Approach to the patient with suspected iron overload

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INTRODUCTION

Iron overload is a potentially serious problem that is often overlooked because the symptoms are nonspecific and often develop gradually.

A number of diagnostic tests are available, but their interpretation can be challenging.

Once iron overload is diagnosed, the options for treatment are relatively straightforward in the majority of individuals. However, untreated individuals can develop life-threatening organ toxicity. It is important to identify iron overload before organ damage occurs.

An approach to evaluating individuals with suspected iron overload is presented here.

Separate topic reviews discuss the regulation of iron balance, the diagnosis of and treatment of hereditary hemochromatosis (HH), and the management of iron overload.

- **Iron balance** – (See "Regulation of iron balance".)
- **HH population screening** – (See "*HFE* and other hemochromatosis genes", section on 'Role of population screening'.)
- **HH diagnosis** – (See "Clinical manifestations and diagnosis of hereditary hemochromatosis".)
- **HH treatment** – (See "Management and prognosis of hereditary hemochromatosis".)

- **HH genetics and genetic test interpretation** – (See "*HFE* and other hemochromatosis genes" and "Gene test interpretation: *HFE* (hereditary hemochromatosis gene)".)

- **Chelation therapy** – (See "Iron chelators: Choice of agent, dosing, and adverse effects".)

- **Therapeutic phlebotomy** – (See "Thalassemia: Management after hematopoietic cell transplantation", section on 'Iron stores' and "Management and prognosis of hereditary hemochromatosis" and "Management and prognosis of hereditary hemochromatosis", section on 'Phlebotomy'.)

NORMAL IRON STORES

The normal iron content of the body is 3 to 4 grams, distributed as follows:

- Hemoglobin in circulating red blood cells (RBCs) – Approximately 2.5 grams
- Iron-containing proteins other than hemoglobin (eg, myoglobin, cytochromes, catalase) – 400 mg
- Iron bound to circulating transferrin – 3 to 7 mg
- Storage iron in the form of ferritin or hemosiderin (typically in bone marrow macrophages)

Adult males have approximately 1 g of storage iron (mostly in liver, spleen, and bone marrow). Adult females often have less storage iron, depending upon the menses, pregnancies, deliveries, and iron intake; some may have no iron stores [1].

Total body iron content is determined by the balance between dietary iron intake (or other sources such as transfusion) and iron loss from bleeding or shedding of iron-containing cells; there are no physiologic mechanisms to eliminate iron from the body when it is present in excess:

- **Intake** – A typical Western diet in resource-rich settings contains approximately 10 to 20 mg of iron; approximately 10 percent of this is absorbed in the upper gastrointestinal tract. Heme iron (eg, iron in meats) is better absorbed than non-heme iron (eg, iron from vegetable sources). Other factors that influence the efficiency of iron absorption are discussed in detail separately. (See "Regulation of iron balance", section on 'Intestinal iron absorption'.)

- **Loss** – Iron is normally lost in sweat, shed skin cells, and gastrointestinal loss at a rate of approximately 1 mg/day. Menstruating females lose additional iron, equivalent to 0.5 to 1.0 mg/day.

- **Recycling** – Iron is recycled from the breakdown of senescent RBCs in the macrophages of the reticuloendothelial system in the liver, spleen, and bone marrow.

While removal of iron from the body is not regulated, the absorption of iron from intestinal cells and the release of storage iron from macrophages is highly controlled, in a process involving a number of transport proteins and their regulators. (See "Regulation of iron balance", section on 'Role of specific proteins'.)

In hereditary hemochromatosis (HH), genetic variants in one of these regulators (typically, homozygous C282Y mutation in the *HFE* gene or compound heterozygosity for C282Y/H63D) leads to excessive intestinal iron absorption; other causes of increased iron stores include ineffective erythropoiesis (eg, in thalassemia), and a large number of red blood cell transfusions for indications other than blood loss (eg, hemoglobinopathies, hematologic neoplasms). (See 'Causes of iron overload' below.)

CAUSES OF IRON OVERLOAD

Overview of causes — Iron overload can be due to increased intake or increased absorption (table 1).

- **Intake** – The major cause of increased iron intake is red blood cell (RBC) transfusions for chronic anemia (thalassemia, sickle cell disease (SCD), hemolytic anemias such as pyruvate kinase deficiency, an inherited bone marrow failure syndrome, or a myelodysplastic syndrome). Less common causes include excessive use of iron supplements or iron-containing medications such as hemin, used to treat certain porphyrias.

- **Absorption** – The major causes of increased iron absorption include hereditary hemochromatosis (HH) due to biallelic *HFE* C282Y; ineffective erythropoiesis in thalassemia, sideroblastic anemias, and certain other inherited anemias; and liver disease, especially alcoholic liver disease and chronic hepatitis. Less common causes include gestational alloimmune liver disease (GALD) and rare genetic variants affecting iron absorption or distribution.

Patients often have more than one cause of iron overload. Classic examples are transfusional iron overload in an individual with beta thalassemia major, HH plus excessive use of iron supplements, HH plus ingestion of alcohol stored in iron-containing barrels, or HH plus alcoholic liver disease.

Elevated serum ferritin (ferritin >300 ng/mL in males, >200 ng/mL in females) may occur in some conditions in the absence of excess iron, as summarized in the table (table 2). Inflammation is a common cause, including malignancies, systemic juvenile idiopathic arthritis, systemic lupus erythematosus (SLE), chronic kidney disease, hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS), and metabolic syndrome [2]. These causes must be distinguished, as treatment is directed towards the underlying condition and does not involve iron reduction methods. (See 'Differential diagnosis' below.)

Transfusional iron overload — Transfusional iron overload occurs when transfusions are given for anemia not caused by iron deficiency. Examples include:

- Thalassemia, in which iron overload is compounded by increased absorption due to ineffective erythropoiesis
- Sickle cell disease (SCD)
- Other inherited anemias
- Aplastic anemia
- Myelodysplastic syndromes
- Other hematologic malignancies
- Hematopoietic stem cell transplantation

For individuals without iron deficiency, transfusion of >15 to 20 units of RBCs (>10 units in smaller children) can cause clinically significant iron overload, as each unit of RBCs contains approximately 250 mg of iron. Some individuals with ineffective erythropoiesis who also have increased iron absorption may develop iron overload after fewer transfusions. The correlation between number of transfusions and iron overload is not exact; clinical judgment is required in determining when to assess for iron overload.

Individuals receiving chronic RBC transfusions are typically monitored using serum ferritin levels and liver and cardiac magnetic resonance imaging (MRI) (algorithm 1). (See 'Sequence and interpretation of testing' below and "Clinical utility of cardiovascular magnetic resonance imaging", section on 'Iron overload'.)

Hereditary hemochromatosis — Hereditary hemochromatosis (HH) is an autosomal recessive disorder with increased iron absorption, which sometimes causes excessive iron stores. HH is caused by variants in the *HFE* gene, typically homozygous C282Y/C282Y or compound heterozygous C282Y/H63D. (See "Gene test interpretation: *HFE* (hereditary hemochromatosis gene)".)

Less common forms of HH include other *HFE* variants and pathogenic variants in other iron regulatory genes:

- Ferroportin
- Hemojuvelin
- Hepcidin
- Ceruloplasmin
- Transferrin receptor 2

Individuals with HH can absorb as much as 2 to 4 mg of dietary iron per day (twice the rate of individuals without HH). This increased absorption can result in as much as an additional 3 mg per day in excess of needs, which are typically 1 to 2 mg per day. (See 'Normal iron stores' above.)

Over time, iron accumulation can occur at a rate of approximately 1 gram per year (10 grams per decade). This explains the typical age of presentation (fourth to fifth decades in males; later in females, due to iron loss with menstruation and/or pregnancy). (See "Clinical manifestations and diagnosis of hereditary hemochromatosis".)

Individuals with a family history of HH should have *HFE* testing (or testing for other familial gene variants) to identify HH if present and prevent permanent end-organ damage. In the Hemochromatosis and Iron Overload Screening (HEIRS) study, self-reported information about the family history had a sensitivity of 81 percent and a specificity of 97 percent for an accurate report, supporting the use of family history as a screening tool [3]. Individuals who are homozygous for *HFE* C282Y or compound heterozygous (C282Y/H63D) should have iron studies and liver function tests. (See 'Sequence and interpretation of testing' below.)

The ideal age to perform genetic testing and/or liver iron assessment has not been determined. Deferring screening until adulthood is reasonable to facilitate informed consent for testing. (See "Genetic testing", section on 'Ethical, legal, and psychosocial issues' and "Clinical manifestations and diagnosis of hereditary hemochromatosis", section on 'Pathophysiology'.)

The appropriate screening tests include *HFE* genetic testing and iron studies. These can be done sequentially (*HFE* testing followed by iron studies only in those with the HH genotype); it may be cost effective to order the testing simultaneously. Screening relatives of an individual with HH and interpretation of the results are discussed separately. (See "Management and prognosis of hereditary hemochromatosis", section on 'Testing and counseling first-degree relatives'.)

Ineffective erythropoiesis — Ineffective erythropoiesis refers to a process in which RBC precursors are destroyed by apoptosis or hemolysis before they differentiate into mature RBCs; this is manifested by intense erythroid hyperplasia in the bone marrow with a low reticulocyte count. This most commonly occurs in thalassemia; other causes include pyruvate kinase (PK) deficiency, congenital dyserythropoietic anemia, and some sideroblastic anemias. The

associated iron overload may be compounded by frequent RBC transfusions for anemia. (See "Pathophysiology of thalassemia", section on 'Ineffective erythropoiesis'.)

Ineffective erythropoiesis can also occur in megaloblastic anemias (vitamin B12 or folate deficiency); however, the underlying condition is usually treated before significant iron accumulates. (See "Causes and pathophysiology of vitamin B12 and folate deficiencies", section on 'Hematopoiesis'.)

SCD and autoimmune hemolytic anemias are not associated with ineffective erythropoiesis; in these anemias, hemolysis primarily affects mature RBCs in the circulation rather than RBC precursors in the bone marrow. Individuals with these disorders can develop transfusional iron overload, but they are not at increased risk of iron overload attributable to their hemolytic anemia. (See 'Transfusional iron overload' above.)

Ineffective erythropoiesis leads to increased intestinal iron absorption by an incompletely understood mechanism [4-9]. Elevated erythroferrone, produced by RBC precursors, suppresses hepcidin production, although the exact mechanism is poorly understood [4-10]. These proteins are discussed separately. (See "Regulation of iron balance" and "Regulation of erythropoiesis".)

Liver disease — Several acute and chronic liver disorders are associated with inflammation and increased acute phase reactants, including ferritin. The liver is also a major site for iron storage, and any process that damages liver cells can release storage iron into the circulation, leading to an increase in ferritin [2,11]. In some cases, there is also increased iron absorption and increased iron deposition in the liver, although typically not to the extent seen in HH. The mechanism of increased iron absorption is incompletely understood; it likely involves decreased hepcidin production by the diseased liver [12,13].

Examples include:

- **GALD** – Gestational alloimmune liver disease (GALD; also called neonatal hemochromatosis or neonatal iron storage disease) is a rare disorder caused by maternal alloantibodies that cross the placenta and cause injury to the fetal liver, leading to severe liver failure and/or cirrhosis in the newborn. Hepatic and extrahepatic iron deposition is often seen, but this is a consequence of liver injury, not a cause. (See "Causes of cholestasis in neonates and young infants", section on 'Gestational alloimmune liver disease (neonatal hemochromatosis)'.)

- **Alcoholic liver disease** – Alcoholic liver disease may be associated with increased stainable liver iron. (See "Clinical manifestations and diagnosis of alcohol-associated fatty liver disease and cirrhosis".)

- **Chronic liver disease** – Other chronic liver diseases such as non-alcoholic fatty liver disease (NAFLD), chronic viral hepatitis, porphyria cutanea tarda (PCT), or chronic hepatitis from other causes may also increase liver iron. Phlebotomy reduces iron deposition. In PCT, phlebotomy also targets the impaired heme biosynthesis. (See "Epidemiology, clinical features, and diagnosis of nonalcoholic fatty liver disease in adults" and "Porphyria cutanea tarda and hepatoerythropoietic porphyria: Pathogenesis, clinical manifestations, and diagnosis", section on 'Central importance of iron in PCT'.)

Some individuals with iron overload from liver disease may also have a genetic component of increased iron absorption that exacerbates liver injury. It may not be clear which came first, liver disease or iron overload. The severity of the initial liver injury may be challenging to determine (eg, unclear amount or duration of excess alcohol intake). This provides the rationale for *HFE* testing in some cases. (See 'Post-diagnostic testing' below.)

Rare causes — Rare causes of iron overload include:

- An iron-loaded diet such as in African iron overload (also called Bantu syndrome or Bantu siderosis), in which homemade beer contains excess iron leached from iron barrels. Rarely, genetic iron overload may occur in African and African American populations [14].
- Hemin treatment for porphyria.
- Intravenous iron infusions in patients with chronic kidney disease [15].
- Unintentional consumption of a prenatal vitamin with iron by a child, or intentional consumption in attempted suicide.

CONSEQUENCES OF EXCESS IRON STORES

Organ damage from reactive oxygen species — As total body iron burden increases beyond that needed for production of hemoglobin for red blood cells (RBCs), myoglobin for muscle cells, and iron-containing enzymes, the iron-binding protein transferrin becomes saturated, eventually exceeding its capacity and resulting in binding of iron to other proteins and molecules, including albumin, citrate, acetate, and others. This iron is referred to as non-transferrin-bound iron (NTBI); it begins to appear once the transferrin saturation (TSAT) exceeds 35 percent and rises significantly with TSAT above 70 percent [16,17].

NTBI is taken up by cells that have active uptake mechanisms such as the L-type calcium channel. This includes parenchymal cells of the liver, heart, and endocrine organs. In these

organs, excess iron can chemically interact with hydrogen peroxide, acting as a Fenton reagent and catalyzing the Haber-Weiss reactions [18]:

$$H_2O_2 + Fe(2+) \longrightarrow OH^- + Fe(3+) + OH\bullet \text{ (hydroxyl radical)}$$
$$O_2^- \text{ (superoxide anion)} + Fe(3+) \longrightarrow O_2 + Fe(2+)$$

SUM: $H_2O_2 + O_2^- \longrightarrow O_2 + OH^- + OH\bullet$

These reactive oxygen species in turn can cause tissue damage, inflammation, and fibrosis [18,19]. The liver, heart, joints, and endocrine organs appear to be especially susceptible. By the time clinical findings have developed (hepatic fibrosis, heart failure, cardiac conduction defect), significant iron deposition and tissue injury have likely occurred. (See 'Typical clinical findings' below.)

Some iron toxicity may be abrogated by the body's antioxidant defenses such as glutathione-S-transferase (GST) [20]. Genetic variants in the GST system are under investigation [21,22].

Typical clinical findings — Iron overload may be suspected with the following (see 'Overview of causes' above):

- Family history of hereditary hemochromatosis (HH)
- Multiple RBC transfusions for anemia other than iron deficiency
- Unexplained organ damage such as liver, heart, endocrine, or joint disease
- Incidental finding of increased serum ferritin or transferrin saturation (TSAT)

Excess total body iron (several grams or more) will cause organ damage. Typical manifestations include one or more of the following:

- Hepatic involvement with biochemical abnormalities in liver function, inflammation, fibrosis, and eventually cirrhosis
- Cardiac involvement with cardiomyopathy, heart failure, and/or arrhythmias
- Pancreatic involvement with diabetes mellitus
- Pituitary and gonadal involvement with hypogonadism, decreased libido, and impotence
- Skin involvement with hyperpigmentation ("bronze diabetes")
- Joint involvement with arthropathy, especially involving the second and third metacarpophalangeal joints, and often with chondrocalcinosis

Evaluation for iron overload is often indicated for individuals with unexplained organ dysfunction, especially liver, heart, gonadal dysfunction. The relative likelihood of iron overload versus other causes of organ dysfunction varies with patient age, family history, other

symptoms, and other comorbidities. As examples, iron overload is more likely to be a cause of organ damage in middle aged males or postmenopausal females, those with a family history of hemochromatosis, and those with a history of transfusions, and less likely in younger individuals or those with a personal or family history that suggests another etiology. (See 'Other cause of organ dysfunction' below.)

SEQUENCE AND INTERPRETATION OF TESTING

Overview of approach — The evaluation for suspected iron overload differs depending on the clinical setting, as discussed in the following sections (algorithm 1) [2,23]. In addition to a thorough clinical evaluation, all patients with suspected iron overload should have the following laboratory tests (see 'CBC, LFTs, and iron studies' below):

- Complete blood count (CBC) with red blood cell (RBC) indices
- Iron studies including serum ferritin and transferrin saturation (TSAT)
- Metabolic panel including hepatic enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST])

Testing for *HFE* C282Y and H63D is an appropriate initial step in individuals with a family history of hereditary hemochromatosis (HH). *HFE* testing is also appropriate in most individuals with documented iron overload as a means of determining the genetic contribution. This is true even in individuals with an acquired cause of iron overload such as liver disease, because there may also be a genetic component. (See 'Post-diagnostic testing' below.)

Other testing such as MRI or liver biopsy with iron staining are generally limited to individuals with laboratory evidence of iron overload, in order to estimate total body iron stores, or in those for whom there is diagnostic confusion, in order to definitively establish or exclude increased tissue iron. (See 'Noninvasive imaging (MRI)' below and 'Other tests for selected individuals' below.)

Our approach is consistent with clinical guidelines published by a number of groups [24-28].

Some of the studies used to diagnose iron overload are also extremely useful for monitoring the progress of treatment with phlebotomy or iron chelation; these uses are discussed separately. (See "Management and prognosis of hereditary hemochromatosis" and "Iron chelators: Choice of agent, dosing, and adverse effects" and "Transfusion in sickle cell disease: Management of complications including iron overload", section on 'Excessive iron stores'.)

CBC, LFTs, and iron studies — The CBC and iron studies are interpreted together; anemia influences the evaluation if present:

- A normal CBC with increased ferritin and TSAT suggests HH or other form of iron overload. If anemia is present, the diagnosis cannot be HH in isolation. (See "Clinical manifestations and diagnosis of hereditary hemochromatosis".)

- Microcytic anemia with increased ferritin and TSAT strongly suggests thalassemia. Transfusion-dependent thalassemia (TDT, also called thalassemia major) or non-transfusion-dependent thalassemia (NTDT, also called thalassemia intermedia) may cause substantial iron overload, which may be exacerbated by transfusions but may also occur without transfusions due to ineffective erythropoiesis. (See 'Ineffective erythropoiesis' above and "Diagnosis of thalassemia (adults and children)".)

- Normocytic anemia with increased ferritin suggests anemia of chronic disease/anemia of inflammation, which may have increased ferritin without increased total body iron stores or rarely may be associated with iron overload from other causes. (See "Anemia of chronic disease/anemia of inflammation".)

- Macrocytic anemia with increased ferritin and/or TSAT suggests an underlying cause of anemia such as hemolysis or megaloblastic anemia, such as vitamin B12 deficiency. (See "Macrocytosis/Macrocytic anemia".)

- Polycythemia with increased ferritin and/or TSAT suggests a primary or secondary process leading to increased production of RBCs. Secondary erythrocytosis may be caused by hypoxia (lung or heart disease) or increased erythropoietin production (liver or kidney disease). Primary erythrocytosis is caused by polycythemia vera or other myeloproliferative neoplasm (MPN). MPNs are often associated with increased ferritin from transfusional iron overload, but MPNs are not associated with total body iron overload in the absence of transfusions. (See "Diagnostic approach to the patient with erythrocytosis/polycythemia".)

LFTs are often helpful because iron studies are more likely to be abnormal in individuals with liver disease regardless of the total body iron burden, and the absence of liver disease eliminates this as a possible cause of abnormal iron studies. This has been illustrated in studies that show a poor correlation between iron studies and total body iron burden in individuals with liver disease of various causes [29].

Routine iron studies include serum iron, transferrin (also reported as total iron binding capacity [TIBC]), and ferritin; TSAT is calculated as the ratio of serum iron to TIBC and expressed as a

percentage (TSAT = iron ÷ TIBC x 100). The results that are most useful for evaluating iron overload are the ferritin and TSAT, both of which are elevated in iron overload [26]:

- **Ferritin** – The normal range for ferritin in plasma or serum is approximately 40 to 200 ng/mL (40 to 200 mcg/L; 89.9 to 449.4 picomoles/L). A ferritin level ≥200 to 300 ng/mL (≥200 to 300 mcg/L) in a male or ≥150 to 200 ng/mL (≥150 to 200 mcg/L) in a female is consistent with iron overload, and a level below these values is good evidence that the patient does not have iron overload. Typically, ferritin levels in iron overload are in the range of up to 2000 to 3000 ng/mL (mcg/L), even higher if iron overload is causing severe liver disease or cardiomyopathy. If the individual has received multiple transfusions, ferritin may also be higher.

  Elevated serum ferritin is a sensitive test for iron overload, but it is not very specific. Numerous conditions other than iron overload can elevate serum ferritin [2]. Ferritin is an acute phase reactant that increases with infection or inflammation. Ferritin can also be elevated in patients with liver disease. These other causes of abnormally high ferritin must be distinguished in order to avoid unnecessary invasive testing and/or delays in treatment. (See 'Differential diagnosis' below.)

  In individuals with transfusional iron overload, there is some correlation between the ferritin level and the total body iron burden (individuals with a ferritin in the range of 500 to 1000 ng/mL are unlikely to have severe iron overload; those with ferritin in the range of 3000 to 4000 ng/mL may have substantial iron burden), but there is variability between individuals and between measurements for the same individual [11]. The correlation between iron stores and ferritin levels may only be reliable at a ferritin below 3000 to 4000 ng/mL [30]. Observational studies have generally found some weak correlations between ferritin and iron burden (assessed by liver biopsy or therapeutic phlebotomy) but results are mixed, and sensitivity and specificity are in the range of 60 to 80 percent [31-38].

  The correlation of ferritin and liver iron concentration is not linear in individuals with a component of non-transfusional iron overload from ineffective erythropoiesis. The correlation is generally weak in regularly transfused patients with sickle cell disease (SCD) compared with thalassemia, though high ferritin levels (>3000 ng/mL) and low ferritin levels (<1000 ng/mL) generally correlate with high and low liver iron concentration, respectively.

- **TSAT** – A high TSAT (≥45 percent in males or ≥40 percent in females; refer to the laboratory's reference range) often occurs with iron overload [2]; a TSAT below these levels

is good evidence that the patient does not have iron overload, even if the ferritin is elevated. If TSAT is not provided by the laboratory, it can be calculated (calculator 1).

An increased TSAT may precede an increased ferritin, and rarely, a person may have an isolated increased TSAT without overt iron overload or organ damage, especially in a younger adult. An elevated TSAT with a normal ferritin suggests that the individual is at risk for, or in the early stages of, iron overload. Such individuals are likely to benefit from further monitoring to determine whether the TSAT normalizes or the ferritin increases. (See 'Organ damage from reactive oxygen species' above.)

Several factors may confound ferritin and TSAT measurements, including diet and comorbidities, especially liver disease [23,39].

- **Liver disease** – Ferritin and TSAT can be elevated in liver disease because dying hepatocytes release storage iron into the circulation, and alcohol may suppress hepcidin synthesis, leading to increased intestinal iron absorption. TSAT may be increased in liver disease caused by excess alcohol because alcohol suppresses liver transferrin synthesis. Ferritin is also an acute phase reactant. Thus, it is ideal to obtain at least two independent measurements. There is no simple algorithm to follow when the ferritin and TSAT are discordant; the clinical context determines the likely interpretation and the subsequent approach. Hematology consultation may be appropriate in these cases.

- **Inflammation** – If the patient is in the midst of an acute infection or inflammation, it may be prudent to delay iron studies testing until the acute event has resolved, or if the studies have already been performed, to repeat them after the acute event has resolved, rather than pursuing more aggressive testing for iron overload such as MRI. An exception is suspected hemophagocytic lymphohistiocytosis (HLH), for which elevated ferritin is one of the diagnostic criteria. If it is not clear whether the patient has an acute infection or inflammatory process, then the C-reactive protein (CRP) can be checked. A normal CRP is inconsistent with inflammation or infection and in most cases eliminates these as an explanation for the increased ferritin. (See "Clinical features and diagnosis of hemophagocytic lymphohistiocytosis", section on 'Diagnostic criteria'.)

- **Fasting** – Some clinicians prefer to use fasting samples for iron studies. This is not supported by data from clinical studies, but it is not unreasonable to use at least one fasting sample, especially in individuals with a borderline result or discordance between clinical and laboratory findings [26]. For an individual with increased ferritin during an ongoing inflammatory process such as malignancy, diabetes, or connective tissue disease,

other testing is likely to be needed to determine whether there is total body iron overload (eg, MRI, course of phlebotomy, biopsy).

Additional information about iron studies is presented separately. (See "Causes and diagnosis of iron deficiency and iron deficiency anemia in adults", section on 'Iron studies (list of available tests)'.)

Noninvasive imaging (MRI) — Noninvasive imaging such as MRI using T2*, R2, and R2* measurements has become increasingly accurate for determining hepatic and cardiac iron deposition and has generally supplanted direct tissue biopsy for assessing iron overload and quantifying its severity (image 1).

We routinely use combined liver and cardiac MRI to confirm iron overload and measure its extent in individuals with increased serum ferritin and TSAT (algorithm 1). This is especially true for those with thalassemia and other severe transfusion-dependent anemias such as Diamond-Blackfan anemia. Imaging of both the liver and heart is important because iron accumulation is not uniform. If the clinical history strongly suggests a cause of iron overload such as a family history of HH, multiple RBC transfusions (>15 to 20 units, for any indication), or non-transfusion-dependent thalassemia in the absence of transfusions, then a ferritin value above the upper limit of normal with TSAT >45 percent is an appropriate threshold for performing MRI.

- **Liver MRI** – A liver iron concentration estimated by MRI >3 mg Fe/g dry weight (equivalent to approximately 53 to 125 micromol/g dry weight) indicates hepatic iron overload. Generally, a LIC of over 5 to 7 indicates the need for treatment. Estimation of liver iron and details of the methods are presented separately. (See "Methods to determine hepatic iron content", section on 'Magnetic resonance imaging'.)

- **Cardiac MRI** – A cardiac T2* by MRI <20 milliseconds (normal: >20 milliseconds) indicates cardiac iron overload [40]. Values <10 milliseconds have been associated with severe myocardial iron loading and high risk of the development of cardiac failure and/or arrhythmias. (See "Clinical utility of cardiovascular magnetic resonance imaging", section on 'Iron overload'.)

- **Other tissues** – MRI of other tissues (pancreas, pituitary gland) has been reported in individuals with known iron overload but is not routinely used to diagnose iron overload [23,41].

MRI assessment of liver and cardiac iron is very useful for transfusional iron overload. The usefulness of MRI for other disorders is mixed, and results must be interpreted in the clinical

context. A 2015 systematic review and meta-analysis of liver MRI to determine iron overload in individuals with HH (20 studies; 819 patients) found substantial heterogeneity, with significant risk of bias and variable sensitivity and specificity; the authors concluded that a negative liver MRI was sufficient to exclude iron overload [42]. The threshold for the presence of iron overload was also inconsistent, ranging from 2 to 15 mg of iron by gram of liver dry weight. The authors considered a value of 7 mg of iron per gram of liver dry weight (equivalent to approximately 125 micromol/gram of dry weight) to indicate iron overload. However, other experts including UpToDate authors use a lower threshold, especially in individuals with known *HFE* C282Y or transfusional iron overload. When following changes in liver iron over time with MRI, the same technique should be used (eg, R2 or R2*), as systematic differences between the two techniques exist [43].

High diagnostic accuracy has been reported using a superconducting quantum interference device (SQUID) [23,44-46]. However, this test is not routinely used because it requires a specialized instrument not available in most institutions.

Computed tomography (CT) scanning has also been used to assess liver iron content (image 2). However, CT involves radiation exposure, and dual-energy scans are required to compensate for background attenuation [11]. CT is thus reserved for individuals who require an imaging study but do not have access to MRI [47].

The degrees of hepatic and myocardial iron overload may be discordant in an individual patient; this subject is discussed in depth separately. (See "Clinical utility of cardiovascular magnetic resonance imaging", section on 'Iron overload'.)

Other tests for selected individuals

Liver biopsy — Liver biopsy is considered by some experts to be the gold standard for determining increased total body iron stores. Others consider the response to phlebotomy to be a better measure, although this cannot be done in all patients. (See 'Response to phlebotomy' below.)

Liver biopsy may be especially useful for individuals with:

- No access to MRI
- Liver injury
- Concomitant viral hepatitis
- Planning to undergo hematopoietic stem cell transplant (HSCT)
- Need to assess liver histology

Most patients do not require a liver (or other) biopsy since noninvasive MRI estimation of iron stores is highly effective for estimating iron burden. Occasionally, liver or endomyocardial biopsy done for histologic diagnosis will reveal iron overload.

We generally reserve liver biopsy for individuals who require precise estimation of liver iron burden and/or concurrent assessment of liver histology. Examples include individuals with elevated hepatic enzymes and a very high ferritin (eg, >1000 ng/mL [>1000 mcg/L]) in whom it is not clear which came first, individuals with thalassemia prior to HSCT with concern for hepatic fibrosis, or those with other causes of liver injury for whom the severity of iron overload and extent of liver injury are unclear from other testing. This practice is consistent with a 2011 guideline from the American Association for the Study of Liver Diseases (AASLD) [26]. (See "Clinical manifestations and diagnosis of alcohol-associated fatty liver disease and cirrhosis", section on 'Liver biopsy' and "Clinical manifestations and diagnosis of hereditary hemochromatosis", section on 'Estimation of iron stores'.)

Liver tissue can be analyzed for hepatic iron content (HIC; also called liver iron content [LIC]). The upper limit of normal for HIC has been variously given as 25 to 32 micromol of iron per gram (equivalent to approximately 1.4 to 1.8 mg/g) of liver dry weight, with any value >2 mg/g being considered abnormal. This procedure is discussed separately. (See "Methods to determine hepatic iron content", section on 'Hepatic iron concentration'.)

In a series of patients with transfusion-dependent beta thalassemia who had undergone HSCT followed by phlebotomy to remove excess iron, there was a strong linear correlation between HIC measured from liver biopsy and total body iron overload based on phlebotomy [48]. Total body iron stores (in mg of iron per kg of body weight) equaled approximately 10.6 times the HIC (in mg of iron per gram of dry liver weight) (figure 1). A 70 kg individual with a HIC of 7 mg/gram of liver weight would have a total body iron burden of approximately 5 grams. (See "Methods to determine hepatic iron content".)

Liver iron can also be estimated semi-quantitatively using a histologic stain for iron (Perls' Prussian blue staining) (picture 1A-B). For individuals who undergo liver biopsy, the specimen can also be evaluated for the degree of liver injury, inflammation, and fibrosis/cirrhosis [48]. Sampling variability can occur with any biopsy-based testing, which is especially likely in individuals with cirrhosis or patchy liver injury. (See "Interpretation of nontargeted liver biopsy findings in adults" and "Histologic scoring systems for chronic liver disease".)

Response to phlebotomy — Response to therapeutic phlebotomy is considered by some experts to be the gold standard for determining total body iron stores [48]. Information about the response to phlebotomy can also be highly useful in individuals for whom the presence or

degree of iron overload is unclear or those who do not have access to MRI. In iron overload, the ferritin will decline as iron is removed. Others use liver biopsy with quantitation of liver iron content. (See 'Liver biopsy' above.)

Phlebotomy can only be safely performed in individuals who do not have significant anemia or other comorbidities that would prevent them from tolerating the procedure. Typical settings for phlebotomy are:

- Individuals with HH
- Individuals with transfusional iron overload who undergo treatments to correct their anemia and thus can tolerate phlebotomy
    - People with SCD treated with exchange transfusion
    - People with thalassemia, SCD, aplastic anemia, or myelodysplastic syndrome who have undergone HSCT and are no longer severely anemic

In these individuals, we generally use noninvasive methods to assess iron stores (ferritin, TSAT, liver MRI) and correlate these results with the number of phlebotomies that can be performed before the patient becomes iron deficient. However, if there is no access to these noninvasive tests, serial phlebotomies with assessment of the number of units of blood removed is a reasonable alternative for determining the total body iron burden.

Each phlebotomy of 500 mL of whole blood will remove approximately 200 to 250 mg of elemental iron. Thus, an individual with total body iron stores of 5 grams (corresponding to a liver iron content of 7 mg/g dry weight) would require approximately 20 phlebotomies to reach an iron deficient state.

We typically perform phlebotomy of 500 mL of blood one to two times per week until the patient's hemoglobin has fallen to approximately 12 g/dL, the RBCs have become slightly microcytic (mean corpuscular volume [MCV] approximately 75 to 80 fL), and the TSAT and ferritin are below normal (<15 percent and <20 ng/mL, respectively), and then we calculate the iron burden from the number of phlebotomies [49].

The schedule and monitoring of therapeutic phlebotomy are discussed in more detail separately. (See "Thalassemia: Management after hematopoietic cell transplantation", section on 'Iron stores' and "Management and prognosis of hereditary hemochromatosis" and "Management and prognosis of hereditary hemochromatosis", section on 'Phlebotomy'.)

Endomyocardial biopsy — Endomyocardial biopsy may be appropriate in individuals with heart failure or conduction abnormalities, in an individual with elevated cardiac iron on MRI, or

those who do not have access to cardiac MRI. In rare cases, cardiac biopsy done for other indications may reveal iron overload that was not expected. (See "Endomyocardial biopsy".)

For all other patients, cardiac MRI is the preferred method for assessing cardiac iron deposition. (See 'Noninvasive imaging (MRI)' above.)

DIAGNOSIS

The diagnosis of iron overload may be made by one or more of the following [11,23,40,41,47,50-56]:

- **Iron studies** – Increased serum or plasma ferritin (≥200 to 300 ng/mL [≥200 to 300 mcg/L] in a man; ≥150 to 200 ng/mL [≥150 to 200 mcg/L] in a woman) in a patient without significant inflammation or infection and with increased transferrin saturation (TSAT; ≥45 percent). Of note, ferritin and TSAT typically are repeated, although there are no data regarding whether repeat values are needed, and the diagnosis is typically confirmed by imaging studies (to quantify the degree of overload) and/or response to phlebotomy or chelation therapy. (See 'CBC, LFTs, and iron studies' above and 'Post-diagnostic testing' below.)

- **MRI** – Evidence of iron overload by MRI of the liver or heart. A liver iron concentration estimated by MRI >3 mg iron per gram of dry liver weight is consistent with hepatic iron overload. A cardiac T2* by MRI <20 milliseconds (normal: >20 milliseconds) is consistent with cardiac iron overload. (See 'Noninvasive imaging (MRI)' above.)

- **Biopsy** – Evidence of iron overload on tissue biopsy (requires iron stain). Levels of hepatic iron >2 mg/g dry weight is consistent with hepatic iron overload. (See 'Liver biopsy' above.)

- **Phlebotomy** – Removal of iron with a course of therapeutic phlebotomy, typically in the range of ≥1.5 to 2 grams (at least five to six phlebotomies) with normalization of the ferritin level. (See 'Response to phlebotomy' above.)

MRI, biopsy, or a course of phlebotomy are generally required to provide an estimate of the extent of the total body iron burden. There are not good data comparing findings from MRI with those from liver biopsy in the same patient [53,57,58]. Additional testing (*HFE* genetic testing) is needed to determine the underlying cause in individuals who do not have known transfusional iron overload or known ineffective erythropoiesis. (See 'Post-diagnostic testing' below.)

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of iron overload includes other causes of elevated serum ferritin and other causes of liver, cardiac, or endocrine dysfunction.

Other causes of high ferritin

- **Acute illnesses with hemophagocytosis** – Certain acute illnesses can cause very high ferritin levels due to hemophagocytosis (table 2). Unlike iron overload, these conditions cause a rapid, acute, and extremely high ferritin level along with other manifestations of disease including fevers, cytopenias, and other worrisome findings.

  - **HLH** – Hemophagocytic lymphohistiocytosis (HLH) is a potentially life-threatening inflammatory condition in which excessive immune activation leads to tissue destruction and acute systemic illness; it can occur in children and adults. In HLH and the related macrophage activation syndrome (MAS; associated with underlying rheumatologic/connective tissue disease), the ferritin is often extremely high, in the range of 5000 to 20,000 ng/mL (or even higher) and the presentation is often acute severe illness with fever, hepatosplenomegaly, rash, neurologic findings, and pancytopenia. Like iron overload, there may be liver and cardiac involvement. Unlike iron overload, patients with HLH are acutely ill with fever, cytopenias, neurologic findings, and abnormal coagulation studies. (See "Clinical features and diagnosis of hemophagocytic lymphohistiocytosis", section on 'Clinical features'.)

  - **HIV infection** – Infection with human immunodeficiency virus (HIV) can cause high ferritin levels independent of iron status, especially if there is advanced disease, low CD4 count, and opportunistic infection such as histoplasmosis or tuberculosis [59-63]. Like iron overload, there may be liver involvement. Unlike iron overload, these individuals are often acutely ill with fever, cytopenias, and evidence of infection. (See "Acute and early HIV infection: Clinical manifestations and diagnosis".)

- **Chronic inflammatory conditions** – In inflammatory conditions (metabolic syndrome, diabetes, Still's disease), ferritin may be increased as an acute phase reactant [39,64,65]. Like iron overload, the ferritin is above normal and the patient may have nonspecific symptoms such as fatigue. Unlike iron overload, in most inflammatory states the degree of ferritin elevation does not exceed two to three times normal, the transferrin saturation (TSAT) typically does not exceed 45 percent, and there are other features of the clinical picture or signs of inflammation such as increased C-reactive protein (CRP) and other acute phase reactants. This was illustrated in a 2012 population-based case-control study

of 766 middle-aged adult outpatients in which 329 met criteria for metabolic syndrome [66]. Compared with controls, the individuals with metabolic syndrome had higher ferritin levels and higher CRP, but similar transferrin receptor (reflective of similar TSAT values). (See "Metabolic syndrome (insulin resistance syndrome or syndrome X)" and "Acute phase reactants".)

- **Liver injury** – In viral hepatitis, alcoholic hepatitis, and nonalcoholic steatohepatitis, injury to hepatocytes may increase serum ferritin despite normal total body iron stores. Alcohol can be hepatotoxic at levels of consumption as low as one to two drinks per day. Like iron overload, there may be increased transaminases and jaundice. Unlike iron overload, in liver disease, total liver iron (as estimated by MRI or measured by liver biopsy) is not increased, and therapeutic phlebotomy would not improve the ferritin level. Importantly, iron overload can cause liver disease, and each can exacerbate the other. Thus, the presence of liver disease does not exclude the possibility of iron overload, and the presence of iron overload does not exclude the possibility of underlying liver disease. (See "Approach to the patient with abnormal liver biochemical and function tests" and "Clinical manifestations and diagnosis of alcohol-associated fatty liver disease and cirrhosis", section on 'When to consider alcohol-associated liver disease'.)

- **Malignancy** – Malignancy can be associated with increased ferritin; in some cases, ferritin can be extremely high. This was illustrated in a 2015 publication that evaluated the cause of a ferritin level >50,000 ng/mL (mcg/L) in a series of 113 adults at a single institution [30]. Of these, 36 (32 percent) had a hematologic malignancy and 5 (4 percent) had a solid tumor.

- **Rare genetic conditions** – Several variants affecting the ferritin light chain (*FTL)* have been described that cause elevated serum ferritin without systemic iron overload, referred to as "benign hyperferritinemia" [67]. We generally do not test for this since it does not affect patient management, which includes assessment for tissue iron and attention to other causes of high ferritin such as alcoholic liver disease or non-alcoholic steatohepatitis. Testing might be used in the rare individual with no other cause of elevated ferritin who is concerned about the finding and/or who wishes to avoid additional testing in the future.

  The hereditary hyperferritinemia-cataract syndrome can cause exceedingly high serum ferritin levels (often >1000 ng/mL) without tissue iron overload, in association with bilateral congenital cataracts. This disorder, which has been termed "hereditary hyperferritinemia-cataract syndrome" is inherited in an autosomal dominant manner and appears to involve a number of different mutations in the iron responsive element of *FTL* [68-71]. A direct relationship between the degree of hyperferritinemia and the severity of

cataracts suggests that the latter is a consequence of excessive ferritin production within the lens fibers [72].

Other cause of organ dysfunction

- **Liver disease** – Other causes of liver disease include inherited and acquired conditions. Like liver disease secondary to iron overload, there may be increased transaminases, liver inflammation, or, in later stages, liver fibrosis/cirrhosis. These conditions are often associated with elevated ferritin, because the liver is the major site for iron storage and liver damage will cause ferritin release into the circulation. (See 'Other causes of high ferritin' above.)

- **Heart disease, diabetes, or hypogonadism** – Like iron overload, other causes of these conditions may occur gradually and present with nonspecific symptoms such as fatigue. Unlike iron overload, these conditions are not associated with evidence of increased iron stores on noninvasive imaging or biopsy. The need for this testing depends on the specific clinical scenario, as discussed in separate topic reviews. (See "Determining the etiology and severity of heart failure or cardiomyopathy" and "Classification of diabetes mellitus and genetic diabetic syndromes" and "Causes of secondary hypogonadism in males".)

POST-DIAGNOSTIC TESTING

Two major issues that need to be addressed once iron overload is documented (or strongly suspected) are:

- The extent of iron overload and severity of tissue damage, which determines the need for and urgency of therapeutic interventions. (See 'Determining the extent and severity' below.)

- The underlying cause(s) of iron overload, which determines other aspects of the treatment plan. (See 'Determining the cause(s)' below.)

Determining the extent and severity — The degree of iron overload can be determined from a combination of the serum ferritin, noninvasive (MRI) imaging, and in some cases, tissue biopsy and/or response to a course of therapeutic phlebotomy. Liver iron is not necessarily predictive of cardiac iron burden, and cardiac MRI is appropriate in individuals with significant iron overload, as well as those with heart failure or cardiac conduction abnormalities [27,73]. (See 'Sequence and interpretation of testing' above and 'Noninvasive imaging (MRI)' above.)

For individuals with transfusional iron overload, the number of transfusions should be tracked as this can also be incorporated into risk estimates. (See 'Transfusional iron overload' above.)

The degree of iron overload that causes organ damage varies among patients. However, as a general rule, total body iron stores above 5 grams and liver iron concentration >7 mg per gram of dry liver weight are associated with an increased risk of iron-induced complications such as hepatic fibrosis and diabetes. In individuals with transfusional iron overload, this corresponds to approximately 20 to 30 transfusions (fewer in those with thalassemia, who have abnormally high iron uptake as well). Liver iron concentration >15 mg per gram of dry liver weight is associated with a substantial risk for hepatic fibrosis, cardiac disease, and increased mortality [11].

Additional testing to characterize organ damage is listed in the table (table 3).

Determining the cause(s) — Causes of iron overload are listed in the table (table 1). Many of these will have already been diagnosed and/or be obvious from a routine history and physical examination and basic laboratory studies such as a complete blood count and liver function studies.

Individuals with hereditary hemochromatosis (HH) may have a positive family history, but a negative family history does not eliminate the possibility of HH, because HH is almost always a recessive trait, and many otherwise healthy carriers are unaware of their genetic status. Moreover, *HFE* HH has low penetrance and is likely to be underdiagnosed.

Regardless of whether an individual is initially diagnosed with an inherited or acquired cause of iron overload, the possibility of other causes of iron overload should also be addressed. A common scenario is an individual with increased ferritin and/or transferrin saturation who uses excess alcohol and has liver disease [74]. In such individuals, it may be difficult to assess the amount of alcohol intake, the degree of total body iron overload, and the contribution of other factors such as *HFE* status. If there is concomitant cirrhosis and/or gastrointestinal bleeding, these estimations may be even more difficult (cirrhosis may affect the distribution of hepatic iron deposition; bleeding may decrease total body iron stores).

These cases require an individualized approach. The following may be helpful:

- ***HFE* testing** – Testing for *HFE* variants should be performed if there is any doubt about the possibility of a contribution of HH to excess iron stores. This includes all adults with iron overload not due to transfusions, and some individuals with transfusional iron overload, especially if the iron burden appears to be out of proportion to the number of transfusions administered. The importance of *HFE* testing was examined in a study involving 132

individuals with liver disease, in which 45 (34 percent) had *HFE* variants and 6 (5 percent) were homozygous for C282Y [75].

- Testing for *HFE* C282Y and H63D is relatively inexpensive; homozygosity for C282Y strongly supports a component of iron overload; compound heterozygosity for C282Y/H63D confirms a likely contribution of iron overload in a middle-aged adult; and negative results essentially eliminate the possibility of HH. The likelihood of iron overload with these and other genotypes is discussed separately. (See "*HFE* and other hemochromatosis genes".)

- Treatment for HH with phlebotomy is low-risk and can greatly reduce the risk of life-threatening organ toxicity. Individuals who are heterozygous for *HFE* C282Y or homozygous or heterozygous for H63D have a lower risk of iron overload but may require serial monitoring. (See "Management and prognosis of hereditary hemochromatosis".)

- **Serial monitoring** – Repeating iron studies after an acute illness has resolved, especially infection or inflammatory condition, may give a more accurate result and may reduce the need for unnecessary additional testing. However, this may not be possible in cases of chronic inflammatory conditions such as diabetes or metabolic syndrome.

- **Phlebotomy** – If there is doubt about the degree or cause of iron overload, therapeutic phlebotomy may be useful in establishing the cause. Significant iron overload in the absence of transfusion is strongly suggestive of a hereditary component. Most individuals with uncomplicated alcoholic liver disease have <4 grams of mobilizable iron, whereas individuals with symptomatic HH typically have ≥5 grams.

HFE testing is widely available. Listings of testing laboratories can be accessed online through the Genetic Testing Registry (www.ncbi.nlm.nih.gov/gtr/).

Interpretation of *HFE* genotypes, additional testing for rare HH variants in those with a strong suspicion of HH who test negative for C282Y and H63D, and appropriate management are discussed separately. (See "Management and prognosis of hereditary hemochromatosis" and "*HFE* and other hemochromatosis genes", section on 'Rare HFE variants' and "*HFE* and other hemochromatosis genes", section on 'Non-HFE hemochromatosis'.)

TREATMENT

The majority of individuals with iron overload should be treated to prevent end-organ damage. Rare exceptions may include those with only modest iron overload who would be unable or unwilling to tolerate therapy.

The major treatments for iron overload include phlebotomy for those without significant anemia and chelation therapy for those with anemia. In some cases, chelation therapy may be deferred until the underlying anemia is treated (eg, after hematopoietic stem cell transplantation [HSCT] for aplastic anemia). These subjects are discussed separately:

- **Phlebotomy** – (See "Thalassemia: Management after hematopoietic cell transplantation", section on 'Iron stores' and "Management and prognosis of hereditary hemochromatosis" and "Management and prognosis of hereditary hemochromatosis", section on 'Phlebotomy'.)

- **Exchange transfusions in sickle cell disease (SCD)** – (See "Red blood cell transfusion in sickle cell disease: Indications and transfusion techniques", section on 'Exchange blood transfusion'.)

- **Chelation therapy** – (See "Iron chelators: Choice of agent, dosing, and adverse effects" and "Transfusion in sickle cell disease: Management of complications including iron overload", section on 'Chelation therapy'.)

Individuals with iron overload should also be educated to avoid inadvertent iron intake (eg, from multivitamins containing iron) and to avoid hepatotoxic medications and alcohol. However, individuals with iron overload should follow a healthy diet and should not feel compelled to avoid red meat or other iron-containing foods. (See "Management and prognosis of hereditary hemochromatosis" and "Management and prognosis of hereditary hemochromatosis", section on 'Addressing concerns about dietary iron'.)

Blood transfusions should be administered as needed; however, unnecessary transfusions should be avoided. (See "Red blood cell transfusion in infants and children: Indications" and "Indications and hemoglobin thresholds for red blood cell transfusion in the adult".)

In some cases, it may be possible to reduce transfusions by using other methods to treat anemia. Examples include:

- Erythropoiesis-stimulating agents in renal failure (see "Treatment of anemia in nondialysis chronic kidney disease")
- Exchange transfusion in SCD (see "Red blood cell transfusion in sickle cell disease: Indications and transfusion techniques", section on 'Simple versus exchange transfusion')

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Hemochromatosis".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Hemochromatosis (The Basics)")
- Beyond the Basics topic (see "Patient education: Hereditary hemochromatosis (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Mechanisms and causes** – There are no physiologic mechanisms to eliminate excess iron from the body. Major causes of iron overload include (table 1):
  - Blood transfusions (typically >15 to 20)
  - Increased uptake of dietary iron due to:
    - Hereditary hemochromatosis (HH)
    - Ineffective erythropoiesis in beta thalassemia, sideroblastic anemia, or other inherited anemias
    - Liver disease, especially alcoholic liver disease and chronic hepatitis

(See 'Normal iron stores' above and 'Causes of iron overload' above.)

- **Clinical manifestations** – Clinically significant iron overload causes increased serum ferritin and transferrin saturation (TSAT). Excess iron produces reactive oxygen species that can cause tissue damage, inflammation, and fibrosis. The liver, heart, joints, skin, and endocrine organs are especially susceptible. (See 'Consequences of excess iron stores' above.)

- **Evaluation** – All patients with suspected iron overload require a thorough clinical evaluation, complete blood count (CBC), and iron studies including ferritin and TSAT. Liver function testing is often helpful. A low or normal serum ferritin or TSAT is helpful in excluding iron overload. Higher values are consistent with iron overload but are nonspecific, and additional testing is often indicated (algorithm 1). (See 'Sequence and interpretation of testing' above.)

- **Diagnosis** – Iron overload may be suspected by one or more of the following findings (see 'Diagnosis' above):

  - Increased serum ferritin (≥200 to 300 ng/mL [≥200 to 300 mcg/L] in males, ≥150 to 200 ng/mL [≥150 to 200 mcg/L] in females) in a patient without significant inflammation, and/or increased TSAT (≥45 percent in males; ≥40 percent in females). The increase in TSAT may precede ferritin. Rarely, an isolated increased TSAT may occur without overt iron overload or organ damage, especially in a younger adult, prompting close monitoring. (See 'CBC, LFTs, and iron studies' above.)

  - Iron overload by MRI (liver iron >3 mg per gram dry liver weight; cardiac T2* MRI <20 milliseconds) or tissue iron stain. (See 'Noninvasive imaging (MRI)' above and 'Liver biopsy' above.)

  - Normalization of the ferritin after five to six (or more) phlebotomies). (See 'Response to phlebotomy' above.)

- **Differential diagnosis** – The differential diagnosis of iron overload includes inflammatory conditions, liver disease, and malignancies (table 2). Extremely high ferritin may occur with hemophagocytic lymphohistiocytosis (HLH); HIV infection, especially with low CD4 count and opportunistic infection; and cancer, especially hematologic malignancies. (See 'Differential diagnosis' above.)

- **Post-diagnostic testing** – Total body iron burden is assessed by liver MRI or biopsy. Other evaluations depend on symptoms (table 3). The cause of iron overload should be

determined; there may be multiple causes. *HFE* testing is appropriate in all adults with iron overload not due to transfusions and some individuals with transfusional iron overload, especially if the iron burden appears to be out of proportion to the number of transfusions. (See 'Post-diagnostic testing' above and "Clinical manifestations and diagnosis of hereditary hemochromatosis".)

- **Testing family members** – Testing asymptomatic first-degree relatives of individuals with HH is addressed separately. (See "Management and prognosis of hereditary hemochromatosis", section on 'Testing and counseling first-degree relatives'.)

- **Management** – Phlebotomy is used in individuals without significant anemia. Chelation therapy is used for individuals with anemia. (See "Iron chelators: Choice of agent, dosing, and adverse effects" and "Thalassemia: Management after hematopoietic cell transplantation", section on 'Iron stores' and "Management and prognosis of hereditary hemochromatosis" and "Management and prognosis of hereditary hemochromatosis", section on 'Phlebotomy' and "Transfusion in sickle cell disease: Management of complications including iron overload", section on 'Chelation therapy'.)

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Topic 7157 Version 94.0

GRAPHICS

Causes of iron overload

Cause	Mechanism
Increased intake	
Transfusional overload (eg, in inherited bone marrow failure syndromes, hemolytic anemias, myelodysplastic syndrome, aplastic anemia)	Iatrogenic, used to treat severe anemia
Iron-loaded diet (eg, "African iron overload")	Dietary, from iron in barrels used to store homemade beer; may have genetic component
Repeated hemin infusions (eg, to treat acute intermittent porphyria)	Iatrogenic, used to treat acute porphyric attacks
Increased absorption (with normal intake)	
Hereditary hemochromatosis due to *HFE* mutation (eg, C282Y/C282Y; C282Y/H63D)	Reduced hepcidin
Hereditary hemochromatosis due to rare mutations (eg, ferroportin, hemojuvelin, hepcidin, ceruloplasmin)	Alterations in known regulators of intestinal iron absorption
Thalassemia major or intermedia	Ineffective erythropoiesis leading to suppression of hepcidin; transfusional iron overload may also contribute
Sideroblastic anemia (inherited or acquired)	Ineffective erythropoiesis leading to suppression of hepcidin
Inherited anemias (eg, CDA, DBA)	Ineffective erythropoiesis leading to suppression of hepcidin
Gestational alloimmune liver disease (GALD)*	Maternal alloantibody causing liver injury in utero
Chronic liver disease, especially alcoholic liver disease, chronic hepatitis, and non-alcoholic fatty liver disease (NAFLD)	Incompletely understood, possible reduced hepcidin production?

Refer to UpToDate content on iron overload, iron balance, and specific disorders for further details.

HFE: hereditary hemochromatosis gene; CDA: congenital dyserythropoietic anemia; DBA: Diamond-Blackfan anemia.

* Many cases of GALD were previously called neonatal hemochromatosis; however, the conditions are not synonymous.

Courtesy of Stan Schrier, MD.

Graphic 105365 Version 2.0

Causes of increased ferritin

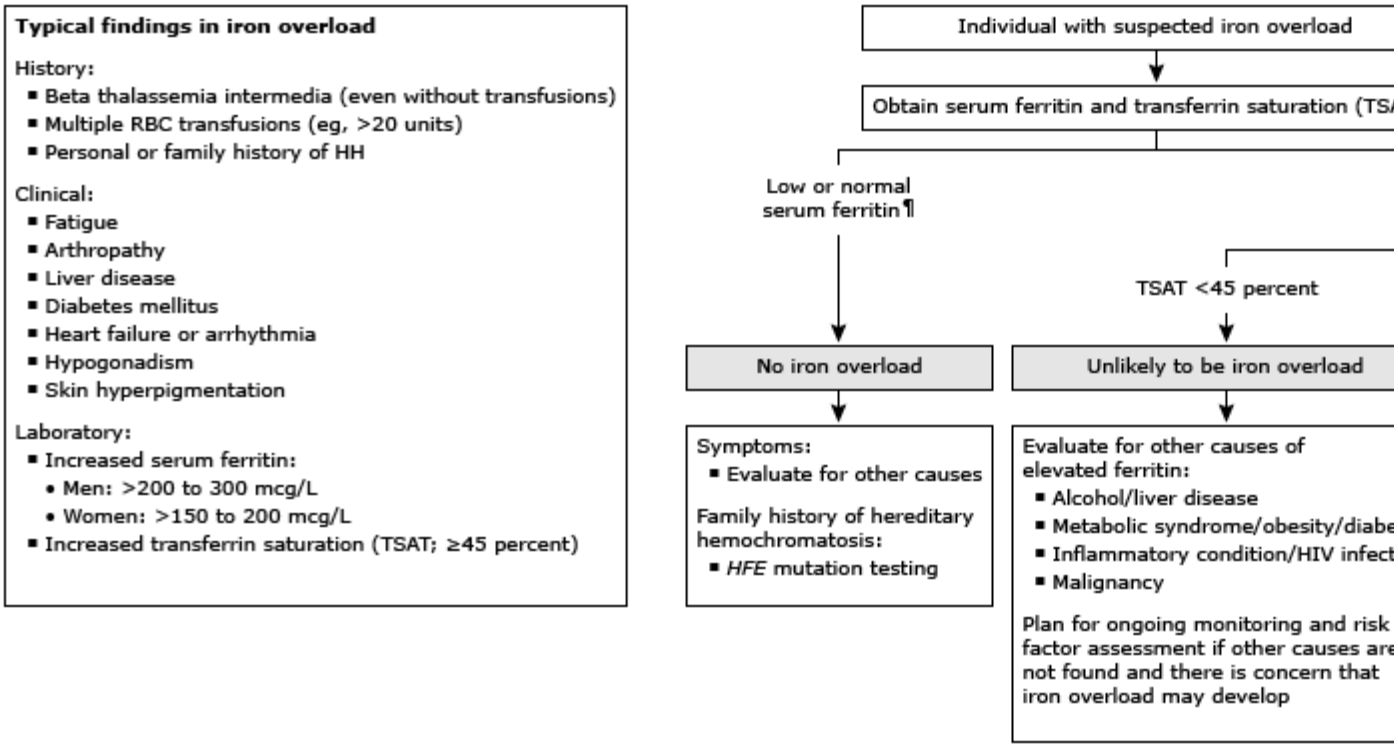
Condition (examples)	Pattern	Management implications
Iron overload ▪ Hereditary hemochromatosis ▪ Transfusional iron overload ▪ Ineffective erythropoiesis (eg, thalassemia)	Progressive/cumulative increase in ferritin over time, eventually causing organ damage if not treated. TSAT will be high (typical value >45%).	Close monitoring with iron removal once there is evidence of excess tissue deposition (from MRI or tissue biopsy) or the ferritin level exceeds a certain threshold (eg, >1000 ng/mL). Phlebotomy is often used in individuals without anemia; iron chelation is generally used for individuals with anemia.
Massive cell/tissue death ▪ HLH ▪ Cancer ▪ Liver failure	Rapid rise in ferritin to very high levels (eg, >3000 ng/mL), usually in the setting of acute illness with immune dysregulation. TSAT will not be increased (typical value <45%).	Aggressive therapy for the underlying condition is usually indicated. Ferritin level may be a useful marker of disease activity.
Inflammatory block ▪ Anemia of chronic disease/anemia of inflammation (ACD/AI, as in diabetes, cancer, chronic infection, or autoimmune disorders) ▪ Anemia of chronic kidney disease ▪ Chronic liver disease	Chronic, modest increase in ferritin (approximately two to three times normal). Ferritin is an acute phase reactant. TSAT will not be increased (typical value <45%).	May be helpful in distinguishing ACD/AI from iron deficiency, but ferritin by itself is a poor indicator of iron stores in the setting of chronic inflammation. A search for the cause may be indicated if not immediately apparent. Therapy is directed to the underlying condition.

Ferritin is a marker of iron stores, but it may also be elevated as an acute phase reactant or due to massive cell and tissue death, especially in the liver and in the setting of hemophagocytosis. The absolute ferritin level cannot be interpreted in isolation and should not be the sole basis for treatment decisions. The pattern of ferritin increase (progressive, acute/marked increase, or chronic mild elevation) as well as the patient's underlying condition must be incorporated in the evaluation.

TSAT: transferrin saturation; MRI: magnetic resonance imaging; HLH: hemophagocytic lymphohistiocytosis; ACD/AI: anemia of chronic disease/anemia of inflammation.

Graphic 115294 Version 2.0

Algorithm for evaluating suspected iron overload



This is a general approach and should not substitute for the judgment of the treating clinician. It presumes examination, and complete blood count (CBC). Refer to UpToDate for details of the evaluation. Other diagnc response to a course of therapeutic phlebotomy may be appropriate in some settings.

RBC: red blood cell; TSAT: transferrin saturation (serum iron ÷ TIBC × 100); HH: hereditary hemochromatosis magnetic resonance imaging; TIBC: total iron-binding capacity.

* Ideally two measurements are performed when the patient is not acutely ill, especially if results are borde

¶ The threshold for ferritin and TSAT above which to pursue additional testing depends on the patient's age number of transfusions received.

Δ Findings of a very high ferritin and TSAT may be sufficient to diagnose iron overload in some individuals (e transfusions). However, quantitation of iron stores remains useful for decisions about when to start and sto

◇ MRI is increasingly accepted as the best test. However, liver biopsy may be preferable in some settings (eg may be done in combination with cardiac MRI in some institutions. Cardiac MRI is important in many cases, erythropoiesis and transfusional iron overload, because hepatic and cardiac iron deposition may not be unif

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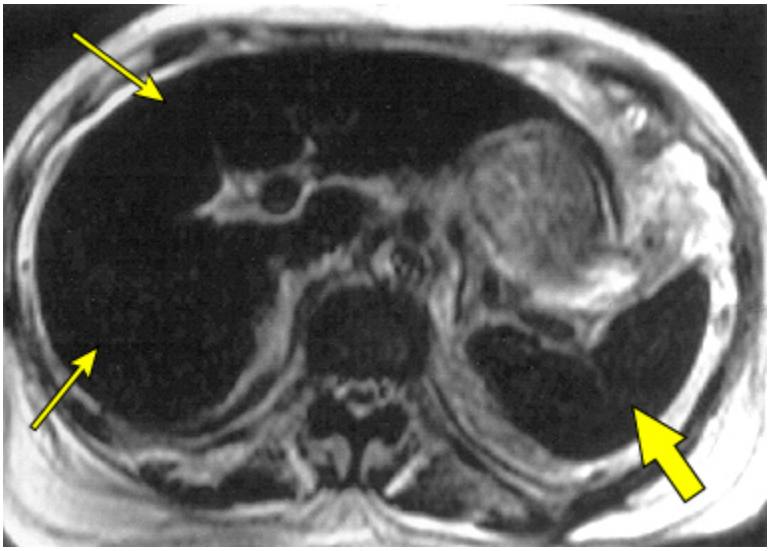
Graphic 111015 Version 2.0

Hemochromatosis on magnetic resonance imaging

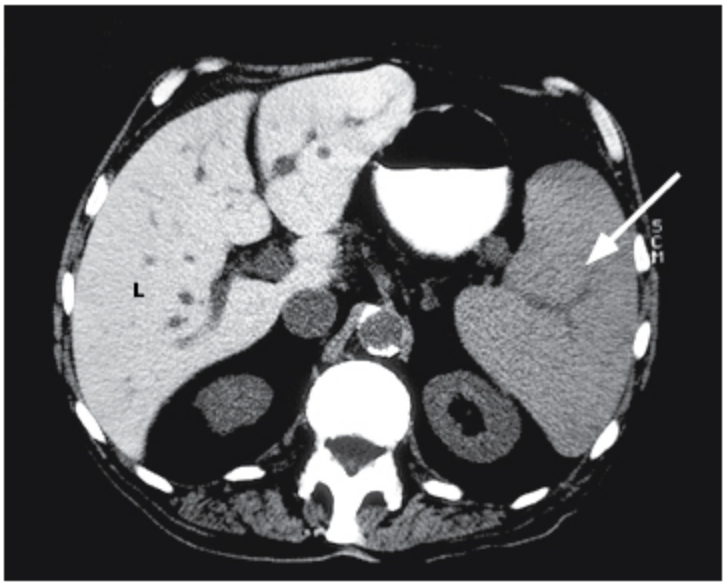


72-year-old female with hemochromatosis suggested by MRI. T1-weighted images show a black hypointense liver characteristic of iron overload (arrows) and a similar low intensity of the spleen (thick arrow).

Courtesy of Martina Morrin, MD.

Graphic 56593 Version 4.0

Hemochromatosis of the liver as evaluated by CT scanning

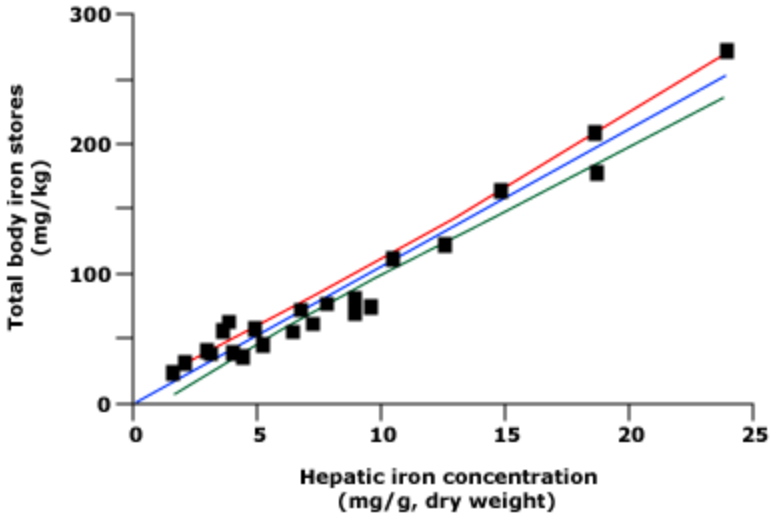


CT scan through the upper abdomen shows high attenuation throughout the liver (L), which normally has a similar attenuation to the spleen (white arrow). Other deposition diseases producing this appearance include amiodarone toxicity.

Courtesy of Jonathan Kruskal, MD.

Graphic 69367 Version 3.0

Correlation between hepatic iron concentration and total body iron stores in thalassemia major patients without cirrhosis

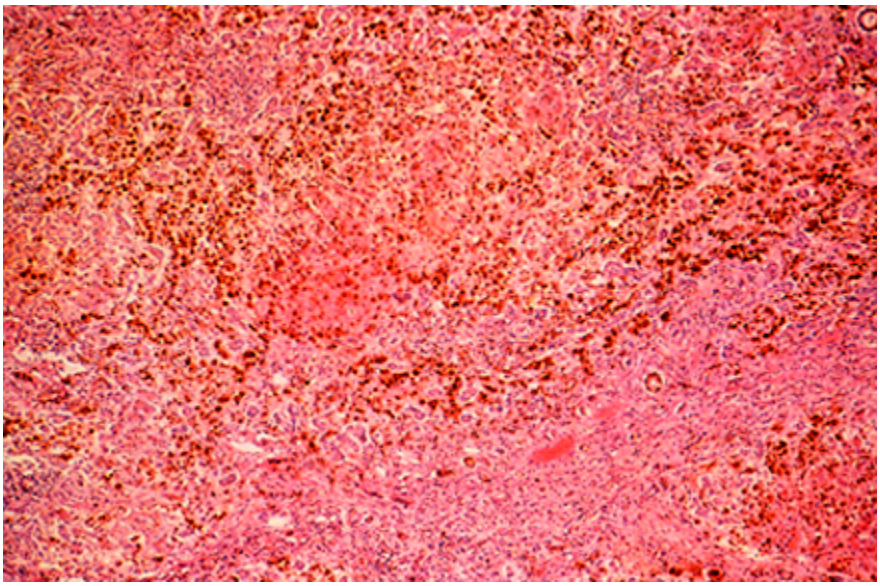


The correlation is shown for 25 patients with liver biopsy samples that had a dry weight of 1.0 mg or more. The regression line (middle blue line) and 95 percent confidence limits (upper red and lower green lines) are shown.

Adapted from: Angelucci E, Brittenham GM, McLaren CE, et al. Hepatic iron concentration and total body iron stores in thalassemia major. N Engl J Med 2000; 343:327.

Graphic 55632 Version 2.0

Liver biopsy in hereditary hemochromatosis (H and E staining)

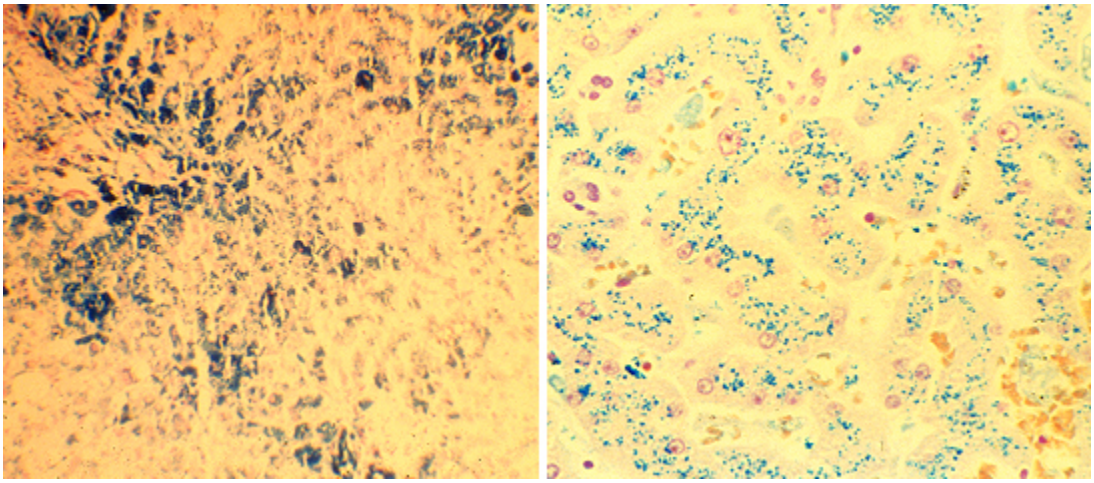


Low power view of a liver biopsy from a patient with hereditary hemochromatosis showing brown pigmentation of hepatocytes due to iron deposition (hematoxylin and eosin stain). The presence of iron can be confirmed by Perls' Prussian blue stain.

Courtesy of Robert Odze, MD.

Graphic 70985 Version 2.0

Liver biopsy in hereditary hemochromatosis (iron stain)



Perls' Prussian blue stain of a liver biopsy from a patient with hereditary hemochromatosis. Left panel: Low power view shows intense iron staining of hepatocytes. The blue-stained iron deposits typically start at the periphery of the liver lobule and extend centrally. Right panel: High power view shows intense iron staining (in blue) of hepatocytes.

Courtesy of Stanley L Schrier, MD.

Graphic 50096 Version 3.0

Suggested evaluation for organ damage based on signs and symptoms in patients with iron overload

Abnormality	Indicated evaluations
Weakness, fatigue, malaise	Evaluation for liver, endocrinologic, and cardiac disorders and for anemia
Elevated hepatic enzyme concentrations	Evaluation for hepatitis B, hepatitis C, and other liver diseases (such as drug-related hepatopathy, alpha-1-antitrypsin deficiency, or metastatic cancer); liver biopsy
Hepatomegaly or hepatic pain	Evaluation for hepatitis B, hepatitis C, and other liver diseases; liver biopsy; measurement of alpha-fetoprotein concentration; hepatic imaging procedures; liver MRI*
Arthralgias or arthropathy	Radiography of affected joints; evaluation for other arthropathies
Thyroid dysfunction	Measurement of thyroid-stimulating hormone, thyroxine, and antithyroid antibody concentration if hypothyroid
Impotence, premature amenorrhea	Measurement of luteinizing hormone, follicle-stimulating hormone, and sex hormone concentrations; CT of anterior pituitary to evaluate for possible pituitary tumor
Cardiac symptoms	Electrocardiography; echocardiographic assessment of ventricular ejection fraction and exercise tolerance; cardiac MRI*
Hyperglycemia or diabetes mellitus	Fasting serum glucose and glycosylated hemoglobin levels

Refer to UpToDate for the approach to the evaluation.

MRI: magnetic resonance imaging; CT: computed tomography.

* Combined liver and heart MRI is available in some institutions.

Adapted from: Barton JC, McDonnell SM, Adams PC. Management of hemochromatosis. Hemochromatosis Management Working Group. Ann Intern Med 1998; 129:932.

Graphic 60117 Version 8.0

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