MEETING THE CHALLENGES IN THE MANAGEMENT OF SICKLE CELL DISEASE

OVERVIEW

No longer a life-threatening disease, sickle cell disease (SCD) has become a chronic disease with life-threatening events that requires coordinated care by a multidisciplinary care team. Join Michael DeBaun, MD, MPH, and Collin Montgomery, APRN, as they discuss the acute and chronic complications experienced by individuals with SCD and the barriers they often encounter. The faculty offer real-world strategies for overcoming these barriers to improve the quality of life and other health outcomes of patients with SCD. Learn about 4 medications approved for treating acute and chronic complications of SCD and how to optimize their use. Case studies are utilized to share the faculty's experience and to facilitate integration into clinical practice.

TARGET AUDIENCE

This activity was developed for pediatric and adult hematologists, hematology nurse practitioners, emergency physicians, primary care physicians, pediatricians and other clinicians involved in the management of patients with sickle cell disease.

LEARNING OBJECTIVES

At the conclusion of this activity, participants should be better able to:

- Describe the causes and consequences of increased morbidity and mortality associated with sickle cell disease (SCD)
- Integrate key SCD management guideline recommendations into practice
- Compare and contrast standard, new, and emerging therapies for SCD—including mechanisms of action, dosing, safety and efficacy
- Employ communication and education strategies to help patients establish goals to improve their quality of life, prevent disease worsening, and have fewer/less severe symptoms

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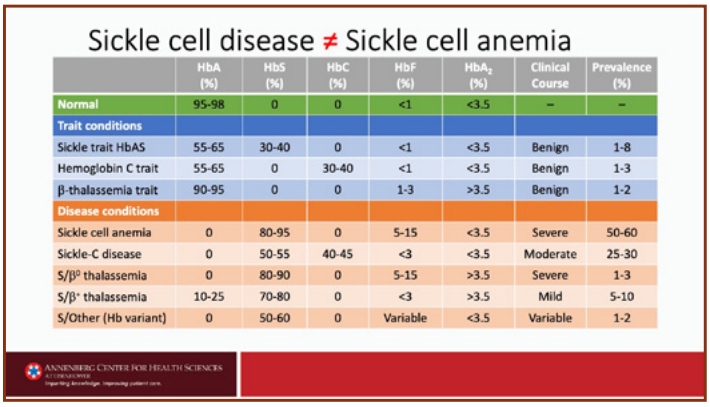
Medication	Approved Indication in the US	Approved Dose in the US
Crizanlizumab	Reduce the frequency of vaso-occlusive crises in adults and pediatric patients age ≥16 years with sickle cell disease	5mg/kg IV on week 0, week 2, and every 4 weeks thereafter
Hydroxyurea	Reduce the frequency of painful crises and reduce the need for blood transfusions in pediatric patients age ≥2 years with sickle cell anemia with recurrent moderate to severe painful crises	20mg/kg orally once daily initially; may increase by 5mg/kg every 8 weeks, or sooner if a severe painful crisis occurs, to a maximum tolerated dose or 35mg/kg is reached if blood counts are in an acceptable range
L-glutamine	Reduce the acute complications of sickle cell disease in adult and pediatric patients age ≥5 years	5g to 15g orally twice daily based on body weight
Voxelotor	Treatment of sickle cell disease in adults and pediatric patients age ≥12 years	1500mg orally once daily

EPIDEMIOLOGY

Michael DeBaun, MD

What is sickle cell disease? It's a group of genetic disorders that are progressively disabling and lead to chronic hemolytic anemia and its sequelae. Typically, in sickle cell disease, red blood cells contain hemoglobin S. More than 50% would cause the cells to sickle, which obstructs the blood flow to your vital organs resulting in tissue ischemia, reperfusion injury, and damage. Sickle cells can also permanently damage, not just your organs, but also can result in significant complications associated with pain referred to as vaso-occlusive pain. And importantly, it often causes necrosis of the bones, which can contribute to the pain.

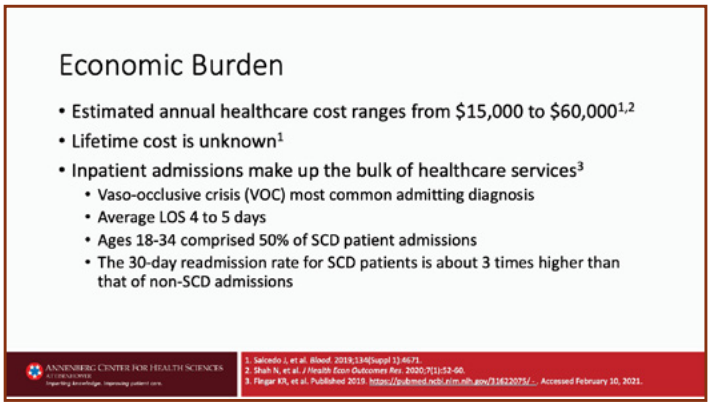


Sickle cell disease is not the same as sickle cell anemia. And one of the challenges in interacting with families of children, and in adults with sickle cell disease, and adolescents with sickle cell disease, is to make sure that they understand the type of sickle cell disease they have, so that they can effectively communicate to the clinician, their type, along with the course of their disease.

Sickle cell disease refers to the umbrella term of sickle cell disease syndromes, which include hemoglobin SS, hemoglobin SC, hemoglobin β thalassemia-plus, hemoglobin S/β thalassemia zero, and other compound heterozygotes, where the hemoglobin S concentration is typically more than 50%. Sickle cell syndromes should be distinguished from sickle cell trait, in which case, the hemoglobin S concentration is usually less than 50%. When we refer to sickle cell disease vs sickle cell anemia, in the case of sickle cell anemia, we're referring specifically to homozygous SS.

Collin Montgomery, APRN

Sickle cell anemia is the most common inherited disorder in the United States. For sickle cell anemia, we have roughly 1400 children born annually. In the United States, sickle cell disease affects about a hundred thousand people. The vast majority of these people are African American. Sickle cell disease is very common in areas where malaria had a high prevalence. Those with malaria in sickle cell trait were more likely to survive, therefore, procreate. Therefore, we have more people born with sickle cell disease.

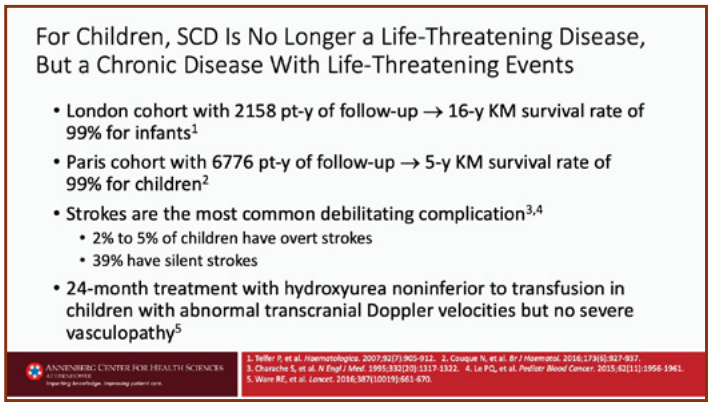


Let's talk about the economic burden of sickle cell disease. Annually, about $15,000 to $60,000 per person is spent on sickle cell disease management. The lifetime cost is unknown. I would think that has something to do with the fact that as time has progressed, it's no longer a disease of childhood, but patients are making it into adulthood. And the research just hasn't caught up. The bulk of these monies are spent on inpatient stays, with the number one presenting diagnosis being vaso-occlusive crisis. Of the money spent, 18-34-year-old adults are consuming most of the healthcare dollars. That's very important because that encompasses our patients in their transition period, which is ages 18-21 years. I'll talk more about that a little later in the presentation. It's also important to know that compared to the general population, sickle cell admissions have a higher 30-day

readmission rate, about 3 times higher than the general population. Beyond the economic burden, patients with sickle cell disease experience significant morbidity that impairs functioning and quality of life.

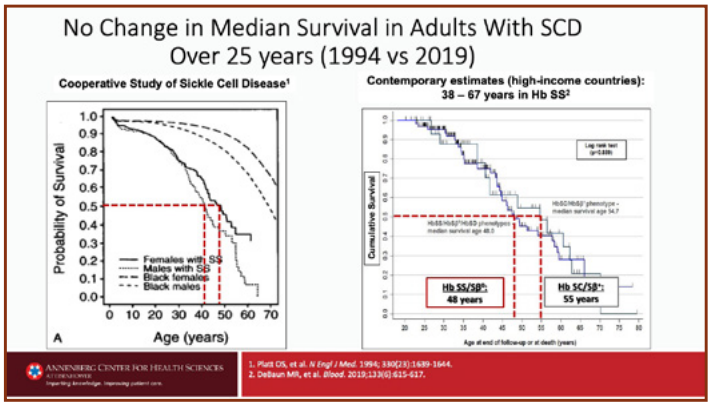
Michael DeBaun, MD

For children with sickle cell disease, sickle cell disease is no longer a life-threatening disease, but a chronic disease with life-threatening events. Several international studies have demonstrated that children with sickle cell disease are expected to live into their 18th birthday, with approximately 99% of those children born even 20 years ago expected to live to their 18th birthday. Unfortunately, survival is not the only component of this disease for children. Strokes are still the most common debilitating complication in this population. With the advent of primary stroke prevention,



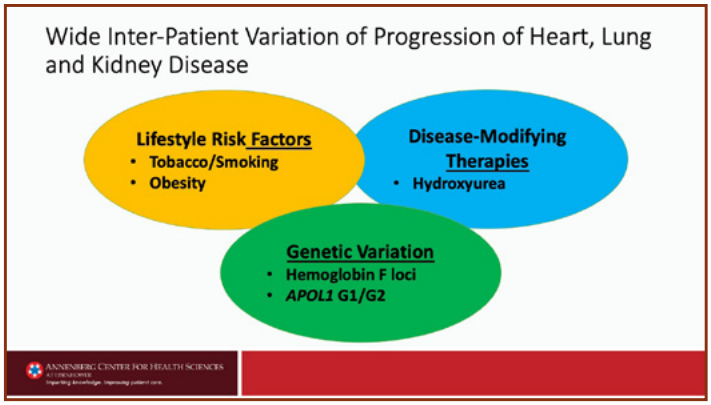
approximately 2%-5% of children will have overt strokes. Unfortunately, the most common complication of this disease that has lifelong sequela is silent strokes, and about 40% of children, before they hit their 18th birthday with sickle cell anemia, will have silent cerebral infarcts.

In adults with sickle cell disease, there's been no change in the median survival in over 25 years. Specifically, in the cooperative study of sickle cell disease that was published in 1994 in the New England Journal of Medicine, the median survival for adults was approximately 48 years of age.



In 2019, combining 2 comprehensive sickle cell disease centers, one from the University of North Carolina, one from Vanderbilt University Medical Center, the median survival was approximately 48 years.

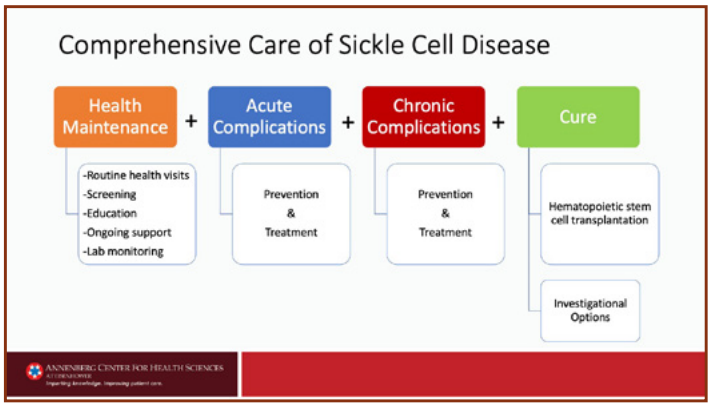
There is wide interpatient variation of progression of heart, lung, and kidney disease in children and adults with sickle cell disease. The factors that contribute to the wide variation are lifestyle risk factors, including tobacco use and obesity; disease-modifying therapy, such as hydroxyurea; and then genetic variation, such as the hemoglobin F loci and APOL1 G1/G2 genetic variation.



COMPREHENSIVE CARE

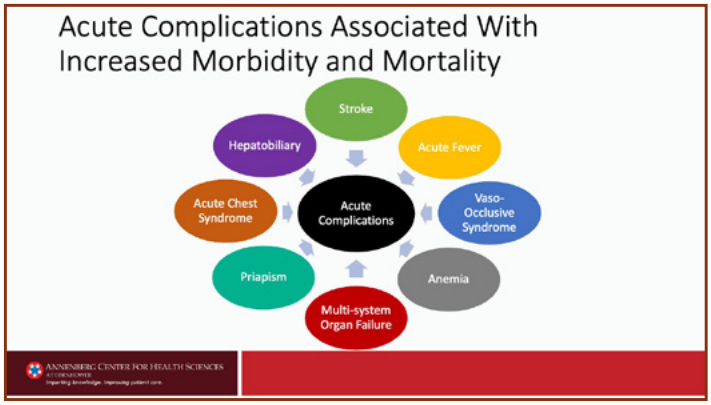
Michael DeBaun, MD

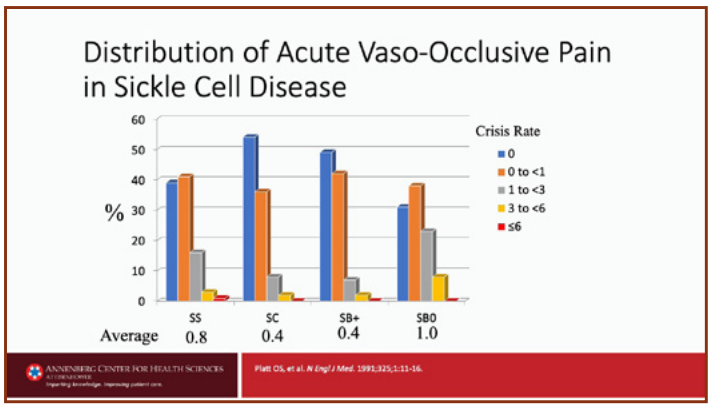
Comprehensive care has improved survival of sickle cell disease. This comprehensive care includes health maintenance, acute management of the disease in the hospital and at home, chronic complications that have been managed better with improvement and knowledge of how to decrease morbidity associated with these chronic complications. And, of course, last but not least, cure of sickle cell disease.



The acute complications associated with sickle cell disease increase not only the morbidity, but also the mortality. The acute complications include stroke, acute fever, which may be associated with life-threatening infection, vaso-occlusive syndrome, acute drop in hemoglobin referred to as anemia, multisystem organ failure, priapism, acute chest syndrome, and liver disease.

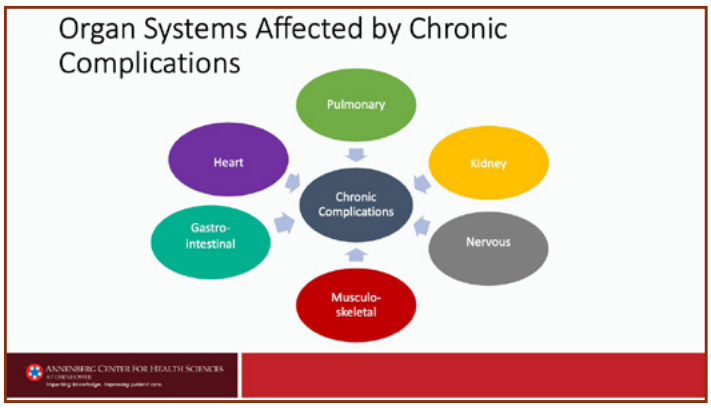
The most common complication of sickle cell disease is acute vaso-occlusive pain. As mentioned earlier, because of the different types of sickle cell disease, you should know the type of sickle cell disease that you have. One of the reasons that this is important is because the rate





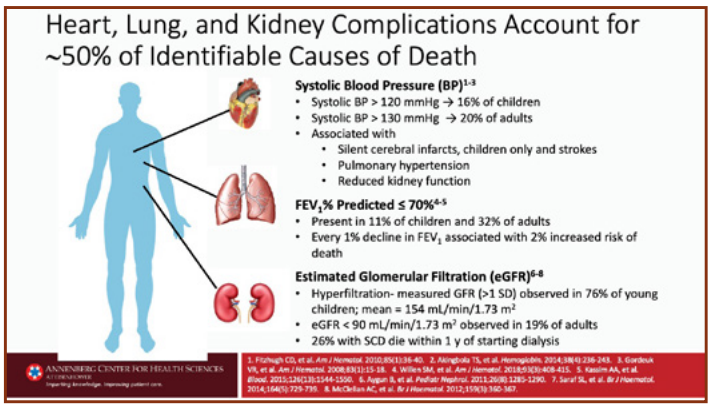
of pain differs dramatically based on the type of sickle cell disease. For adults with hemoglobin SS, we expect them to have approximately 1 pain event per year, whereas for patients with hemoglobin SC, we expect them to have less than 1, approximately 0.4 pain events per year.

What is equally important, in terms of knowing the type of sickle cell disease, is understanding the mental health of individuals with sickle cell disease, particularly the adolescents and young adults. The PiSCES observational study is easily the strongest study to describe the clinical history of acute vaso-occlusive pain in young adults and adults with sickle cell disease. This was a study that involved daily pain diaries for 6 months in 232 individuals with sickle cell disease. Pain was reported on 54% of the patient days. Healthcare utilization only occurred in 3.5% of the patient days, indicating that among patients with pain, most of these individuals elected to stay at home and were not seen by their primary care provider or the hematologist in the outpatient setting, nor were they seen in the emergency room or admitted to the hospital. 29% of these individuals reported pain most days of the week and 14.2% reported pain in less than 5% of the diary days.



Sickle cell disease affects every organ of the body, including the lungs, the kidneys, the brain, the musculoskeletal system, the gastrointestinal (GI) system, and the heart. Manifestation of both acute and chronic problems requires integration of care with the hematologist and the primary care provider.

Heart, lung, and kidney diseases account for 50% of all identifiable causes of death in adults with sickle cell disease. Systolic blood pressure is a major manifestation of complications associated with sickle cell disease and higher systolic blood pressures in individuals with sickle cell disease are associated with overt strokes, silent strokes, and pulmonary hypertension, as well as decreasing kidney function. Lung function is critical in sickle cell disease because the lungs are actually the only organ that can reverse the sickle cells during a circulation because of the access to the oxygen and the exchange between the blood flow red blood cells



in the pulmonary artery and the lungs. Lung disease, as manifested by a decrease in FEV_1% predicted less than 70%, is associated with an increased rate of death when compared to adults with higher FEV_1% predicted. And these are young adults. For every 1% decline in the FEV 1% predicted, there is an associated 2% increased risk of death. As mentioned, kidney function is an important component of survival in sickle cell disease. For adults and children with decreased kidney function, you can expect there to be an increase in the likelihood of earlier mortality. Reduced glomerular filtration rate (GFR) is associated with 3-fold greater risk of death in adults with sickle cell disease.

Collin Montgomery, APRN

With respect to some of the common challenges with taking care of this patient population, I've highlighted just 3 here. One is frequent healthcare utilization, which is an issue that we face in our healthcare institution where I work. Also, failed transition from pediatric to adult care and then limited clinical expertise.

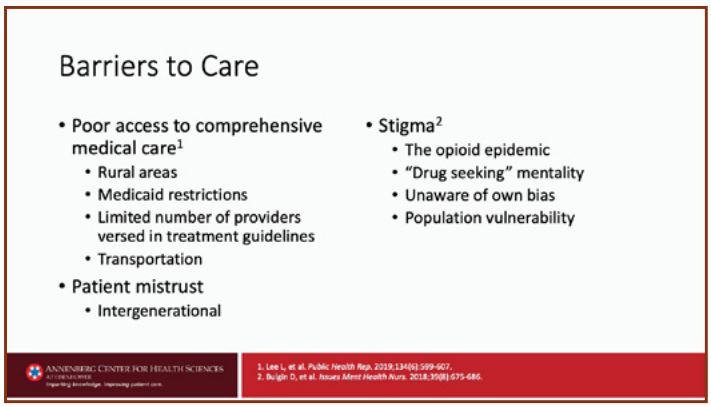
Let's talk about healthcare utilization. One thing that significantly contributes to health care utilization is obviously pain being the hallmark symptom of sickle cell disease. So, poorly managed pain at home contributes, and under-managed or unmanaged mental health disorders also contribute to frequent healthcare utilization. And I'll talk about that a little later.

Failed transition from pediatric to adult care. I'm an adult provider. So, a lot of times I like to say that sickle cell patients, up until their second to third decade of life for most patients, have not really had any significant complications other than pain. So, sometimes they don't understand the necessity of linking up with an adult provider for chronic disease management because they haven't had any complications. This also contributes to increased healthcare utilization in this population. So, your transition age is from about ages 18 to 21.

And as it pertains to limited clinical expertise, this is more on the adult side of things. The vast majority of pediatric patients are cared for by a pediatric hematologist, but for adult patients—because sickle cell disease was once considered a disease of childhood—the number of adult providers does not compare to pediatric providers. So, many adult patients are being cared for by general practitioners.

As for barriers to care, poor access to comprehensive medical care is definitely a contributing factor. I'm in a rural state. I'm in the center of the state. So, I have patients that travel 2-3 hours to come see me for their comprehensive care. That's a significant burden for patients time-wise and also financially.

Patient mistrust is a very significant issue among this population. Nearly all of my patients, by the time I receive them, have had some type of

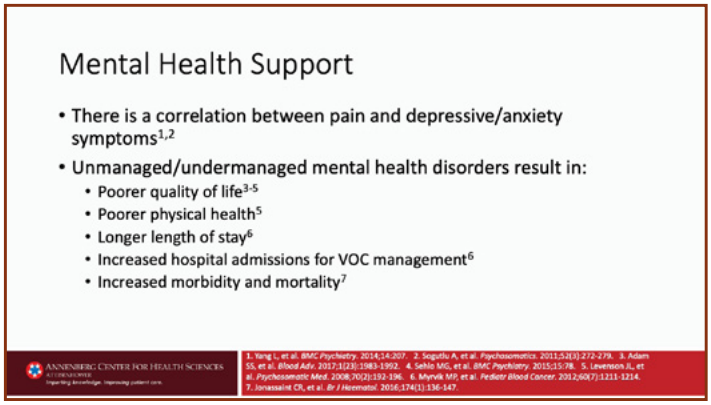


negative experience from a healthcare provider or a healthcare visit. And there's definitely a component for the intergenerational. My grandparents are old enough to tell me about how poor the treatment was for African American patients. Those things are passed down from generations, and then, with my patients, it's reinforced when they, too, have negative healthcare experiences.

Another thing that's very important also is stigma. These patients are highly stigmatized. As my pediatric partner often says, they're very cute when they're little and they're hurting and everybody wants them to stop hurting. As they transition into adolescents, the stigma kind of starts to set in, typically more so in the males than the females. And I will say the opioid epidemic has definitely contributed to the stigma. Sickle cell patients have become an unintended victim of the opioid epidemic. People are hypervigilant for drug-seeking behavior and opioid addiction and a lot of times my patients are mislabeled for those things.

As it pertains to drug-seeking mentality, the things that we're taught in medical education as drug-seeking are often the same things that I teach my patients to be as a knowledgeable sickle cell patient. So, I expect when they present to the ER that they are able to say, this medicine works for me, this medicine doesn't work for me, I need medicine for itching and nausea and all those things. Well, when patients come in with specific medicines at specific doses, sometimes in sickle cell patients it is misinterpreted for drug-seeking vs them just being a knowledgeable patient.

Bias is inherent, as providers. We have to be aware of our own bias. We need to be able to identify it and we need to be able to manage it. I think one effective way of doing that is having an interdisciplinary team to manage these patients. It helps with like an internal checks and balances. And then the population vulnerability. Often, I say I'm a voice for patients that don't have a voice. They are typically of lower socioeconomic status, lower healthcare literacy, lower overall education. So, sometimes their advocacy efforts go unnoticed or they're not really taken seriously.



Let's talk about mental health and its significant impact in sickle cell disease management. There's definitely a correlation between depression and anxiety and days with pain. For the patient that has unmanaged depression, anxiety, or any mental health disorder, they typically have more utilization. When they are admitted, those stays are much longer compared to their counterparts. And with sickle cell disease, the more inpatient admissions and healthcare utilization that they have is associated with an increase of morbidity and mortality.

Regarding educational and vocational support, for your patients that are in primary school and secondary school, 504 plans or IEP may be necessary. IEP being individualized education program. Your 504 plans just give the basic accommodations that they need just because they have sickle cell disease. So, avoiding extreme temperatures, frequent restroom breaks, having access to hydration, the nurse, things of that nature. And then for your IEP, that's your patient that may have some cognitive issues after having a stroke and getting them the necessary accommodations. For higher education. I feel like this is a really big thing for our college students. Again, a lot of times this age group has not experienced anything very significant in their healthcare. So, they are not as prone to register with the disability services at their college or university. But that's very important because I've had some patients that have gotten some acute complication that caused them to be out of school. And it was very hard for us to assist them, to get the accommodations that they needed, because they weren't registered with the disability service and then ADA accommodations for employment.

The first evidence-based guidelines for sickle cell disease were published in 2014. Since then, we've had some new updates come out in the past couple of years, and they're actually highlighted here. In the adult world, I deal with a lot of pain, so I have a lot of experience with that pain guideline. And the biggest thing I like about the pain guidelines is it encourages a multimodal approach.

Regarding health maintenance, it is very important that, in addition to the things specific to sickle cell, the sickle cell patients also receive the things that the general population is recommended to receive. For pneumococcal infection, patients should be on penicillin prophylaxis until they are 5 years old and have been vaccinated for pneumococcal infection. For renal disease, they need to be screened for proteinuria starting at 10 years of age. And then, if indicated, they should have referral for nephrology for management. For pulmonary hypertension, if your patient is presenting with any type of symptoms suggestive of pulmonary hypertension, it's important to go ahead and get an echocardiogram. Again, that's 1 of the complications that is associated with a shortened life expectancy. It's also not recommended to do any screening echocardiogram.

Hypertension, again, contributes to morbidity and mortality in this group. If the patient does have hypertension, you want to do screening, and then the standard of care management. For retinopathy, you want to start those screenings at 10 years of age for the dilated eye exam. I will tell you as an adult provider, I've had several patients that have come to my clinic that were diagnosed with sickle cell disease based on their eye exam. They were older. They were too old to have been screened at birth for sickle cell disease, but definitely went in and had sickle cell retinopathy. And that's how they got a referral to my clinic. As for strokes, you want to do your transcranial Doppler (TCD) for ages 2-16 years in your S/β thalassemia zero group and then your SS patients. And adequate referral, if necessary, if they have abnormal TCDs. Transfusion support may be needed and that can be taken care of by hematology.

And then reproductive counseling. It's very important when we put our patients on hydroxyurea to encourage contraception for the concerns with teratogenic effects of hydroxyurea. And it's also very important that in the reproductive years we teach the inheritance pattern of sickle cell disease. What I find a lot of is people actually know that they have sickle cell trait—well, the parents find out at birth that they have sickle cell trait—they may pass it on to the child. They may not pass it on to the child, like telling them about it, but they don't know what that really means as it pertains to reproduction and the likelihood of having a child with sickle cell disease. I can't overemphasize enough that prevention is critical.

Here are some nonmedical therapies that can help sickle cell patients, as I say, live their best life. Healthy living, good diet, exercise, getting good sleep, and definitely making sure that we're doing thorough assessments for depression and anxiety. A thorough assessment not being, do you have depression and anxiety? A lot of times patients are very shocked when we explain that there's concerns for depression and anxiety and my LCSW that's in my clinic, her assessment looks like a conversation. And I will say a lot of my patients have like a somatic presentation of depression and anxiety that is often misinterpreted as sickle cell-related pain.

MANAGEMENT OF COMPLICATIONS

Michael DeBaun, MD

Acute management of sickle cell disease complications requires early recognition and rapid intervention. One of the first acute complications of sickle cell disease is a temperature elevation or fever. In infants, this is a medical emergency. Prompt evaluation should occur in the emergency room where blood cultures are obtained and intravenous antibiotics or intramuscular antibiotics are given.

Acute vaso-occlusive pain is a very common complication. Perhaps the most common complication in this population. Management of acute vaso-occlusive pain should start with knowledge of how to manage the pain at home first. And the management should include nonpharmacologic strategies for acute management of pain, and then a stepwise approach for management of pain with initially nonsteroidal anti-inflammatory drugs for several days, hydrocodone, and then more potent opioids that can be taken orally.

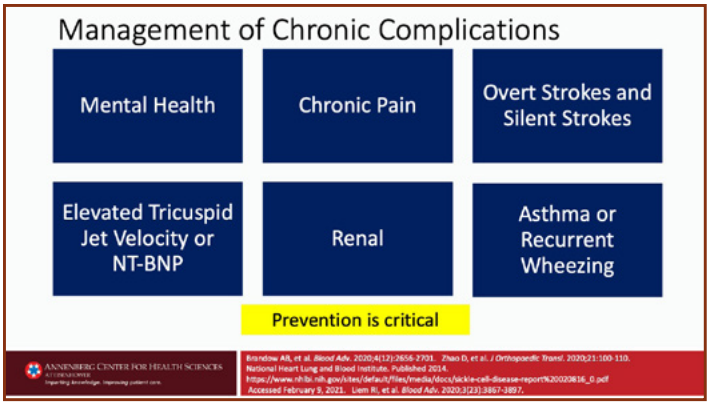
One of the challenges with managing sickle cell disease is when children and adults have acute pain, they often become dehydrated. As a result of the dehydration, they can actually have decreased perfusion to the rest of their body. And so adequate oral hydration is important in the management of the disease. What's important to note is that you will not abate or stop a vaso-occlusive pain episode with hydration. The goal is just to make sure that they are what we refer to as euvolemic—neither dehydrated or over hydration is necessary in acute vaso-occlusive pain. In fact, too much fluid may actually cause complications in the lung.

Acute drops in the hemoglobin. Severe anemia is a major complication of sickle cell disease. And for those individuals, they need to have a CBC and reticulocyte count, typically more frequently than every 24 hours. It's important to confirm the cause of the acute drop in the hemoglobin and to be prepared for red blood cell transfusion. In the event that the services are not available for red blood cell transfusion for patients who've had an acute drop in hemoglobin, they should be transferred to a facility that has the ability to offer that service.

Hepatobiliary complications acutely are a challenge. They should be referred to the hematologist for management. And then also general surgeon. There is no optimal timing for management of acute hepatic biliary complications because of the acute illness, which can often be associated with acute chest syndrome. I typically hold off on acute surgical removal of the gallbladder in a case of gallbladder disease causing the complications, but there's no optimal timing that's been described in the literature. Typically, prior to surgery, we would perform a simple transfusion to get the hemoglobin up to about 10 g/dL. This is because there's clear evidence that in patients with hemoglobin SS and hemoglobin S/β thalassemia zero, that increasing the hemoglobin to 10 g/dL prior to the surgery will decrease the incidence of life-threatening acute chest syndrome postoperatively.

Acute chest syndrome is a life-threatening complication in sickle cell disease. Characteristics of acute chest syndrome include increase in the respiratory rate, a decrease in the oxygen saturation, and increase in the work of breathing. What's important here is to recognize that children and adults with asthma or recurrent wheezing have a much higher rate of acute chest syndrome. And also what's important is that once the hemoglobin starts to drop 2 g/dL below the base line, and there's an oxygen requirement, that consideration should be for at least simple transfusion to improve the oxygen-carrying capacity of the blood. And then, potentially, if the acute chest syndrome episode becomes even more severe, then to be prepared for an exchange transfusion. If the facility does not have the capacity to perform exchange transfusion, patients should be considered to transfer to a facility where an exchange transfusion can be performed. It's a red blood cell exchange transfusion because that is one of the few approaches to abate progression of severe acute chest syndrome that can be life-threatening and result in respiratory failure.

Multiorgan failure can occur in sickle cell disease. Again, the optimal therapy is supportive care with red blood cell exchange transfusion, oxygen treatment, and evaluation for kidney, lung, and heart disease, as well as evaluation for potential strokes, which requires a neurological consultation. In general, when a patient has multiorgan failure, then an admission to the ICU for integrated and comprehensive medical care within various subspecialties is recommended.



The management of chronic complications of sickle cell disease requires ongoing care. Our strategy as the best way to facilitate care for a child or an adult with sickle cell is to empower them with the knowledge of their chronic disease and the manifestations of the complications that may occur in the different organs.

Mental health cannot be overemphasized as a major comorbidity in sickle cell disease. There should be ongoing assessment of depression and anxiety with almost every routine visit. Individuals with sickle cell disease, particularly the adults, are best managed when they have a primary care provider coupled with a specialist in sickle cell disease. Typically, because many of the complications that now occur in sickle cell disease are outside of the expertise of the hematologist, such as management of depression, chronic back pain, and other complications that occur in the disease and in the general population. In the event that there is anxiety or depression, patients should be managed by a healthcare specialist with expertise in this area, often a primary care provider or a mental health therapist.

Chronic pain is another complication that occurs, particularly in the adult population, with the formal definition of chronic pain. But before patients with chronic pain are referred outside of the hematology clinic, they should be evaluated for other causes of chronic pain that can occur in sickle cell disease, which include avascular necrosis of the hip or the humerus, as well as compression fractures of the spine. There should be an individualized approach to managing the chronic pain, which is based on strategies which are a nonpharmacologic, as well as pharmacologic strategy. There should be a formal evaluation for depression, as well as anxiety. There should be, if possible, buy-in with the family on how the chronic pain should be managed, as well as referral to a primary care provider to address, as mentioned, mental health comorbidities.

Overt strokes and silent strokes are extremely common in children and adults with sickle cell disease. About 40% of children or young adults, before they finish high school, will have silent strokes. Those strokes have dropped dramatically because of primary stroke prevention and the use of transcranial Doppler with the initial regular blood transfusion therapy monthly for at least a year. And then ultimately switched over to hydroxyurea.

Children and young adults, as well as adults with silent strokes, may not be aware of their cognitive impairments, and ongoing evaluation for progression of silent strokes should be considered once they've been identified with a screening MRI of the brain, which is the only way to detect the silent stroke in children and adults with sickle cell disease.

Elevated tricuspid jet velocity is associated with earlier death in sickle cell disease. And so, as a result of the recommendations from the American Society of Hematology (ASH) and the American Thoracic Society, there should be at least some recognition that screening should only be done in symptomatic adults with cardiopulmonary manifestations. The recommendation from the American Thoracic Society is that every adult should be evaluated at least once with a 2-dimensional echocardiogram to evaluate the tricuspid jet velocity.

Renal complications in sickle cell disease are common. They are often manifested as having albuminuria or an elevated urine albumin-to-creatinine ratio. In general, we start screening for increase in the urine albumin-to-creatinine ratio as soon as they can start to void in a cup. So, anywhere between 5-6 years of age is when we start. We typically have repeated evaluations once an initial evaluation is abnormal, because of the high rate of false positives. And we prefer for the second or even a third evaluation to be done early in the morning before we refer the patients to the nephrologist for treatment of an angiotensin converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB).

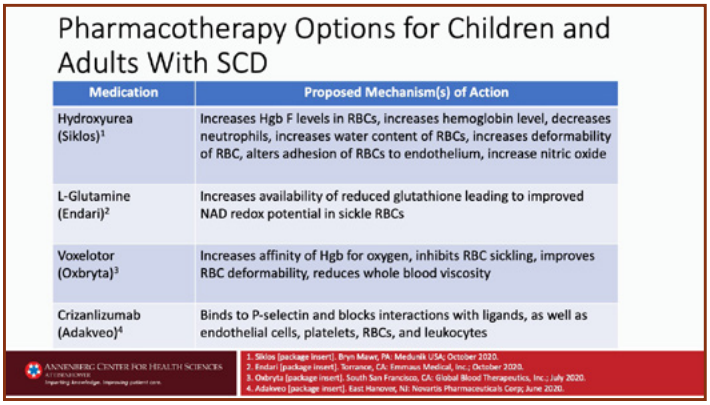
Asthma or recurrent wheezing is a common complication in children and adults without sickle cell disease. And because asthma and recurrent wheezing is common, what's important to know about asthma or recurrent wheezing in sickle cell disease is that in children with asthma, there's a higher rate of acute chest syndrome. There's a higher rate of admission to the hospital for pain with asthma. And there's a higher rate of mortality as they become older. In adults, the diagnosis of asthma is more challenging. And what we have found is that in adults with recurrent wheezing, they have essentially the same increase in disease prevalence as children with asthma. Namely, adults with recurrent wheezing have an increased rate of vaso-occlusive pain that requires hospitalization. They have an increased rate of acute chest syndrome and adults who have recurrent wheezing have an increased rate of earlier mortality.

In summary, acute and chronic manifestations of sickle cell disease require a multidisciplinary care team across the lifespan that includes, but is not limited to, a primary care provider, a mental health specialist, a hematologist, neurologist, pulmonologist, nephrologist, and an orthopedic surgeon.

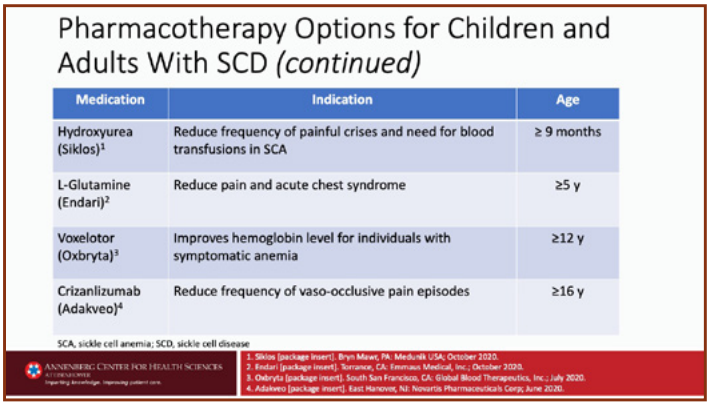
PHARMACOTHERAPY OVERVIEW

Michael DeBaun, MD

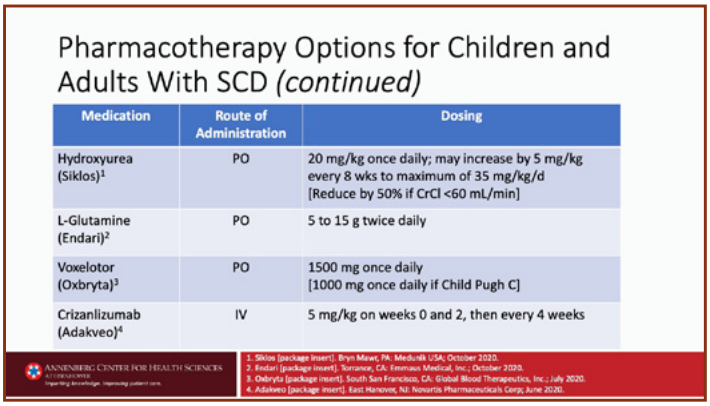
The pharmacologic options for children and adults with sickle cell disease include 4 FDA-approved drugs: hydroxyurea, L-glutamine, voxelotor, and crizanlizumab. Hydroxyurea's major mechanism of action is that it increases hemoglobin F levels, increases the total hemoglobin level, decreases the neutrophils, which are associated with inflammation, and increases the water content of red blood cells, which is associated with decreased rate of polymerization. Basically, the hemoglobin S does not polymerize as quickly, increases the formability and, importantly, alters the adhesion of red blood cells to the endothelium. And hydroxyurea increases nitric oxide.



L-glutamine increases availability of reduced glutathione, leading to improvement in NAD redox potential in sickled red blood cells. Voxelotor increases affinity of hemoglobin for oxygen, inhibits red blood cell sickling, and improves red blood cell deformability, and reduces whole blood viscosity. Crizanlizumab blocks P-selectin and blocks interactions with ligands, as well as endothelial cells, platelets, red blood cells, and leukocytes, essentially making the red blood cells less adhesive to each other and to the other cells within the blood vessels.

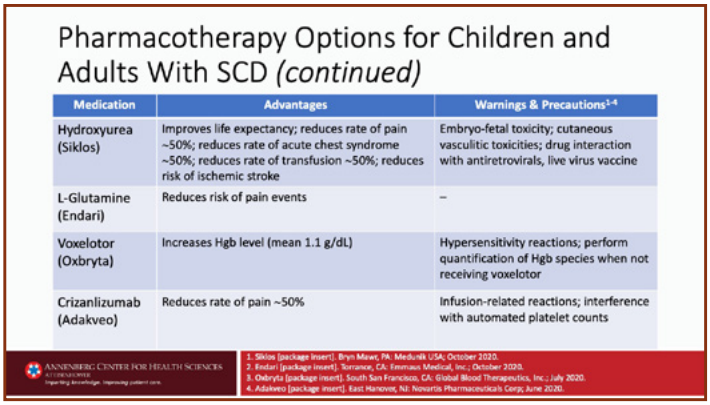


Hydroxyurea, the indication is typically for children greater than 9 months of age. The indication, according to the NHL BI guidelines published in 2014, is they should be offered to children with hemoglobin SS and hemoglobin S/β thalassemia zero with encouragement for the families to start the medication at that age. For L- glutamine, the indication is to reduce pain and acute chest syndrome for children greater than 5 years of age. For voxelotor, the indication is for symptomatic anemia in children over 12 years of age and adults. For crizanlizumab, the indication is for individuals who have repetitive vaso-occlusive pain episodes, who are at least 16 years of age.



The route of administration for hydroxyurea, L-glutamine, and voxelotor is all oral. Hydroxyurea is typically once a day. For L-glutamine, it's twice a day. And voxelotor it's once a day. For crizanlizumab, there's an initial intravenous (IV) infusion over a short window of time in a clinic, typically less than an hour. And then there's a second infusion 2 weeks later. And then every 4 weeks thereafter. For crizanlizumab, the administration of the medication must be done intravenously.

What are the benefits of these 4 FDA-approved medications that are used in sickle cell disease? For hydroxyurea, specifically for children and adults with hemoglobin SS and S/β thalassemia zero, there's evidence that hydroxyurea improves the life expectancy of adults with sickle cell disease, reduces the rate of pain by about 50%, reduces the rate of acute chest syndrome by about 50%, reduces the rate of transfusions by about



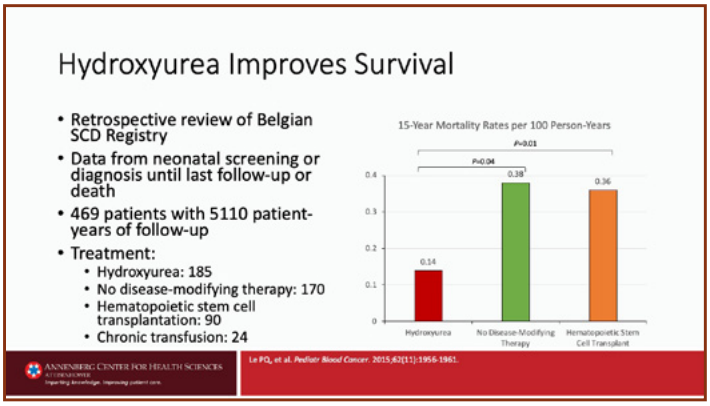
50%, and reduces the risk of stroke. Although the degree of decline based on use of hydroxyurea is not well-defined, we clearly have evidence that hydroxyurea in children with sickle cell disease will decrease the transcranial Doppler measurement, which is a risk factor for strokes in children with hemoglobin SS and hemoglobin S/β thalassemia zero.

L-glutamine reduces the risk of pain events and acute chest syndrome. For voxelotor, it increases the hemoglobin by a mean of 1.1 g/dL. And for crizanlizumab, it reduces the rate of pain by about 50%.

PHARMACOTHERAPY

Michael DeBaun, MD

I think one of the biggest selling points that I have when I talk to young adults and parents of young children with this disease is that there are multiple studies now in the literature that have demonstrated the survival advantage of hydroxyurea. Specifically, one of the first studies to demonstrate the benefit of hydroxyurea was published in Belgium. And it's referred to as the Belgian Sickle Cell Disease Registry. In the 15-year study, the group of patients with the greatest survival were the patients

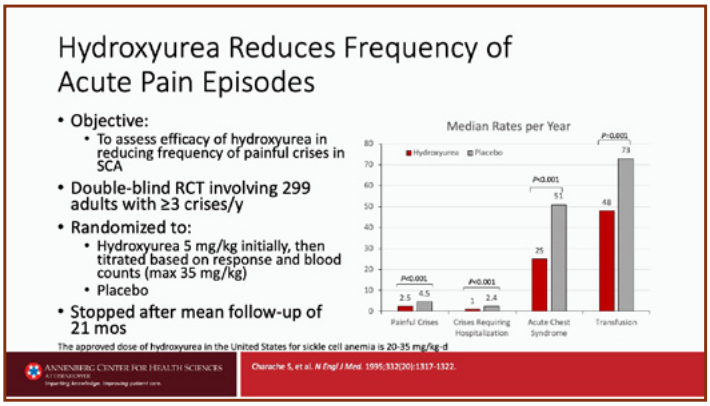


who were thought to have the most severe sickle cell disease because they only reserved hydroxyurea for the patients with multiple pain episodes or multiple acute chest syndrome episodes. In that group of patients, the rate of death was very low when compared to that group of patients who had the least severe disease, ie, those are the patients who didn't come into the hospital for pain and didn't come into the hospital with acute chest syndrome. That is, they were normal, and therefore the parents didn't see a need. And there was no indication, at the time, for those individuals to be treated with hydroxyurea. But yet that group of patients had the highest rate of death, therefore indicating that the event rate that you would expect to occur, did not occur. We would have expected that children and adults who had no manifestations of sickle cell disease in terms of pain and ACS would be the well group. But it turns out that the group that was initially

treated with hydroxyurea because of severe disease did far better than a group of children and adults that were considered as being asymptomatic, but had a higher death rate.

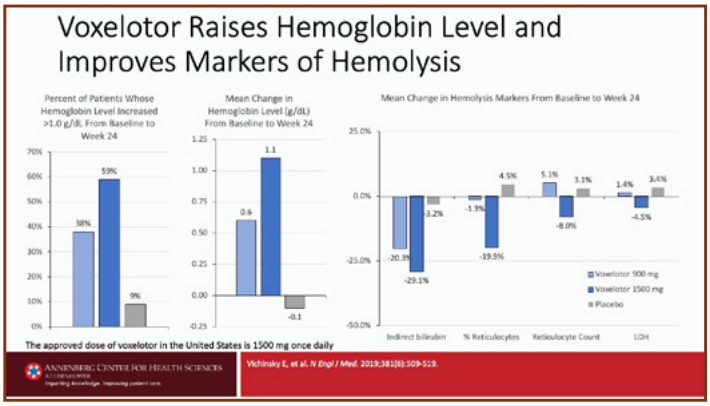
Collin Montgomery, APRN

Let's look at the influence on hydroxyurea on acute pain. Hydroxyurea was the very first medicine approved for sickle cell disease management in 1980. Dr. DeBaun has done a great job of talking about that study. Here's a few of the benefits he was talking about. So, there are less episodes of painful crisis among patients that are on hydroxyurea. Hospitalizations, secondary to crisis, are lower. Acute chest, which is the medical emergency and can be life-threatening, significantly decrease, and then transfusion requirements also decrease. That's very important because the more transfusions patients get, the more iron they're exposed to.



Michael DeBaun, MD

I am going to discuss briefly the safety and efficacy of voxelotor. The assessment of safety and efficacy of voxelotor was performed in 2 doses. In the trial, the patients are receiving either 900 mg of voxelotor or 1500 mg or no active drug at all. The median follow-up was 42.3 weeks. And what's important to note is that many patients received hydroxyurea as hydroxyurea was not excluded as an entry criterion in the trial. But it's important to know about the use of voxelotor is that there was an increase in the total amount of hemoglobin, so that increase was approximately a gram per deciliter. To be exact, it was 1.1 g/dL with the higher dose of voxelotor. What's important to know about the use of voxelotor with the mean change in hemolysis is that, as you would expect, there was a decrease in the indirect bilirubin. There was a decrease in percent reticulocytes, and there was a decrease in reticulocyte count.



Now, about hydroxyurea and its clinical role in patients with hemoglobin SS and hemoglobin S/β thalassemia zero. It's recommended, as Michael said, to start these patients on hydroxyurea at 9 months, irrespective of their disease severity. In adult management, this may be a bit different. Sometimes, I kind of receive patients that families maybe didn't want on hydroxyurea or I've received adults that just have never been offered hydroxyurea. And then, in that case, you can start hydroxyurea for those patients that have had had 3 or more painful crises that required IV opioids or IV nonsteroidal anti-inflammatory drugs (NSAIDs). In addition to decreasing pain, acute chest syndrome, and hospitalizations, it definitely improves quality of life. And it can also improve the cognitive function in patients that have had abnormal TCDs.

L-glutamine was associated with lower acute pain crises and decreased hospitalizations. I think it's an excellent option to add to your multimodal pain approach for sickle cell patients. The study found the chief adverse side effect to be constipation, which I think is very interesting because a lot of patients suffer with constipation, especially those that are on opioids. For L-glutamine, you can give that with hydroxyurea.

What is also important to note is that in patients with recurrent pain, there was no evidence that voxelotor actually decreased the rate of acute vaso-occlusive pain episodes. At this point, the evidence is that if you have patients with sickle cell anemia or patients with hemoglobin SC disease with low hemoglobin that are symptomatic, then you may want to consider voxelotor as the drug of choice to increase the hemoglobin by at least a gram per deciliter.

Safety and efficacy of voxelotor was described in the trial. The major manifestation of voxelotor at the 1500 mg dosing level was the presence of headaches. But what should be noticed is that in the placebo group, the rate of headaches was about the same. There's about twice as many participants in the 1500 mg group that had diarrhea. There was a slight increase in nausea, but other clinical manifestations associated with the drug did not occur at a dramatically different rate when compared to placebo, except for abdominal pain. So, in general, my experience has been that this is a medication that is very well tolerated, except there tend to be gastrointestinal (GI) complications, which include diarrhea, nausea, and abdominal pain. In a phase 2 randomized controlled trial, which was

Safety and Efficacy of L-Glutamine *(continued)*

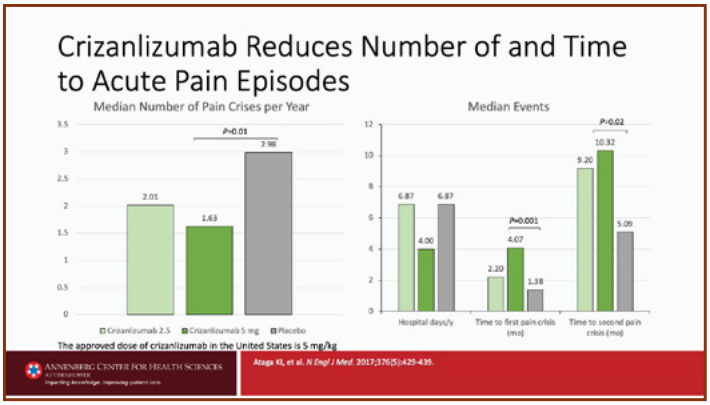
Adverse Event	L-Glutamine (n-151)	Placebo (n=78)
Constipation	25.2%	24.4%
Nausea	22.5%	16.7%
Headache	21.2%	17.9%
Pain in extremity	15.9%	7.7%
Vomiting	14.6%	12.8%
Chest pain- noncardiac	13.9%	9.0%
Back pain	13.2%	6.4%
Abdominal pain- upper	10.6%	7.7%

The approved dose of L-glutamine in the United States is 5-15 g twice daily
Niihara Y, et al. N Engl J Med. 2018;379(3):226-235.

Safety and Efficacy of Voxelotor *(continued)*

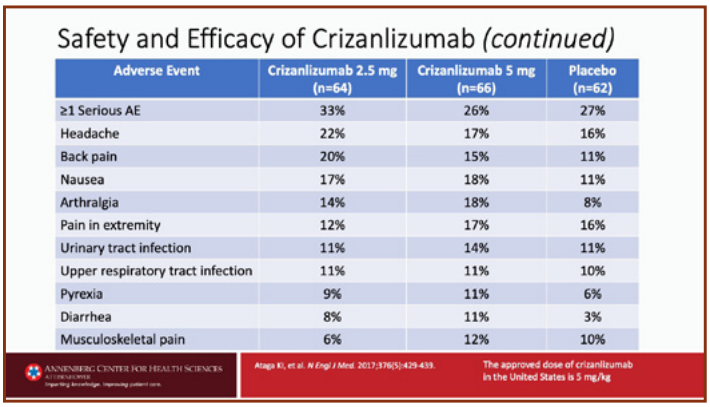
	Voxelotor 900 mg (n=92)	Voxelotor 1500 mg (n=88)	Placebo (n=91)
Headache	15%	26%	22%
Diarrhea	17%	20%	10%
Nausea	16%	17%	10%
Arthralgia	12%	15%	12%
Upper respiratory tract infection	18%	14%	11%
Abdominal pain	14%	14%	8%
Fatigue	13%	14%	10%
Rash	11%	14%	10%
Pyrexia	11%	12%	7%

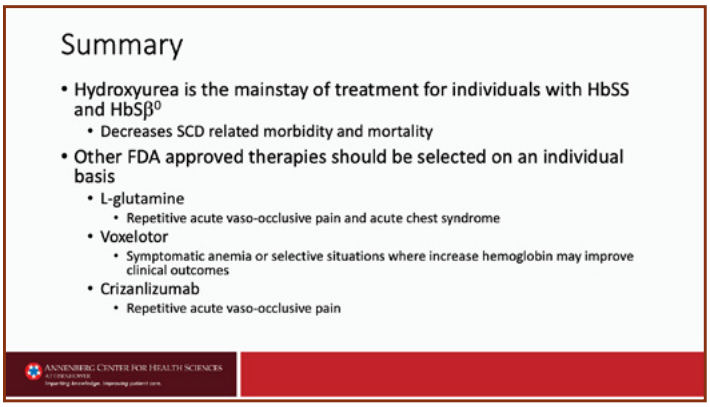
The approved dose of voxelotor in the United States is 1500 mg once daily
Vichinsky E, et al. N Engl J Med. 2019;381(6):509-519.



double-blind, patients with sickle cell disease were randomly allocated to either receive crizanlizumab at 2.5 mg/kg or 5 mg/kg or placebo. What's important to note is that hydroxyurea was allowed in this trial. Even though this was only a phase 2 trial, the results indicated that crizanlizumab reduced the number of, and time to, acute pain episodes. Specifically, the median number of pain episodes for the patients who were treated with 5 mg was 1.63 per year vs, in the placebo group, where it was 2.98. This was significant at the 0.01 level. In addition, the median events, time to second pain event, was also decreased in the group of patients who received the 5 mg/kg dose vs the group of patients who received the placebo dose.

In terms of safety and efficacy of crizanlizumab, what's important to note is that the drug was generally very well tolerated. For the patients who were receiving crizanlizumab at the 5 mg dose, when compared to the placebo dose, what we found was that there was a higher rate of nausea when compared to placebo and a higher rate of fever onset, and there was a higher rate of diarrhea, but those were generally the most common features that distinguished crizanlizumab from the placebo group.





CURATIVE THERAPY

Michael DeBaun, MD

Hematopoietic stem cell transplant is an option for cure in sickle cell disease. Matched related donor hematopoietic stem cell transplant has been available for selected groups of children and adults with sickle cell disease for over 25 years. The biggest challenge has been low donor pool for matched related donors. About 15% of children with sickle cell disease will have available donors. That's the majority of children and adults who elect to have a matched related donor who will not have an option for curative therapy using this strategy. Also of note is that there's nonmyeloablative and myeloablative transplant. The nonmyeloablative transplant is the preferred strategy for adults because many of the adults, as mentioned earlier, have heart, lung, or kidney disease, and their body simply cannot tolerate the myeloablative treatment regimen. So, nonmyeloablative hematopoietic stem cell transplant, which is matched related donor, is the preferred route for individuals over 18 years of age. Myeloablative matched related donor transplant has been the mainstay of therapy for children over the last 25 years.

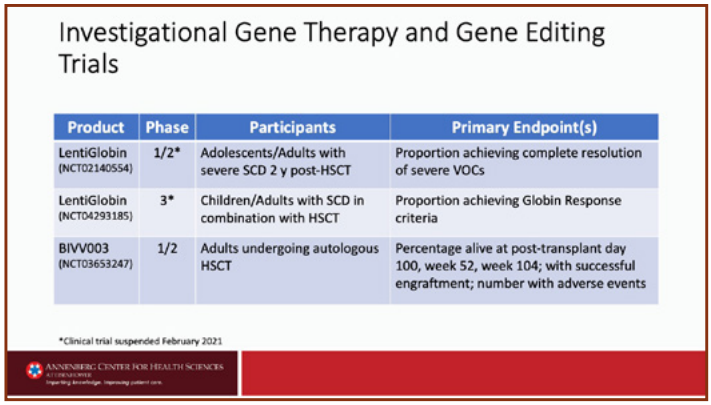
Generally, for children and adults, we reserve a curative therapy for stroke. For adults, we reserve the treatment for recurrent vaso-occlusive pain episodes and for our selective children where the quality of life has been dramatically impaired by repetitive pain episode that is not associated with social determinants of health, as well as appropriate mental health evaluation. Individuals who have recurrent transfusions or heavily alloimmunized may also be considered for a hematopoietic stem cell transplant. Individuals with moderate renal damage can be considered for the nonmyeloablative approach. Other severe disease complications include priapism or progressive debilitation of ambulatory status due to avascular necrosis of the hip. These indications have never really been identified with a consensus panel and should really be based on individualized decision-making between the primary care provider, the hematologist, the transplant provider, and the family.

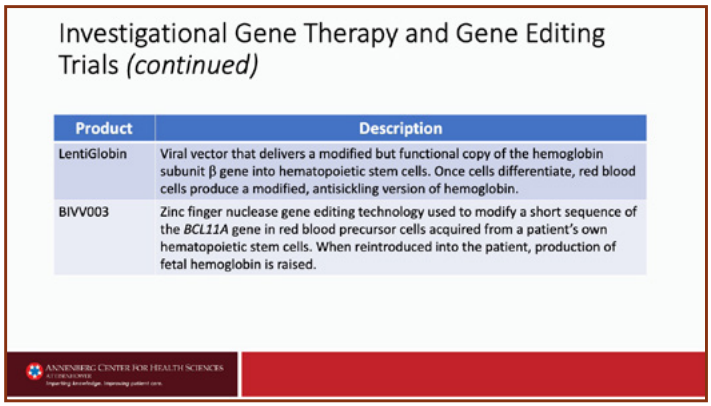
On the horizon is the use of haploidentical transplant with post-transplant cyclophosphamide. The importance of this strategy is that it is nonmyeloablative. Therefore, most adults can undergo this transplant due to the fact that even if you have significant heart, lung, and kidney disease, you can still be eligible for these types of transplant trials. And then also what's important is that because it's a haploidentical transplant, you only need half of a match. Most clinical trials that have been done in this area have indicated that more than 90% of the adults with sickle cell disease, and almost every child with sickle cell disease, will have an available donor due to the requirement of having only half of a match required, which can be a sibling, a parent or, in fact, a son or daughter.

Transplant complications can often be more serious than the disease itself. And for this reason, there should be careful consideration about whether the benefits of current disease-modifying therapy outweigh the risks associated with curative therapy. The complications include graft-vs-host disease, death, and morbidity associated with complications with the transplant, and even a malignancy that may occur after the curative therapy.

As is the case for hematopoietic stem cell transplant where we do not have a definitive therapy, our recommendation is that all children and adults who engage in curative therapy, whether it's hematopoietic stem cell transplant, gene therapy, or gene editing, be engaged in a clinical trial.

There are several trials available for curing sickle cell disease with gene therapy and gene editing. There's the lentiglobin phase 1/2 trial. There's a lentiglobin phase 3 trial. And BIVV003 that's in a phase 1/2 trial.

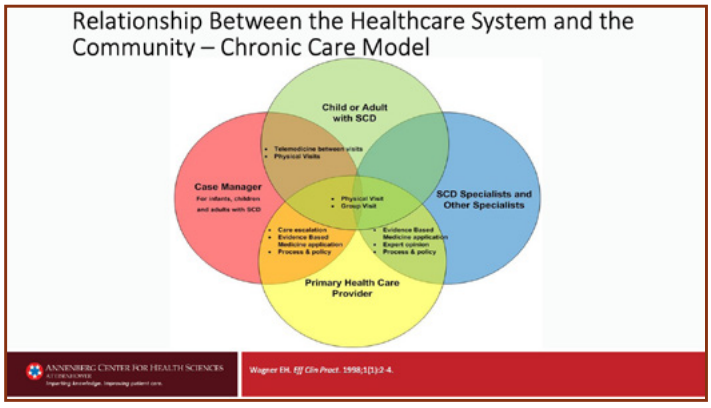




COORDINATED CARE

Collin Montgomery, APRN

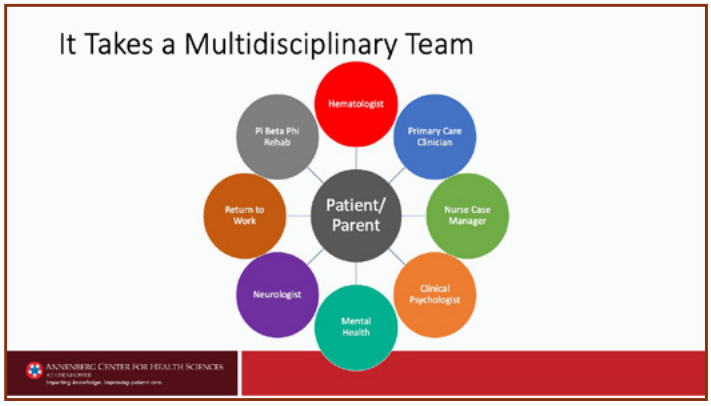
The Ed Wagner chronic care model is a strategy to facilitate care for children and adults with sickle cell disease. It starts off with empowering individuals with the disease to know about sickle cell disease and to try to have a patient-centered approach to their care. In the era of COVID, this may mean that we have telemedicine visits as opposed to families commuting 2 hours to see us for a 30- or 45-minute visit. But in addition, there should be physical visits, as needed, to address the needs of the



families. That also includes visits that occur on the weekends for our families who work Monday-Friday, and also in the evening for our students who have challenges getting out of school, as you would expect, to see a physician on a routine basis. This model also includes sickle cell disease specialists, as well as other specialists who manage the chronic manifestations of the disease. As mentioned, chronic lung disease or acute chest syndrome, which may have sequelae, or asthma or recurrent wheezing, kidney complications that may occur, cardiopulmonary complications that may require referral to a pulmonologist or cardiologist to address pulmonary hypertension.

The primary care health provider in the management of children and adults with sickle cell disease is absolutely key to improving the total care for this patient population, particularly given the high rate of mental health complications that occur in this population, specifically depression and anxiety. We believe that every individual with sickle cell disease, particularly every adolescent and adult, should have a primary care provider to facilitate their care and to be a partner in the care with their sickle cell expert.

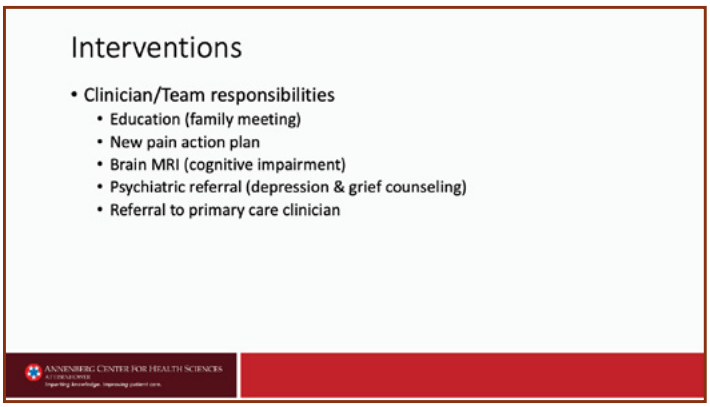
Last but not least, is the nurse case manager for infants, children, and adults with sickle cell disease. Again, embracing the Ed Wagner chronic care model, most of the work in terms of managing children and adults with sickle cell disease occurs in between the visits. The case manager spends an inordinate amount of time making sure the families are well educated about the disease, anticipatory guidance in terms of management of complications, including having a pain action plan that's available and knowledgeable and is followed, including scheduling visits for the multitude of specialists and evaluations that are required for children and adults with sickle cell disease, and also facilitating the care once they come to clinic to make sure that their knowledge base about the disease is sufficient to allow for those patients and their families to be self-sufficient and empowered to make informed decisions about their treatment options.



In summary, this chronic care model is a multidisciplinary team that requires the hematologist, the primary care provider, the nurse case manager, a psychologist or mental health specialist, or neurologist if there's concern about a stroke, on strategies to improve that patient's ability to go back to work when they're ill or go back to school, or to be an advocate for those students who have difficulty with academic performance due to silent strokes or overt strokes, and then rehabilitation as it relates to acute strokes that may occur, and then the chronic rehab component for those individuals.

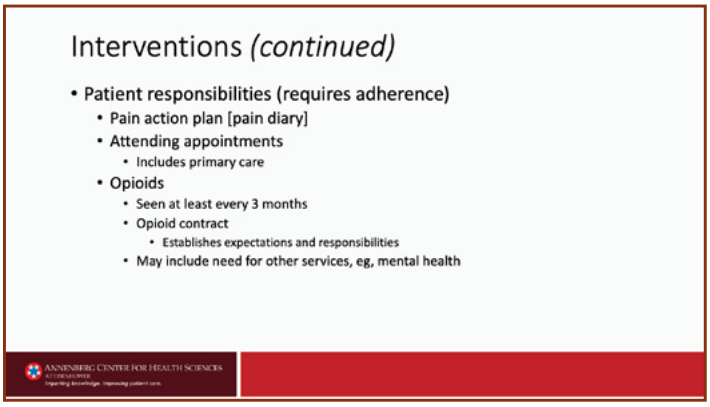
The multidisciplinary team is key to improving patient outcomes with the sickle cell population. Let's talk about the roles of the team and the patient. As the team, education, education, education, education, is so important for these patients. Understanding the need for primary care services, knowing what are acute complications, what can be life-threatening, what are chronic complications and how to manage those.

I definitely like to involve family when caring for patients because I need to know what their support system looks like. Patients with support systems also have better outcomes. The new pain action plan. I definitely want to have a pain plan because there's nothing like meeting a new patient and like reinventing the wheel. I want to know what's worked best. It's



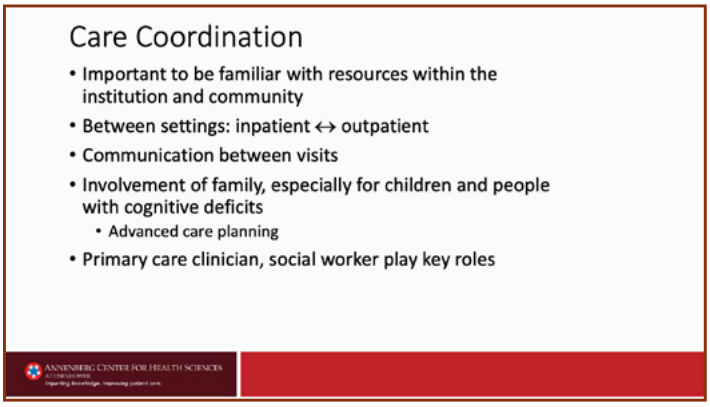
important to know what's worked best for them in the past. What hasn't worked in the past. If they have any preferences. When developing a pain plan, the patient should be an integral part of that. And then brain MRIs. So, involving neurology if we have any concerns for cognitive impairment. Again, psychiatric referral is absolutely necessary because under-managed and unmanaged mental health disorders contribute to morbidity and mortality in this population, longer lengths of stay, more frequent utilization. And then again, primary care. Knowing your resources in your area to make sure that your patients are getting the primary care services they need.

Now let's talk about the patient's responsibility. A pain diary, I absolutely love pain diaries. I see my patients roughly every 2-6 months, but it's a way for them to capture what their pain looks like over that time period. What's worked for them? When did they notice they were having pain? What makes that pain worse? Because a lot of times our clinic visits are so short, it is hard for the patient to remember everything that's happened in 3 months. But when they bring me the diary, I'm able to look through and ask the questions I need to better meet their needs.



And then attending appointments is very important. And that is sickle cell appointments, as well as primary care appointments. As patients are aging, they're having chronic medical issues that are well within the scope of the general practitioner to care for vs the hematology specialists. Also, the CDC recommends that patients that are on chronic opioids are seen at least at a minimum every 3 months by their provider. Obviously, that's more frequent when we're doing dose adjustments. And then, the opioid contract, very important. It just sets forth the expectations of the provider as it pertains to opioid prescribing for patients. One key feature that I encourage in opioid contracts is to put a component in there about mental health services. If you feel that the patient needs mental health services, that can be a requirement of your opioid contract because it's not uncommon for patients to chemically cope with medicines. Because again, patients are often confused and they have a somatic presentation of their mental health disorder and they assume it is sickle cell-related pain, but it's really not the actual source of pain.

Care coordination is essential. If you're in a large institution, care coordination can be very easy because you typically have all the specialties there in-house. However, if the institution is not large, it is important to know your community allies and who can you send your patients to in order to get the services they need, whether they be mental health services, orthopedic services, neurology services, endocrinology,

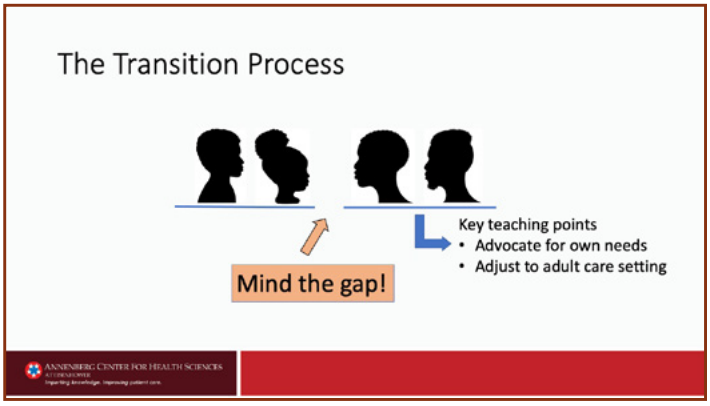


just make sure that you are aware of your community resources to help better care for these patients because it definitely takes a team to optimize management. Coordinating between inpatient and outpatient definitely improves patient outcomes and a shortened length of stay. If chronic transfusion is needed, again, know your resources in your community in the event that your facility is unable to provide that. And then reminder phone calls. I found that with my tech-savvy population, phone calls are not really what they like to do. So, they respond best from text messages. And that also helps with your patients— and especially your patients that have cognitive deficits—making sure they attend their appointments.

Another thing with care coordination, especially, you know, with patients with cognitive deficits, that it's important to get the family involved and help the patient identify someone that we can talk to if they are unable to make their decisions that even may be advance care planning. We do a lot of that in sickle cell disease as well.

As for the primary care clinicians and the challenges that they face. Again, adherence, adherence, adherence, as patients are just not as adherent to their primary care appointments as they typically are for sickle cell. So, educating on the importance of attending those appointments and also educate on disease and disease management.

Transition process. This is a very important part. As you recall, the highest rate of morbidity and mortality in sickle cell disease patients is in the young adult population, which encompasses your transition period ages



18-21 years. It is imperative that you have a social worker as a part of this process. They are able to identify the needs of the patients and address the needs of the patients.

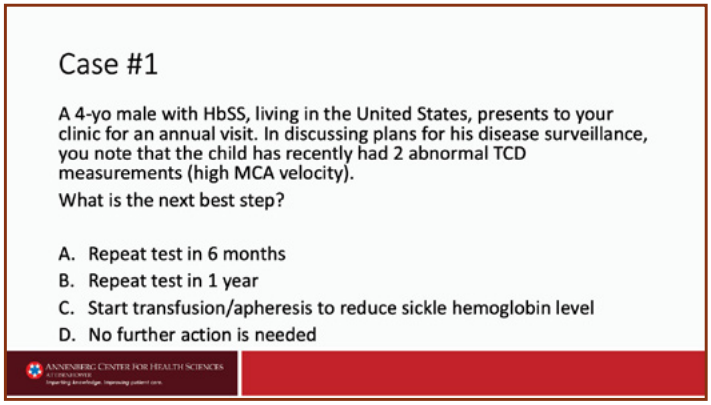
There are some standardized tools to assess transition readiness. You can start that with your adolescents, early adolescence into late adolescence, and you just need to have a good plan on how to successfully transition. Some key things that should be in that transition plan is preparing the patient to be their own advocate, which is very different when you're going from pediatrics to adults, because typically the parent is speaking. So, teaching the patient how to advocate for their own needs. Also, I think the hardest thing for my patients that transition is they often talk about the culture of the adult setting vs the pediatric setting. It is very different and that is kind of a hardship sometimes for patients to get over.

In summary, the complex needs of the sickle cell population are best met by a multidisciplinary team. This team includes primary care services, specialty services, mental health services, care management and coordination. These things are essential to produce the best outcomes in this population. Also, a very critical part in the sickle cell patient's life is the transition process, which is typically between ages 18 and 21 years. Unsuccessful transition is related to increased morbidity and mortality. So, we want to have a solid transition plan that includes standardized readiness tools to assess whether or not the patient is ready. We also want to be able to meet their barriers that they may have related to transition. And we have to emphasize the importance of preventative care measures and a primary care provider to manage the other chronic diseases that may be co-occurring with sickle cell disease.

CASE SCENARIOS

Michael DeBaun, MD & Collin Montgomery, APRN

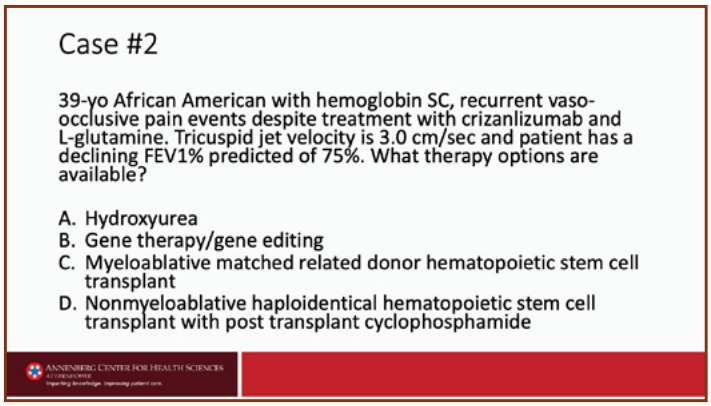
CASE #1



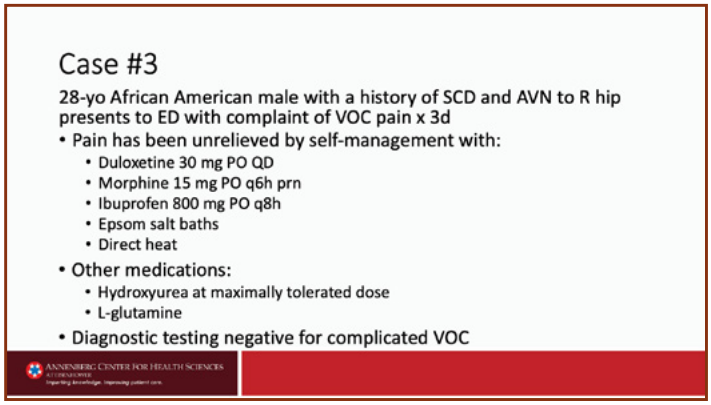
The correct answer is option C. After discussion with the family, this child should be started on regular blood transfusion therapy to decrease the hemoglobin S level to less than 30% to keep the hemoglobin level above 9 g/dL. And this can be done with simple transfusions or preferably with red blood cell exchange apheresis.

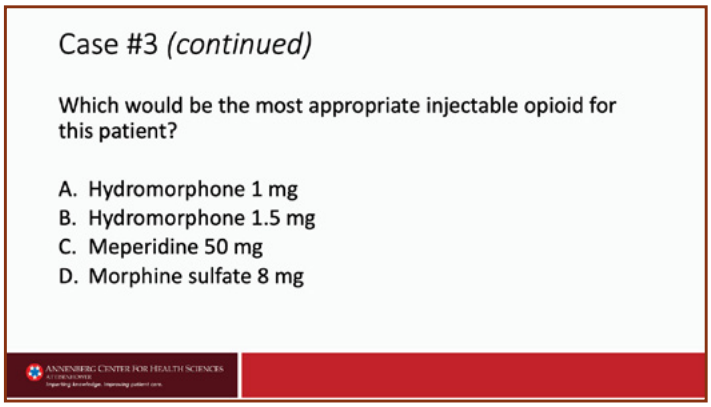
CASE #2

This is a challenging case. And generally speaking, this is an adult who has end organ disease. Specifically, he has a tricuspid jet velocity greater than 2.5 cm/second, which is associated with premature death. Also has a low FEV 1% predicted. So, myeloablative therapy, whether it's myeloablative gene therapy or gene editing, myeloablative matched related donor hematopoietic stem cell transplant would not be the safest option for this individual. The option that I would prefer—and the literature would support as the best option for this individual—would be nonmyeloablative haploidentical hematopoietic stem cell transplant with post-transplant cyclophosphamide. There is an alternative, although not on the list, which is nonmyeloablative matched related donor hematopoietic stem cell transplant, which has been offered to adults who have an HLA-matched sibling donor.



CASE #3





The answer would be hydromorphone 1 mg because it is the closest to their home medicine, which you should do. Your injectables should be equivalent to the home oral dosing. And that's a good starting point for patients for relief. You can increase by 25% with subsequent dosing.

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