

HEMATOLOGY eDIGEST

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Program Information

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Welcome to the June edition of Hematology eDigest. We hope you enjoy Dr. Robert J. Adams' discussion on the topic of stroke and sickle cell disease.

Please note:

Hematology eDigest will be taking off for the next couple of months, returning to publication in the fall of 2006. During that time, our [Newsletter archive](#) section will continue to be available, as well as the post-tests for CME credit.

Thank you for your loyalty and support for the 2005 – 2006 editions Hematology eDigest. We'll see you next fall.

In this Issue...

Stroke is one of the most common and significant complications of Sickle Cell Disease (SCD). It results from either blockage of arteries (rarely veins) producing cerebral infarction, or from rupture of intracerebral arteries either in the substance of the brain (producing intraparenchymal hemorrhage) or in the Circle of Willis (producing subarachnoid hemorrhage). Most neurologists consider "stroke" a clinical syndrome with an acute and defined onset and a picture that usually involves focal signs and symptoms.

While there is significant literature on so-called "silent infarctions" in SCD (i.e. those without a clear onset and overt symptoms), in this issue we focus solely on overt stroke, reviewing recent information on the prevention of stroke, and discussing treatment studies and recent advances that, if applied, should improve outcomes

and serve as evidence-based guides to clinical practice.

Commentary & Reviews by:

Robert J. Adams, M.D.

Guest Editor of the Month:



Robert J. Adams, M.D.

Presidential Distinguished
Chair
Regents Professor of
Neurology
Professor of Pediatrics Medical
College of Georgia
Augusta, Georgia

Commentary & Reviews

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Guest Faculty Disclosures

Robert J. Adams, M.D.

Faculty Disclosure: Dr. Adams has indicated a financial relationship in the form of honoraria from Novartis Pharmaceuticals.

Unlabelled/ Unapproved Uses

No faculty member has indicated that their presentation will include information on off label products.

Commentary

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It has been known for some time that SCD causes stroke in children and adults¹. New imaging methods, especially magnetic resonance imaging and angiography, have added to the appreciation of the burden of vascular disease². In addition to clinical stroke in 10-15% of the patients, subclinical abnormal areas on MRI are present in another 20% of children³. The rate of silent infarcts in adults with SCD is also under study, and there are new data on genetic predictors of stroke in SCD⁴ which may one day lead to predictive models that can be used prospectively.

While the list of potential risk factors for stroke in SCD continues to be expand⁵, risk stratification for first stroke is based on transcranial Doppler testing⁶. TCD screening was used in the selection of subjects for the only two randomized controlled trials of stroke prevention in SCD (STOP⁷ and STOP II⁸). Based on these studies, regular transfusion has become well established for primary stroke prevention in children with SCD. While the STOP strategy is not universally accepted (due primarily to concerns about duration of transfusion),

it does represent an important evidence-based approach to stroke prevention.

Although there have been no randomized trials, regular transfusion is also well accepted as an effective treatment to prevent recurrent stroke⁹. There are new uncontrolled data on the use of hydroxyurea to prevent first and recurrent stroke in SCD, and a Phase III randomized trial is now beginning enrollment^{10,11,12,13}. There is also a randomized trial underway comparing regular transfusion to no transfusion in children with silent MRI lesions who do not meet STOP TCD criteria for prophylactic transfusion¹⁴.

Bone marrow transplantation has been used in SCD and appears to prevent worsening of cerebrovascular disease¹⁵. In contrast to the growing evidence base in children with SCD, there have been no new data presented on stroke in adults with SCD since the 1998 Cooperative Study of Sickle Cell Disease report by Frempong et al¹⁶, even while survival continues to improve. Further, there are no systematic data involving SCD patients on the use of agents known to prevent stroke in adults without SCD, such as antiplatelet agents and warfarin — indicating the need for further studies in these areas.

There continues to be the hope that better understanding of the mechanism(s) of stroke and the beneficial effects of transfusion¹⁷, especially on large vessel vasculopathy involving the Circle of Willis arteries, will lead to targeted interventions that are safer than transfusion but just as effective.

Stroke prevention and treatment in SCD remain important goals. Data from the STOP and STOP II studies provide evidence-based guidance for screening for risk, use, and duration of prophylactic blood transfusion to prevent stroke, and have documented some of transfusion's other benefits. While it is not realistic to think that all strokes could be prevented, screening of children starting at an early age, repeated on a judicious basis and backed up by intervention, should markedly reduce the burden of stroke from large artery disease. There is some support for the position that hydroxyurea prevents first and recurrent stroke, but definitive evidence from controlled trials remains to be developed. Two ongoing randomized trials, one comparing hydroxyurea to transfusion in secondary stroke prevention, and one using transfusion in children with silent lesions on MRI, will add to our evidence base in the next few years.

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PRIMARY PREVENTION OF STROKE IN CHILDREN WITH SCD

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In 1997, a Clinical Alert was issued by NHLBI based on the results of a randomized clinical trial (RCT) called the Stroke Prevention in Sickle Cell Anemia — the STOP study. STOP was the first RCT testing any approach to stroke prevention in SCD, and the first RCT involving regular blood transfusion in SCD for any indication.

The key to this study was the selection of children at risk for first stroke using transcranial Doppler (TCD). TCD had been reported to identify a high risk subset with a >10%/year risk of stroke if not treated. This is compared to about a .5%/year risk of stroke in children with SCD generally based on the Cooperative Study of Sickle Cell Disease.

In STOP, children age 2-16 years of age with homozygous SCD and no history of stroke were screened with TCD. Children were eligible for randomization if they had a TCD indicating high stroke risk on two examinations. (TCD estimates blood flow in the arteries of the Circle of Willis using pulsed ultrasound; the higher the blood flow and/or the more narrow or stenotic the artery, the higher the blood flow velocity.) The selection criteria used was 200 cm/sec, which was found in about 10% of children with SCD. These 10% are presumed to be those at highest risk.

The children randomized were either given regular transfusion every 3-4 weeks (simple or exchange methods were acceptable with a Hb S target of 30% or less as a fraction of total Hb measured just before the next transfusion) or standard care, which was either no or only episodic transfusions for specific and accepted short term problems. The main outcome was stroke, as judged by a blinded panel based on history, examination and MRI taken after a possible stroke.

After the planned enrollment of 130 children had been followed for about 2 years, the study was halted by the Monitoring Committee when there were 11 strokes among 67 children randomized to standard care and only one of 63 randomized to transfusion. The stroke risk was 10%/year among those randomized to standard care but <1% in the transfusion arm (p=0.002). These robust results led to the recommendations by NHLBI and the American Stroke Association that all children with homozygous (or Sbeta 0 thal) be screened starting at age 2 years and thereafter at regular intervals (not clearly determined but suggested as every 6-12 month) to look for TCD results that meet the criteria for prophylactic blood transfusion.

In addition to the main finding, a number of secondary reports have been produced that:

1. elucidated rise in ferritin with transfusion;
2. reported low rates of alloimmunization using a matching protocol for blood;
3. showed that silent infarcts and significant non-neurological events were also reduced by regular transfusion;
4. showed that a minority of children with high risk TCD have markedly abnormal magnetic resonance angiograms of the Circle of Willis, and that those higher TCD velocities (>250 cm/sec) rarely drop significantly with treatment, while those with more normal appearing MRA studies may revert to normal TCD with prolonged treatment;
5. showed that transfusion was highly effective even if the child missed some transfusions and that those with Hb S of >30% but <40% were also protected from stroke¹.

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☰ CAN TRANSFUSION FOR PRIMARY STROKE PREVENTION BE SAFELY STOPPED

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Despite the results of STOP, acceptance of transfusion as a highly effective stroke prevention strategy was limited by the uncertain duration of transfusion with iron overload and other related problems. A second study, again an RCT funded by NHLBI, looked at what happens when transfusion is removed in a low risk subset treated according to the STOP protocol for at least 30 months. In STOP II, 23 centers participated and 79 children of a planned 100 were enrolled before this study too was halted prematurely, this time for safety reasons. In STOP II, children 5 years of age or older who had initially abnormal TCD which reverted to low risk (defined as <170 cm/sec) during a minimum treatment period of 30 months of regular transfusion were randomized to continue transfusion or have it abruptly stopped. After randomization both groups had regular follow up with TCD, with the idea that those that could not tolerate withdrawal would first show return of high risk TCD before becoming at risk for stroke. The study used a composite endpoint which could either be a stroke or a TCD that showed return of high risk.

This surveillance strategy worked, but only partially. The study was halted when there were 16 events, all in the halt transfusion arm. Fourteen were reversions to high risk TCD without stroke and two were strokes. In the two patients with strokes, a high risk TCD was initially observed — but in the 3-4 weeks allowed by the protocol to obtain a second confirmatory high risk TCD before declaring an endpoint and restarting transfusion, two children developed stroke. Thus, while the TCD did give an indication of return of risk, the time to respond was short.

About 25% of those taken off transfusion appeared to tolerate staying off transfusion at least to 1-2 years. However, there were no distinctive features of these children, in that the only indicator of higher risk of reversion to abnormal TCD or stroke after stopping transfusion was a higher average TCD observed before ever initiating regular transfusion — and this was not a powerful indicator ($p=0.05$). By one year after stopping transfusion, about half the children had been restarted on transfusion, either due to stroke or stroke risk, or other indications such as pain or acute chest. While the duration of transfusion remains to be determined, STOP II was interpreted as indicating ongoing risk in most cases even after prolonged transfusion, arguing for the need for continued treatment. The search is ongoing for a less intensive “maintenance” therapy that could substitute for transfusion, either as first or follow-on therapy.

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☰ CAN HYDROXUREA SUBSTITUTE FOR TRANSFUSION AS EITHER MAINTENANCE OR INITIAL THERAPY TO PREVENT STROKE?

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The evidence base for stroke prevention based on RCTs continues to grow. This summer (2006), enrollment will begin in SWITCH, a Phase III randomized clinical trial that will compare two treatments for the prevention of a recurrent stroke (secondary stroke prevention) and treatment of iron overload in children with sickle cell anemia. Standard treatment (monthly blood transfusions for stroke prevention and iron chelation for the prevention of iron overload) will be compared to hydroxyurea to prevent recurrent stroke and phlebotomy (the removal of blood) to treat iron overload.

The trial design is based on the experience of Russell Ware and colleagues, who in 2004 reported the outcome of this sort of approach in an open label uncontrolled study of 35 patients with SCD and stroke. At first hydroxyurea was started two weeks after stopping transfusion, at an initial dose of 15-20 mg/kg, then escalated by 5 mg/kg every 8 weeks as tolerated (or up to 30-35 mg/kg). The protocol was changed to incorporate an overlap of both treatments in which transfusion was continued until maximum hydroxyurea dosing was achieved. The latter approach appeared more effective and is being used in SWITCH. Stroke recurrence was 5.7 events per 100 patients years (7 of 35 had strokes, all cerebral infarctions) — but when considering only the 20 patients with overlap of therapy, there were only two events (estimated rate of 3.6 per 100 patients years). The average HU dose was 26.7 mg/kg, and all but 5 patients were believed to have good compliance. As expected with regular phlebotomy, serum ferritin decreased markedly and liver biopsies were normal.

This group is to be applauded for this systematic open label study (adding to other smaller studies of HU in this setting such as Sumoza A, de Bisotti R, Sumoza D, Fairbanks V. Hydroxyurea (HU) for prevention of recurrent stroke in sickle cell anemia (SCA). *Am J Hem.* 2002;71:161-165) and for pursuing this approach in a randomized controlled Phase III study.

Also in 2004, the report by Gulbis et al appeared on the experience of using HU in 127 SCD patients in a treatment registry, including 18 at risk for stroke. The Belgian Registry began in 1993, enrolling children with SCD into open label treatment with HU if one or more risk factors for a severe course were present (99 for 3 or more recent vaso-occlusive crises, 21 for acute chest, 7 for stroke, and 1 for TIA) or if the patient had two abnormal TCD's using the STOP criteria only. Mean age at entry was 6 years (range 8 months-19 years). In this registry the authors identify 34 patients at risk for first stroke based on abnormal TCD. In this group, follow up on HU of about 3 years on average was reported, with only one event (seizure) observed.

If these patients were comparable to the standard care arm of STOP, which they appear to be, there should have been at least 6 strokes if HU was no more effective than standard care. While it is indeed encouraging that primary stroke prevention with HU will work, and may even be comparable to transfusion, it would be highly desirable to see this result more adequately confirmed in a randomized controlled trial.

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1. Ware RE, Zimmerman SA, Sylvestre PB, et al. Prevention of secondary stroke and resolution of transfusional iron overload in children with sickle cell anemia using hydroxyurea and phlebotomy. *J Pediatr* 2004;145(3):346-52.



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☰ HYDROXYUREA AS MAINTENANCE THERAPY FOR PRIMARY STROKE PREVENTION

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Target Audience

This activity has been developed for Hematologists. There are no fees or prerequisites for this activity.

Learning Objectives

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

- Identify the indications for risk screening with Transcranial Doppler for primary prevention of stroke in children with SCD;
- Identify the indications for prophylactic blood transfusions in children with SCD, including primary and secondary stroke prevention;
- Compare the use of hydroxurea to transfusion for stroke prevention in SCD.

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