

TRANSFUSION MEDICINE UPDATE



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Iron Overload in Transfusion Medicine

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INTRODUCTION

Poor iron intake and blood loss are well-known causes of chronic anemia. Many other types of chronic anemia (e.g., sickle cell disease, thalassemia major, and myelofibrosis), are *not* due to iron deficiency but to ineffective erythropoiesis or shortened red cell survival, and actually provoke inappropriate iron absorption. In addition, without treatment, chronically transfused patients eventually develop toxic iron overload. This Transfusion Update briefly reviews iron physiology, the pathophysiology of iron overload, and the role of transfusion medicine in its prevention and treatment.

IRON HOMEOSTASIS

Although many biological molecules cannot function without iron, free ferrous iron causes severe oxidative molecular damage. Iron must be closely regulated and shepherded around the body bound within cytochromes such as heme or to an array of transport and storage proteins. Normal body iron stores total 3 to 4 grams, most of it within the erythropoietic cycle. American diets contain 10 to 30 mg of daily iron; 5 to 10% is normally absorbed. Men and non-menstruating women typically lose 1 mg of iron/day via skin, GI, and urinary routes; menstruating women lose about 4 mg per day, and may be in slight negative iron balance. Pregnancy, menorrhagia, and bleeding aggravate iron deficiency, but it is important to remember that there is no physiologic mechanism for excretion of excess iron.

The small intestine is the principal regulator of body iron stores: low iron stores increase absorption, and iron surplus normally diminishes it. Iron moves from the gut lumen into enterocytes for storage within hollow spheres of intracellular ferritin while awaiting transfer to plasma via the membrane protein ferroportin. Untransferred iron leaves the body with shed enterocytes within a few days. Transfer of iron to plasma increases in anemias, and can be inhibited by the acute phase reactant liver protein hepcidin, which in turn is normally stimulated by iron excess, inflammation, increased plasma transferrin, and the HFE gene product (which is defective in hereditary hemochromatosis). Liver disease thus dysregulates

iron transfer into plasma, playing a central role in both anemia of chronic illness and iron overload.

IRON TRANSPORT AND STORAGE

Within the circulation, ferric iron binds to transferrin, a liver-produced iron transport protein, normally occupying about 1/3 of transferrin binding sites, such that normal serum iron is 100 mcg/dL and iron binding capacity is 300 mcg/dL. Iron-laden transferrin enters red cell precursors via endocytosis, and apotransferrin returns to the circulation. Red cell mitochondria synthesize heme, incorporating ferrous iron into the completed protoporphyrin ring. Each globin chain of the hemoglobin tetramer harbors a heme molecule which binds molecular oxygen in the lungs and releases it in tissues. Surplus erythrocyte iron is also stored within ferritin. Although circulating apoferritin does not store or transport iron, its levels correlate with intracellular ferritin-iron stores and the body iron burden. Apoferritin is an acute phase reactant; low serum levels accurately reflect iron deficiency, while high levels usually (but not always) bespeak excess.

IRON RECYCLING

Splenic macrophages scavenge aging RBCs and recycle their components, storing recovered iron in ferritin or returning it to circulating transferrin. Macrophages also transport excess plasma iron or ferritin/hemosiderin scavenged from tissue hemorrhage to the marrow. Continuous recycling of iron normally keeps replacement requirements low.

IRON OVERLOAD

Certain diseases and dietary factors disrupt normal iron absorption. Oral overdoses of iron (and vitamin C) may overwhelm the usual defenses, permitting rapid uptake. Disorders of hepcidin secretion or mutations affecting ferroportin function or its response to hepcidin may allow excessive transfer of enterocyte storage iron into plasma even if dietary intake is normal or reduced. Red blood cell transfusion (1 mg of iron per ml) of course bypasses GI regulation altogether, and a lifetime transfusion history of as few as 10 units of PRBCs may lead to overload. Absent blood loss, unchecked absorption and repeated

transfusions stockpile unneeded iron. At first, the surplus resides within marrow, reticulo-endothelial macrophages, and macrophage-like cells in other organs, e.g., Kupffer cells in the liver. When this storage capacity is at last overwhelmed, iron accumulates in other tissues. This is well tolerated at first; iron deposition without cellular damage is called *hemosiderosis*. Continued accumulation leads to cellular toxicity and damage to many organs, particularly the liver, myocardium, and endocrine glands, resulting in *hemochromatosis*.

IRON TOXICITY

Iron-mediated organ damage follows a predictable course regardless of the cause. Liver parenchymal toxicity leads to early fibrosis, progressing over years to cirrhosis and hepatocellular carcinoma. Early damage to the specialized myocardium of the conduction system causes dysrhythmias, and, with time, global cardiomyopathy and congestive failure. Iron overload in the anterior pituitary leads to hypogonadism, whereas damage to the thyroid, parathyroid glands and pancreatic beta islet cells produces hypothyroidism, hypoparathyroidism and diabetes. Skin manifestations include hair loss and “bronzing” due to iron and melanin deposition. Iron accumulation in joints produces destructive arthritis. Central nervous system toxicity manifests as memory loss and vertigo.

Progressive iron overload is eventually fatal. Transfusion-related iron overload shortens life expectancy even as RBC transfusion staves off morbidity from chronic anemias (e.g. thalassemias), or prevents serious complications of sickle cell anemia (e.g., stroke). Fear of iron toxicity may discourage beneficial transfusion therapy, paradoxically prolonging life while diminishing its quality.

TREATMENT OF IRON OVERLOAD

Three categories of iron overload therapy are phlebotomy, red blood cell exchange, and chelation. Each is appropriate in particular circumstances.

Phlebotomy is technically simple, and is most appropriate for symptomatic polycythemia. Since the volume removed is typically not replaced, most patients can tolerate withdrawal of only about 500 mL of blood per session. Assuming a net loss of 250 mg per treatment, it takes many weeks to reduce a large iron burden.

Isovolemic large volume erythrocytapheresis or red cell exchange with saline replacement is an alternative which permits withdrawal of larger volumes of red cells. The procedure can potentially be performed manually, but an automated apheresis technique has been described for the rapid reduction of hematocrit in polycythemia vera to reduce the risk of hyperviscosity and thrombo-embolism by removing a mean of 1100 mL of RBC within 1 to 2 hours, equivalent to 5 or 6

conventional phlebotomies with a single treatment.¹ Maintenance of a normal hematocrit afterwards was attributed in this study to massive removal of iron, depriving the abnormal clone of needed substrate.

More common indications for erythrocytapheresis are serious complications of sickle cell disease such as stroke and acute chest syndrome. Unlike abnormal red cells in other anemias, which are merely short-lived or dysfunctional, sickled cells are actually harmful, causing ischemia by occluding the microcirculation. Simple transfusion (with fewer units) reduces the proportion of circulating sickle hemoglobin, but does not actually remove any sickle cells, and of course predisposes to iron overload. Red cell exchange (with more units) reduces both the concentration of sickled cells and their numbers. While it would seem that volume for volume exchange of normal RBCs for sickle cells should produce no net change in body iron burden, several investigators have reported decreases in serum ferritin levels via red cell exchange in iron overloaded sickle cell patients previously treated with simple transfusion.^{2,3,4}

Chelators are a class of compounds which bind iron for biliary excretion. These drugs treat iron overload in transfusion-dependent anemias such as beta thalassemia, and, combined with simple transfusion, are an alternative to red cell exchange in sickle cell disease. Deferoxamine was formerly the only chelator approved in the U.S. Although effective in controlled trials, its administration requires prolonged, painful, nightly subcutaneous infusion. Poor compliance limits its real world efficacy. A newer once-daily oral chelator, deferasirox (Exjade®) offers hope for better compliance, partially restoring the relative advantages of simple transfusion in chronic anemias.

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