Evaluation and Treatment of Transfusional Iron Overload in Children

Hannah M. Ware, Janet L. Kwiatkowski, MD, MSCE*

KEYWORDS

• Transfusion • Iron overload • Chelation • Magnetic resonance imaging

KEY POINTS

- Regular red cell transfusions lead to progressive iron accumulation that causes liver, heart, and endocrine organ toxicity.
- Transfusional iron burden is monitored with serum ferritin levels and liver and cardiac magnetic resonance imaging.
- Three different chelators are available for clinical use in the United States: deferoxamine, deferasirox, and deferiprone.
- Trends in iron burden, transfusional iron intake, patient/family preferences, adverse effect profiles, and adherence are factors to consider in individualizing chelation plans.

INTRODUCTION

Transfusions are increasingly being used in the management of blood disorders in children. Regular red cell transfusions have been used to alleviate the severe anemia and suppress ineffective erythropoiesis in patients with thalassemia major for many years, and are increasingly being used in the management of children with sickle cell disease (SCD). In SCD, the goal of regular transfusions generally is to reduce the hemoglobin S level to less than 30% to 50% to prevent or treat disease complications, such as stroke. An estimated 1000 to 2000 individuals with thalassemia and 100,000 individuals with SCD live in the United States,[1] and therefore patients with SCD account for a larger proportion of transfused individuals. Other hematologic disorders treated with transfusions include bone marrow failure syndromes, such as Diamond-Blackfan anemia (DBA), and hemolytic anemias, such as pyruvate kinase deficiency.

The monitoring and treatment guidelines for transfusional iron overload generally have been derived from the experience with patients with thalassemia and are described herein. However, differences in transfusional iron loading and its clinical

Division of Hematology, Department of Pediatrics, Children's Hospital of Philadelphia, University of Pennsylvania, 34th Street, Civic Center Boulevard, Philadelphia, PA 19104, USA
* Corresponding author. Children's Hospital of Philadelphia, 3501 Civic Center Boulevard, Colket Building, Room 11024, Philadelphia, PA 19104.
E-mail address: kwiatkowski@email.chop.edu

Pediatr Clin N Am 60 (2013) 1393–1406
http://dx.doi.org/10.1016/j.pcl.2013.09.003 **pediatric.theclinics.com**
0031-3955/13/$ – see front matter

manifestations between patients with thalassemia and other blood disorders are becoming better understood. These differences and the implications for clinical management are discussed where applicable.

HOW TRANSFUSIONS LEAD TO IRON OVERLOAD

Typical regular transfusion regimens involve the administration of 10 to 15 mL/kg of packed red blood cells every 3 to 5 weeks. Each milliliter of pure packed red cells (hematocrit 100%) contains just more than 1 mg of iron. Humans do not have the physiologic ability to excrete excess iron, and therefore chronic red cell transfusion therapy leads to progressive iron accumulation. Chelation therapy is necessary to prevent iron accumulation and/or to remove excess iron. In children with SCD, exchange transfusion also may be used, which limits transfusional iron loading and may obviate the need for chelation.[2]

TOXICITY OF IRON

Free iron is toxic; therefore, iron is usually bound to proteins within the body. For example, iron in plasma is bound to transferrin, a transport protein. However, transferrin becomes saturated in iron overload states, leading to the presence of non–transferrin-bound iron (NTBI) forms.[3] Labile plasma iron (LPI), a form of NTBI, is taken up into cells and causes oxidative damage. The heart, liver, and endocrine organs are most susceptible to iron-related injury.

Cardiac toxicity, including congestive heart failure and atrial and ventricular arrhythmias, is the leading cause of death related to iron overload in patients with thalassemia major.[4] Iron-related heart disease generally does not become evident until the teen years in patients with thalassemia who are poorly chelated.[5] Furthermore, iron-associated cardiac disease is uncommon in transfused individuals with SCD, even at older ages.[6] However, children with DBA and sideroblastic anemias may be at risk for iron-related heart disease at younger ages.[7]

Hepatic toxicity from iron overload includes inflammation, fibrosis, and cirrhosis.[8] It is important to vaccinate children against hepatitis A and B viruses and to counsel against alcohol abuse to avoid exposure to additional hepatotoxins. Iron also damages endocrine organs, leading to growth failure, growth hormone deficiency, delayed puberty,[9] hypogonadotropic hypogonadism, impaired glucose metabolism and insulin-dependent diabetes mellitus, osteopenia, hypothyroidism, and hypoparathyroidism.[5] In a registry of North American patients with thalassemia, almost half of patients in the 16- to 24-year-old age group had developed endocrinopathies.[5] Iron-associated endocrinopathies are less common in patients with SCD than in those with thalassemia, but may occur at earlier ages in patients with DBA.[7,10] Good control of iron burden in children is important because organ damage likely results from cumulative exposure to iron.

EVALUATION OF IRON OVERLOAD

Several different tests can be used to monitor the degree of iron overload. Measured with a simple blood test, the serum ferritin level is the easiest and least expensive test to obtain. Although the ferritin level correlates with total body iron burden in patients receiving chronic transfusions,[11] the utility of the test is limited because infection, inflammation, and ascorbate deficiency can either raise or lower serum ferritin levels, altering the ability to accurately predict iron stores. In particular, the serum ferritin may not correlate well with the degree of transfusional iron loading in patients with SCD.[12] Ferritin levels also do not predict cardiac iron loading accurately.[13]