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NURSING CONSIDERATIONS IN THE MANAGEMENT OF PATIENTS WITH CHRONIC TRANSFUSIONAL IRON OVERLOAD

INTRODUCTION

Nurses play a crucial role in monitoring and managing patients who develop transfusion-related iron overload from receiving red blood cell (RBC) transfusions for chronic anemia.[1] Iron overload is a "silent killer" in that it damages organs long before a patient experiences clinical symptoms.[1] Understanding iron overload is critical to preventing life-threatening consequences, including end-organ damage, among patients most at risk[1]: those with beta-thalassemia, sickle cell disease (SCD), myelodysplastic syndromes (MDS), and other rare anemias (eg, Diamond Blackfan).

This article addresses the most common diseases in which iron overload can be problematic: beta-thalassemia, SCD, and MDS. Discussed are the cellular and molecular mechanisms of iron metabolism; the pathophysiology of beta-thalassemia, SCD, and MDS; the development of chronic transfusional iron overload; signs and symptoms of the condition; monitoring patients; the role of nurses in iron chelation therapy; medications used to treat iron overload; and improving patient management, patient education, and adherence to therapy. Case histories and resources for healthcare providers and patients are included.

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THE ROLE OF IRON IN THE BODY

Iron plays an essential role in physiologic processes such as respiration and DNA synthesis. The human body has many mechanisms to absorb, transfer, and store iron, but none to excrete it. When the human body is in normal iron balance, 1 mg to 2 mg of iron enters and is lost daily, leaving only trace amounts of circulating iron. Dietary iron is absorbed and circulates in plasma bound to a globulin, transferrin, where it is utilized in muscle and bone marrow. Most of the iron, however, is incorporated into hemoglobin and mature red cells and stored in the liver, ready to be mobilized for reuse.[1,2]

Chronic Transfusional Iron Overload

Many patients with beta-thalassemia, SCD, or MDS receive regular transfusions with RBCs as supportive therapy to improve their hemoglobin levels.[1] Each unit of RBCs transfused contains 200 mg to 250 mg of iron; therefore, a patient who receives two units per month will accumulate 5 g to 6 g of iron annually.[1] The primary complication that results from these frequent blood transfusions is chronic iron overload,[3] which can occur after as few as 10 transfusions (ie, 20 units of RBCs).[1]

Normally, iron ions bound to plasma transferrin circulate within the body, accumulating within cells in the form of ferritin. Iron overload occurs when transferrin becomes saturated, increasing levels of non–transferrin-bound iron (NTBI). As high levels of toxic NTBI accumulate in the blood, they are absorbed into the surrounding tissues, leading to increased pools of unbound iron. This excess iron initially accumulates in the reticuloendothelial system, then the liver, heart, pancreas, pituitary gland, and parathyroid glands.[1,2]

Iron overload has serious clinical sequelae: if left untreated, transfusional hemosiderosis—accumulation of iron in the heart, liver, and endocrine glands—can result in organ compromise and, eventually, death.[4] The consequences of iron deposition vary; the pituitary, thyroidal, gonadal, heart, liver, and pancreas are the most common glands and organs affected.

HEMOGLOBIN DISORDERS

Hemoglobin disorders are hereditary and consist primarily of the thalassemias and SCD. Approximately 7% of the world's population are carriers of hemoglobin disorders; 300,000 to 500,000 children are born annually worldwide with the most severe forms of the disease.[5] In chronically transfused patients with thalassemia and SCD, mortality is three times greater than in the general population of the United States. The most common cause of morbidity is iron overload-induced cardiomyopathy.[6]

Beta-thalassemia

Normal adult hemoglobin is made up of two alpha and two beta chains folded onto each other and held together by the heme group containing iron. Oxygen binds onto the iron molecule. Production of normal hemoglobin may be partly or completely suppressed due to inheritance of mutations or deletions in the gene responsible for the synthesis of one or more globin chains; beta-thalassemia refers to the affected globin chain.[7]

Beta-thalassemia is classified into two types, depending on symptom severity: thalassemia major (also known as Cooley's anemia), which is more severe, and thalassemia intermedia.[7] Inheriting two defective beta-globin genes can result in ineffective erythropoiesis, leading to severe, life-threatening anemia, which usually presents in the first year of life and, if not treated, can be fatal during infancy or childhood.[3] Primary treatment is transfusions with RBCs,[3] which relieve severe anemia, suppress compensatory bone marrow hyperplasia, and prolong life.[8]

Thalassemia is most prevalent in the Mediterranean basin, the Middle East, Southern and Eastern Asia, the South Pacific, and South China, where reported carrier rates range from 2% to 25%.[5] An estimated 1000 individuals are living with thalassemia major in the US.[9] Signs and symptoms of beta-thalassemia are evident within the first 2 years of life and include life-threatening anemia, failure to thrive, and jaundice.[7]

Sickle Cell Disease

Sickle cell disease is a group of inherited genetic disorders in which hemoglobin polymerizes when deoxygenated, leading to hemolysis, blood vessel obstruction by sickled RBCs, and tissue hypoxia.[10] Two-thirds of patients have SCD-SS, in which a child inherits a sickle (S) gene from each parent.[11] Patients with SCD suffer chronic and episodic pain, reduced quality of life, and life-threatening complications, including stroke.[10]

Sub-Saharan Africa accounts for more than 70% of births affected by SCD.[5] Approximately 2000 infants with SCD are identified by neonatal screening programs in the US annually.[11] Timely diagnostic testing, parental education, and comprehensive care can markedly reduce morbidity and mortality from SCD in infancy and early childhood.[11] Increasingly, hospitals are adopting recommendations that

chronic transfusions be instituted for risk of stroke in children with SCD, increasing the need for iron chelation.[12]

MYELODYSPLASTIC SYNDROMES

Myelodysplastic syndromes are a group of heterogeneous disorders characterized by the presence of dysplastic changes in at least two of three hematopoietic cell lines.[3,13] Patients with MDS usually present with anemia and other cytopenias[14] and are classified as having one of five subtypes of disease: refractory anemia (RA), RA with ringed sideroblasts (RARS), RA with excess of blasts (RAEB), RAEB in transformation (RAEB-T), and chronic myelomonocytic leukemia. The proportion of individuals whose MDS evolves to acute myeloid leukemia (AML) ranges from 5% to 15% in the low-risk RA/RARS group and from 40% to 50% in the RAEB/RAEB-T group.[13]

The International Prognostic Scoring System (IPSS) stratifies patients with MDS into four distinct risk groups in terms of survival and evolution of AML based on three major variables: marrow blast percentage, cytogenetic subgroup, and number of cytopenias. The four risk groups and percentage of the population are: low (33%), intermediate-1 (Int-1–38%), intermediate-2 (Int-2–22%), and high (7%). Median survival in the absence of therapy ranges from 5.7 years for those in the low risk category to 0.4 years in the high risk category.[13] Males experience poorer survival than females.[15]

MDS is primarily a disease of the elderly. Among individuals >70 years of age, incidence is 22 to 45 individuals per 100,000 people, which increases further with age. Morbidities caused by cytopenias and the potential of MDS to evolve into AML are the major clinical problems observed in patients with MDS.[16]

SCREENING PATIENTS FOR TRANSFUSION-INDUCED IRON OVERLOAD

Blood transfusions are increasingly prevalent in the treatment of individuals with beta-thalassemia, SCD, and MDS,[1] primarily because these patients have a better prognosis.[16,17] This is due to an improved understanding of the disorders and to newly available treatments. Therefore, regular screening for iron overload is more important than ever. One unit of packed RBCs contains approximately 200 mg to 250 mg of iron. Patients who are chronically transfused will have an iron excess of approximately 0.4 mg/kg/day to 0.5 mg/kg/day (1 g/month).[18] With repeated transfusions, iron accumulation and signs of iron overload may be apparent after 10 to 20 transfusions **(Table 1)**.

Accurate assessment of iron burden in the body—by monitoring serum ferritin levels, liver iron concentration (LIC), and cardiac iron—is necessary not only to diagnose iron overload but also to manage therapy effectively.[19]

Serum ferritin, the most commonly used test for estimated iron burden, is inexpensive and noninvasive. The normal range for males is 12 mcg/L to 300 mcg/L; for females, it is 12 mcg/L to 150 mcg/L.[20] Consistently high levels of serum ferritin indicate high iron burden[21]; ≥1000 mcg/L is the clinical benchmark for transfusion-induced iron overload.[5,21] Measuring serum ferritin levels has disadvantages. It is an indirect measurement of iron burden; it can be influenced by complications (eg, infection, inflammation, ascorbate deficiency); and it requires serial measurements and/or interpretation with other indicators of iron overload.[1]

LIC, the most valid surrogate marker for total body iron burden, can be measured by liver biopsy, superconducting

TABLE 1. Clinical Signs and Symptoms of Transfusion-Induced Iron Overload

SYSTEM	SIGNS AND SYMPTOMS
General	• Weight loss • Fatigue • Bronze/gray skin
Hematologic	• Underlying anemia • Transfusion dependence • Duration of transfusion dependence • Number of transfusions each year • Chelation history and compliance
Cardiac – Heart failure	• Dyspnea • Orthopnea • Paroxysmal nocturnal dyspnea • Swelling of lower extremities
Gastrointestinal – Cirrhosis	• Abdominal distention • Abdominal pain • Hematemesis • Melena • Encephalopathy
Endocrine	• Stunted growth • Delayed puberty • Decreased libido • Delayed menarche • Diabetes mellitus – Polyuria – Polydipsia – Polyphagia
Musculoskeletal	• Arthralgias

Source: Mir.[22]

quantum interference device, and magnetic resonance imaging (MRI)[19] **(Table 2)**. Normal LIC values are <1.2 mg Fe/g dry weight; values for mild, moderate, and severe iron load are 3 mg Fe/g to 7 mg Fe/g dry weight, 8 mg Fe/g to 15 mg Fe/g dry weight, and >15 mg Fe/g dry weight, respectively.[1]

ROLE OF NURSE SPECIALISTS

A key role for nurse specialists in caring for patients with beta-thalassemia, SCD, or MDS is identifying and monitoring those at risk for iron overload. Once blood transfusions are initiated, a patient should be provided with a chart for tracking the number of RBC units transfused, since iron overload can occur after only 10 transfusions. A baseline serum ferritin level should also be recorded, as consistently high levels can be an indication for treatment with iron-chelating agents.[1] Samples of both charts are downloadable at www.ironoverloadnurses.com.

Iron Chelation Therapy

Iron chelation therapy, which removes excess iron from plasma and cells in organs, has been in use for more than 40 years.[3] The rationale for use of an iron chelator is to maintain safe levels of NTBI[5]; however, to work effectively, chelator levels must be maintained at pharmacologically active concentrations[1] or NTBI returns to cause oxidative damage. Therefore, patient adherence to therapy is critical for the effective management of iron overload. Two drugs are currently approved by the US Food and Drug Administration (FDA) for iron chelation therapy: deferoxamine mesylate (Desferal®) and deferasirox (Exjade®).

Deferoxamine mesylate: Introduced in the 1960s, deferoxamine is indicated for the treatment of acute iron intoxication and of chronic iron overload due to transfusion-dependent anemias. Iron chelation with deferoxamine is currently the reference standard to which new chelating agents are compared.[1] Doses are administered intravenously or subcutaneously using a small portable pump capable of providing continuous infusions 8 to 24 hours/day 5 to 7 days per week, due to its short plasma half-life. The duration of infusion must be individualized. For patients with beta-thalassemia in particular, the introduction of deferoxamine meant survival improved significantly beyond infancy or childhood; for the first time, conditions related

TABLE 2. Overview of Iron Overload Tests

METHOD	ADVANTAGES	DISADVANTAGES
Serum ferritin	• Noninvasive • Easy to assess • Inexpensive • Can be performed frequently, allowing regular monitoring • Positive correlation with morbidity and mortality • Allows longitudinal follow-up	• Indirect measurement of iron burden • Levels are influenced by many factors, including nutrition, infection, and inflammation • Serial measurement and/or combination with other indicators is required
Liver biopsy	• Validated reference standard • Direct measurement that provides accurate information • Allows non-heme storage iron to be measured • Allows accurate assessment of disease progression • Positive correlation with morbidity and mortality	• Invasive, painful, potentially serious complications • Requires skilled professional personnel and standardized laboratory procedures • Small biopsy may not be representative of tissue iron distribution • Spurious measurements may occur as a result of certain hepatic diseases • Poorly correlated with cardiac iron • Difficult follow-up
MRI	• Noninvasive • Able to analyze whole organ • Pathologic status of the liver can be assessed in parallel • Allows longitudinal follow-up of patients	• Requires imager with a dedicated imaging method • Indirect measurement of LIC
SQUID	• Noninvasive • Measurement may be repeated frequently • Linear correlation with LIC assessed by biopsy	• Limited availability • High cost • Indirect measurement of LIC • Complex procedure requiring trained personnel • Underestimates LIC versus biopsy

LIC = liver iron concentration; MRI = magnetic resonance imaging; SQUID = super conducting quantum interference device.
Source: Cappellini[5]; www.irontoxicity.com.[19]

CASE 1

IN BETA-THALASSEMIA, LOW LIVER IRON DOES NOT NECESSARILY INDICATE THAT CARDIAC IRON IS NOT PRESENT

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Liver iron has long been thought to be a reliable indicator of total body iron burden, including the likelihood of cardiac iron. In patients with beta-thalassemia, however, that is not always the case.

INITIAL PRESENTATION

Aalia M., 12-year-old girl of South Asian descent, presented with her mother at a thalassemia treatment center for a blood transfusion to manage her beta-thalassemia; previously, she had been transfused every 3 weeks at another institution, where she adhered to chelation therapy with deferoxamine and had no obvious organ damage secondary to iron overload. Aalia's ferritin levels were mildly high—in the 800 mcg/L to 1000 mcg/L range—and a previous liver biopsy showed her to have a hepatic iron content of 3.2 mg Fe/g dry weight, which is low.

DIAGNOSIS AND TREATMENT

Shortly after her transfer to the thalassemia treatment center, Aalia was switched to deferasirox at her and her mother's request so that she could take an oral medication rather than undergo 10-hour subcutaneous nightly infusions, as was necessary with deferoxamine. Aalia was started on a daily dose of 20 mg/kg of deferasirox to minimize adverse events, which are dose-dependent, and slowly titrated up to 30 mg/kg/day over several months. (With patients who have beta-thalassemia, medication doses are generally increased to trend serum ferritin levels downward toward 500 mcg/L, as long as monthly laboratory tests show no elevation of liver enzymes or creatinine and the patient is experiencing no serious adverse events.) Aalia was also scheduled for an MRI of her heart and liver to assess her iron overload. While her levels of liver iron were still low (3.1 mg Fe/g dry weight), she also had a low T2* (15 ms), indicating iron in the heart, a serious and potentially fatal condition; her ejection fraction was normal (63%).

Aalia was continued on deferasirox 30 mg/kg/day and her ferritin levels were tracked each month. However, her ferritin remained in the 800 mcg/L to 1000 mcg/L range, about where it was on her initial presentation at the center; as a result, her dosage of deferasirox was increased to 35 mg/kg/day in an attempt to bring her ferritin down.

Aalia's ferritin finally began to trend downward on the 35 mg/kg/day dose; MRIs, repeated at 6-month intervals, confirmed this trend. Aalia experienced some gastrointestinal upset (ie, nausea and cramping) on the higher dosage, but switching from morning to evening dosing ameliorated these side effects. Adherence and proper administration were reviewed at each monthly visit with Aalia and her mother.

FOLLOW-UP

After 1 year of aggressive, high-dose chelation with deferasirox, Aalia's T2* returned to normal; her liver iron level of 1.5 mg Fe/g dry weight was near normal. She was monitored closely for any renal or liver toxicities secondary to chelation therapy during this period, including monthly laboratory analyses and regular screenings by the ophthalmology and audiology departments. Her serum ferritin levels are currently stable—in the 500 mcg/L to 600 mcg/L range—and her deferasirox dosage is adjusted as necessary to keep her levels within this range as she grows and gains weight.

DISCUSSION

Cardiac failure secondary to cardiac iron remains the major killer of thalassemia patients. Liver iron, usually an excellent direct measure of total body iron, does not always reflect the level of cardiac iron in these patients. MRI is the gold standard for measuring liver and cardiac iron and is standard equipment in thalassemia centers in the United States.

Evidence of cardiac iron calls for aggressive treatment; if detected early, it can be reversed before dysfunction occurs. Deviations from the treatment regimen, as well as any side effects, should be reported. Monitoring for potential adverse events is necessary to ensure proper, regular administration of deferasirox.

Adverse events and toxicity of chelators tend to increase as total body weight declines; treatment is therefore a balancing act. Serum ferritin levels in patients with beta-thalassemia traditionally have been kept slightly higher than normal serum ferritin levels. However, the emphasis now is increasingly on tighter control.

to iron overload, such as heart disease, could be prevented.[1] The safety of deferoxamine is well established. The majority of patients do not experience complications even after decades of use; for this reason, some individuals may prefer to start chelation therapy on deferoxamine rather than deferasirox.[1] In addition to injection-site soreness and other reactions related to infusion (eg, itching, erythema, and induration), adverse events include allergic reactions, cardiovascular (tachycardia, hypotension, shock), hematologic, musculoskeletal, nervous system, special senses (eg, high-frequency sensorineural hearing loss and/or tinnitus), respiratory, and urogenital. Deferoxamine is contraindicated in patients with severe renal disease or anuria, since the drug and the iron chelate are excreted primarily by the kidney.[23]

Deferasirox: Approved by the FDA in 2005, deferasirox is an orally administered iron chelating agent indicated for the treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older.[21] Results of phase II and III deferasirox clinical trials have shown a dose-dependent efficacy across a range of anemias[21,24-28]; the drug is well tolerated and safe, including in pediatric patients with beta-thalassemia.[25] Five-year safety data are now available.[29] Common adverse events include gastrointestinal upset, diarrhea, nausea, vomiting, abdominal pain, and skin rash.[21] Deferasirox may cause serious renal, hepatic, and cytopenic adverse reactions, including multiorgan dysfunction and fatalities in patients. These events are more frequently observed in patients with advanced age, high-risk MDS, thrombocytopenia, or underlying renal or hepatic impairment. Deferasirox is contraindicated in patients with creatinine clearance <40 mL/min or serum creatinine >2 times the age-appropriate upper limit of normal, in patients with poor performance status and high-risk MDS or advanced malignancies, in patients with platelet counts <50 x 10^9L, and in patients with hypersensitivity to deferasirox or any of its components.[21]

CLINICAL TRIALS FOR DEFERASIROX

Three efficacy and safety studies supported the approval of deferasirox:

- A randomized comparative study of deferasirox (n=296) vs deferoxamine (n=290) in patients 2 years of age or older (mean age, 17.1 years; range, 2-53 years; 52% female and 88% white) with beta-thalassemia and transfusional hemosiderosis found that deferasirox removed iron from the body in proportion to the amount of the drug administered.[24]
- In an open-label, non-comparative trial, deferasirox was given for 1 year to patients with chronic anemias and transfusional hemosiderosis: those with either beta-thalassemia who could not be properly chelated with deferoxamine (n=85) or with rare anemias requiring chelation therapy (n=99); 19% of patients were <16 years of age and 16% were ≥65 years of age. The primary end point—maintenance or reduction of LIC—was demonstrated with an absolute reduction of -4.2 mg Fe/g dry weight.[27]
- In a multicenter, open-label, randomized trial of deferasirox (n=132) vs deferoxamine (n=63) given for 1 year in patients with SCD and transfusional hemosiderosis, the primary objective was to demonstrate safety and tolerability. Adverse events were found to be generally mild to moderate in severity in both groups. Forty-four percent of the patients were <16 years of age.[28,30]

Other key trials involving deferasirox have continued to explore its use in patients with beta-thalassemia, SCD, and MDS. For example, the Evaluation of Patient Iron Chelation With Exjade (EPIC) trial has been the largest prospective multicenter study conducted for any iron chelator to date. It included 1744 patients across a number of transfusion-dependent anemias. The EPIC study was the first trial to confirm that fixed starting doses of deferasirox—based on ongoing transfusional iron intake, with subsequent dose titration guided by serum ferritin trends and safety markers—are clinically acceptable for chelation therapy.[31] In a subgroup of patients with MDS, deferasirox provided significant reduction in serum ferritin levels over 1 year of treatment, with appropriate dose adjustments every 3 months based on serum ferritin trends and safety markers.[32]

Another trial, the 1-year ESCALATOR study, evaluated the effects of treatment with deferasirox on LIC in heavily iron-loaded patients with beta-thalassemia unable to achieve successful chelation. When deferasirox doses were adjusted based on serum ferritin levels and transfusional iron intake, patients maintained or reduced their iron burden as measured by LIC.[33] An additional year of treatment found overall safety was maintained.[34]

Cardiac Efficacy

Several clinical trials have investigated the effect of deferasirox on cardiac iron loading, cardiac iron removal, and cardiac function, as measured by left ventricular ejection fraction (LVEF), primarily in patients with beta-thalassemia **(Table 3)**. Myocardial MRI T2* values of <20 ms indicate a progressive and significant decline in LVEF; the lower

Table 3. Deferasirox Clinical Trials Measuring Cardiac Efficacy

STUDY	POPULATION	DOSE	RESULTS
Removal of myocardial iron			
EPIC 1-year cardiac reduction substudy[35]	Heavily transfused patients with beta-thalassemia and mild, moderate, and severe myocardial siderosis (n=114)	30 mg/kg/day (dose adjustments allowed based on safety and efficacy monitoring: 5 mg/kg/day-40 mg/kg/day)	**Over 12 months of therapy (n=105):** • Cardiac T2* significantly improved • LVEF remained stable • Myocardial T2* was inversely correlated with LIC
US04 18-month study with 6-month extension[36]	Iron-overloaded patients with beta-thalassemia (n=26)	30 mg/kg/day (dose adjustments allowed based on safety and efficacy monitoring to 40 mg/kg/day)	**Over 18 months of therapy (n=12):** • Cardiac T2* significantly improved • LVEF trended upward • 83.3% of patients responded (≥4% increase in T2*) • Patients with both baseline LIC <18.5 mg Fe/g dw and cardiac T2* >6 ms showed improvement in T2* >1% per month
2203 Baseline cardiac MRI scans prior to therapy and a follow-up scan 1 to 2 years later[37]	Patients with thalassemia major (n=19) were divided into two groups: baseline cardiac T2* >20 ms or T2* <20 ms	20 mg/kg/day to 35 mg/kg/day	**Over a mean treatment period of 488 days:** • T2* significantly improved in 9 patients with myocardial iron loading and T2* <20 ms • In 10 patients with T2* >20 ms, T2* was maintained after 2 years
107/108 Pooled analysis of a subpopulation of two studies, a phase III randomized trial of deferasirox vs deferoxamine followed by deferasirox only for 4 years, and a phase II noncomparative trial[38]	Patients with transfusion-dependent beta-thalassemia (n=29) or rare anemias (eg, MDS, Diamond Blackfan, other) (n=6)	Doses at baseline and 1 year calculated from baseline and 1-year LIC, respectively Dose adjustment after 1 year based on serum ferritin trends **Mean starting dose:** 21 mg/kg/day (range: 10 mg/kg/day–30 mg/kg/day) Mean final dose: 29 mg/kg/day (range: 7.5 mg/kg/day–40 mg/kg/day)	**Over 4 years:** • Cardiac T2* significantly improved • Mean T2* improved to 0.7 ms (within normal range) • Greatest improvement in T2* occurred in the first year of treatment (0.16 ms/month) and least improvement occurred in the final treatment year • Median change: 1.27 ms/year • LVEF was maintained over 4 years
Prevention of myocardial siderosis			
EPIC 1-year cardiac prevention substudy[39]	Beta-thalassemia major with normal cardiac function and no cardiac iron overload (n=78)	20 mg/kg/day or 30 mg/kg/day (dose adjustments allowed based on safety and efficacy monitoring)	**Over 12 months of therapy (n=78):** • Myocardial iron accumulation was maintained in normal range in patients with T2* ≥20 ms • Cardiac function, as measured by LVEF, improved in patients with LVEF in the normal range • Myocardial T2* was inversely correlated with serum ferritin

dw = dry weight; LIC = liver iron concentration; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging.
Sources: Pennell[35]; Wood[36]; Reyal[37]; Garbowski[38]; Pennell.[39]

the value, the higher the risk of cardiac dysfunction.[40]

These studies demonstrate that deferasirox is efficacious in lowering myocardial iron burden in patients with beta-thalassemia who have mild, moderate, and severe cardiac siderosis.[35-37] Deferasirox is also efficacious in preventing myocardial iron accumulation in patients with beta-thalassemia and normal baseline myocardial iron levels.[39] This highlights the importance of early intervention to prevent disease progression and to avoid future cardiac events resulting from myocardial siderosis.

Deferasirox maintained[34,39] or improved[35,36] cardiac function (ie, LVEF) in these trials. However, appropriate doses are needed to have an impact on cardiac iron, with doses of 30 mg/kg/day to 40 mg/kg/day shown to

IMPROVE YOUR SKILLS IN MONITORING FOR IRON OVERLOAD AND PROVIDING PATIENT EDUCATION

The Iron Overload Nurse Ambassador (IONA) program is a nationwide community of nurses dedicated to educating patients, nurse colleagues, and physicians about the risks of transfusional iron overload and the importance of monitoring at-risk patients. The IONA Web site discusses the causes, consequences, diagnosis, and management of iron toxicity. Tables, figures, flow charts, animations, and other aids clarify core concepts. A serum ferritin tracker, transfusion tracker, patient education protocol, and monitoring protocol are available as downloadable PDF files. A quarterly digital newsletter, IONA Links, shares best practices for the care of patients receiving blood transfusions. A resources section includes links to Webcasts on treatment of iron overload and other educational programs. Membership in IONA is free; a membership application form is available on the Web site at http://www.ironoverloadnurses.com.

reduce cardiac iron, and with doses of 20 mg/kg/day to 30 mg/kg/day shown to prevent myocardial iron accumulation.

Ongoing Clinical Trials

Studies are ongoing to determine long-term benefits and risks of deferasirox. In 2009, the safety profile of deferasirox in patients with beta-thalassemia (n=951), MDS (n=584), and other anemias (n=263) was characterized in a 1-year study of pooled data that emphasized renal safety. Results suggest deferasirox may be used in patients with a baseline creatinine clearance of >60 mL/minute, while individuals with a creatinine clearance of 40 mL/min to <60 mL/min need close monitoring, and those with a creatinine clearance of <40 mL/min should not receive deferasirox. In patients with MDS and liver iron overload, alanine aminotransferase and aspartate aminotransferase levels decreased from baseline over the study year, indicating iron chelation therapy improves these markers of liver function.[41]

Two observational studies of deferasirox were conducted in 167 patients with MDS: 123 individuals who were chelation-naïve and 44 individuals who had received chelation (80% with deferoxamine) for a median of 2 years (range: 0.3–16.4 years). Those who were chelation-naïve had a high baseline median serum ferritin level of 2679 ng/mL (range, 184 ng/m–16,500 ng/m) at study entry, indicating that iron chelation therapy was started relatively late in this population. Those who had received chelation with deferoxamine prior to the study had a median serum ferritin of 2442 ng/mL (range, 521 ng/mL–8565 ng/mL), suggesting that deferoxamine therapy was suboptimal in most patients.[42] After 1 year of treatment with deferasirox, however, serum ferritin levels decreased significantly—by 662 ng/mL in the chelation-naïve population and by 716 ng/mL in those previously chelated. In patients with MDS with transfusion-dependent iron overload, deferasirox substantially reduced serum ferritin levels, indicating that deferasirox was a viable daily treatment option. Deferasirox was also safe. The most common drug-related adverse events were diarrhea, nausea, and rash.[42]

A phase II open-label trial (lasting 1 year followed by a 2-year extension phase) was conducted to evaluate long-term safety and tolerability of deferasirox in 83 patients with low or Int-1 IPSS-risk MDS. Mean age was 68 years (range, 21-90 years) and mean serum ferritin level was 3312.7 mcg/L. Despite ongoing transfusion therapy (mean rate of 3.6 units/month), 31 of 50 patients who completed 2 years of treatment with deferasirox had a decrease in serum ferritin of at least 200 mcg/L (mean decrease: 1088 mcg/L). To determine whether decreases in serum ferritin correlate with clinical benefits, a large, prospective,

TABLE 4. Monitoring Treatment With Deferasirox

TEST	FREQUENCY
Complete blood count	Monthly or more frequently if patient is at increased risk of complications (eg, preexisting kidney condition, elderly, has multiple medical conditions, or is taking medication that may affect organs)
Serum ferritin	Monthly, with dose adjustment based on 3 to 6 month trends
Serum creatinine and creatinine clearance	2 times prior to therapy and monthly thereafter; in patients with underlying renal impairment or risk factors for renal impairment, monitor creatinine and/or creatinine clearance weekly for the first month, then monthly thereafter
Proteinuria	Monthly
Liver function (serum transaminase and bilirubin)	Prior to initiation of therapy; every 2 weeks during the first month; and monthly thereafter
Auditory and ophthalmic	Testing recommended prior to therapy and yearly thereafter

Source: Exjade.[21]

randomized, controlled trial in low and Int-1 MDS patients is currently enrolling participants.[43]

MANAGEMENT OF PATIENTS ON DEFERASIROX

Evidence-based guidelines for treating patients with beta-thalassemia, SCD, and MDS include recommendations for monitoring iron overload when they receive chronic blood transfusions. The National Heart, Lung and Blood Institute recommends that even if patients with SCD receive only intermittent transfusions, a comprehensive program to monitor and treat iron overload is necessary, beginning with baseline serum ferritin testing at transfusion onset.[11] The National Comprehensive Cancer Network guidelines recommend that patients with low or Int-1 IPSS-risk MDS be monitored after 20 or more RBC transfusions; when ongoing RBC transfusions are anticipated; and when serum ferritin levels are >2500 mcg/L, with the goal of decreasing ferritin levels to <1000 mcg/L. The Thalassaemia International Federation recommends serum ferritin and LIC testing as iron chelation regimens are tailored to the specific needs of individual patients.[5]

The goal of chelation therapy, regardless of which drug is used, is to provide the maximum therapeutic benefit with the fewest adverse events. That is a primary reason patients undergoing daily infusions of deferoxamine are generally amenable to switching to oral therapy with deferasirox tablets: studies show that, when compared with deferoxamine, deferasirox was preferred by patients because of convenience, no injection-site soreness or other reactions associated with infusion therapy, and less daily disruption of life (more free time and greater mobility from not having to endure lengthy daily infusions).[5,44,45] In addition, patient satisfaction is higher with deferasirox.[44,46]

Deferasirox dosages are initiated at 20 mg/kg per day; if the patient does not respond while adhering to and tolerating treatment, slowly titrate up in 5 mg/kg/day to 10 mg/kg/day increments over 3 to 6 months according to serum ferritin level trends. Doses of up to 40 mg/kg are FDA approved; doses above 40 mg/kg are not recommended. Deferasirox therapy requires close patient monitoring, including measurement of serum creatinine and/or creatinine clearance prior to initiation of therapy and monthly thereafter **(Table 4)**.[21] Concomitant use of deferasirox with cholestyramine may result in a decrease in efficacy of deferasirox. For adults, reduce the daily dose of deferasirox by 10 mg/kg if a rise in serum creatinine to >33% above the average of the pretreatment measurements is seen at two consecutive visits and cannot be attributed to other causes. For pediatric patients, reduce the dose by 10 mg/kg if serum creatinine levels rise above the age-appropriate upper limit of normal at two consecutive visits.

In clinical trials, elderly patients (eg, ≥65 years), primarily those with MDS, had a higher frequency of adverse events than younger patients.[21] Therefore, elderly patients should be closely monitored for early signs or symptoms of adverse events that may require a dose adjustment. Elderly patients are at increased risk for deferasirox toxicity due to the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Table 5. Management of Common Adverse Events Associated With Deferasirox

ADVERSE EVENT	MANAGEMENT RECOMMENDATIONS
Gastrointestinal	• Take dose in the evening; many patients will sleep through any reactions
Diarrhea	• Increase dietary bran and fiber • If lactose intolerant, avoid dairy products • Stay hydrated • Take antidiarrheal medications for up to 2 days (not recommended in pediatric patients)
Nausea/vomiting	• Stay hydrated (eg, electrolyte solutions)
Abdominal pain	• Drink small, steady amounts of clear liquids, such as electrolyte solutions • Avoid solid foods for first few hours after taking dose • Avoid narcotic pain medications and nonsteroidal anti-inflammatory drugs, such as aspirin or ibuprofen
Skin rash	• Occurs in 8% to 10% of patients • Generally appears on the trunk and face within the first few weeks of starting therapy • Patients experience discomfort and interference with activities of daily living • Use OTC medications such as corticosteroids or long-acting antihistamines until rash resolves or symptoms improve • Rash should abate as patient stays on medication and becomes sensitized • If rash progresses or recurs, instruct patients to call the doctor • If rash is severe, consider dose interruption or adjustment

Sources: Ault[1]; Cappellini[3]; Exjade[21]; Pilo[47]; Vinchinsky.[48]

Patients receiving deferasirox should be appropriately screened and monitored for risk of gastrointestinal hemorrhage and for serious allergic reactions, such as skin rashes.[21] If the latter are severe, treatment should be stopped and patients should contact their healthcare provider immediately.

Deferasirox tablets should be dissolved completely in water, orange juice, or apple juice, which should be drunk immediately. Any residue should be re-suspended in liquid and swallowed. The tablets should not be swallowed whole, chewed, or crushed.[21] Deferasirox should be optimally administered at least 30 minutes prior to a meal; when administered less than 30 minutes beforehand, bioavailability becomes more dependent on food content, increasing as the fat content increases. Consistency in administration can limit this variability.[12] Deferasirox should not be taken with aluminum-containing antacids.[21]

While deferasirox oral therapy does not cause the adverse events associated with deferoxamine infusions, it is nevertheless associated with common adverse events, which must be managed **(Table 5)**. In pivotal clinical trials of deferasirox, mild, nonprogressive increases in serum creatinine occurred in about one-third of patients; levels returned spontaneously to baseline in more than two-thirds of these individuals while on therapy.[3]

Improving Patient Management and Education

Managing patients with beta-thalassemia, SCD, MDS, and transfusion-induced iron overload requires a collaborative approach that involves physicians and nurses, as well as the patients themselves. A protocol for such collaboration is shown in **(Figure 1)**. It is also important to have a system for patient education and monitoring **(Figure 2)**. To provide quality care, the Iron Overload Nurse Ambassador (IONA) program (www.ironoverloadnurses.com) also recommends the following[49]:

- Check the transfusion history of all patients to help ensure that intermittently transfused patients are monitored appropriately, as some may be nearing their 20th unit of RBCs. Reviewing records for the potential risk of iron overload and other problems improves patient care.
- Make consistent communication with other team members a priority. This is essential to improve and maintain quality care. Speak directly with physicians to offer information about patients. This encourages everyone on the team to monitor risk for iron overload.
- Create a communication sheet to include with each patient's chart, noting the date when the healthcare team has been notified of a patient's iron overload status. This provides a record of potential risk and ensures that everyone involved in that patient's care has been notified of risk alerts in a timely fashion.

For more, see *Improve Your Skills in Monitoring for Iron Overload and Providing Patient Education* on page 8 and *Resources for Healthcare Providers and Patients* on page 14.

Improving adherence to therapy

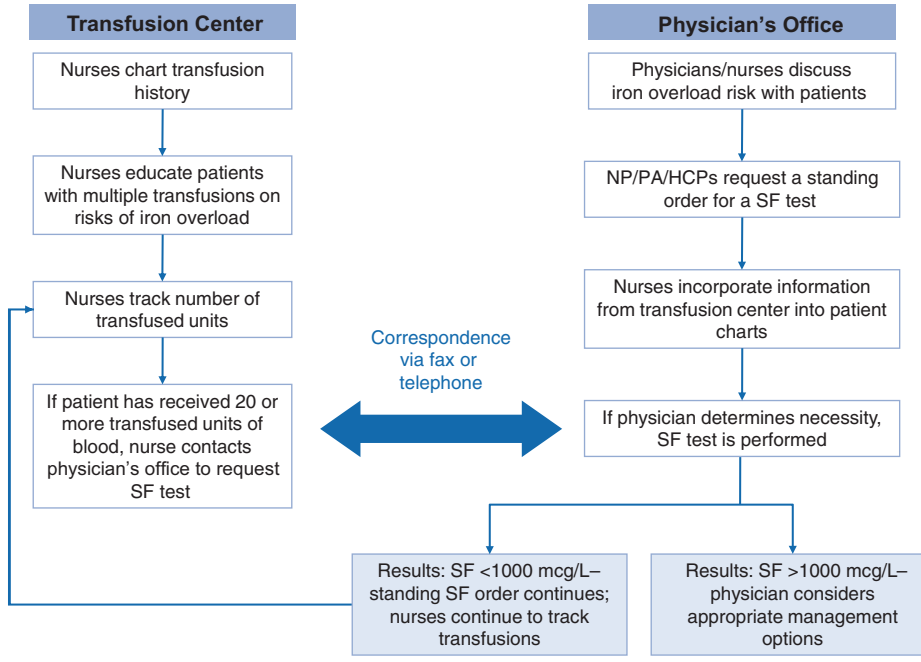
As iron chelation therapy becomes increasingly tailored to the specific needs of individual patients,[50] adherence to the treatment regimen is critical, especially since iron overload is asymptomatic until serious problems arise. Graphics with simple illustrations can help educate patients about iron overload and its potential health risks. For example, a serum ferritin tracking chart can help patients see the positive effects of chelation (ie, a decreasing serum ferritin level). Managing adverse events effectively and keeping the medication regimen simple can also help with adherence.

Even though deferasirox is preferred by patients due to convenience, no injection-site soreness, and improved quality of life,[44] issues with nonadherence remain. In a study of patients with SCD taking deferasirox, reasons cited for nonadherence included difficulty with insurance coverage, taste, forgetfulness, somatic complaints, a subjective feeling that chelation therapy was not needed, and uncertainty about the proper dose.[51]

Managing patients with beta-thalassemia, SCD, or MDS and iron overload requires a collaborative approach.

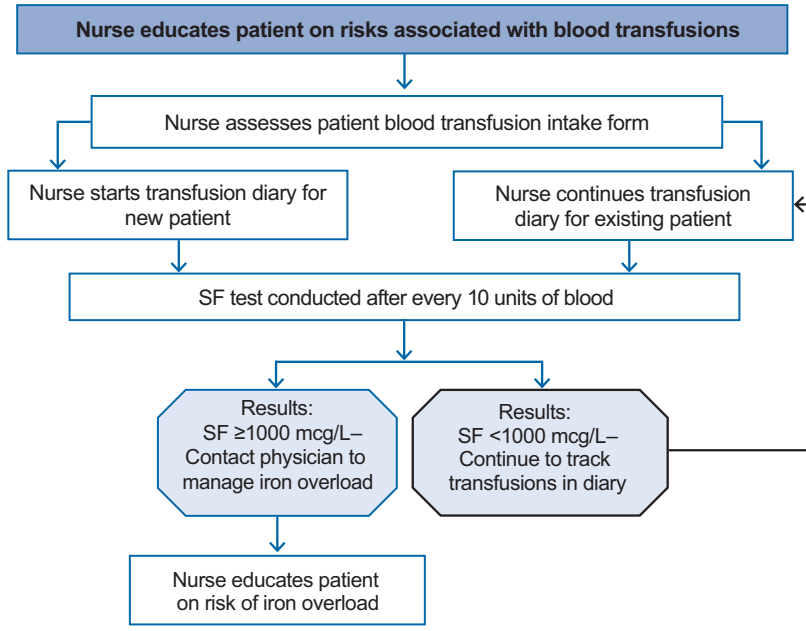
Given such potential obstacles, providing positive reinforcement to patients is important. Continuing education is necessary—and not just for its knowledge value; patients are influenced by whether they perceive that their healthcare providers believe something is important. If necessary, ask the patient directly whether the prescribed medication is being taken—and taken as directed. If not, ask why. Then try to address those reasons. Parental and family support is also recommended, especially when patients are children or adolescents. Every attempt should be made to accommodate use of chelating agents within the patient's and the patient's family's existing lifestyle.[18]

FIGURE 1. Iron Overload Healthcare Team Collaboration Protocol



SF = Serum ferritin.
Source: Adapted from www.ironoverloadnurses.com.[49]

FIGURE 2. Patient Education and Monitoring Protocol



SF = Serum ferritin.
Source: Adapted from www.ironoverloadnurses.com.[49]

CASE 2

IN SICKLE CELL DISEASE, ENDOCRINE DYSFUNCTION MAY SIGNAL IRON OVERLOAD

Joyce A. Brownlee, MSN, ARNP

Frequent blood transfusions are necessary in sickle cell disease to manage chronic—often severe—anemia. Chronic transfusions can lead to iron overload, manifestations that may appear indirectly as endocrine function disorders, such as hypothyroidism. Testing, however, can reveal the underlying cause.

INITIAL PRESENTATION

Nancy A. is an African-American woman 32 years of age, married, mother of two young daughters, and currently unemployed. She has SS genotype sickle cell disease (SCD). She presented to a sickle cell center for a follow-up visit with complaints of extreme fatigue and intermittent pain in her back and shins that had persisted for the past 3 days. Her pain was reported as 5/10 on the linear pain scale (0 = no pain, 10 = excruciating pain).

DIAGNOSIS AND TREATMENT

Nancy was diagnosed with chronic anemia due to hemolysis of the sickled red cells. Intermittent blood transfusions might be required if her hemoglobin fell 2 g/dL below her baseline, which is 8 g/dL. A blood test yielded these results: hemoglobin 8.6 g/dL; hematocrit 24.9%; white blood count 12.2 mcg/L; reticulocyte count 9.4%; thyroid-stimulating hormone (TSH) 6.56 mIU/L; ferritin 3226.0 mcg/L (which was high); mean corpuscular volume 106.2 fL; and fetal hemoglobin 15.7%.

Nancy was scheduled for a thyroid ultrasound to check for thyroid nodules. Because of her high serum ferritin, she was placed on daily chelation therapy with deferasirox 1500 mg daily (based on 20 mg/kg—the minimum approved initial dosage with the maximum efficacy and the fewest side effects). With deferasirox, the dosage can be increased to 25 mg/kg to 30 mg/kg over time (3-6 months) if a patient shows no response to therapy; 40 mg/kg is the maximum approved dosage.

Nancy underwent ophthalmic and auditory exams prior to starting deferasirox, as ocular and aural disturbances have been reported with deferasirox usage. She was taught how to adhere to the medication regimen. She was advised that deferasirox may cause stomach upset, nausea, and diarrhea, but that by increasing fiber in her diet, these side effects may be lessened. She was educated on the importance of tracking her transfusions and units of red blood cells transfused, and of adhering to monthly follow-up visits for laboratory tests to monitor her ferritin, kidney and liver functions, and complete blood count. She was given a personal medical record booklet to note her test results and advised to bring it with her to each doctor visit.

FOLLOW-UP

Nancy received a thyroid ultrasound that revealed mild thyromegaly but no thyroid nodules. Her ophthalmic and auditory exams were normal. She continues with daily deferasirox therapy and has monthly tests to monitor her ferritin and TSH levels. Her most recent ferritin level was 2644.0 mcg/L (normal range is 13.0 mcg/L-150 mcg/L); her TSH level was 4.90 mIU/L (normal range is 0.27 mIU/L-4.2 mIU/L). As is typical with patients with SCD who have chronic transfusional iron overload, chelation therapy with deferasirox is initiated whenever Nancy's ferritin levels reach >1000 mcg/L; patients with ferritin levels of 500 mcg/L to 1000 mcg/L should be educated about iron overload and monitored. With Nancy, this is an ongoing process.

DISCUSSION

Iron overload affects such endocrine organs as the thyroid gland, pancreas, ovaries, testes, liver, and pituitary gland, as well as the heart and brain. Early signs of hypothyroidism, diabetes, and menstrual disorders may be related to iron overload in patients with SCD. Nurses should be alert for such signs and target patients who are at risk.

CASE 3

IRON OVERLOAD INCREASINGLY IS A CONCERN IN PATIENTS WITH MYELODYSPLASTIC SYNDROME

Phyllis McKiernan, MSN, OCN, APN-C

Supportive care and symptom management traditionally have been the focus of treatment for patients with myelodysplastic syndrome (MDS). Recent advances in therapeutic modalities, however, have increased the lifespan of patients with MDS, who are now receiving red blood cell transfusions for their chronic anemia, resulting in iron overload.

INITIAL PRESENTATION

In 2002, Walter P., a white, 71-year-old retired banker, widowed, with two adult sons, presented at a myelodysplastic syndrome (MDS) treatment center for a repeat bone marrow biopsy. He first saw his primary care physician in 1998 with complaints of fatigue and dyspnea. Blood testing revealed a mean corpuscular volume of 102 fL, indicating a macrocytic anemia. Results of a bone marrow biopsy showed a normocellular marrow with dysplastic changes and no myeloid blasts. A cytogenetic evaluation was not performed because of inadequate genetic material in the specimen. He was diagnosed with MDS, classified as refractory anemia. He was then referred to a community oncologist and treated with folic acid and blood transfusions. His anemia persisted, however. When his transfusion requirement eventually increased to 2 units per month, he was referred to the center.

DIAGNOSIS AND TREATMENT

Walter received a bone marrow biopsy, which found dysplasia and ringed sideroblasts but no myeloid blasts. Ringed sideroblasts indicate the amount of iron in red blood cell (RBC) precursors seen on a bone marrow biopsy and are a morphologic hallmark of MDS.[13] Cytogenetic testing showed a 20q deletion chromosomal abnormality.

Walter's diagnosis was then revised to refractory anemia with ringed sideroblasts with an International Prognostic Scoring System score of 0 (low risk).[52] Erythropoietin 40,000 units subcutaneously weekly was initiated. After 4 weeks, no response was observed and filgrastim 300 mcg subcutaneously biweekly was added. The addition of filgrastim to erythropoietin has been shown to have a synergistic effect, notably in patients with ringed sideroblasts.[53] No response was observed, however, and Walter continued to require 2 units/month to 4 units/month of packed RBCs.

In 2005, Walter developed iron overload from his transfusions. To manage it, he was offered chelation therapy with deferoxamine. (Deferasirox would be approved later that year.) He declined, not wanting to endure the lengthy daily infusions deferoxamine necessitates. However, once deferasirox—an orally administered, once-daily regimen—received an indication from the FDA as a chelator in iron overload, Walter was willing to begin treatment; his serum ferritin at that time was elevated (2600 mcg/L). Treatment with deferasirox 20 mg/kg/day, the recommended initial dosage, was initiated. Serum ferritin was monitored every 3 months; the goal was to decrease Walter's ferritin to 500 mcg/L.

In 2006, Walter's ferritin level had decreased to 1250 mcg/L; in 2007, it was 850 mcg/L; in 2008, it was 400 mcg/L. Deferasirox was then discontinued. Later that year, however, his ferritin increased to 1200 mcg/L; deferasirox was reinitiated at 20 mg/kg/day. In 2009, his ferritin level was back down to 600 mcg/L, indicating chelation therapy was working.

FOLLOW-UP

Due to Walter's persistent transfusion requirement and the risk for iron overload, he continues chelation with deferasirox 20 mg/kg/day, as well as erythropoietin 40,000 units/week and filgrastim 300 mcg/week to maintain his current transfusion rate. His serum ferritin is monitored every 4 months. He has no reported side effects to deferasirox and the decrease in his serum ferritin indicates continued response to treatment. Now 79 years of age, he feels well and continues to be active.

DISCUSSION

Nurses should provide patients who receive chronic transfusions with information regarding the clinical sequelae and consequences of iron overload, as well as the treatment options. In addition, barriers to adherence to therapy need to be identified and addressed. At a time when deferoxamine was his only option for chelation therapy, Walter was educated on iron overload and the available treatment; he made an informed decision not to proceed, due to the significant negative impact on his quality of life. Once deferasirox became available, he began treatment and has achieved a therapeutic benefit.

Sources: NCCN[13]; Hellstrom-Lindberg[52]; Hellstrom-Lindberg.[53]

RESOURCES FOR HEALTHCARE PROVIDERS AND PATIENTS

A wealth of information is available on the Internet on iron overload, beta-thalassemia, sickle cell disease, myelodysplastic syndromes, and related subjects both for healthcare providers and for patients. Programs and organizations also exist online to assist qualified patients in paying for their medications. Here is a sampling:

FINANCIAL ASSISTANCE

Exjade® Patient Assistance and Support Services (EPASS™) Complete Care
http://www.us.exjade.com/patient/epass-complete-care.jsp

Novartis Patient Assistance Foundation
http://www.pharma.us.novartis.com/about-us/our-patient-caregiver-resources/paf-enrollment.jsp
1-800-277-2254

Patient Assistance Now
http://www.patientassistancenow.com

IRON OVERLOAD

Be Transfusion Smart. Be Iron Smart
http://www.betransfusionsmart.com

EXJADE® Web site
http://www.us.exjade.com

Iron Overload Nurse Ambassador Program
www.ironoverloadnurses.com

Iron Toxicity.com
http://www.irontoxicity.com

THALASSEMIA

Cooley's Anemia Foundation
http://www.cooleysanemia.org

Diamond Blackfan Anemia Foundation
http://dbafoundation.org

March of Dimes
http://www.marchofdimes.com

National Heart, Lung and Blood Institute
http://www.nhlbi.nih.gov/health/dci/Diseases/Thalassemia/Thalassemia_WhatIs.html

Thalassaemia International Federation
http://www.thalassaemia.org.cy

SICKLE CELL DISEASE

American Sickle Cell Anemia Association (ASCAA)
http://www.ascaa.org

International Association of Sickle Cell Nurses & Physician Assistants
http://www.iascnapa.org

National Heart, Lung and Blood Institute
http://www.nhlbi.nih.gov/health/prof/blood/sickle/index.htm

Sickle Cell Disease Association of America
http://www.sicklecelldisease.org

Sickle Cell Information Center
http://www.scinfo.org

SickleCellKids.org
http://www.sicklecellkids.org

MYELODYSPLASTIC SYNDROMES (MDS)

Aplastic Anemia & MDS International Foundation
http://www.aamds.org

Leukemia and Lymphoma Society
http://www.leukemia-lymphoma.org

Myelodysplastic Syndromes Foundation
http://www.mds-foundation.org

National Cancer Institute
http://www.cancer.gov/cancertopics/pdq/treatment/myelodysplastic/Patient

CONCLUSION

Patients with beta-thalassemia, SCD, and MDS increasingly receive blood transfusions for chronic anemia because it improves outcomes. This creates a risk for developing transfusion-related iron overload. Iron overload is asymptomatic until diagnostic testing reveals it, which makes monitoring for this potentially lethal condition crucial for nurses who care for patients receiving regular transfusions. Iron overload not only represents a serious health risk and could affect how well patients feel, but if left undiagnosed and untreated, it can complicate the course of their disease, making it more difficult to manage. Managing adverse events resulting from chelation therapy is important for adherence. Patient education is important for adherence, too, and should be an ongoing part of care.

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