

Managing Sickle Cell Disease in Patients for Whom Blood Transfusion Is Not an Option

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ORIGINAL RESEARCH REPORT

Managing Sickle Cell Disease in Patients for Whom Blood Transfusion Is Not an Option

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Abstract

Sickle Cell Disease (SCD) is a hereditary blood disorder affecting beta hemoglobin. This disorder causes sickle-shaped red blood cells with decreased oxygen-carrying capacity resulting in vaso-occlusive crises. These crises are often treated with analgesics, antibiotics, IV fluids, supplementary oxygen, and allogeneic blood transfusion. This treatment regimen becomes complicated when caring for SCD patients for whom blood transfusion is not an option. Blood transfusion may not be an option due to the patient's religious, personal, or medical concerns and in scenarios where blood is not available for transfusion. Some examples include the patient being a Jehovah's Witness, blood-borne pathogens concerns, or prior history of multiple alloantibodies and severe transfusion reactions. The number of patients in these categories is growing. The patients and their autonomy should be respected during treatment. This review focuses on the currently available modalities to best manage this subgroup of SCD patients without blood transfusion, including new professional guidelines and new therapies to reduce the severity of SCD as approved by the Food and Drug Administration since 2017.

Keywords: Sickle cell disease, Blood transfusion, Bloodless medicine, Pain management, Vaso-occlusive crisis, Blood substitute

1. Introduction

SCD is an autosomal recessive disorder that causes abnormal beta hemoglobin known as HbS. A missense mutation of glutamic acids causes this abnormal beta hemoglobin to valine at the sixth position on Chromosome 11. This mutation leads to distortion of the RBC, giving them their sickle shape [1]. These sickle-shaped RBCs have shorter survival in circulation (10–20 days compared to 90–120 days for normal RBC), often leading to symptoms such as fatigue and jaundice typically seen in patients with

SCD. These cells can occlude smaller blood vessels causing vaso-occlusive crises, leading to other complications like organ failure, stroke, proliferative retinopathy due to ischemic damages, and Acute Chest Syndrome (ACS). SCD is typically asymptomatic during early infancy when fetal hemoglobin is dominant [2]. Whether symptomatic or not, diagnosis is made through hemoglobin analysis: electrophoresis, high-performance liquid chromatography, thin-layer isoelectric focusing, solubility testing, and examination of the peripheral blood smear [2].

Abbreviations: SCD, sickle cell disease; RBC, red blood cells; Hb, hemoglobin; JW, Jehovah's Witness; FDA, Food and Drug Administration; ACS, acute chest syndrome; GI, gastrointestinal; EPO, erythropoietin; OTAs, oxygen therapeutic agents; PFCs, perfluorocarbons; HBOCs, hemoglobin-based oxygen carriers; PEG-Hb, PEGylated hemoglobin,

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The primary treatment for SCD consists of hydroxyurea, which increases patient production of fetal hemoglobin, thus reducing pain and other vaso-occlusive complications while decreasing hospitalization and improving survival [3]. Another treatment modality is managing vaso-occlusive pain with analgesia, hydration with normal saline, and allogeneic blood transfusions. Specific indications for blood transfusion include preparation for surgery, symptomatic anemia, prevention and treatment of acute stroke, multiorgan failure, prevention and treatment of ACS, and recurrent priapism [3]. Treatment becomes complicated for SCD patients for whom blood transfusion is not an option when these indications arise. The reason why blood transfusion might not be an option may vary amongst patients, including personal, religious, or medical reasons. SCD patients also have a higher incidence of alloimmunization against donor red blood cells. Finding compatible blood units to transfuse might be difficult for some patients with SCD. It can become challenging for some healthcare providers to manage the difference in care for these patients when a blood transfusion is no longer an option.

2. Prevention and immunization

The most appropriate way to manage patients with SCD is by taking preventive measures to minimize vaso-occlusive crises. These crises can be triggered by but are not limited to hypoxemia, dehydration, and changes in body temperature. Prevention of hypoxemia is complex due to the decreased O₂ carrying capacity of the sickle cells. However, keeping SCD patients well hydrated with adequate oral fluid intake helps prevent the cells from taking on a sickled form, therefore decreasing hypoxemia. Another form of prevention of hypoxemia is the first-line medication for SCD, hydroxyurea. Hydroxyurea is a ribonucleotide reductase inhibitor that increases the patient's level of fetal hemoglobin. Fetal hemoglobin is composed of subunits alpha 2 and gamma 2; therefore, it is not affected by the beta subunit mutation seen in SCD. Fetal hemoglobin also has a higher oxygen-carrying capacity due to its higher binding affinity for oxygen than adult hemoglobin. This makes fetal hemoglobin very beneficial for SCD patients. It reduces RBC sickling and allows more oxygen delivery to the tissues, ultimately decreasing hypoxemia and minimizing vaso-occlusive crises. Hydroxyurea can also reduce RBC adhesiveness to vascular endothelium, minimizing vaso-occlusive crises.

Preventing dehydration does not just reduce hypoxemia. It also minimizes the occurrence of vaso-occlusive crises. As mentioned, recommending proper hydration for SCD patients can prevent the cells from taking on their sickle shapes. Adequate hydration can also help blood flow through the venous and arterial systems, improving tissue perfusion. SCD patients are advised to drink twice as much water as the average individual. The Boston Medical Center Department of Food and Nutrition Services recommends over 13 8-oz cups or bottles a day for SCD patients over 100 pounds. Hydration is essential as SCD patients often have difficulty concentrating their urine and diuresing more water. Moreover, fluid intake should increase during hot weather and exercise due to additional fluid loss through sweat. Despite the patient's hydration status, fluid hydration is always recommended for managing vaso-occlusive crises. Hydrating patients in vaso-occlusive situations slows or stops the sickling process by increasing the plasma volume. This decreases blood viscosity and indirectly reduces red cells dehydration and intracellular concentration of HbS. Supplemental fluids may be given either orally, intravenously, nasogastrically, subcutaneously, or rectally. The optimal quantity, administration rate, and type of fluid for treating a vaso-occlusive crisis is still not well defined, and often these decisions are made on an individualized basis [2,4].

Another way to prevent vaso-occlusive crises involves staying up to date with immunization. Due to absent or decreased splenic function, SCD patients have a greater risk of developing bacterial infections or sepsis. Moreover, children with SCD are at a higher risk of being affected by an invasive pneumococcal disease. Therefore, prophylactic oral penicillin is recommended for all infants and children, in addition to two doses of 23 valent polysaccharide pneumococcal vaccine separated by 5 years, if two years or older. This should begin 8 weeks after completion of recommended doses of pneumococcal conjugate vaccine. Other vaccines that should be administered include the influenza vaccine for patients 6 months and older, the meningococcal vaccination for patients 2 months and older, and now vaccination against severe acute respiratory syndrome coronavirus 2 [5]. Vaccinations should be monitored and administered routinely to help develop the patient's immunity and reduce complications associated with infection.

Iron supplementation is not generally advised in SCD patients for preventive measures. In high-income countries, dietary iron is sufficient, and transfusional iron overload is prevalent in patients with

SCD that can accept blood transfusions. Therefore, empiric iron supplementation is discouraged for SCD in high-income countries. The situation might be different in low/middle-income countries where access to blood transfusion is limited, and many people have poor dietary iron intake. Microcytosis is not reliable as a sole indicator of iron deficiency, because microcytosis is associated with alpha thalassemia trait, hemoglobin C, and other hemoglobinopathies. When iron stores are measured by ferritin, children with SCD have a low incidence of iron deficiency. Therefore, the evidence does not support empiric iron supplementation for SCD. Iron supplements should be limited to documented iron deficiency or for the acute short-term augmentation of erythropoiesis-stimulating agents.

2.1. Therapies to reduce severity of SCD

Tremendous progress has been made in medications to reduce the severity of SCD in all patients. One of these medications briefly mentioned above is hydroxyurea. The FDA approved hydroxyurea in 2017 for treating SCD in children as SiklosTM (Medunik USA). The FDA approved it for adult SCD in 1998. Hydroxyurea is a manufactured chemical not made from blood products. Hydroxyurea treatment for SCD is taken once a day, with dosage selected based on the individual needs. The benefit of hydroxyurea is usually related to the dosage, with a great deal of individual variation. Lab results are followed every 1–3 months to monitor for the medication's benefits and any side effects. Hydroxyurea usually reduces pain and other vaso-occlusive complications, decreases hospitalization rates, and improves survival [3]. Many studies have also shown that hydroxyurea can be neuroprotective from the effects of SCD. A good safety profile and similar benefits of hydroxyurea have been observed in SCD populations globally. The one disadvantage of hydroxyurea is its potential to cause birth defects; therefore, it should not be used during pregnancy.

Glutamine is an amino acid occurring naturally in many foods. It was approved in 2017 for treating SCD patients 5 years and older. Glutamine (EndariTM, Emmaus) is processed from sugar cane to pharmaceutical-grade purity. It is taken twice a day using powder packets mixed with food or drink to treat SCD. Glutamine can reduce the frequency of pain, ACS, and hospitalizations. Side effects, including headaches and/or gastrointestinal (GI) symptoms, were reported in only 10% of people taking glutamine. Lab monitoring is not needed for glutamine. Data shows that glutamine therapy is safe during pregnancy.

Voxelotor (OxbrytaTM, Global Blood Therapeutics), approved by the FDA to treat SCD patients 12 years and up, covalently binds to valine within hemoglobin, increasing its affinity to oxygen, and thereby preventing sickling of the RBC [6]. Voxelotor (OxbrytaTM) is produced as a chemical, not as a blood product. It is administered as three oral capsules per day. Voxelotor can raise the hemoglobin level and reduce the premature breakdown of sickled RBCs by blocking the crystallization of sickle hemoglobin. Symptoms of yellow eyes (from jaundice) are usually reduced, and patients report less fatigue. The benefits of voxelotor for sickle cell pain are less clear. Lab monitoring ensures that blood counts do not rise too high. Side effects reported for voxelotor include headaches, GI symptoms, and interference with lab analysis of hemoglobin fraction. Voxelotor is cleared from the body through the liver and has potential interactions with other medications that are also cleared by the cytochrome P450 system. We are unaware of any data showing the safety of taking voxelotor during pregnancy.

Crizanlizumab (AdakveoTM, Novartis) blocks abnormal stickiness of sickle RBCs to the blood vessel wall. The FDA approved crizanlizumab to treat SCD in patients 16 years and up. Crizanlizumab is produced in industrial cell culture, containing no blood products. It is administered as an intravenous infusion over about 30 min, first with loading doses 2 weeks apart and then regular booster doses every 4 weeks. Crizanlizumab can reduce the frequency of sickle vaso-occlusive pain. No lab monitoring is needed for crizanlizumab. Side effects reported for crizanlizumab include headaches, GI symptoms, and infusion reactions. We are unaware of any data showing the safety of taking crizanlizumab during pregnancy [7,8].

These three newest medications for SCD disease are expensive but can usually be covered by insurance with physician prescription and documentation justifying their use. Hydroxyurea for SCD is less expensive and can be covered by insurance with a physician's prescription. These treatments are highly beneficial in preventing complications that may lead to the need for a blood transfusion and should be recommended for all SCD patients for whom transfusion is not an option. Discussion points for patient education about these therapies are provided in [Table 1](#).

3. Treating vaso-occlusive crises

Though less frequent and severe, vaso-occlusive crises can still occur despite preventive measures. As mentioned above, it can present in many ways in

Table 1. Advantages and disadvantages of the four approved non-transfusion therapies for SCD. These are educational notes not intended to replace prescribing information.

Therapies	Advantages	Disadvantages
Hydroxyurea FDA approved for adults 1998, for children 2017	<ul style="list-style-type: none"> • Produced with no blood products • Increases production of fetal hemoglobin • Reduces RBC- endothelial adhesion • Reduces pain events and hospitalizations by one half • Raises hemoglobin by 1 g/dL • Reduces the occurrence of priapism • Increases lifespan • Neuroprotective • Low cost 	<ul style="list-style-type: none"> • Contraindicated in pregnancy due to possible teratogenicity • Dose-related neutropenia requires routine laboratory monitoring of WBC and renal function
Glutamine FDA approved for age 5 years and up, 2017	<ul style="list-style-type: none"> • Produced with no blood products • It does not require routine laboratory monitoring • Reduces the frequency of pain, ACS, and hospitalizations • Reduces oxidative stress, which sickle cells are more susceptible to • Safe during pregnancy 	<ul style="list-style-type: none"> • Side effects may include GI symptoms and headaches
Voxelotor FDA approved for age 12 years and up, 2019	<ul style="list-style-type: none"> • Produced with no blood products • Blocks sickling of RBC • Reduces hemolysis • Raises hemoglobin by 1 g/dL • Reduces jaundice in eyes 	<ul style="list-style-type: none"> • Side effects include headaches, GI symptoms • Interference with lab analysis of hemoglobin fraction • Potential interactions with other medications also cleared by the cytochrome P450 system • Requires routine laboratory monitoring to make sure blood count does not rise too high • Safety in pregnancy unknown
Crizanlizumab FDA approved for age 16 years and up, 2019	<ul style="list-style-type: none"> • Produced with no blood products • Reduces RBC- endothelial adhesion • Reduces pain frequency • Administered by intravenous infusion • It does not require routine laboratory monitoring 	<ul style="list-style-type: none"> • Side effects include headaches, GI symptoms, and infusion reactions • Interferes with some lab tests by clumping the platelets • Safety in pregnancy unknown

SCD patients, such as pain, stroke, ACS, dactylitis, and priapism, and the treatment often involves blood transfusion. Blood transfusion could be considered for acute therapeutic or prophylactic indications. In the case of acute anemia, blood transfusion is considered when hemoglobin decreases below 2 g/dL and the patient is symptomatic (e.g., dizziness, syncope, headache, weakness). In symptomatic ACS with Hb > 1.0 g/dL below the baseline, or where oxygen saturation cannot be maintained >92% on room air, or if oxygen requirements increase, a transfusion to a Hb level of 10–11 g/dL could be considered. For acute ischemic stroke, international guidelines recommend that patients should be treated with exchange

transfusion aiming for Hb of 10 g/dL and HbS <30%. For acutely unwell SCD patients with multi-organ failure, exchange transfusion could be performed, aiming for HbS <30% and Hb of >10 g/dL [9,10]. For prophylactic prevention of vaso-occlusive crisis after surgery, it is recommended to increase Hb level to 10 g/dL before surgery [10].

However, new evidence-based guidelines for SCD care from 2014 to 2020 include discussions on medically recommended blood transfusions when balancing medical risks and benefits for SCD (independent of religious objection) [11–13]. A principal concern is that people with SCD have a high risk of RBC alloimmunization: forming an antibody against the transfused RBCs. Transfusion is not

recommended for sickle cell pain alone: “Do not administer a blood transfusion unless there are other indications for transfusion in children and adults with a vaso-occlusive crisis” [13]. Transfusions are recommended when major complications develop, such as severe ACS, a complicated pregnancy, or an acute stroke. It is important to note that these expert guidelines do not recommend a specific hemoglobin threshold for transfusion in SCD, instead emphasizing pathophysiologic situations. The benefits of transfusion include reducing HbS percentage and increasing oxygen delivery to tissues.

Managing SCD without allogeneic blood transfusion can be challenging, but many competing strategies have been implemented. One successful method increases the body's natural production of RBC through erythropoiesis via the administration of high-dose recombinant erythropoietin (EPO) or other erythropoiesis-stimulating agents like darbepoetin. EPO is a representative of this class. The kidneys synthesize EPO, which stimulates the bone marrow to produce RBC. EPO is naturally elevated in SCD as compensation for hemolytic anemia. Therefore, higher doses of EPO are administered in SCD than in people without anemia at baseline [14]. In previous studies of preoperative management for anemic Jehovah's Witness (JW) patients, surgeons took advantage of this natural process and achieved correction of anemia through administering high-dose exogenous EPO 3–4 weeks before surgery [15]. This approach might be applied to SCD patients with an acute exacerbation of anemia for whom blood transfusion is not an option. Though it might take 3–4 weeks to correct the anemia, it might still be beneficial to administer EPO to these patients. The main contraindication for EPO is hyperviscosity and thrombosis when Hb is at 11 g/dL or above. Still, this Hb level is rarely encountered in SCD patients with profound anemia. Also, the young age of most individuals with SCD makes atherosclerotic heart disease unlikely. Patients should also be given high-dose iron, vitamin B12, and folate to help the bone marrow to reach maximal RBC production.

Another way to treat these patients is to manage hemoglobin decrease by preventing blood loss. Studies of iatrogenic anemia have shown phlebotomy for hospitalized patients to result in 5–10 mL of blood loss at each blood draw [16]. This is not significant blood loss for a non-anemic adult (representing 0.1–0.2% of total red blood cell mass) but has a disproportionately higher impact for a severely anemic SCD patient, especially in small children. Decreasing blood draws and using microtubes such as those used for newborns on

these patients can help maintain their hemoglobin levels and prevent exacerbation of anemia. Another method to prevent blood loss is withholding medications that can cause increased blood loss in non-major and major trauma. The use of anticoagulants should be stopped if there is significant bleeding, but prophylactic anticoagulation is prudent for the increased thrombotic risks when an SCD patient is bedbound [17]. In female patients, hormonal therapy could be administered to prevent blood loss from menses. It is known that blood loss from menses can trigger sickle cell crises in female SCD patients and anemia in healthy female patients, so preventing menses with hormonal therapy helps maintain hemoglobin levels for female SCD patients. Progestin-based birth control is recommended for females with SCD, as they have been shown to have a lower risk of thrombosis in these patients compared to combined birth control. Birth control should be advised and discussed with any female SCD patient of childbearing age.

Aggressive measures can be taken if these patients develop severe anemia exacerbation that becomes life-threatening despite sufficient hydration, increasing natural erythropoietin, and decreasing blood loss. Patients can be intubated and placed on ventilatory support to increase oxygen delivery to tissues and reduce the work of breathing. Patients could also be sedated and administered neuromuscular blockade to minimize energy expenditure [18]. High-dose EPO, iron, vitamin B12, and folate should continue to be administered to patients in this state to maintain erythropoiesis. Using the above methods of increasing natural erythropoietin, decreasing blood loss, intubation, and sedation successfully treated a JW SCD patient with ACS. The patient's hemoglobin declined to 3.1 g/dL during hospitalization, and in 5 weeks, the patient recovered from ACS and was discharged with a hemoglobin of 7.7 g/dL [18]. These methods of treatment could be imitated until further research is carried out. Examples of approaches to treating SCD patients without blood transfusion are shown in Fig. 1.

4. Blood substitutes (Oxygen Therapeutic Agents)

Blood substitutes are currently being researched as a treatment for patients who cannot accept blood transfusions. The main functions of these blood substitutes are to transport oxygen and carbon dioxide throughout the body. Oxygen Therapeutic Agents (OTAs) or oxygen carriers can be produced through synthetic production, chemical isolation, or

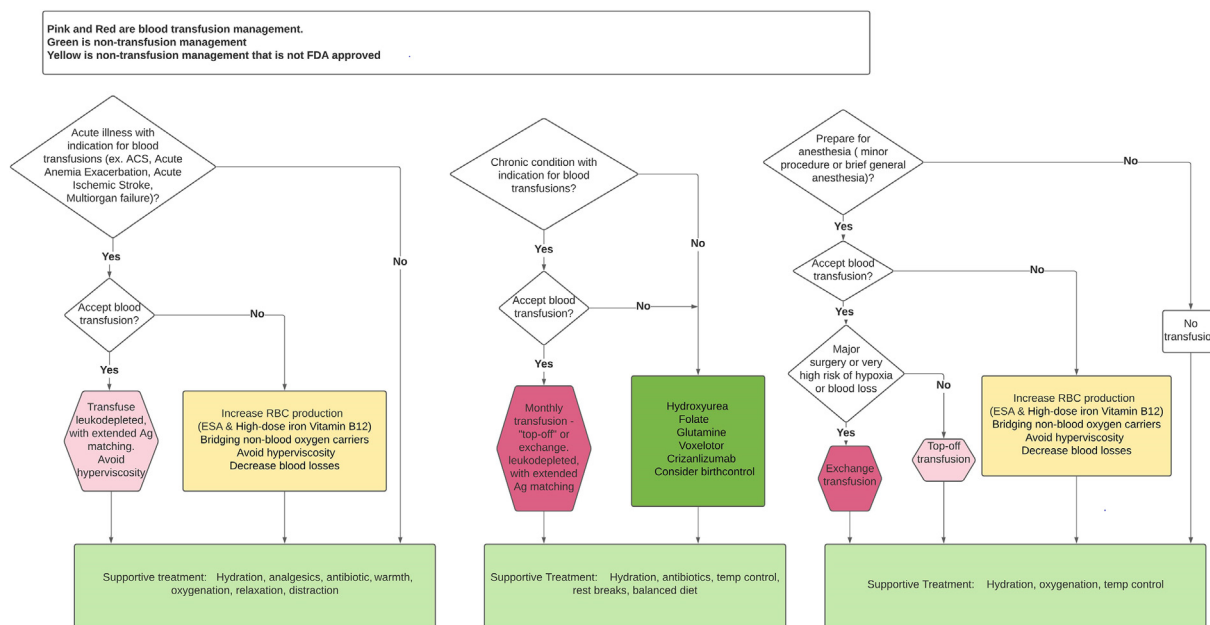


Fig. 1. Treating SCD patients without blood transfusion.

recombinant biochemical technology. The development of OTAs followed two main approaches: Perfluorocarbons (PFCs) and hemoglobin-based oxygen carriers (HBOC) [19]. The short half-lives of the OTAs limit their utility for the chronic anemia of SCD, but they could be considered a “bridge” therapy for acute exacerbation of anemia. Table 2 compares the advantages and disadvantages of the two main OTAs approaches.

PFCs are long-chain polymers primarily of carbon and fluorine that are more effective than blood plasma in dissolving and absorbing oxygen [19,20]. It was first used in Japan on a patient with a severe GI bleed. However, PFCs need more development as the first generation was not soluble in water and carried less oxygen compared to other OTAs. In addition, flu-like symptoms have also been reported with PFCs. Some PFCs are currently used in Russia and Mexico. However, more clinical trials are

required in the United States before FDA approval can be granted [21].

HBOCs are synthetic blood-based carriers of hemoglobin that take advantage of hemoglobin's natural function to covalently bond oxygen and transfer oxygen from the lung throughout the body [19]. Hemopure is a type of HBOC that is approved in South Africa and is available in the United States for life-threatening anemia under the FDA Expanded Access Program [21]. In a recent case study, a patient with a severe hemorrhage who declined blood transfusion due to religious reasons was stabilized from a hemoglobin level of 3.3, with 7 units of hemopure using the FDA Expanded Access Program [22]. Limitations of HBOCs include oxygen toxicity due to rapid unloading of oxygen and vasoconstriction due to vasoactivity properties from nitric oxide scavenging, leading to hypo-oxygenation, systemic hypertension, and pulmonary hypertension [21].

HBOCs can be chemically modified to prevent these side effects. PEGylated hemoglobin (PEG-Hb) is a high-potent HBOC that is vaso-inactive with a strong plasma expanding ability. It has increased oxygen affinity and minimal nitric oxide scavenging ability in comparison to prior HBOCs, therefore, it is not likely to cause oxygen toxicity and vasoconstriction. PEG-Hb has been used successfully in stabilizing an SCD patient with acute hyperhemolysis who was unable to receive blood transfusion due to fear of further hemolysis and bone marrow suppression. She was able to receive 40 mg/

Table 2. Advantages and disadvantages of the two main approaches to OTAs. These are educational notes not intended to replace prescribing information.

OTAs	Advantages	Disadvantages
PFC	<ul style="list-style-type: none"> Dissolves and absorb a significant amount of gas compared to plasma 	<ul style="list-style-type: none"> Poor oxygen carrier Flu-like symptoms
HBOCs	<ul style="list-style-type: none"> High oxygen affinity Good oxygen carrier 	<ul style="list-style-type: none"> Oxygen toxicity Vasoconstrictive properties

mL from manufacturers under an emergency investigational new drug approval [23]. Sanguinate, a type of PEG-Hb, has been granted FDA approval as an orphan drug for usage in SCD [21].

5. Discussion

Treating SCD patients for whom blood transfusion is not an option remains challenging for health care providers. Preventive measures should be taken to help reduce the frequency of SCD emergencies. Previously, the only preventive measures were good self-care (hydration, rest, temperature control, healthy diet, and vaccinations). Now exciting progress in SCD clinical research has been made with four medications available by prescription to reduce the severity of SCD: hydroxyurea, glutamine, voxelotor, and crizanlizumab. Acute and chronic complications can still occur despite preventive measures. However, patients can now receive curative approaches with hematopoietic stem cell transplant and gene therapy, which are beyond the scope of this paper. Supportive treatment and methods that increase natural erythropoiesis and decrease blood loss are also available. Until non-blood oxygen-carrying agents become more available and safe for patient use, alternative ways to treat this growing population of patients should continue to be researched. Patients are encouraged to keep up to date with advances in SCD therapy so that emergencies become less likely. This growing population might also benefit others with SCD to drive faster progress in clinical research on non-transfusion treatments and improve effective care.

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