back. Anywhere there's bone, you can get AVN. Sickle cell is a multiorgan dysfunction disease.

Vaso-occlusive Episodes (VOEs) in Children

- Pain is the hallmark feature of SCD in pediatric patients
  - Complex, multidimensional pain
  - Nociceptive or neuropathic
  - Visceral or somatic
- Pain from VOE starts as early as the first 6-12 months of life
  - Dactylitis is often the first indicator of SCD
  - Involvement shifts to arms, leg, back, and pelvis as child ages
- VOEs typically last 3-9 days

Challenges in the Management of Pediatric Pain in Sickle Cell Disease. https://cme.dannemiller.com/articles/activity?id=310&f=1

Vaso-occlusive episodes in children. This pain is a hallmark, we know, feature of pediatric patients. It is contributed, it's complex. It could be just repeated painful episodes, but it can be multidimensional. You can have AVN, you can have acute osteomyelitis, you have trauma. It can be visceral or somatic, meaning that most of the visceral can be inside the organs. You can have splenic pain. You can have GI pain. Neuropathic pain is important because, after repeated episodes of pain, you can get neuropathic pain.

Pain crisis can start as early as six months of age with swelling of the hands and feet but then evolve into arms legs, back pelvis as the child ages. The vaso-occlusive events of pain crisis can last about three to nine days. Some of those patients will need hospitalizations for that.

Pain Management in Children

- Acetaminophen
  - Exceeding recommended daily dose can result in hepatic toxicity
- NSAIDs
  - Pain relief and peripheral anti-inflammatory activity
  - Conflicting evidence of efficacy in children
- Opioids
  - Benefits
    - Potent, centrally-mediated analgesic action
    - Multiple routes for delivery
    - Lack of ceiling effect
  - Drawbacks
    - Side effects (nausea, vomiting, pruritus, constipation, urinary retention, respiratory depression, oversedation)
    - Tolerance = higher and higher doses necessary
    - Risk for dependence

Challenges in the Management of Pediatric Pain in Sickle Cell Disease. https://cme.dannemiller.com/articles/activity?id=310&f=1

Pain management in children, generally we start with acetaminophen making sure they don't have too much. Try to do no more than four times a day. NSAIDs like Ibuprofen, we use that every six hours. We try to use those first. If those two medicines fail or they have severe and we go to opioids, it does work in most patients but does have a ceiling effect. If you keep going up and up and up, the drawbacks is just the side effects; itching, constipation, nausea, vomiting, developing high tolerance over time. Increasing the dose over time can lead to intolerance, but also a risk for dependence.

Sickle Cell FDA-approved Drugs (4)

Agent	Mode of Action	FDA Approved	Indicated Pediatric Age
Hydroxyurea[1]	Increases fetal hemoglobin Anti-inflammatory Anti-adhesion	Adults: 1998 Children: 12/2017	18 y/o and older 2 years and older
L-glutamine[2]	Anti-oxidant	2017	5 years and older
Crizanlizumab[3]	Anti-adhesion	Children and adults: 11/2019	16 years and older
Voxelotor[4]	Increases hemoglobin Red blood cell allosteric modifier (increases O_2 to sickle cells)	Children and adults: 11/2019	12 years and older

1. US Food and Drug Administration. FDA approves hydroxyurea for treatment of pediatric patients with sickle cell anemia [press release]. December 21, 2017.; 2. US Food and Drug Administration. FDA approved L-glutamine powder for the treatment of sickle cell disease [press release]. July 2, 2017.; 3. US Food and Drug Administration. FDA approves crizanlizumab-tcma for sickle cell disease. [press release]. November 19, 2019.; 4. US Food and Drug Administration. FDA approves novel treatment to target abnormality in sickle cell disease [press release]. November 25, 2019.

What are the four FDA-approved drugs that we have right now 2021? We know the hydroxyurea is approved right now. What is the mode of action? It increases fetal hemoglobin, decreases inflammation, decreases adhesion. It's FDA-approved in adults in 1998, but it took all the way to December 2017 to be approved in children two years and older.

L-glutamine, Endari is another name, is an antioxidant. Approved in July of 2017 in kids five years and older. We'll talk about that. Crizanlizumab, anti-adhesion. Used primarily to prevent pain. Also glutamine is used to prevent pain and crizanlizumab is used to prevent pain. That was approved in adolescents and adults 16 and older in November 2019. Voxelotor increases hemoglobin and improves oxygen delivery to the tissues in children and adults 12 years and older.

Considerations for the Type of Treatment: Age, How is it Given, Side Effects, Indications

- Considerations
  - Age eligibility (2 y/o, 5 y/o, 12 y/o, 16, y/o, 18 y/o)
  - Route of delivery (oral vs IV); tablet vs solution
  - Side-effect profile
- Indications
  - Prevention of ongoing end organ damage
  - Decrease the frequency of symptoms/complications
    - Pain episodes
    - Acute chest syndrome
    - Priapism
    - Lack of energy

Considerations. When we think about therapies, what do we think about? Briefly, we think about considerations. Age, route of delivery, oral versus IV. Side effect profile, if they're having lots of GI side effects. Some of these drugs can cause side effects. Prevention. What are the indications? Prevention of end-organ damage. For example, hydroxyurea, we want to just give them to prevent end-organ damage. Decrease the frequency of symptoms, painful episodes, acute chest. For painful episodes, we're thinking about not only hydroxyurea, crizanlizumab (Adakveo), and also L-glutamine (Endari). Priapism and also lack of energy. With lack of energy, you can think about voxelotor because that increases the hemoglobin level.

Sickle Cell Disease - Types of Therapies

- Categories
  - Disease modifying
    - Change the course of the disease without cure
      - Hydroxyurea
      - Crizanlizumab
      - Voxelotor
      - L-glutamine
  - Curative therapies
    - Bone marrow (stem cell) transplantation
      - Sibling match
      - Haplo (half match, ie, parent) identical match
      - Match unrelated donor
  - Gene therapy

Onimoe G, Rotz S. *Cleve Clinic J Med.* 2020;87(1):19-27.

The types of therapies put them in three different categories. You have disease-modifying therapies as we talked about. Change the course of the disease without cure. Curative therapies, for example, bone marrow transplant. They're two types. You have sibling match bone marrow transplant, you have haplo transplant, meaning half matching the parents. The other one is a match unrelated. The most common one we use is the sibling match transplant has the best outcomes. We are still studying haplo transplant from a parent because only 15% of patients will have a sibling that have a full HLA match for bone marrow transplant.

Haplo transplant is now being used more and more under clinical trial settings. Gene therapy, we'll talk about that as something that is right now experimental. About 40 to 45 patients so far have been cured of sickle cell disease right now through one clinical trial that we know of at this point.

Sickle Cell Disease - Types of Therapies

- Quality of life
  - Effective in improving or maintaining an acceptable quality of life
- Risks and benefits
  - Side effects
  - Short-term risks
  - Long-term risks
    - Development of another chronic disease (ie, GVHD) or worsening the health of another organ (ie, kidney)
    - Mortality (chance of dying from this therapy)
    - Reproductive health
      - Spermatogenesis/sperm count
      - Oocyte (eggs) damage
      - Sperm collection pre BMT
      - Oocyte (eggs) preservation pre-BMT/?

We think about the quality of life. Thinking about therapies. How can it improve their quality of life? Side effects. What's the risk and benefits? Short term, long term. Long-term, you think about developing another chronic disease such as graft versus host disease or worsening another organ system.

In going through with a curative therapy, for example, mortality, what's the chance of dying from this therapy? We know that bone marrow transplant, there is a chance to die because you can get an overwhelming infection in so some transplants that gives you lots of chemo, increased risk of infections and that can happen. You can have risk of strokes there. Transplant, if certain drugs put you at risk for that. There's lots of things to think about. Reproductive health. If there's chemotherapy involved and any of these curative therapies, you got to think about your ability to reproduce. Oocytes preservation. Those are all things that we need to think about.

Sickle Cell Disease - Clinical Scenarios

- Low hemoglobin (ie, Hgb <9.0) on maximum tolerated dose on hydroxyurea
  - Voxelotor
  - Erythropoietin-stimulating agents
- Persistent pain on hydroxyurea on maximum tolerated dose on hydroxyurea
  - Crizanlizumab
  - L-Glutamine
- Development of severe red blood cell antibodies or history of hyperhemolysis
  - Erythropoietin ± hydroxyurea
  - Voxelotor

Also in terms of clinical scenarios, low hemoglobin, think about voxelotor during a maximum tolerated dose hydroxyurea or erythropoietin. We can use that too to further increase the hemoglobin level. Persistent pain or hydroxyurea in a maximum tolerated dose. We can give L-glutamine. We can give crizanlizumab also. Also, these clinical trials all had hydroxyurea as part of their patients that were enrolled in the study, they showed to be effective in addition to being on hydroxyurea. Those who were on hydroxyurea, they also benefited of having these drugs added to their regimen to decrease pain or increase hemoglobin. Also, someone who has a lot of red blood or antibody from repeated blood transfusions, erythropoietin plus hydroxyurea. Voxelotor is also optional.

Recommended Treatment Approaches

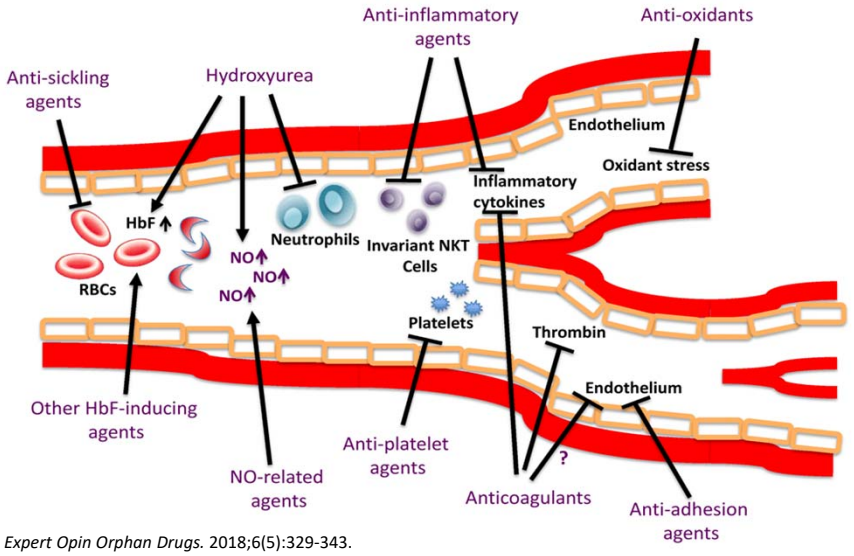
Treatment Approach	Dose and Frequency	Duration	Recommendation	Evidence Quality	Availability in Low Resource Areas
Prevention of infection					
Penicillin V	62.5-250 mg twice daily	At least until 5 yr of age	Strong	Moderate	Available
Pneumococcal vaccines	Every 5 yr, starting at 2 yr of age	Lifelong	Strong	Moderate	Limited availability
Malarial prophylaxis when appropriate	Daily (eg, proguanil), weekly (eg, pyrimethamine), or intermittent (eg, mefloquine-artesunate or sulfadoxine-pyrimethamine plus amodiaquine)	Lifelong (in malarious area)	Strong	Low	Available
Blood transfusion					
Acute care					
Treatment of anemia	Simple transfusion; target Hb level 10 g/dl	Limited	Strong	Low	Limited availability
Preoperative transfusion (if Hb <8.5 g/dl)	Simple transfusion, performed once; target Hb level 10 g/dl		Strong	Moderate	Limited availability
Ongoing care					
Primary stroke prevention	Target HbS <30%; transfusions every 3-6 wk	Indefinite	Strong	High	Very limited availability
Secondary stroke prevention	Target HbS <30% or <50%; transfusions every 3-6 wk	Indefinite	Moderate	Low	Very limited availability
Prevention of additional silent cerebral infections	Target HbS <30%; transfusions every 3-6 wk	Indefinite	Moderate	Moderate	Very limited availability
Hydroxyurea					
Universal use	20-35 mg/kg/day	Indefinite	Moderate	Moderate	Limited availability
Prevention of acute complications	15-35 mg/kg/day	Indefinite	Strong	High	Limited availability
Primary stroke prevention	15-35 mg/kg/day	Indefinite	Strong	Moderate	Limited availability

*Data on recommended treatments, the strength of the recommendation, and the quality of the evidence are from DeBaun MR, et al. *N Engl J Med.* 2014;371:699-710., Ware RE, et al. *Lancet.* 2016;387:661-670.; and Yawn BP, et al. *JAMA.* 2014;312:1033-1048. Data availability in low resource area are from Bello-Manga H,et al. *Expert Rev Hematol.* 2016;9:1031-1042. HbS denotes sickle hemoglobin

Piel FD, et al. *N Engl J Med.* 2017;376(16):1561-1573.

I know it's very hard to read. I'm not going to go into detail here. This is a nice summary slide from *The New England Journal of Medicine* just showing you all the dose and frequency of all the treatments that we give. Testing pediatrics pneumococcal vaccines, malaria prophylaxis in subterranean Africa, penicillin, then blood transfusions for acute care, those who have elevated TCD velocities, stroke prevention, or secondary stroke prevention. You see all those. The duration recommendation and then hydroxyurea here. These are the summaries I thought was really nice in 2017, but now we have two new ones.

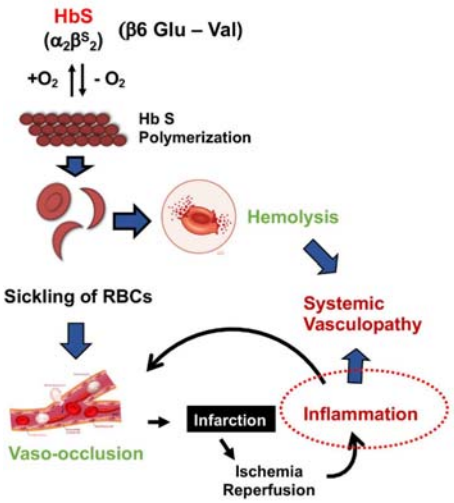
How Do New Sickle Cell Treatments Work?



Ataga KI, Desai PC. *Expert Opin Orphan Drugs.* 2018;6(5):329-343.

How does sickle cell treatments work? Again, this is just a quick schematic diagram just showing you now this is very cut complex. As we understand sickle cell disease, you see how hydroxyurea works; no white cells, increased fetal hemoglobin, improving nitric oxide delivery, anti-inflammatories, anti-antioxidants, for example, L-glutamine (Endari), antiplatelet agents . All throughout the vessel wall, you can see all of these factors. Inflammatory factors, adhesion factors, and coagulation factors all play a role, we think, in the genesis of sickling.

Targets of Treatments for SCD



- Change the genotype
  - Allogeneic BMT
  - Autologous HSCT modification
- Target HbS polymerization
  - Increase fetal hemoglobin
    - Genetic and genomic approaches
      - Suppressing BCL11A
      - Simulate HPFH variants
    - Pharmacologically (eg, hydroxyurea)
  - Hb O_2 affinity
- Targeting vaso-occlusion
  - Inhibiting adhesive interactions between cells and endothelium
- Targeting inflammation
  - Feedback loop of sterile inflammation that promotes further vaso-occlusion
  - L-glutamine
  - Inflammasome inhibition

Salinas Cisneros G, Thein SL. *Front Physiol.* 2020;11:435.

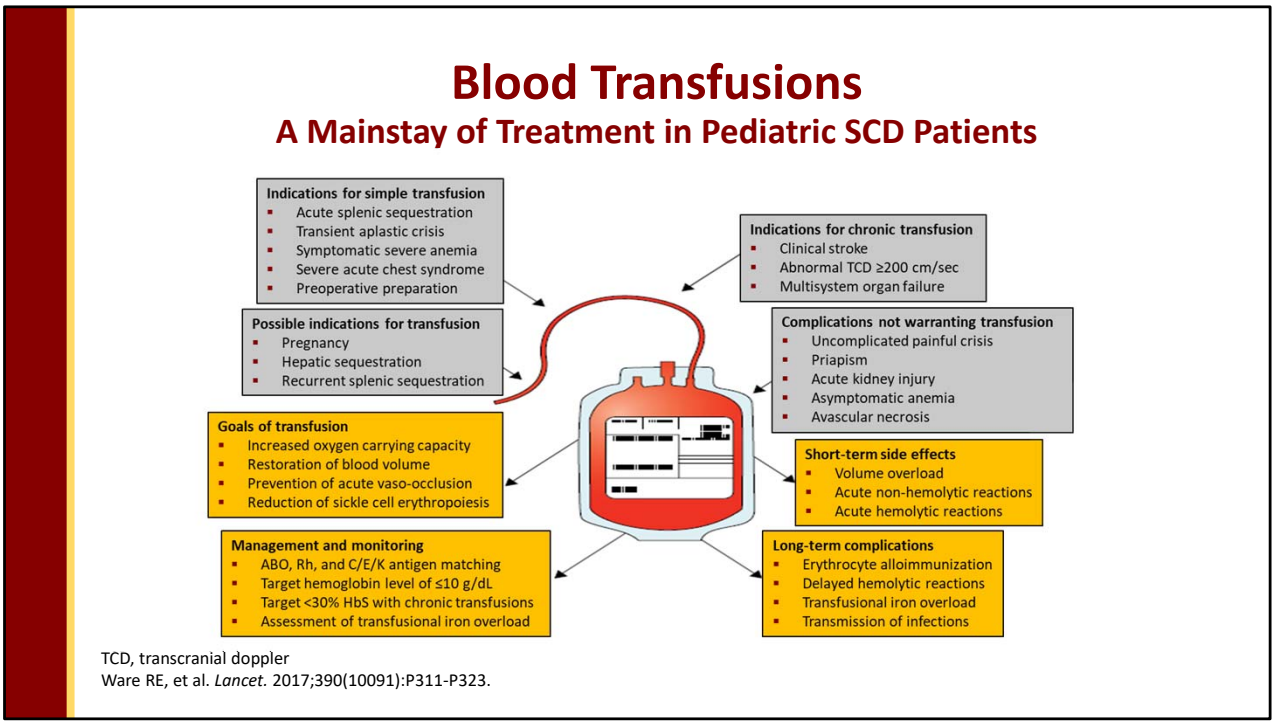
This is just another schematic diagram just showing on the left how these all play a role at the genetic level, how the sickle cell polymer-- There is this loop of how the sickling happens in red blood cell and then you have hemolysis. On the other side, you have sickling. Once you break down hemolysis, that causes systemic vasculopathy that feeds into inflammation, the inflammation feeds into vaso-occlusion. When we think about treatments, we are also targeting these areas of the genotype with transplant and a hemoglobin S polymerization with fetal hemoglobin. Things like voxelotor targets vaso-occlusion. Also, crizanlizumab (Adakveo) targets vaso-occlusion, and also inflammation like L-glutamine.

Categories of Treatment Options

	Hydroxyurea (FDA approved)	Ribonucleotide diphosphate reductase inhibitor
Hemoglobin S polymerization	LBH589/panobinostat (NCT01245179)	Pan histone deacetylase inhibitor
	Voxelotor/GBT440 (NCT03036813) (FDA approved)	α-Globin reversible binding
	Decitabine/THU (NCT01685515)	DNMT1 inhibition
	Sanguinate (NCT02411708)	Targeting carbon monoxide delivery
Vaso-occlusion	IMR-687 (NCT04053803)	Phosphodiesterase 9 inhibitor
	L-Glutamine (FDA approved)	Increase NADH and NAD redox potential
	Crizanlizumab (NCT03264989) (FDA approved)	P-selectin inhibitor
	Heparinoids: Sevuparin (NCT02515838)	P-selectin and L-selectin inhibitor
	Poloxamer and Vepoloxamer	Nonionic block copolymer surfactant
Inflammation	Prasugrel, ticagrelor (NCT02482298)	P2Y2 inhibitors
	Intravenous immunoglobulin (NCT01783691)	Effects on neutrophils and monocytes activation
	Simvastatin (NCT03599609)	Vascular endothelium
	Rivaroxaban (NCT02072668)	Anti factor Xa
	N-Acetylcysteine (NCT01800526)	Oxidative stress reduction

THU, tetrahydrouridine; DNMT1, DNA methyltransferase type 1
Salinas Cisneros G, Thein SL. *Front Physiol.* 2020;11:435.

These are the treatment categories just showing you each one of those. I won't go into detail. Some of these drugs right now are in clinical trials. We have got new ones. You can see showing you in the left is basically the different types. Crizanlizumab is a P-selected inhibitor L-glutamine increases NDH. These are just all of the overall treatments categories that we talk about.



Blood transfusions, I won't go over into detail. We have acute goals of transfusions and then we have chronic goals of transfusions. We talked about this before for simple transfusions, splenic sequestration, acute crisis, aplastic crisis, severe acute chest syndrome, pre-operative preparation, pregnancy. You can go on and on. Then prevention for chronic blood transfusions on the right, that's for chronic strokes. Elevated transcranial Doppler velocity more than 200 centimeters per second, multiorgan failure so that would be something that we also look at.

Benefits of Each Therapy

Hydroxyurea	
Anemia/hemolysis	⬇
Vaso-occlusion	⬇
Acute chest syndrome	⬇
Stroke	?
Nephropathy	?
Pulmonary hypertension	?
Fatigue and QOL	⬇ for some patients
Mortality	⬇

L-Glutamine	
Anemia/hemolysis	➡
Vaso-occlusion	⬇
Acute chest syndrome	⬇
Stroke	No evidence
Nephropathy	No evidence
Pulmonary hypertension	No evidence
Fatigue and QOL	➡
Mortality	No evidence

Voxelotor	
Anemia/hemolysis	⬇
Vaso-occlusion	➡
Acute chest syndrome	➡
Stroke	No evidence
Nephropathy	No evidence
Pulmonary hypertension	No evidence
Fatigue and QOL	➡
Mortality	No evidence

Crizanlizumab	
Anemia/hemolysis	➡
Vaso-occlusion	⬇
Acute chest syndrome	➡
Stroke	No evidence
Nephropathy	No evidence
Pulmonary hypertension	No evidence
Fatigue and QOL	➡
Mortality	No evidence

These are the benefits, a nice summary slide of benefits of each treatment. I'm going to wrap it up in a couple of minutes because I'm going to talk about this.
Really the hydroxyurea decreases hemolysis, vaso-occlusion, acute chest syndrome. L-glutamine does the same with vaso-occlusive acute chest syndrome. The fatigue and quality of life both for L-glutamine and hydroxyurea as it relates to voxelotor and crizanlizumab. Voxelotor decreases anemia and hemolysis primarily, and then crizanlizumab improves vaso-occlusion primarily.

Hydroxyurea

- The most effective disease-modifying drug in sickle cell disease in adults and children
- Offered to children 9 months and older.[1] FDA approved for children aged 2 years and older in 2017
- MSH (adults): HU reduced frequency of pain crisis, hospitalization, acute chest syndrome to by 50%; decreased mortality in adults[2]
- BABY HUG: safety and efficacy in infants with SCA[3]
- Common adverse effects: suppression of blood counts, rash, stomach discomfort

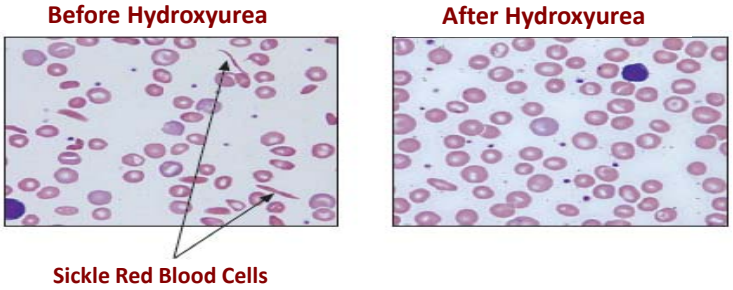
1. NHLBI Publications and Resources. Evidence-based management of sickle cell disease: expert panel report, 2014. Accessed January 6, 2021.
2. Charache S, et al. *N Engl J Med.* 1995;332(20):1317-1322. 3. Thornburg CD, et al. *Blood.* 2012;120(22):4304-4310.

Basically, hydroxyurea is the most effective disease-modifying treatment in adults and children. Decrease pain crisis by 50%, hospitalization by 50%, acute chest syndrome by 50%, decreased mortality in adults.

Hydroxyurea - How Does it Work

Red Blood Cell Changes

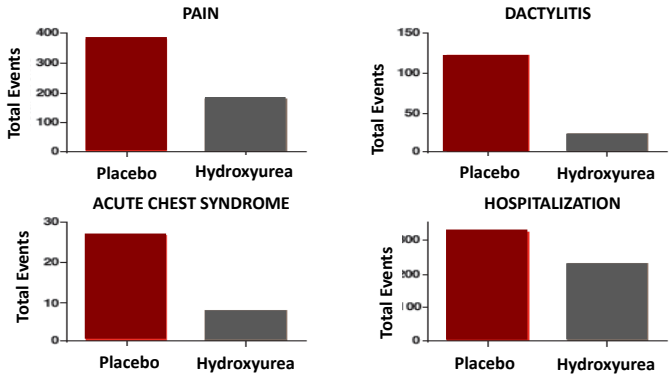
- How does hydroxyurea work?
  - Makes increases red blood cell (Hgb F) size and less likely to sickle
  - Increases fetal hemoglobin (Hgb F) and decreases inflammation in SCD patients



Ware RE. *Blood.* 2010;115(26):5300-5311.; Thornburg CD, et al. *Blood.* 2012;120(22):4304-4310.

I'm just showing you the before and after changes in hydroxyurea on the peripheral blood smear.

Baby HUG Study Results



- **In this study, hydroxyurea did not cause any serious side effects**
- Children treated with hydroxyurea did not have more infections
- Children treated with hydroxyurea did not have more liver or kidney problems

Thornburg CD, et al. *Blood.* 2012;120(22):4304-4310.

Then this is from the BABY HUG study in babies showing you that hydroxyurea significantly lowered pain rates in babies on the average of 12 months of age versus the placebo group. Pain and dactylitis, dactylitis is another form of pain crisis in baby acute chest syndrome and even hospitalizations.

Current Curative Therapies/Strategies

Changing the genotype		
(1) Allogeneic stem cell transplant	Myeloablative regimens (MAC), reduced intensity regimens (RC), and non-myeloablative regimens (NMA)	50 clinical trials listed in ClinicalTrials.gov
(2) Autologous transplant		10 clinical trials listed in ClinicalTrials.gov
	a) Gene therapy Lentiviral strategies (NCT02247843, NCT02140554, NCT02186418)	
	Inducing fetal hemoglobin	Downregulation of *BCL11A* (NCT03282656) Globin chromatin structure manipulation Downregulating beta globin expression
	b) Gene editing Using zinc finger nucleosomes (ZFN), transcription activator-like effector nucleases (TALENs), CRISPR/Cas9 techniques (NCT03745287)	Downregulation of *BCL11A* Reactivation of HbF by HPFH mutations Globin gene repair

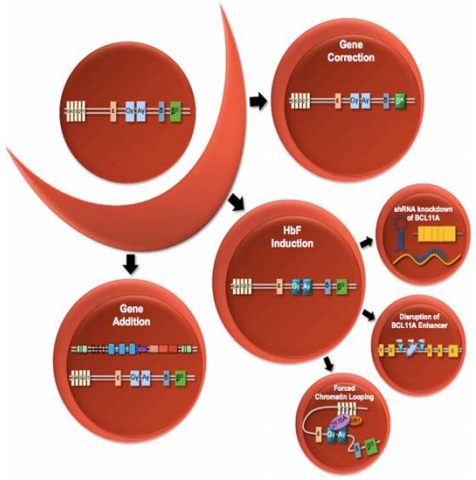
Salinas Cisneros G, Thein SL. *Front Physiol.* 2020;11:435.

Curative therapies. Right now, there's over 50 clinical trials for allogeneic transplant, autologous transplant, gene therapies. We have a number of gene therapies.
Gene therapy and gene editing, there are at least four to five right now that we have ongoing targeting different-- There's lentiviral targeted strategy that's called gene addition to add a new hemoglobin, a fetal hemoglobin inside the gene to make them like a trait patient. Then gene editing where you're changing one of the molecular markers in the red blood cells the one that's telling them to make more fetal hemoglobin so turning fetal hemoglobin back on. Making substantial amounts of fetal hemoglobin. They can do that through CRISPR technology or TALEN's transcription activator like a factor nucleases or zinc-finger nucleases. All of these are new gene-editing techniques that we're still learning today early on in clinical trials.

Gene Therapies
"Disease Modifying" vs "Curative-Like Results"

- Approaches to Gene Therapy:

1. Addition of a helpful gene (Gene Addition)→ the level of production of this" new hemoglobin" determines how well it changes the course of the SCD
2. Gene knockdown (eg, Bcl11A) to Improve hemoglobin F levels → level of production fetal Hgb determines how well it changes the course of disease



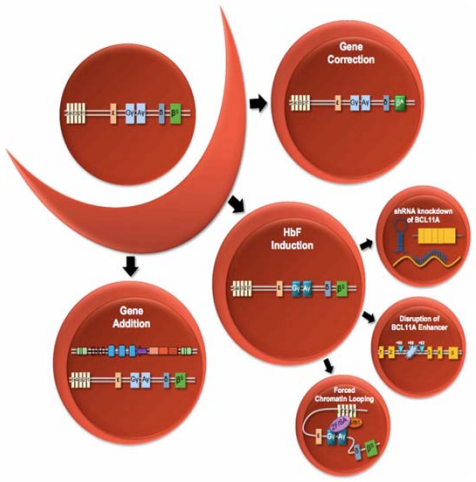
Salinas Cisneros G, Thein SL. *Front Physiol.* 2020;11:435.

These are all the disease-modifying versus curative therapies. Like I talked about before, either adding a new gene versus knocking down a gene such as BCL11A that reactivates fetal hemoglobin.

Gene Therapies
"Disease Modifying" vs "Curative-Like Results"

- Approaches to Gene Therapy:

3. Direct globin gene editing to "correct" the mutation present (eg, changing a hemoglobin S [HbS]–encoding gene to one encoding hemoglobin A)
4. Gene editing of globin regulatory elements, to at least partially reverse the normal hemoglobin switching from fetal to adult hemoglobin



Salinas Cisneros G, Thein SL. *Front Physiol.* 2020;11:435.

I'll just keep going here. I'm not going to go over this too much.

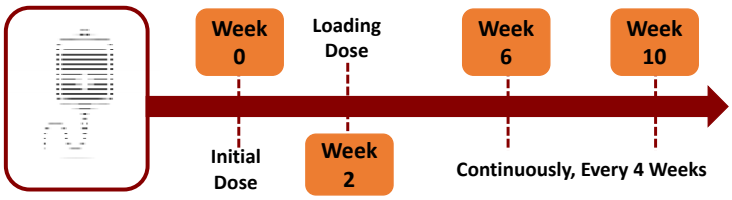
Indications for HSCT Balanced with Donor: Risk/Benefit Ratio Consideration Availability

Matched sibling donor	Matched unrelated donor or minimally mismatched good quality cord product	Mismatched marrow donor, haploidentical donor
• Stroke • Elevated TCD velocity • Acute chest syndrome • VOC • Pulmonary Hypertension/tricuspid regurgitation jet velocity.2.5 m/s • Osteonecrosis/AVN • Red cell alloimmunization • Silent stroke specially with cognitive impairment • Recurrent priapism • Sickle nephropathy	• Stroke • Elevated TCD velocity • Recurrent acute chest syndrome despite supportive care • Recurrent severe VOC despite supportive care • Red cell alloimmunization despite intervention plus established indication for chronic transfusion therapy • Pulmonary hypertension	• Recurrent stroke despite adequate chronic transfusion therapy • Inability to tolerate supportive care though strongly indicated, e.g., red cell alloimmunization, severe VOC and inability to take hydroxyurea

Salinas Cisneros G, Thein SL. *Front Physiol.* 2020;11:435.

I think we talked about this in terms of your sibling donor match, unrelated donor, and a mismatch haploidentical, why we would do each one of those? You can see a match sibling donor, the indications are very, very wide. For the unrelated donor or a haploidentical donor, the indications are actually more narrow. For the haploidentical identical donor, right now they're using silent infarction in strokes as an indication for that group.

Crizanlizumab: Anti-stickiness/Adhesion of Cells to the Vessel Wall and to Each Other (Anti-P Selectin)



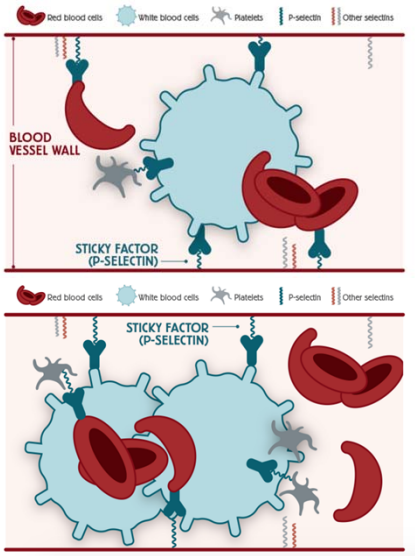
- Approved to decrease the frequency of vaso-occlusive crises in adults and children 16 y/o and older
- Given as an IV infusion every 4 weeks after after initial and loading doses during Week 0 and Week 2

Ataga KI, et al. *N Engl J Med.* 2017;376(5):429-439.

Crizanlizumab. The last three or four slides are just to say that crizanlizumab is anti-stickiness, anti-adhesion. This slide is showing you that basically to do this, it has to be in generally an infusion center. We give them two loading doses, week 0 and week 2, and we give it every month. Basically, every four weeks thereafter. It takes about six months to see a response to say they're a responder or not. It takes a while to see.

Crizanlizumab

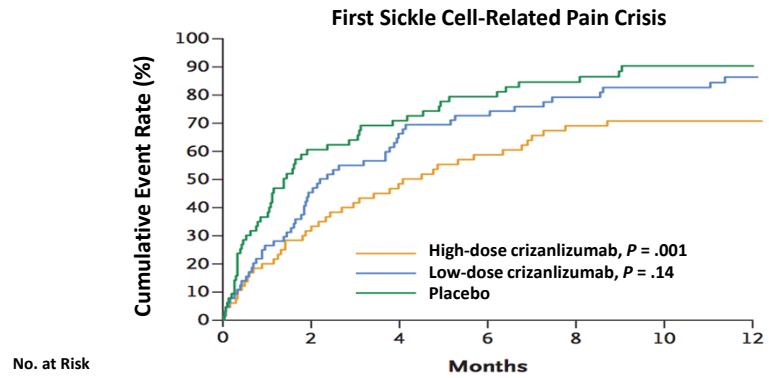
- **Crizanlizumab attaches to P-selectin,** which plays a key role in vaso-occlusion
- By attaching to P-selectin, **crizanlizumab blocks connections** between certain cells such as red blood cells, white blood cells, and platelets



Ataga KI, et al. *N Engl J Med.* 2017;376(5):429-439.

It attaches to the vessel wall. We talked about P-selectin and that's a sticky protein that actually causes white cells and platelets to stick to each other. What crizanlizumab does, it blocks the P-selectin interaction of these cells in the vessel wall.

Crizanlizumab (Anti P-Selectin)



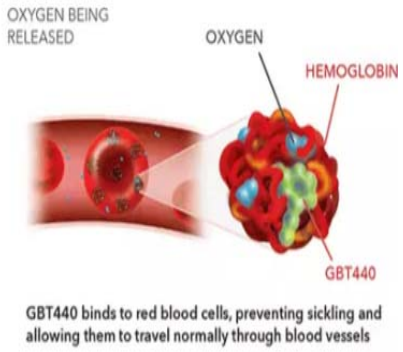
No. at Risk												
High-Dose Crizanlizumab	67	49	41	35	30	26	24	20	18	17	16	15	7
Low-Dose Crizanlizumab	66	47	34	28	21	19	17	15	12	10	10	10	3
Placebo	65	37	23	21	17	13	12	9	8	6	5	4	1

Crizanlizumab significantly **reduced** the median annual rate of VOCs by **approximately 45% vs placebo** (**1.63 vs 2.98, respectively; *P* =.010)**.
Reductions in VOC frequency were observed regardless of SC disease genotype and/or hydroxyurea use.
Ataga KI, et al. *N Engl J Med.* 2017;376(5):429-439.

It showed a significant decrease in pain crisis; 45% decrease. Annualized pain crisis rate, 1.63 versus 2.98, which is statistically significant.

Voxelotor

Mechanism of Action and Potential for Disease Modification



- Voxelotor binds to the a-globin chain of Hb resulting in an allosteric modification of Hb which increases Hb-O_2 affinity; leftward shift in Oxy-Hb dissociation curve
- Decreases polymerization tendency of deoxy-HbS
- Improves sickle red cell survival increases in Hb and decrease reticulocyte count

Blyden G, et al. *Am J Hematol.* 2018 May 12. doi: 10.1002/ajh.25139.; Howard J, et al. *Blood.* 2019; 133(17): 1865-1875.; Hutchaleelaha A, et al. *Br J Clin Pharmacol.* 2019; 85(6): 1290-1302

Voxelotor is our other one I want to talk about. Mechanism of action, it binds to the alpha-globin chain, causes the chains to change, the hemoglobin to change, increases oxygen affinity, and it allows the sickle cells to actually buy more oxygen and to deliver more oxygen to the tissues. It improves that.

Voxelotor

- Hemoglobin S polymerization inhibitor indicated for the treatment of sickle cell disease in adults and pediatric patients 12 years of age and older[1]
- Given once-daily (1500 mg) as 500 mg tablets[1]
- Voxelotor is designed to work by ***helping hemoglobin,*** the molecules inside red blood cells, ***hold onto more oxygen as the red blood cells*** travel through the body[2]
- This keeps red blood cells in their normal shape and helps stop sickling[2]

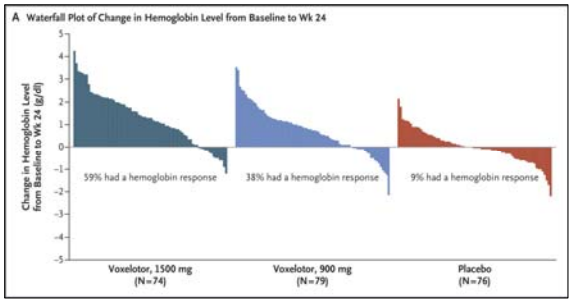
Reduce dose to 1000 mg daily in severe liver disease or if the patient is taking strong CYP3A4 inhibitors; increase dose to 2500 mg QD with CYP3A4 inducers

QD=daily

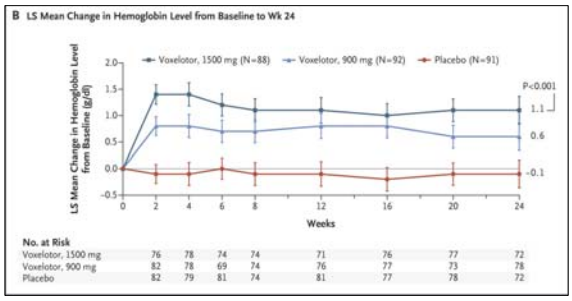
1. Oxbryta® (voxelotor) [package insert]. Global Blood Therapeutics, Inc: South San Francisco, CA. 2019. 2. Vichinsky E, et al. *N Engl J Med.* 2019;381(6):509-519.

One of the things we just want to say is given to kids 12 and older but we need to reduce the dose from the 1,500 milligrams. As it's FDA-labeled use 1,500 milligrams a day, decrease it to 1,000 in a severe liver disease or taking any strong CYP3A4 inhibitors and increase the dose if they're taking CY3A4 inducers. We talked about why it helps.

Voxelotor Improves Hemoglobin in Majority of Patients – HOPE Study Results From Baseline to Week 24



59% of those on 1500 mg demonstrated a hemoglobin response compared to only 9% in placebo group



1500 mg dose group had mean change of 1.1 in hemoglobin from baseline compared to 0.1 in placebo group

Vichinsky E, et al. *N Engl J Med*. 2019;381:509-519.

This is just showing you in the study from the HOPE trial showing that it increased, 59% of those patients, demonstrated a hemoglobin response. That was very encouraging versus only 9% of placebo group. The mean change of hemoglobin is 1.1 from baseline compared to 0.1 versus the placebo group that's on the right.

HOPE Study – Phase 3 Trial of Voxelotor in SCD

- 274 participants were randomly assigned in a 1:1:1 ratio to receive a once-daily oral dose of 1500 mg, 900 mg of voxelotor, or placebo
- 90% had severe genotype homozygous hemoglobin S or hemoglobin SB0 – thalassemia
- Approximately two-thirds (65%) were receiving hydroxyurea at baseline
- Voxelotor significantly increased hemoglobin levels and reduced markers of hemolysis

Vichinsky E, et al. *N Engl J Med*. 2019; 381(6):509-519.

In the HOPE trial, the updated trial is showing you out of 274 participants, approximately 65% were receiving hydroxyurea at baseline. They significantly increase hemoglobin levels and reduce markers of hemolysis in those groups.

Voxelotor Ongoing Trials

HOPE Kids 1 Study Phase IIa Ongoing

- Safety , pharmacokinetics, and early effectiveness in up to 155 children with SCD
- Four-part study each involving ages ranging from 9 months to 17 years
- Assigned to single or multiple doses of therapy

https://clinicaltrials.gov/ct2/show/NCT03036813.; https://clinicaltrials.gov/ct2/show/NCT02850406.; https://www.gbt.com/pipeline/sickle-cell-disease

We're also looking at it in children. Right now, up to 155 patients with sickle cell disease, 9 months to 17 years of age assigned a single dose of multiple doses of therapy so this is something that's ongoing looking at children.

L-Glutamine

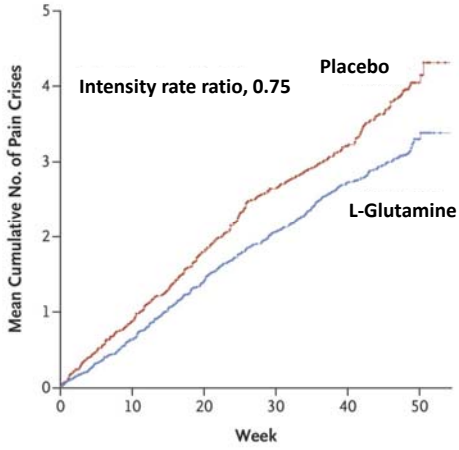
- Essential amino acid
- Increased levels are needed in certain conditions (such as stress in the red blood cell)
- Indicated to ***reduce the acute complications of sickle cell disease*** in adult and pediatric patients 5 years of age and older
- Uptake of L-glutamine is several times **greater in sickle red cells** than in normal red cells primarily to increase the total intracellular NAD level

Endari® (L-glutamine oral powder) [package insert]. Emmaus Medical, Inc: Torrance, CA. 2020.

The last disease-modifying group is L-glutamine which is to reduce the rate of acute complications of sickle cell disease in children 5 years and older. The L-glutamine uptake in sickle cells is several times greater than normal red blood cells.

Recurrent Events of Sickle Cell-Related Pain Crisis Over Time, According to Trial Group

- The cumulative number of painful crises was 25% lower in the L-glutamine group than in the placebo group over the entire 48-week treatment period



Niihara Y, et al. *N Engl J Med.* 2018;379(3):226-235.

You can see that there's a 25% reduction of pain-related crisis versus placebo in those patients taking hydroxyurea over 48-week treatments on trial.

L-Glutamine

- 5 g to 15 g orally, twice daily based on body weight
- Each dose of L-glutamine should be mixed in 8 oz. (240 mL) of cold or room temperature beverage or 4 oz. to 6 oz. of food before

Recommended Dosing

Weight (kilograms)	Weight (pounds)	Per dose in grams	Per day in grams	Packets per dose	Packets per day
Less than 30	Less than 66	5	10	1	2
30 to 65	66 to 143	10	20	2	4
Greater than 65	Greater than 143	15	30	3	6

Endari® (L-glutamine oral powder) [package insert]. Emmaus Medical, Inc: Torrance, CA. 2020.

One of the last slides is just showing you basically the bottom line is L-glutamine is given in packets 5-, 10-, and 15-milligram packets based on weight. You can give one to two to three packets per day to a maximum of 30 milligrams daily.

Exciting Times Are Here!

- SCD: Chronic, lifelong, debilitating condition resulting in multiorgan dysfunction and decreased lifespan
- BUT new therapies are here and are on the horizon!!

Exciting times are here. Sickle cell is a chronic, lifelong debilitating condition resulting in multiorgan dysfunction and decreased lifespan while we have exciting new therapies are here on the horizon. Thank you so much for listening. Now I'll pass on the baton to Dr. Lanetta Bronté-Hall. Thank you.

Sunshine Sickle Cell Project: A Quality Improvement Initiative

Therapies for Pediatric Patients with Sickle Cell Disease

The Sunshine Sickle Cell Project Quality Improvement Initiative

- **Goal**: Improve the quality of care for adult and pediatric patients with SCD in Florida
- **Participants**: Clinicians across Florida who participated in the educational interventions and provide care for patients with SCD
- **Lead investigator**: Dr. Lanetta Bronté-Hall

Dr. Lanetta Bronté-Hall: You've heard a wonderful presentation. With everything, we always try to figure out how do we actually implement and monitor the standard of care that we do want to implement. The Sunshine Sickle Cell Project Quality Improvement Initiative will do just that. Our goal is to improve the quality of care for adult and pediatric patients with sickle cell disease in the State of Florida. We want to work with clinicians across Florida who participate in the educational interventions and provide care to patients with sickle cell disease. I'm your lead investigator.

Why Should I Participate in a SCD QI Project?

- Disparities in care exist for patients with SCD and their families, which contributes to suboptimal outcomes
- Reimbursement for care has shifted from fee-for-service to value-based models in which payments are tied to the quality of services delivered, as opposed to the volume
- Quality improvement projects allow clinicians, working within a team, to identify an issue and implement interventions that can result in improvements in healthcare quality that result in improved outcomes for patients with SCD

What gaps in care have you identified in your practice setting?

Why should you participate in a sickle cell disease QI project? We know disparities in care exist for patients with sickle cell disease in their families. Ultimately, this contributes to sub-optimal outcomes.

Reimbursement for care has shifted from fee-for-service to value-based models where payments are tied to quality of services delivered. We've proven, for example, where we've saved the health plan $342 per person per month based on the quality initiatives that we have with that particular plan. Quality improvement projects allow clinicians working within a team to identify an issue and implement interventions that can result in improvements in healthcare quality that result in improved outcomes for patients with sickle cell disease.

What we want to do is identify your gaps in care in your setting and it may be setting specific. You may have gaps that are very different from another practice but our goal is to work within your practice and your resources.

Examples of Successful QI Projects in SCD

- Balsamo L, Shabanova V, Carbonella J, et al. Improving Care for Sickle Cell Pain Crisis Using a Multidisciplinary Approach. *Pediatrics.* 2019;143(5):e20182218; DOI: https://doi.org/10.1542/peds.2018-2218
- Adams-Graves P, Ostric E, Martin M, et al. Sickle cell hospital unit: a disease-specific model. *J Healthc Manag.* 2008;53(5):305-315; discussion 316-317.
- Kanter J, Jordan LB. Improving the healthcare model for management of adults with sickle cell disease in the PPACA era. *J Hematol Transfus.* 2015;3(1):1037.
- Third Annual Sickle Cell Disease Research and Educational Symposium and Grant Writing Institute and Annual National Sickle Cell Disease Scientific Meeting. Jordan L, Bruce B. Joint Commission Sickle Cell Disease Specific Care-Accountability that Works. 2009. Abstract# 403.
- **Memorial Sickle Cell Day Hospital at Memorial Regional Hospital-A Solution That Works. 2011.**
- LaVista JM, Treise DM, Dunbar LN, et al. Development and evaluation of a patient empowerment video to promote hydroxyurea adoption in sickle cell disease. *J Natl Med Assoc.* 2009;101(3):251-257. doi: 10.1016/s0027-9684(15)30853-1.
- Florida Health Care Transition Services Task Force for Youth and Young Adults with Disabilities. Report and Recommendations Implementation of Senate Bill 988. Ensuring successful transition from pediatric to adult health care. http://www.floir.com/siteDocuments/2009_fl_hct_task_force_report-cms.pdf

What are some examples of a successful QI project? I've actually participated and created one at Memorial Regional Hospital where I was for 11 years. That QI project came along with being certified by the Joint Commission for Sickle Cell Disease. I know that it can't be done, but it will take some resources and some interest from your perspective.

What We Look at and How We Measure

Qualitative measures
- Routine health care maintenance
- Care planning for SCD patients
- Acute care
- Assessment, treatment, and management of acute pain crises
- Patient satisfaction with care
- Patient-reported outcomes measurement; PROMS

Quantitative measures
- Health care use
- ED visits
- Hospital readmission rates
- ICU admission rates

What does it look like in terms of what we measure? We look at both qualitative and quantitative measures. On the qualitative side, there can be indicators for routine healthcare maintenance, care planning. Some of these are already built into your EHRs, so you get credit for these working with your plans already, but we can tweak them a little bit and make some enhancements specifically for sickle cell disease.

Management of acute pain crisis, for example, how satisfied are the patients with care? We know that they do have some issues with some of the providers and they do make complaints a lot to administrators. Some of you may have been on the opposite end of that where you've received some of those complaints. We want to be proactive and actually understand if you are receiving complaints, how we can make that better for you as well.

On the quantitative side, what about the healthcare use? Are the patients going to the ED a lot? Are they having long lengths of stay? What about the ICU admissions? We'll work with you so that we can create a tool to actually monitor some of these indicators.

Quality Improvement Indicators

- ↑ Increase in care planning and management
- ↑ Increase in the appropriate assessment, treatment and management of sickle cell disease
- ↑ Increase in patient/family education and shared decision making
- ↓ Reduction in the number of ED visits for acute vaso-occlusive crisis

We will increase the care planning and management of your patients. Again, we'll do that within a team. We'll increase the appropriate assessment treatment and management of sickle cell disease using standard practice guidelines from the National Institutes of Health and also the American Society of Hematology. We'll increase patient and family education and shared decision-making, which is so important for this patient population, and for any patient population is really to include patient and families in the decision-making process. Overall, these initiatives will lead to a reduction in ED visits and acute vaso-occlusive crises.

Quality Improvement Action Planning℠

6 Steps	4 Plans
1. What is the problem?	1. Plan A: Immediate actions to minimize harm
2. What is causing the problem?	2. Plan to get data
3. What is the goal?	3. Plan to act
4. What steps will we take to reach the goal?	4. Plan to validate
5. How will we know the staff are following the plan?	
6. How will we know the plan is working?	

We'll identify in six steps by asking these six pertinent questions. What is the problem? What is causing the problem? What is the goal? What steps will we take to reach the goal? How will we know the staff are following the plan? How will we know the plan is working? Yes, you may have an office manager who does overall management and may be addressing some of these but there's a way that we can go in and provide some additional resources so that at the end of the day, we'll have some plans. An immediate action plan, we have a plan to get data, a plan to act, and then also a plan to validate. It's a very strategic process.

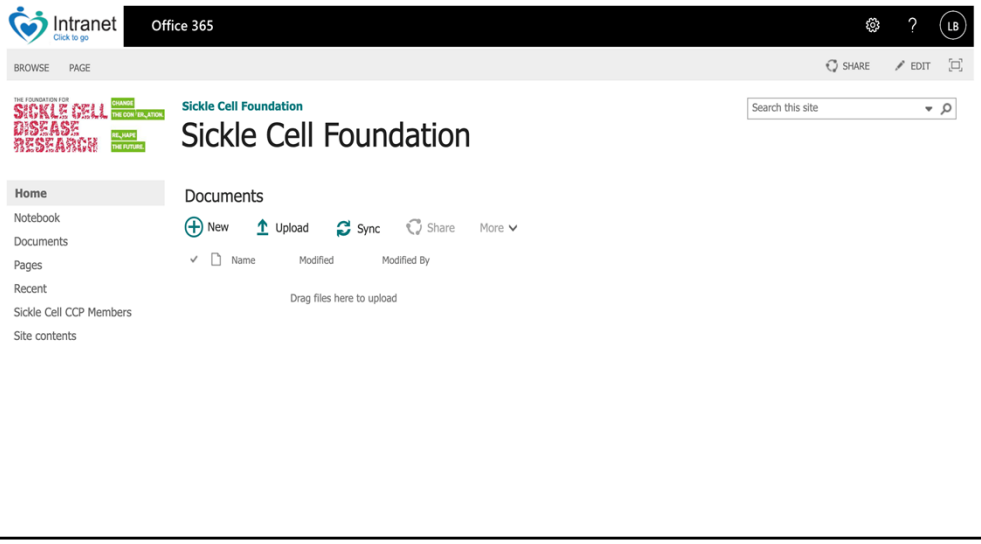
Personal Plans of Action

- **Write down *five things* you can do to improve healthcare quality for your patients with SCD**
- Example: I will:
  1. Study the barriers to best practices for my SCD patient population in the pediatric ED setting
  2. Implement a quality improvement project, utilizing measures selected from the Sunshine Sickle Cell Project quality improvement indicators, specifically focusing on pain management in the ED for pediatric patients with SCD in Florida
  3. Evaluate the impact of the quality improvement initiative by analyzing patient data and contributing to the larger body of research in Florida through the Sunshine Sickle Cell Project

What makes you unique?
What are your issues?
What would you like to study?

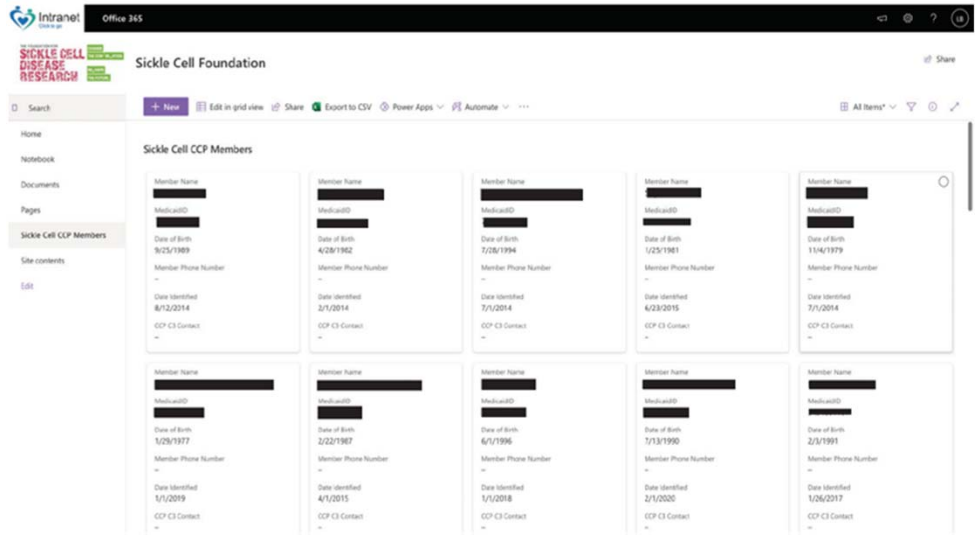
These personal plans of action is where you'll get an opportunity to write down five things that you can do to improve healthcare quality for your patients with sickle cell disease. Of those five that you write down, we'll select the top three because we don't want you to feel overwhelmed. Typically, about three items is what we can manage in terms of implementing, monitoring, validating, and making any tweaks that we need to make.

Example QI Monitoring Tool – Sharepoint Dashboard View



Here's an example of a QI monitoring tool using SharePoint. This is with one of my health plans, community care plan. They actually created the SharePoint drive for us.

Example QI Monitoring Tool – Sharepoint
Easy Monitoring Tool Available to You During Project



We go into the system where we're able to get the patient's information, what day the case management contacted the patient. We actually know who the case manager is and then we're able to interact with that case manager, either through secured emails. We get a lot of information from the case managers and work very closely with them because they do have a population of patients that they follow.

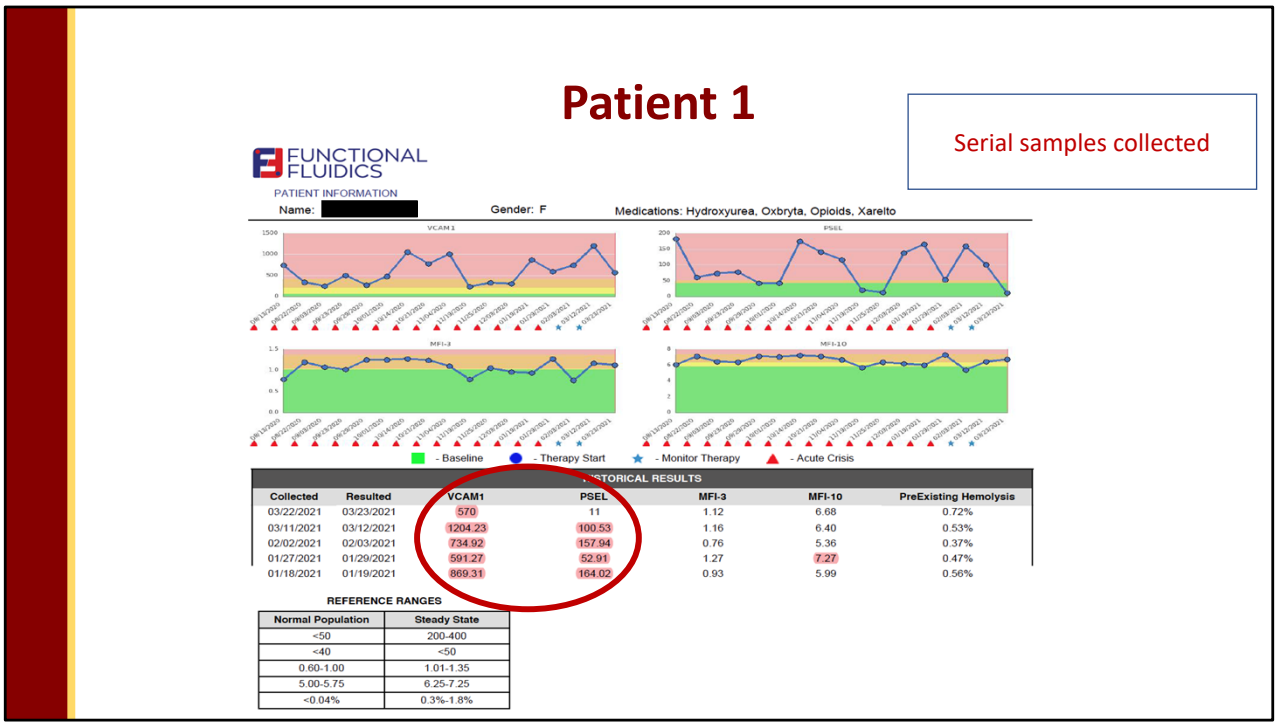
Biomarkers – Support of Subjective Pain Score

Biomarker critical value in one or more of the following areas:

Whole Blood Cell Adhesion on VCAM1 (>400)
Whole Blood Cell Adhesion on PSEL (>50)
Red Blood Cell Membrane Fragility Index at 3 min (>1.35) and 10 min (>7.25)

We also track biomarkers on our patients and we're very excited about this. We work with an outside lab called Functional Fluidics.

What these biomarkers assess, Dr. Campbell spoke about the inflammatory biomarkers, VCAM and P-selectin and also the red blood cell fragility and the medications that can target these biomarkers. Crizanlizumab, for example, targets the VCAM and the P-selectin, and the voxelotor targets the red blood cell membrane fragility. We actually have about 1,500 samples that we have sent to Functional Fluidics. What we're now starting to receive back is how much pain are the patients actually in because that's always the question at the end of the day, is this objective score really valid?

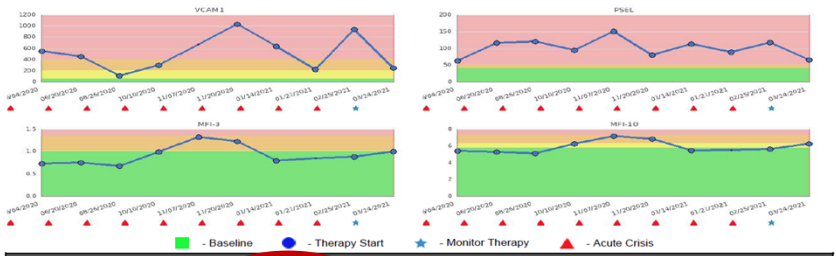


The points that you see that are in the red, so this is a critical lab just as you would receive from Quest or LabCorp and they call you up and say, "Doc, I got a critical lab that I need to report." What we're seeing is that the patients are always in a critical zone in terms of their inflammatory response to sickle cell. This is pretty amazing that we now have a way to validate that pain score. I can tell you that the patients who come in for pain, they all look like this, versus the ones that we never see for pain. They have a profile that's more normal, you don't see the increase in the inflammatory markers. We're so excited to be able to bring you this data.

Patient 2

FUNCTIONAL FLUIDICS

PATIENT INFORMATION
Name: [redacted] Gender: F Medications: Adakveo, Opioids



HISTORICAL RESULTS

Collected	Resulted	VCAM1	PSEL	MFI-3	MFI-10	PreExisting Hemolysis
03/23/2021	03/24/2021	251	66	1.00	6.26	0.46%
02/23/2021	02/25/2021	939.15	117.99	0.89	5.65	0.71%
01/20/2021	01/21/2021	225.40	89.42	Failed	Failed	0.55%
01/12/2021	01/14/2021	636.51	113.23	0.80	5.44	0.29%

REFERENCE RANGES

Normal Population	Steady State
<50	200-400
<40	<50
0.60-1.00	1.01-1.35
5.00-5.75	6.25-7.25
<0.04%	0.3%-1.8%

Dr. Campbell is also sharing data from his institution, so we know that across all academic or in the community, these data are valid. Again, this is another patient and you can see they're in the red zone. Your patients are in the pain that they're telling you they're in and we're here to help you get them hopefully assessed for these new medications and get them in a better state of health.

What Your Report Will Look Like

Example QI Monitoring Tool - Sharepoint

4/7/2021 Foundation for Sickle Cell Disease Research Mail - Sickle Cell CCP Members [redacted]

Lanetta Bronté-Hall <lbronte@fscdr.org>

Sickle Cell CCP Members - [redacted]
1 message

Sickle Cell Foundation <no-reply@sharepointonline.com> Fri, Feb 26, 2021 at 11:41 AM
Reply-To: no-reply@sharepointonline.com
To: lbronte@fscdr.org

[redacted] has been changed

[redacted]
2/26/2021 8:40 AM

Medicaid ID [redacted]
Member Name [redacted]
Member Has Another Insurance N/A
Date of Birth 8/31/2001
Member Phone Number [redacted]
Date Identified 1/20/2021
CCP C3 Contact [redacted]
CM following: [redacted]
Notes [redacted]

DaysSinceLast6MinuteWalk	60 days
DaysSinceLastPulmonaryFunctionStudy	120 days
DaysSinceLastComprehensiveLabs	150 days
DaysSinceLastUrinalysis	30 days
DaysSinceLastEchocardiogram	120 days
DaysSinceLastSerumFerritin	88 days
DaysSinceLastTranscranialDoppler	60 days
Next Scheduled Office Visit:	2/26/2021 Edited
DaysSinceLastOfficeVisit	40 days
MedicaidID	[redacted]

Standard of care tests and procedures are completed every 6 months unless clinically indicated to complete sooner.

Modify my alert settings|View Sickle Cell CCP Members

This is what a report can look like. Again, I'm working with Community Care Plan. I get this information by email, and then I'm able to see when the patient is due for X, Y, or Z and so we'll be able to provide a similar report for you.

Example Methodology

- Create and implement a protocol for pain management in the ED for patients with SCD in Florida with the goals of improving:
  - Mean time from triage to first analgesic dose
  - Percentage of patients that received their first analgesic dose within 30 minutes of triage, and
  - Percentage of patients who had pain assessment performed within 30 minutes of triage and who were re-assessed within 30 minutes after the first analgesic dose
  - Health plan per member per month health care utilization decrease and cost savings
  - Assess differential diagnosis for pain
  - Assess new therapeutic treatment options

The example methodology, we will create and implement a protocol for pain management in the ED. For example, if you're attached to an institution where you constantly have patients that are going back and forth from the ED, and these are patients that you monitor. Primary care doctors, for example, will have patients who they may not see very frequently but they get reports that the patient is going back and forth to the ED. That's the patient we want to help manage with you so that you can improve those metrics with that plan that you're enrolled in. Things that will be able to help you track or meantime for triage to first analgesic dose, for example, if it's an ED protocol. It just depends on the protocol and depends on the location.

Next Steps – How Do You Participate?

- Approximately three months following conclusion of all educational interventions, interviews (60–90 minutes) will be conducted with multiple stakeholders at the patient-, provider-, and clinic-level using semi-structured interview guides
- In addition, quantitative data will be obtained from **chart reviews and ICD-10 codes provided by participating clinicians**
- Data will be collected and analyzed concurrently using the quantitative + qualitative approach
- Qualitative data will be secondary to the quantitative assessment
- The target participation in the QI initiative is 50-100 clinicians

What are the next steps and how do you participate? About three months following the conclusion of all educational interventions, there will be interviews about 60 to 90 minutes. I'll be reaching out to the stakeholders, the patients, the providers, people at the clinic level, and we'll use a semi-structured interview guide to get your understanding of QI and then also what gaps you've identified in your organization. In addition to the quantitative data that we'll be collecting, there'll also be some chart reviews and pulling out some of those ICD codes.

We'll collect the data, analyze it concurrently, again, using both quantitative and qualitative approach. We hope to include 50 to 100 clinicians. You'll have a dashboard where you'll be able to see how your patient population is doing and you'll be able to compare to other clinicians that are participating. Although the patient information will be blinded, you'll be able to see to see your patient information but not the other clinicians' information.

Interested in Participating?

- Click the "Complete Form" button below the video window and complete an interest form
- Once your form is submitted, you will receive an email from *ManagingSCD.com*