

# ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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## Principles and Indications of Chronic Transfusion Therapy for Children With Sickle Cell Disease

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**H&O** What are the indications for chronic transfusion therapy in children with sickle cell disease?

**RW** The most common indication to begin and maintain a chronic transfusion program for children with sickle cell disease (SCD) is cerebrovascular complications. SCD affects the brain in a large percentage of pediatric patients, and transfusions are used most often to prevent either a first (primary) stroke or a subsequent (secondary) stroke. Overall in sickle cell anemia (SCA), which is the most common and severe form of SCD (sometimes referred to as hemoglobin SS or homozygous sickle cell anemia), approximately 8–10% of children will experience a stroke before reaching adulthood. Yet, if a child has already had a stroke, he or she has a 50–90% chance of experiencing a second stroke.

The most agreed-upon indication for chronic transfusions is stroke prophylaxis, sometimes called secondary stroke prevention. In the setting of a child with a previous stroke, the risk of a second stroke is reduced to approximately 10–20% with regular monthly transfusions. This common indication has never been tested in a clinical trial but it has been accepted in clinical practice over the last 30 years or so.

More recently, prevention of a first stroke has generated interest clinically. The problem with trying to prevent an initial stroke was predicting which 8–10% of children would have that event. Transcranial Doppler (TCD) screening has emerged as a screening tool with good pre-

dictive value; TCD screening is a means by which children with SCA can have a noninvasive, nonpainful assessment of the blood vessels in their brain. This technique identifies children at high risk for stroke. If children have a TCD flow velocity exceeding 200 cm/s, and that value is repeated and confirmed, then they have an approximate 30% chance of having a primary stroke in the near future (ie, the next 3 years). This threshold of 200 cm/s is a surrogate marker for stenosis in the large intracranial arteries, which increases the risk of stroke. Patients exceeding that threshold are thought to be at high enough risk to warrant prophylactic transfusions, typically given every month. Data from the Stroke Prevention Trial in Sickle Cell Anemia (STOP), a study looking at children who reached that 200 cm/s threshold and received either transfusions or observation on a randomized basis, indicated that chronic transfusion therapy was successful in preventing stroke. Primary stroke prevention after TCD screening and secondary stroke prevention after a documented stroke are the two most common reasons for transfusion therapy in children with SCA in the United States today.

**H&O** Once a patient is found to require chronic transfusion therapy, what is the next step?

**RW** After a stroke or a finding of flow velocity over the threshold of 200 cm/s by TCD and an explanation of the transfusion regimen to the parents and child, a periodic transfusion program commences. The frequency of the transfusions is typically monthly (ie, between 3 and 5 weeks); the precise interval depends on several factors including the child's baseline hemoglobin levels and response to transfusions. The blood transfusions can be administered in several different ways. The most common method, called simple transfusion, is to hang the blood and let it run into the bloodstream. This method is safe and effective, but it adds to the iron burden. At the other end of the spectrum is an automated red blood cell (RBC)

exchange transfusion, known as erythrocytapheresis. In this setting, a machine exchanges the old blood with fresh blood. The advantages are that this method achieves the same end transfusion result but with little net iron gain. The disadvantage is that erythrocytapheresis requires two intravenous lines, more expense, and more blood exposure. Furthermore, this method requires specialized equipment, therefore many centers do not currently perform apheresis procedures on children with SCD. There is also an intermediate method, called a partial exchange procedure, in which some amount of blood is removed manually from the patient prior to a simple transfusion, thus removing some blood and iron before the fresh blood enters the system.

The goal of a monthly transfusion regimen is to shut off the patient's own RBC production; raising the hemoglobin level by transfusion will lower the patient's endogenous sickle erythropoiesis. Hence, the transfused blood is able to predominate within the blood stream. The fresh blood cannot sickle and the hemoglobin level is raised, leading to less anemia. These benefits are easily measured—the desired result is for the percentage of sickle hemoglobin (the percentage of the patient's blood that is his or her own) to be less than 30%. Clinically, this level is effective in preventing a primary or secondary stroke. In practice, the target of 30% hemoglobin S is not always achieved. The clinician can judge whether the amount of blood administered, the method used, or the interval are appropriate based on how close the patient's level of sickle hemoglobin is to 30%. These factors can be modified from month to month to achieve a successful transfusion regimen.

### **H&O** What are less common indications for chronic transfusion therapy in children?

**RW** The two indications I discussed comprise approximately 75% of the transfusion patients in the United States in pediatric academic centers. Another indication for transfusion therapy is central nervous system (CNS) indications not in those two stroke categories, such as transient ischemic attacks (clinical events without radiologic changes) or silent infarcts (changes in the brain detectable by magnetic resonance imaging that are not true clinical strokes). Another indication is repeated episodes of acute chest syndrome. Other much less clear indications include priapism or recurrent debilitating pain. Most pediatric centers have 10–15% of their SCA populations on chronic transfusion therapy. Patients with the milder forms of SCD, such as HbSC or HbS/beta-plus thalassemia, rarely receive this therapy. The number of patients on chronic transfusion therapy has changed in recent years with the advent of hydroxyurea, another

therapeutic option for children with SCA, particularly patients with pain, acute chest syndrome, and non-CNS indications.

### **H&O** Could you describe the use of hydroxyurea?

**RW** Hydroxyurea is an important addition to the armamentarium for children with SCA. This agent was originally developed in the 1960s as an antineoplastic agent. In SCD, it works differently, though the mechanisms of action are not entirely clear. The benefits include an increase in the amount of fetal hemoglobin (hemoglobin F), which helps prevent sickling. Hydroxyurea also lowers the white blood cell count, reduces hemolysis, and changes the shape and flow characteristics, known as the rheology, of the RBCs, all of which are beneficial laboratory effects that lead to the clinical effect. Hydroxyurea is easy to administer: it is given orally, once a day, and has very few short-term side-effects. A phase I/II trial examining the use of hydroxyurea in children with SCA was published in 1999, and there has been a progressive increase in its usage since then. A phase III trial examining the efficacy of hydroxyurea for the prevention of chronic organ damage in infants and toddlers is currently underway. There have been some concerns about optimal dosing and in how young a child hydroxyurea can be safely administered. Safety is a concern because hydroxyurea is an antineoplastic agent that affects DNA, and there are worries that it could be leukemogenic. The long-term safety of hydroxyurea for children with SCA is not known, however, with 10–15 years of experience in children and adults with SCA, there has been no observed increased risk of malignancy.

### **H&O** Could you discuss quality of life in relation to chronic transfusion therapy?

**RW** It is not possible to state definitively whether a child's quality of life is always improved by chronic transfusion therapy because two opposing forces are active in this setting. On the one hand, the child usually feels better on chronic transfusion therapy. This therapy not only does what it is intended to do, such as prevent a stroke, but another benefit is that by ameliorating the anemia and preventing hemolysis, the child feels better, grows better, and has fewer painful events and acute chest syndrome episodes. On the other hand, the child now has to return to the clinic once a month, undergo intravenous line placement, have blood drawn and blood transfused, and the family's school and work schedule are changed. The risks of transfusion are low but real, too. Even though the risk of infectious complications or contaminated blood has been greatly reduced, problems remain with antigen

matching, deriving from the fact that most patients with SCD in the United States are African American and most blood donors are white, leading to antigen mismatches. The more long-term, insidious problem of transfusion-acquired iron overload is also something that ultimately would affect quality of life after several years. Most children who begin a chronic transfusion regimen become iron overloaded after several years and need to begin chelation therapy. For many years, the only effective chelator was deferoxamine, which required a subcutaneous infusion with a pump and was difficult for patients to administer. Although deferoxamine worked, noncompliance was common. In the last 2 years, an oral iron chelator known as deferasirox (Exjade, Novartis) has emerged, which promises to be a better alternative, though its long-term effects, risks, and benefits have not yet been delineated.

### **H&O** What is the status of stem cell transplantation as a treatment method for SCD?

**RW** Worldwide, there have been over 300 stem cell transplants for patients with SCD, with more occurring each year. Currently, stem cell transplantation is the only curative treatment option. Yet problems exist, which keep this method from being employed more widely. The primary problem is patient selection: should a clinician wait for a patient to experience a devastating stroke and then consider him or her a candidate for transplantation, or, should a more healthy individual be considered? Second, problems exist with finding matched sibling donors; only 15% of children have such a donor. A third problem is the actual transplant itself. If the best rates of event-free survival are 85%, then 15% of patients will experience substantial morbidity or even mortality. Finally, sterility from the transplant conditioning regimen almost always occurs, which is difficult for many families of small children to accept. Until the rates of success are improved further, and the morbidity of the procedure is reduced, stem cell transplantation will likely not gain a firm foothold as a treatment option for the child with SCD who is not severely affected.

### **H&O** What are some specific future directions of research in this setting?

**RW** The advent of the oral iron chelator is an important event in transfusion therapy, because the main obstacles clinicians have with starting children on chronic transfu-

sions are the ability to manage iron overload in the long term and the recognized noncompliance with subcutaneous injections. If the oral iron chelator is found to be safe, effective, and well-tolerated in the long term, clinicians will be able to relax their concerns about starting children on chronic transfusion therapy. We will be able to focus more on the tractable issues of access, matching blood, and infectious risks.

There are several important ongoing prospective clinical trials that involve transfusions in children with SCD. The Silent Infarct Transfusion Trial (SITT) run by the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health (NIH) is assessing rates of silent infarcts in children with SCA who are assigned to receive either transfusions or observation on a randomized basis. This trial is in enrollment now. Another trial, run by the Heart, Lung, and Blood Institute of the NIH, Stroke With Transfusions Changing to Hydroxyurea (SWiTCH), is enrolling children who have had a stroke and are receiving transfusion therapy, who are randomized to receive a standard treatment or an alternative treatment. The standard treatment is to stay on transfusion therapy and receive the oral iron chelator, and the alternative treatment is to come off transfusion therapy and switch to hydroxyurea, and then undergo a serial phlebotomy program with removal of blood once a month. That trial is in enrollment now as well. There is a third important trial with hydroxyurea (though no transfusions) run by The National Heart, Lung, and Blood Institute called BABY HUG, which is a phase III trial in which infants receive either hydroxyurea or placebo on a double-blind, randomized basis for the prevention of chronic organ damage. Enrollment is completed for this trial and results should be known in the next 18–24 months.

### **Suggested Readings**

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