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# HEMATOLOGY eDIGEST


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## Course Directors

<p>→ <b>Jerry L. Spivak, MD</b> Professor of Medicine and Oncology The Johns Hopkins University School of Medicine</p>	<p>→ <b>Kwaku Ohene-Frempong, MD</b> Professor of Pediatrics Director, Sickle Cell Program and Comprehensive Sickle Cell Center The Children's Hospital of Philadelphia</p>	<p>→ <b>Cage S. Johnson, MD</b> Professor of Medicine Keck School of Medicine University of Southern California</p>	
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## Welcome...

To the premier issue of the newest CME-accredited resource for in-depth information about key issues in the field of Hematology. Over the next year, Hematology e-Digest will be reviewing current research in a wide variety of topics critical to understanding the on-going developments in our specialty, including: Myelodysplasia, Iron Chelation Therapy, Chronic Myelogenous Leukemia, ITP, and more.

Thank you for joining us.

## In this Issue... *Complications of Transfusion in sickle cell disease*

In recent years, the indications for acute and chronic transfusion therapy in the sickle cell diseases have been expanded to include acute anemia, primary and secondary prevention of stroke, the acute chest syndrome, splenic or hepatic sequestration, pulmonary hypertension, priapism, and preparation for surgery.

The clinical benefits of red cell transfusion are substantial. Transfusion dilutes sickle erythrocytes, improving microcirculatory flow, increasing tissue perfusion and oxygenation, reducing cardiac workload and reducing the tendency for cell-cell and cell-vascular endothelium interactions that participate in vaso-occlusion.

In this month's issue, we examine two common complications of transfusion therapy in sickle cell disease: alloimmunization and iron overload and discuss approaches to diagnosis and management.



improved tissue oxygenation; dilution of sickle cells by normal ones, thereby reducing the opportunity for abnormal cell-cell and cell-vessel wall interactions; suppression of erythropoiesis, thereby reducing the production of reticulocytes, which are the immediate progenitors of irreversibly sickled cells, as well as reducing the number of cells contributing to intravascular hemolysis, and thereby reducing nitric oxide (NO) scavenging by free hemoglobin, and finally, a reduction in cardiac work.

Blood transfusion, in addition to its cost and inconvenience, is, unfortunately, not without risks. Although the risk of HIV transmission is less than that of a fatal hemolytic transfusion reaction, other risks are not nearly so negligible. While there is a proven commonality of gene expression across all ethnic groups, sufficient ethnic variation in the expression of blood group antigens (particularly the minor ones), and the reduced representation of minority ethnic groups in the blood donor pool, make red cell alloimmunization an unavoidable issue. Indeed, rates as high as 50% have been observed with a risk of 3% per unit transfused. Extended red phenotyping involving not rare blood groups but the less commonly tested ones (i.e. E, C and Kell) can reduce this figure to 0.5%; in addition, DNA phenotyping can improve accuracy in multiply-transfused patients. In spite of this, however, a recent survey of over 1100 blood banks revealed that only 37% conducted such extended phenotyping. This not a trivial issue because alloimmunization can lead to difficulties in obtaining matched blood and is a risk for delayed hemolytic transfusion reactions and Transfusion-Related Acute Lung Injury (TRALI) in a group of patients whose lungs and kidneys cannot afford such challenges. Furthermore, alloimmunization is associated with both the development of red cell autoantibodies, possibly as a consequence of immunosuppression, and hyperhemolysis with the host's red cells involved as innocent bystanders.

Iron overload is a delayed but common risk of blood transfusion that is better understood in thalassemia or myelodysplasia patients than sickle cell patients, in part because in the past relatively few sickle cell patients had received chronic transfusion therapy for the length of time required for the development of severe organ damage from hemochromatosis. In addition, iron overload had not previously been recognized as a potential cause of organ failure in sickle cell patients. When carefully monitored, sickle cell patients on chronic transfusion accumulate iron at rates similar to those with thalassemia. Confounding the situation in chronically transfused sickle cell patients is the poor correlation of serum ferritin with the transfusion burden. Furthermore, there appears to be a lag between liver iron overload and significant myocardial iron overload, at least as determined by MRI T2\*. Discrepancies between thalassemics and sickle cell patients in this regard may merely reflect differences in transfusion burden – yet, at the same time, iron absorption may be greater in thalassemic patients because of their greater degree of ineffective erythropoiesis, possibly combined with differences in urinary iron loss. Nevertheless – given the usefulness of transfusion therapy in sickle cell anemia, the difficulties in assessing the cardiac iron burden, and both the compliance issues with iron chelation therapy as well as its risk for Yersinia sepsis – until the genetic challenge of sickle cell anemia is met, the first order of business should be the identification of an effective and nontoxic oral iron chelator.

## ALLOIMMUNIZATION AND DELAYED HEMOLYTIC TRANSFUSION REACTIONS

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In a large series of patients reported by Rosse in the Cooperative Study of Sickle Cell Disease, alloimmunization occurred with a frequency of 42.3%, with multiple allo-antibodies found in 10.2%. Alloimmunization was more common in sickle cell anemia than in the other sickle genotypes, and was less common in those who received their first transfusion as children (9.6%) compared with those receiving initial transfusion after age 10 (20.7%). The risk of sensitization was found to rise with increasing transfusion exposure at a rate of 3% per unit transfused. The most common allo-antibodies are directed at the C, E K, fy<sup>a</sup> and jk<sup>b</sup> antigens.

Alloimmunization causes delays in finding compatible donor units and leads to the delayed hemolytic transfusion reaction/hyperhemolysis syndrome (DHTR/H). Both the Vichinsky and Talano studies report that the DHTR/H syndrome occurred in 11% of patients and caused profound anemia with destruction of both donor and autologous erythrocytes. Talano further reported that, in addition to life-threatening anemia, these episodes were associated with the acute chest syndrome or acute renal failure. In addition, in about one-half of cases the DAT remained negative, with no new antibodies detected.

Serial quantification of hemoglobins A and S can demonstrate the accelerated disappearance of Hb A. Differential agglutination can be used to demonstrate the loss of donor erythrocytes. Treatment of an acute DHTR/H syndrome consists of stopping further transfusion, a difficult posture to adopt in the face of life-threatening anemia. The Win report demonstrated that transfusion can be successfully accomplished following intravenous methylprednisolone (0.5 g/day) and IVIg (0.4 g/day x 5) plus rhEPO in doses of 6000 units three times per week.

Prevention of alloimmunization can be accomplished by extended phenotype matching of transfusions. In Vichinsky's prospective study of transfusion for the primary prevention of stroke, all transfusions were matched for C, E and K. The rate of alloimmunization was reduced to 0.5% per unit exposure, with an accompanying decrease

in DHTR to 0.11%. Despite these data supporting extended phenotype matching, Osby's recent (2005) survey reported that only 37% of 1182 blood banks performed extended phenotype matching for non-alloimmunized patients.

The majority of institutions follow the practice of performing extended phenotype matching only after the patient develops the first allo-antibody. Extended phenotype matching has the benefit of preventing alloimmunization and its attendant morbidity, mortality and hospital costs. As reported by Aygun, however, other institutions argue that the data supporting a reduction in DHTR/H are insufficient to offset the cost of the labor and resources required to perform extended phenotype matching in all cases. Thus, there is a lack of consensus on the utility of red cell phenotype information for selection of transfusion units in this patient population because the costs relative to the benefit have not been clearly demonstrated. Development of a national standard of care awaits the results of well-designed studies that provide objective evidence supporting the clinical necessity for phenotype-matched transfusions for these patients.

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## IRON OVERLOAD

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Transfusion therapy leads to the storage of iron in the endocrine organs, liver and myocardium with subsequent organ dysfunction. Excess iron is toxic because of its ability to induce free radical formation, resulting in molecular, cellular and tissue damage. According to the Stroke Prevention Trial in Sickle Cell Anemia (STOP Trial), as reported by Files in 2002, the iron burden increases by approximately 70 mg for every 100 ml of packed RBCs transfused. In study subjects who received transfusion for primary stroke prevention, the serum ferritin increased from a mean of  $163 \pm 157$  ng/ml (n=50) at baseline to  $1,806 \pm 825$  (n=43) at one year and  $2,761 \pm 1268$  (n=26) at two years.

While liver biopsy remains the gold standard for quantification of iron stores, it is invasive, and the perceived risks have limited its applicability, especially for repeated measurements to assess the progression/regression of iron burden. A liver iron concentration (LIC) of 7-15 mg Fe/g liver (dry weight) correlates with hepatic toxicity, and levels greater than 15 mg Fe/g liver are associated with a high risk of cardiomyopathy. MRI techniques using the T2 or T2\* relaxation times permit an assessment of iron stores in the heart, liver and other tissues. Voskaridou's study of patients with thalassemia syndromes and sickle cell disease showed that LIC values correlated positively with serum ferritin and that liver T2 had a close negative correlation with LIC and ferritin. Cardiac T2 followed the same

pattern and showed a modest correlation with LVEF.

Standard therapy for iron overload consists of subcutaneous infusion of desferrioxamine (DFO) at a dose of 40 mg/kg over 8-12 hours and has been shown to be effective in reducing iron burden and improving organ function. Toxicity is unusual unless doses exceed the therapeutic index of the drug (mean daily dose in mg/kg divided by serum ferritin), i.e.  $>0.025$ . Aggressive continuous intravenous regimens have been used to rapidly reduce the biomarkers of iron overload and improve organ function. In Anderson's prospective study using T2\* cardiovascular magnetic resonance, intravenous infusion of 40-50 mg/kg/day over 24 hours, 7 days per week in seven thalassemic patients produced a decrease in LIC from a mean of  $9.6 \pm 4.3$  mg/g dry weight to  $2.1 \pm 1.5$  mg/g after one year. There was an 11% improvement in LVEF associated with improvements in both liver and cardiac T2\*; however, cardiac T2\* improved more slowly than the hepatic measure, indicating a greater difficulty in mobilizing cardiac hemosiderosis. Other series show demonstrable improvement in cardiac performance within weeks of initiating DFO.

Compliance with therapy is the major problem with DFO and has led to the development of alternative methods of administration, such as twice-daily subcutaneous injections which appear to promote urinary excretion of iron in amounts similar to that achieved with continuous subcutaneous infusion. The expense and inconvenience of DFO has led to the development of oral iron chelators. Deferiprone has been used in Europe with some success but has not been approved in the US; its major toxicity is agranulocytosis. Additionally, a new oral bis-hydroxyphenyl-triazole (ICL 670) is in clinical trials and appears promising.

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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:

- Understand the rationale for transfusion in sickle cell disease;
- Identify the common complications of transfusion in sickle cell disease;
- Understand the limitations of the current studies on therapy for these conditions.

The Johns Hopkins University School of Medicine takes responsibility for the content, quality, and scientific integrity of this CME activity.

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- Dr. Frempong has no relationship with financial supporters.
- Dr. Johnson has indicated a financial relationship of grant/research support from the NIH and the NHLBI. He has also acted as consultant to Novartis, SuperGen, Thios and Icagen.

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