Management and prognosis of hereditary hemochromatosis

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INTRODUCTION

Hereditary hemochromatosis (HH, genetic hemochromatosis) is an inherited disorder most commonly caused by biallelic C282Y point mutations in the *HFE* gene, or, less commonly, other genes related to iron regulation. These disorders result in increased intestinal iron absorption that can eventually cause iron overload and serious tissue damage.

This topic describes our approach to the management of HH and its prognosis with and without treatment.

Related aspects of care are discussed in detail separately.

- Clinical features and diagnosis – (See "Clinical manifestations and diagnosis of hereditary hemochromatosis".)
- Genetics – (See "*HFE* and other hemochromatosis genes".)
- *HFE* genetic test interpretation – (See "Gene test interpretation: *HFE* (hereditary hemochromatosis gene)".)
- Other causes of iron overload – (See "Approach to the patient with suspected iron overload".)

PRETREATMENT TESTING

Iron stores — Many patients with HH will have had an assessment of iron stores and tissue iron by the time of diagnosis. (See "Clinical manifestations and diagnosis of hereditary hemochromatosis", section on 'Diagnostic evaluation'.)

For those who have not, we obtain the following testing, as illustrated in the flowchart (algorithm 1):

- Serum ferritin (repeat if the result was borderline or if the individual was ill at the time of initial testing, since ferritin is an acute phase reactant).
- Magnetic resonance imaging (MRI) of the liver or liver biopsy, for individuals with one or more of the following:
  - Elevated transaminases
  - Hepatomegaly or findings suggestive of liver disease (ascites, skeletal muscle wasting)
  - Ferritin >1000 ng/mL
- Cardiac MRI for individuals with one or more of the following:
  - Signs of heart failure on history (eg, exertional dyspnea), examination (eg, rales, peripheral edema), or echocardiography
  - Unexplained conduction abnormalities on electrocardiography
  - Significant liver iron deposition (some cases)

In some institutions, combined liver and heart MRI are done as a single imaging test. It is important to discuss with the local radiologist to optimize the imaging options.

In selected individuals, biopsy may be done instead of MRI. Examples include individuals who undergo liver biopsy to evaluate for other causes of liver disease or endomyocardial biopsy to evaluate for other causes of heart failure. Biopsies are invasive and the associated risks and benefits should be discussed. (See "Approach to the patient with suspected iron overload", section on 'Other tests for selected individuals'.)

In individuals with significant concern for iron overload, a trial of therapeutic phlebotomy can be used as a means to both reduce body iron load and determine the degree of iron overload. Phlebotomy-mobilized iron, derived from the number of phlebotomies required to deplete iron stores, can serve as a surrogate measure of body iron overload and thereby guide future management [1].

***HFE* genetic testing** — Most individuals diagnosed with HH will have already had genetic testing for the most commonly implicated *HFE* variant, C282Y. Many will have had testing for the

H63D variant. Most clinical laboratories test for these two variants; some do more extensive testing.

We perform testing for C282Y and H63D *HFE* mutations if not done previously, since there are implications for testing and management of first-degree relatives. (See "Clinical manifestations and diagnosis of hereditary hemochromatosis", section on 'HFE genetic testing'.)

If initial *HFE* testing is negative, more extensive testing (for *HFE* variants that were not tested previously or for pathogenic variants in other iron regulatory genes) is appropriate for individuals with significant iron overload that is otherwise unexplained (not due to thalassemia or transfusional iron overload).

The sequence of testing (gene panel versus individual gene testing) depends on available resources and whether a specific variant has already been identified in the family. Other HH-associated genes are discussed separately. (See "*HFE* and other hemochromatosis genes", section on 'Non-HFE hemochromatosis'.)

In contrast, *HFE* testing is generally not done in unselected populations without iron overload who do not have a family history of HH. (See "*HFE* and other hemochromatosis genes", section on 'Role of population screening'.)

Other testing — Other testing for signs of organ involvement depend on the severity of iron overload and the presence of symptoms.

The following testing is reasonable in individuals with evidence of iron overload (ferritin >1000 ng/mL or tissue iron >3 mg [3000 mcg] iron [Fe] per gram of dry weight):

- Liver function tests, including transaminases, prothrombin time with international normalized ratio (PT/INR), and albumin (transaminases are also done on patients with HH who have any ferritin elevation, especially if other cofactors are present such as high body mass index or dyslipidemia)
- Testosterone level in males with low libido or reduced sexual function
- Bone densitometry (dual energy x-ray absorptiometry [DEXA] scan)
- Thyroid function (TSH, total thyroxine [T4] plus triiodothyronine [T3] uptake, or free T4)

Endocrine testing is presented separately (see "Diagnostic testing for hypopituitarism" and "Screening for osteoporosis in postmenopausal women and men"):

OVERVIEW OF MANAGEMENT APPROACH

The goal of treatment is to prevent organ dysfunction from excess iron and/or to improve organ function if it has already been affected. Manifestations of organ damage are summarized in the table (table 1).

- Individuals with iron overload (or at risk for iron overload based on high ferritin) are treated with phlebotomy (algorithm 1). Those who cannot tolerate phlebotomy (eg, due to concomitant anemia) may be treated with an iron chelator instead if iron overload is significant. (See 'People with organ injury from excess iron' below and 'People with isolated high ferritin and/or TSAT' below.)

- Individuals without iron overload who have an HH genotype (homozygosity for *HFE* C282Y or compound heterozygosity for C282Y and another *HFE* variant) can be monitored regularly. (See 'HFE C282Y homozygous individuals without iron overload' below.)

- Individuals who are heterozygous for C282Y or other *HFE* variants generally do **not** require phlebotomy. All individuals (including heterozygous individuals) should have attention paid to other contributing factors such as alcohol use if relevant. (See 'Heterozygous individuals' below.)

Our approach is largely consistent with that of other experts, including a 2019 practice guideline from the American College of Gastroenterology, a 2017 practice guideline from the British Society for Haematology, a 2011 practice guideline from the American Association for the Study of Liver Diseases, and a 2022 guideline from the European Association for the Study of the Liver [2-7]. Links to external guidelines are presented separately. (See 'Society guideline links' below.)

People with organ injury from excess iron — The need for rapid and aggressive intervention is greatest in individuals who have developed organ injury from excess tissue iron deposition. These individuals should initiate a program of regular phlebotomy without delay. The schedule and procedure are described below. (See 'Procedure, schedule, and target ferritin level' below.)

Organ injury (or significant iron deposition likely to cause injury) is inferred from one or more of the following findings:

- Significant liver iron (eg, >3 mg [>3000 mcg] per gram of dry weight) by liver biopsy or magnetic resonance imaging (MRI); liver fibrosis by transient elastography (TE; eg, FibroScan), or increased liver function tests without another cause. Phlebotomy-mobilized iron is also a useful surrogate, with 3.5 g being equivalent to a liver iron content of approximately 4400 mcg per gram of dry weight [8].

- Cardiac iron <20 msec on MRI, reduced ejection fraction on echocardiography, or cardiac iron on endomyocardial biopsy. Endomyocardial biopsy is not commonly used for evaluating cardiac iron but may be performed to evaluate unexplained cardiomyopathy.

- Ferritin >1000 ng/mL (>2247 pmol/L) and biallelic *HFE* variants (or pathogenic variants in other genes strongly associated with HH).

Many individuals with HH who have organ injury from iron overload also have contributing comorbidities that may exacerbate symptoms and the risks of complications (eg, excess alcohol, viral hepatitis). Addressing these is an important component of management. In some cases, organ dysfunction may be due exclusively (or preferentially) to a comorbidity such as excess alcohol rather than to iron overload. This was illustrated in a case report of a premenopausal woman who was homozygous for *HFE* C282Y and had a ferritin level of 1000 ng/mL (2247 pmol/L); she was initially treated with phlebotomy for several years until it was determined that her ferritin elevation was likely due to excess alcohol use rather than HH [9]. (See 'Liver disease' below.)

Additional interventions directed at specific sites of organ toxicity, including screening for hepatocellular cancer in those with cirrhosis, are discussed separately. (See 'Screening for HCC and other complications' below.)

People with isolated high ferritin and/or TSAT — Some individuals with an HH genotype (biallelic *HFE* variants or pathogenic variants in other genes strongly associated with HH) and a high ferritin will have evidence of organ iron deposition on MRI or liver biopsy.

However, there may be cases in which organ iron deposition has not yet occurred (cases in which the liver MRI or liver biopsy do not show increased iron but the ferritin is increased). The decision to intervene is more challenging in such individuals because it is possible that the increased ferritin is due to another condition such as alcoholic liver disease and that clinically significant iron overload will not occur.

Studies have suggested that individuals with a positive family history of iron overload are likely to have a greater risk of developing organ injury than individuals with a negative family history who are found to have a high ferritin incidentally (eg, when tested as part of a population screening program, which we do not recommend for the general population) [10-12]. The reasons are not well understood; individuals with a positive family history may share other genetic or environmental exposures that contribute to iron overload. (See "Clinical manifestations and diagnosis of hereditary hemochromatosis", section on 'Pathophysiology'.)

Phlebotomy and expectant management are both options for individuals with an HH genotype who have an isolated high ferritin without significant iron on MRI or liver biopsy (algorithm 1):

- **Phlebotomy** – If the risk of progression to organ injury is suspected to be increased due to a persistent ferritin elevation above normal, patients are generally treated with phlebotomy, although some may reasonably choose close monitoring of the ferritin level to determine whether it is increasing. Controlled phlebotomy in this circumstance allows determination of phlebotomy-mobilized iron. In general, we tend to recommend a trial of phlebotomy in younger patients without significant comorbidity, since there is little risk, and determination of phlebotomy-mobilized iron can be useful to determine need for maintenance phlebotomy. Expert groups vary in their opinion regarding a specific ferritin threshold at which phlebotomy is clearly indicated, as discussed below. (See 'Phlebotomy' below.)

- **Expectant management** – If the risk of progression is suspected to be low (eg, negative family history, ferritin in normal range, and normal liver function tests), patients can be monitored annually, reserving phlebotomy for those who have a progressively increasing ferritin level and/or evidence of disease progression.

  Monitoring for individuals who are being managed expectantly includes:

  - Physical evaluation of the skin, heart, liver, joints, and endocrine organs (eg, hypothyroidism, hypogonadism, diabetes)
  - Yearly iron studies (iron, total iron binding capacity, ferritin, and calculation of transferrin saturation [TSAT])
  - Additional studies (eg, liver function testing, echocardiography) if/when disease progression is evident (eg, if ferritin continues to rise)

  The monitoring interval may be extended if the iron studies results remain stable and other testing remains negative.

  For females who stop having menstrual periods (postmenopausal or another reason), increased scrutiny may be appropriate.

***HFE* C282Y homozygous individuals without iron overload** — The TSAT may be elevated in this group, but a normal serum ferritin generally indicates no increase in body iron stores. Some of these individuals may develop iron overload over time, and routine monitoring of iron studies, particularly serum ferritin, is recommended at a minimum frequency of every two to three years.

Heterozygous individuals — Iron overload is extremely rare in individuals who are heterozygous for *HFE* C282Y or H63D. However, a finding of a moderately increased ferritin level in heterozygous individuals (above normal but <1000 ng/mL) is relatively common. There is often concomitant alcoholic or nonalcoholic liver disease.

Management in these individuals is not well established, and we individualize our approach depending on their clinical status and presence of comorbidities that could contribute to (or be caused by) abnormal iron studies. If we are unsure of the degree of iron overload, we often obtain an MRI study of the liver or ultrasound-based hepatic elastography to determine the presence of iron deposition and/or fibrosis. Alternatively, liver biopsy can be performed. (See "Noninvasive assessment of hepatic fibrosis: Ultrasound-based elastography" and "Approach to the patient with suspected iron overload", section on 'Noninvasive imaging (MRI)'.)

- For individuals with evidence of serious iron overload (eg, TSAT >45 percent; ferritin >1000 ng/mL; evidence of tissue iron overload on MRI or other imaging or liver biopsy), we question whether they are in fact heterozygotes rather than compound heterozygotes for a common plus a rare *HFE* variant or affected by a pathogenic variant in a non-*HFE* gene. We confirm the original genotyping and, if accurate, test for less common *HFE* variants or test non-*HFE* genes that control iron absorption (see "*HFE* and other hemochromatosis genes"). This is especially true for families in which more than one member is affected. Identifying another relevant disease variant confirms the diagnosis of HH and the value of treating the patient as needed (eg, with phlebotomy), and it allows accurate testing of first-degree relatives.

- For those with a high ferritin but <1000 ng/mL and no sign of tissue iron deposition on MRI, a period of observation may be appropriate, as described above, to determine the trend in ferritin and TSAT. (See 'People with isolated high ferritin and/or TSAT' above.)

- For those with evidence of alcoholic or nonalcoholic liver disease, we counsel abstinence from alcohol use, particularly while the patient is being treated. If they have other liver disease, efforts for appropriate treatment should be pursued, particularly in patients who have nonalcoholic steatohepatitis, where fatty liver and iron deposition can lead to progressive liver disease. (See 'Liver disease' below.)

IRON REMOVAL

Removing excess iron, typically by phlebotomy, is the mainstay of treatment for individuals with HH who have iron overload.

Phlebotomy

Indications and contraindications — Therapeutic phlebotomy is the preferred approach to removing iron in individuals with HH because it is highly effective and relatively devoid of toxicities, as long as the patient is not severely anemic.

Therapeutic phlebotomy is appropriate for individuals with an HH genotype (homozygosity for *HFE* C282Y or variants in other genes strongly associated with HH) and iron overload, as manifested by one or more of the following:

- Serum ferritin >300 ng/mL in males or >200 ng/mL in females, especially if ≥1000 ng/mL (≥2247 pmol/L)
- Evidence of tissue injury (eg, increased hepatic transaminase levels, reduced hormone levels, reduced cardiac ejection fraction)
- Increased tissue iron by magnetic resonance imaging (MRI), other imaging study, or tissue biopsy

This approach is consistent with several practice guidelines, although expert groups vary in their opinion regarding a specific ferritin threshold at which phlebotomy is clearly indicated [6,7,13-15].

In contrast, phlebotomy is not used in individuals who are asymptomatic with normal serum ferritin levels and no tissue iron on MRI, regardless of their *HFE* genotype. A lack of iron on MRI (or other testing such as liver biopsy, if performed) indicates that tissue iron has not accumulated. A large proportion of individuals who have an *HFE* variant (including C282Y) will never develop iron overload, and there is no reason to subject these individuals to phlebotomy unnecessarily.

Possible contraindications to phlebotomy are relatively limited and include anemia or hemodynamic compromise that would make the shift in blood volume difficult to tolerate, or limited life expectancy due to other diseases. However, phlebotomy should not be withheld based upon advanced age alone or in patients who are asymptomatic but have iron studies (or other evidence) consistent with iron overload.

For individuals who cannot tolerate phlebotomy, other options may include a more limited phlebotomy schedule or volume, erythrocytapheresis, or iron chelation. (See 'Alternatives to phlebotomy' below.)

Evidence for efficacy — The efficacy of phlebotomy has not been evaluated in randomized trials, but numerous observational studies and clinical experience have consistently demonstrated improvements in many parameters including life expectancy [16]. The table lists outcomes that are expected to be improved with phlebotomy rather than symptomatic treatment (table 2). The following illustrate some of the results from larger studies:

- **Survival** – A study from 1976 compared outcomes in 85 individuals with HH who were treated with phlebotomy compared with 26 who were not treated [17]. Compared with untreated patients, those who were treated had a higher survival rate at 5 years (18 versus 66 percent) and at 10 years (6 versus 32 percent). The benefit persisted on covariate analysis.

  A study from 1996 evaluated outcomes in a cohort of 251 individuals with HH with a mean age of 46 years who were followed for a mean of 14 years [18]. Cumulative survival at 5, 10, and 15 years was 93, 77, and 62 percent, respectively. These values were lower than population controls; however, when individuals with cirrhosis were censored from the analysis, survival was similar to the general population. For those who had adequate iron removal by phlebotomy, a requirement for fewer than 80 phlebotomy procedures was associated with a better survival rate than requiring >80 phlebotomies, suggesting an association of greater iron burden with worse survival despite treatment. Survival improved in patients treated later in the study (eg, between 1970 and 1991 versus 1947 to 1969).

  A study from 2001 evaluated outcomes in 179 patients with HH who were followed for a median of 8.5 years [19]. Those who were adequately treated with phlebotomy (median iron removal, 14 g) had a higher survival rate than those inadequately treated (survival rate, 16 versus 4.5 years).

  Additional details regarding prognosis are discussed below. (See 'Prognosis' below.)

- **Hepatic fibrosis** – In a study involving individuals with an HH genotype who were followed longitudinally, the fibrosis score decreased in all 20 who had at least one biopsy before and after treatment [20]. Other observational studies have demonstrated improvement or resolution of esophageal varices with treatment [21].

- **Cardiomyopathy** – Several case reports described major improvements in cardiac function with iron removal by phlebotomy or chelation therapy [22-24]. However, severe cardiomyopathy may not improve [25]. (See 'Prognosis' below.)

Other studies have found that hypogonadism improves in males, although this benefit may be limited to younger individuals [25-28]. In contrast, arthritis and diabetes mellitus do not appear to improve in the same way as other complications [29,30]. (See "Clinical manifestations and diagnosis of hereditary hemochromatosis", section on 'Clinical manifestations' and "Arthritis and bone disease associated with hereditary hemochromatosis", section on 'Treatment'.)

Procedure, schedule, and target ferritin level

- **Procedure** – Therapeutic phlebotomy is essentially the same procedure as blood donation, with removal of one unit of blood over a period of two or more hours. It can be performed in a medical office, blood bank or other hospital facility, or at the patient's home by a trained phlebotomist.

  Some individuals, such as those with the following, may better tolerate removal of one-half of a unit of blood per session instead of a whole unit of blood [31,32].

  - Lower body weight (eg, weight <50 kg)
  - Older age
  - Cardiopulmonary disease
  - Ferroportin mutations

  Patients should be encouraged to maintain hydration and avoid vigorous exercise within 24 hours of phlebotomy. Symptoms of hypovolemia are more likely in patients who have a hemoglobin concentration <12 g/dL (hematocrit <36 percent) prior to phlebotomy. Patients may become mildly anemic during intensive phlebotomy. Storage iron will be mobilized to generate new red blood cells (RBCs). Reticulocytosis may be used as evidence of ongoing erythropoiesis and can be monitored periodically (eg, monthly), especially if the hemoglobin level starts to decline.

- **Schedule** – The optimal schedule for phlebotomies has not been established, and the frequency can be tailored to the patient's clinical status and hemoglobin level.

  - **Children** – Children, particularly those with non-*HFE* hemochromatosis variants, may sometimes also need phlebotomy. (See "*HFE* and other hemochromatosis genes", section on 'Non-HFE hemochromatosis'.)

    In general, 5 to 10 mL of blood per kg of body weight is removed at each procedure, initially every week and then less frequently as the serum ferritin decreases to within the target range [33].

  - **Adults** – Most experts recommend once-weekly phlebotomy initially [2].

- More frequent phlebotomies are appropriate for those with more severe iron overload, if tolerated. Patients with signs of organ injury should deplete excess tissue iron as rapidly as possible without causing undue burdens and symptoms. Twice-weekly phlebotomies may be possible as long as the hemoglobin level remains in a safe range (eg, >11 g/dL) and the patient tolerates the procedure hemodynamically.

  In one study, patients who could not be depleted of excess iron over a period of 18 months had a worse prognosis than those who could be depleted in <18 months, but this may have been a surrogate for greater degree of organ injury rather than evidence that the pace of phlebotomy affects outcomes [34].

- Less frequent procedures or temporary interruption of the schedule can be used for individuals who have less severe iron overload, those who develop anemia, and/or those for whom the procedure is less well tolerated. Some experts also temporarily interrupt the schedule if the hemoglobin or hematocrit falls by more than 20 percent from prior values.

  Patients should not be unduly worried about missing or postponing a phlebotomy appointment, if necessary, especially if their tissue iron has been mostly depleted, and some patients may reasonably extend the phlebotomies to once every two weeks. It is important to maintain a regular schedule and educate the patient about the need to fully deplete the excess iron, followed by maintenance phlebotomies as needed. (See 'Maintenance' below.)

- **Monitoring** – In addition to monitoring the patient's clinical status, the following laboratory tests are monitored periodically [6,7,13]:

  - Complete blood count (CBC), hemoglobin, or hematocrit every month or at the time of each phlebotomy.

  - Serum ferritin every month until the desired level is reached; the frequency can be increased (eg, to every two weeks) as the ferritin level gets closer to the desired target.

  In contrast with ferritin, monitoring TSAT is **not** recommended by guidelines, due to known fluctuations and the lack of evidence-based target levels. TSAT can remain increased even with serum ferritin levels are consistently within the target range.

  These intervals vary slightly among clinicians and can be adjusted as needed [35].

- **Duration/number** – The total number of phlebotomies needed to remove the excess tissue iron depends on the degree of accumulated iron. Each 500 mL unit of blood donated contains 200 to 250 mg of iron. Thus, for an individual with 10 grams of excess iron, 40 to 50 phlebotomies (approximately one per week for one year) would be expected to fully deplete the excess iron. This is significantly less than the 70 to 100 phlebotomies that were often required to remove the enormous iron stores in patients who presented with severe symptoms in the era before *HFE* testing. In a series of 40 newly diagnosed patients who were seen between 1990 and 1995, removal of approximately 30 units of blood (equivalent to approximately 7.5 g of iron) was required to normalize body iron stores (defined as a serum ferritin concentration <50 ng/mL and TSAT <50 percent) [36].

  Despite the correlation with the number of phlebotomies, the initial serum ferritin level or hepatic iron content is not entirely accurate in predicting the phlebotomy requirement [37]. Thus, while an estimate can be calculated to help inform the patient of what to expect, in practice the number and frequency is adjusted over time. The hemoglobin and ferritin values generally become available after the phlebotomy procedure has started and are used to determine the following week's procedure.

- **Target ferritin and other laboratory parameters** – Phlebotomy should continue until iron stores have been reduced, typically assessed by the serum ferritin level. There may be some variation among experts on when this point has been reached (ie, whether it is necessary to induce iron deficiency or merely to deplete excess iron stores).

  The 2011 guideline from the American Association for the Study of Liver Diseases, a 2022 guideline from the European Association for the Study of the Liver, and many experts use a target ferritin level in the low normal range [3,13,38]. This is variously defined as approximately 50 ng/mL (112 pmol/L); or between 50 and 150 ng/mL (112 and 137 pmol/L).

  Any of these approaches is reasonable, provided the patient has ongoing monitoring and maintenance phlebotomy to keep the ferritin near the target level. There is some evidence that iron absorption increases as the ferritin level enters the iron-deficient range with exacerbation of hepcidin deficiency, and thus it is not necessary or advisable to completely eliminate all iron stores [39].

Maintenance — Iron generally reaccumulates over time due to ongoing absorption from food. Maintenance phlebotomy (periodic phlebotomy performed after the target ferritin level has been reached) is used to prevent reaccumulation in most individuals.

We typically check the CBC and ferritin level at approximately six months after completion of phlebotomy. If the ferritin level has increased and the increase is interpreted to be due to iron reaccumulation (provided there is not another explanation such as an intercurrent illness), we perform maintenance phlebotomies. Typically, removal of one unit of blood approximately three to six times per year is required (approximately once every two to four months). We target a ferritin level in the low normal range (between 50 and 150 ng/mL). More frequent phlebotomies may be needed for certain individuals who have greater iron absorption; less frequent procedures may be reasonable for those with less accumulation or for whom the procedure is especially burdensome.

If significant iron reaccumulation occurs (eg, if the individual is not adherent with maintenance phlebotomies and/or the ferritin is >500 ng/mL), we perform more intensive phlebotomies as done for initial treatment. (See 'Procedure, schedule, and target ferritin level' above.)

In older individuals, it is prudent to take note of a decrease in the requirement for maintenance phlebotomies, as this could indicate another source of iron loss that requires investigation such as gastrointestinal or urinary blood loss. All individuals should adhere to general population guidelines for colon cancer screening (or more intensive screening, if indicated, for those with higher than average baseline risk) [40]. (See "Causes and diagnosis of iron deficiency and iron deficiency anemia in adults", section on 'Search for source of blood and iron loss' and "Screening for colorectal cancer: Strategies in patients at average risk".)

Donation of phlebotomized blood — Many patients would prefer that phlebotomized blood be added to the general blood donation pool to be used for transfusion. HH does not affect RBCs adversely; the iron content of the cells is likely to be very good.

In some centers, blood removed during therapeutic phlebotomy is donated into the general donor pool, provided pretransfusion testing does not identify another reason for exclusion. These programs may be referred to as "hemochromatosis donor programs" or "hemochromatosis phlebotomy programs"; they typically perform phlebotomy without cost to the patient and use the blood in their transfusion service.

The European Association for the Study of the Liver 2022 guidelines explicitly favor this option [7].

However, some regulatory agencies may prohibit the use of blood from individuals with HH, as discussed separately. (See "Blood donor screening: Overview of recipient and donor protections", section on 'Hereditary hemochromatosis'.)

Alternatives to phlebotomy — Other options are available for the rare individual who cannot tolerate phlebotomy. These generally are not used for individuals with isolated ferritin elevations below 1000 ng/mL because the adverse effects are likely to outweigh the benefits.

- **Erythrocytapheresis** – Erythrocytapheresis is a form of therapeutic apheresis in which RBCs are removed in an isovolemic manner and the patient's plasma is returned in a closed circuit. This procedure requires specialized expertise and equipment and is not commonly performed in HH. (See "Therapeutic apheresis (plasma exchange or cytapheresis): Indications and technology", section on 'Common uses of therapeutic cytapheresis'.)

- **Iron chelation** – Iron chelation involves administration of an oral or parenteral iron-chelating agent. This approach is commonly used in individuals with hemoglobinopathies such as sickle cell disease or thalassemia that cause both anemia and iron overload. Iron chelation is not commonly used in HH but has been reported [24,41,42]. (See "Iron chelators: Choice of agent, dosing, and adverse effects".)

  Use of chelation has also been reported in individuals with aceruloplasminemia, for whom phlebotomy may not be effective in promoting release of iron from body stores [43,44]. (See "*HFE* and other hemochromatosis genes", section on 'Ferroportin (SLC40A1; FPN1)' and "Bradykinetic movement disorders in children", section on 'Neurodegeneration with brain iron accumulation'.)

TREATMENT AND PREVENTION OF COMORBIDITIES

In many cases, organ dysfunction can be reversed with removal of iron. However, patients may require additional treatments to manage organ injury.

Liver disease — Liver chemistry abnormalities are common in the general population, especially mild to moderate elevation of the hepatic transaminases [45]. In individuals with HH, elevated transaminases may be due to excess iron, but it is important to eliminate the possibility of other contributing factors, especially alcohol, drug-induced hepatic injury, viral hepatitis, and nonalcoholic fatty liver disease. This evaluation is discussed separately. (See "Approach to the patient with abnormal liver biochemical and function tests", section on 'Elevated serum aminotransferases'.)

For individuals with hepatitis C virus infection and iron overload, we typically treat the hepatitis C virus infection first since it may be contributing to ferritin elevation. (See "Overview of the management of chronic hepatitis C virus infection".)

Limiting alcohol — Alcohol can be hepatotoxic with intake as low as 30 grams or more per day (equivalent to approximately two standard mixed drinks, 24 ounces of beer, or 10 ounces of wine). Alcohol content of these and other drinks is summarized in the figure (figure 1). However, many individuals with this level of intake will not develop serious liver disease. More alcohol confers greater risk, but the correlation with liver disease is not linear. Further, alcohol inhibits hepcidin and thus can exacerbate iron overload in individuals with HH [46]. (See "Clinical manifestations and diagnosis of alcohol-associated fatty liver disease and cirrhosis".)

Observational studies have shown higher prevalence of cirrhosis and in some cases high incidence of hepatocellular cancer (HCC) in individuals with HH who consume alcohol [47,48]. Iron overload and alcohol may have an additive or synergistic effect on the liver. Limiting alcohol is especially important until excess iron has been removed. Following iron removal, it may be possible to consume alcohol on a limited basis (not more than one to two drinks per day). (See "Cardiovascular benefits and risks of moderate alcohol consumption", section on 'Advice to patients regarding alcohol use'.)

Screening for HCC and other complications — Patients with HH and advanced hepatic fibrosis (stage 3 or stage 4 [cirrhosis]) are at risk for HCC and should undergo surveillance on a periodic basis. Surveillance guidelines are discussed separately. The details of HCC screening and interventions appropriate for individuals with cirrhosis are discussed separately. (See "Surveillance for hepatocellular carcinoma in adults" and "Cirrhosis in adults: Overview of complications, general management, and prognosis".)

Liver transplantation — Individuals with HH-associated cirrhosis or HCC can undergo liver transplantation if indicated. (See "Liver transplantation in adults: Patient selection and pretransplantation evaluation".)

Outcomes from available series include the following:

- A 2023 series of 479 individuals with HH who underwent liver transplantation reported that survival was similar to propensity matched controls with other chronic liver diseases (one-year survival 89 percent, 95% CI 85-91 percent; five-year survival 75 percent, 95% CI 73-81 percent) [49]. The leading causes of death post-transplant were cancer (26 percent) and sepsis (24 percent).

- In a 2007 series of 177 patents with HH undergoing liver transplantation, survival improved between the first and second decades of the study [50]. Five-year survival was 65 percent in those transplanted between 1990 and 1996 and 77 percent in those transplanted from 1997 to 2006. The latter was similar to the general liver transplant population in the same period.

- A 2005 series of 260 individuals with end-stage liver disease and iron overload who participated in the national hemochromatosis transplant registry (13 percent homozygous for *HFE* C282Y or compound heterozygous [C282Y/H63D]) reported that post-transplant survival was lower for those with HH (five-year survival, 34 percent) and in those with iron overload without an HH mutation [51].

- In 2000 series of 456 consecutive individuals with HH who underwent liver transplantation, five-year survival in those with hepatic iron overload was 48 percent compared with 77 percent in matched controls without excess iron [52].

Data are somewhat mixed regarding whether iron overload can recur in the transplanted liver [51,53]. Management following liver transplantation is presented separately. (See "Liver transplantation in adults: Long-term management of transplant recipients".)

Heart failure and arrhythmias — In addition to phlebotomy, other interventions may be appropriate for the management of heart failure and arrhythmias, as discussed separately. (See "Arrhythmia management for the primary care clinician" and "Overview of the management of heart failure with reduced ejection fraction in adults".)

Endocrine abnormalities — Hormone replacement is used, as for individuals without HH:

- Type 2 diabetes mellitus – (See "Initial management of hyperglycemia in adults with type 2 diabetes mellitus".)
- Hypothyroidism – (See "Treatment of primary hypothyroidism in adults".)
- Hypogonadism – (See "Testosterone treatment of male hypogonadism".)
- Osteoporosis – (See "Overview of the management of osteoporosis in postmenopausal women" and "Treatment of osteoporosis in men".)

Discontinuation of hormone therapy following removal of excess iron may be discussed with the consulting endocrinologist; data on this subject are limited.

Patients with arthritis — Arthritis is one of the manifestations of iron overload from HH that is least likely to be improved with iron removal, as discussed in detail separately. (See "Arthritis and bone disease associated with hereditary hemochromatosis".)

Treatment of HH-associated arthritis is similar to treatment of osteoarthritis or calcium pyrophosphate deposition disease (CPPD; also called pseudogout). (See "Overview of the management of osteoarthritis" and "Treatment of calcium pyrophosphate crystal deposition (CPPD) disease".)

OTHER ASPECTS OF MANAGEMENT

Addressing concerns about dietary iron — Patients are often concerned about the effect of specific foods but a balanced, healthy diet (without specific restrictions) is generally appropriate. The following summarizes our approach to dietary advice:

- **Meat** – We do not advise dietary restriction of red meat or organ meats, especially in individuals undergoing regular phlebotomy. This is because the amount of dietary iron absorbed in people with HH (0.5 to 1 mg of iron per day) is far exceeded by the removal of iron by each phlebotomy (200 to 250 mg per unit of blood). However, some individuals may absorb substantially greater amounts of iron. Dietary iron restriction has not been evaluated in randomized trials [54].

- **Supplements** – It is important to inform patients with HH about the need to avoid vitamins or supplements that contain extra iron. Multivitamins with iron can contain up to approximately 18 mg of iron per tablet, which is much greater than the amount of iron in a healthy diet. People who choose to take a vitamin supplement should read the ingredients and only select products that do not contain additional iron.

- **Other dietary changes** – We generally do not provide specific recommendations about avoiding foods that increase dietary iron absorption or consuming foods that reduce iron absorption. None of these dietary modifications have been studied systematically, and their effect would be expected to be small. If patients ask, we provide information on the general effects on bioavailability but emphasize that dietary changes are not necessary and that a healthy diet is more important than avoiding or increasing specific foods.

    - Iron absorption is decreased with intake of tannates (eg, in tea), phytates, oxalates, calcium, and phosphates. Coffee also reduces absorption [55]. In one study, non-citrus fruit intake was associated with reduced ferritin [56].

    - Iron absorption may be increased by intake of vitamin C, orange juice, or other citrus fruits. One case report described heart failure and fatal cardiac arrhythmia in an individual who ingested large amounts of vitamin C over the course of one year (1 gram per day along with orange juice supplemented with vitamin C) and who had hemochromatosis that was not diagnosed until his death [57]. This suggests that excess vitamin C should be avoided in individuals with untreated HH, although the upper limit of safe ingestion is debated [58].

In contrast with this dietary advice, avoidance of excess alcohol is very important to reduce the risk of serious liver injury. (See 'Limiting alcohol' above.)

- **Medications that reduce gastric acidity** – Iron is best absorbed in the normal acidic pH of the upper gastrointestinal tract. Some small studies suggested that iron absorption and phlebotomy requirement were reduced in individuals who took a proton pump inhibitor [59,60]. While use of such medications is appropriate for individuals with standard indications, we do not advise patients to take antiacid medications solely to reduce iron absorption.

Avoiding vibrio infection (contaminated shellfish) — As noted separately, individuals with HH are at risk for infections with siderophilic organisms (bacteria that thrive in high plasma iron concentrations such as *Listeria monocytogenes*, *Yersinia enterocolitica*, and *Vibrio vulnificus*). (See "Clinical manifestations and diagnosis of hereditary hemochromatosis", section on 'Susceptibility to infection'.)

Accordingly, it is recommended that patients with HH avoid consumption of uncooked seafood until iron overload has been treated [61]. Caution is generally appropriate, although the quality of the evidence is weak for specific types of seafoods.

Skin exposure to contaminated water may also be a concern for some individuals, as discussed separately. (See "Soft tissue infections following water exposure" and "Vibrio vulnificus infections".)

Testing and counseling first-degree relatives — It is appropriate to test first-degree relatives of individuals with *HFE* C282Y or H63D, or other heritable causes of iron overload, as recommended by practice guidelines from the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver [3,7]. These individuals should be informed about the inheritance pattern of the disorder (autosomal recessive with incomplete penetrance), which means that approximately one-fourth of siblings of an affected individual will be homozygous or compound heterozygous for *HFE* variants, assuming both parents are heterozygotes.

It is generally appropriate to delay testing until adulthood, when informed consent can be given. Iron overload rarely becomes clinically significant until late adulthood. (See "Genetic testing", section on 'Ethical, legal, and psychosocial issues' and "Genetic testing", section on 'Obtaining informed consent'.)

One exception is individuals with a family history of juvenile hemochromatosis (eg, due to a pathogenic variant affecting hemojuvelin [*HJV*], hepcidin [*HAMP*], or transferrin receptor 2

[*TFR2*]). Testing for these variants should be performed earlier in adulthood for those with an adult presentation and in childhood for those with a presentation in childhood. (See "*HFE* and other hemochromatosis genes", section on 'Juvenile hemochromatosis'.)

For family members who test positive for a variant associated with iron overload, iron studies are obtained. In some cases it is reasonable to obtain the genetic testing and the iron studies in the same visit (eg, if there is concern about the burdens and costs of returning for a second blood draw). The importance of avoiding other causes of liver injury such as excess alcohol may be stressed; additional aspects of management depend on the genotype and the presence of iron overload. (See 'Overview of management approach' above.)

The scope of findings in first-degree relatives was illustrated in a study involving 214 C282Y/C282Y homozygous relatives of 291 C282Y/C282Y individuals with iron overload [62]. More than one-half of the male relatives over age 50 and 68 percent of the female relatives had iron overload. Other studies have reported similar findings [63].

Pregnancy — People with HH can have a successful pregnancy and generally are not treated as high risk unless they have organ injury from iron overload, which is extremely rare in this age group. Pregnancy depletes as much as 1000 mg of total body iron (equivalent to approximately four phlebotomies), which is generally more than is absorbed from food over the course of the pregnancy. (See "Anemia in pregnancy", section on 'Iron deficiency'.)

Often it is advisable to comanage with the hematologist and the obstetrician, agreeing on a desired hemoglobin level and ferritin level over the course of the pregnancy.

We monitor the complete blood count (CBC) and ferritin level periodically, with the interval dependent on iron status [38]. Depending on the iron stores, iron supplementation may be avoided or may be given cautiously.

- If the ferritin level is low, we ensure that iron deficiency is not present, as this may adversely affect the developing fetus. Iron deficiency can be judiciously treated with iron to prevent iron deficiency in the neonate. (See "Anemia in pregnancy", section on 'Supporting evidence'.)
- If the ferritin level is normal, we generally do not provide supplementary iron.
- If the ferritin level is high, we generally do not perform phlebotomies unless there is evidence of organ injury.

Values can be rechecked after delivery and appropriate interventions made as for a nonpregnant person.

PROGNOSIS

Untreated, HH can lead to early death. Common causes of mortality in the pre-phlebotomy era included heart failure, cirrhosis, diabetes mellitus, and hepatocellular cancer (HCC) [18,34,64,65]. These risks persist in populations who are diagnosed with HH at a late stage of iron accumulation.

In the era of active treatment, prognosis depends on the extent of organ injury at the time treatment is initiated and the extent of iron removal. Survival appears to be normal in those with a serum ferritin <2000 ng/mL at the time of diagnosis [66]. With phlebotomy, many outcomes are improved including survival, liver disease, cardiomyopathy, and endocrine dysfunction; others such as hepatic cirrhosis and arthropathy often persist despite iron removal. (See 'Evidence for efficacy' above.)

- A population-based cohort study analyzed data collected from 1990 through 2007 on 3832 patients with HH and their 14,496 first-degree relatives, as well as 38,969 population controls and their 143,349 first-degree relatives [65]. Patients with HH who were identified based on hospitalization had a significantly increased risk of death (relative risk [RR] 2.45, 95% CI 2.27-2.64). Those identified by other means (eg, screening of family members, routine outpatient testing) had a lower mortality than that of those identified in the hospital but a marginally higher mortality than unaffected controls (RR 1.15, 95% CI 1.00-1.33).

- A cohort of 1085 individuals diagnosed with C282Y/C282Y HH from 1996 to 2009 was followed for approximately eight years to assess prognosis [66]. The overall standardized mortality ratio (SMR) was similar to the general population; however, those with serum ferritin ≥2000 ng/mL had increased liver-related deaths (SMR 23.9, 95% CI 13.9-38.2), mostly due to HCC (SMR 49.1, 95% CI 24.5-87.9). Those with serum ferritin <1000 ng/mL had a lower mortality than the general population (SMR 0.27, 95% CI 0.1-0.5). On multivariate analysis, factors associated with an increased risk of death included age at diagnosis ≥56 years, diabetes, alcohol consumption, and liver fibrosis stage F3 or F4. (See "Noninvasive assessment of hepatic fibrosis: Overview of serologic tests and imaging examinations", section on 'Stages of fibrosis'.)

Several smaller studies have also shown a strong correlation between the presence of cirrhosis and early death, as well as between cirrhosis and development of HCC [18,19,34,67].

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

- **Assess iron overload** – Most individuals diagnosed with hereditary hemochromatosis (HH) will have had testing to determine whether iron stores are increased, the severity of iron overload, the presence of *HFE* mutations, and other evaluations for organ injury if appropriate (table 1). This testing should be performed if it was not done already. (See 'Pretreatment testing' above.)
- **Indications for phlebotomy** – The flowchart summarizes our approach (algorithm 1).
  - **Urgent (organ injury)** – The need for rapid and aggressive intervention is greatest in individuals with organ injury from excess tissue iron or ferritin level >1000 ng/mL (>2247 pmol/L). For these individuals, we recommend phlebotomy (**Grade 1B**). Although there are no randomized trials, observational studies have shown that phlebotomy is associated with improved survival and reduced severity of liver and

heart disease in these individuals. (See 'People with organ injury from excess iron' above.)

- **Less urgent (increased ferritin)** – We also suggest phlebotomy for individuals with isolated substantial increases in serum ferritin (eg, >300 ng/mL in males or >200 ng/mL in females), especially if they have a positive family history of iron overload (**Grade 2C**). (See 'People with isolated high ferritin and/or TSAT' above.)

Phlebotomy allows determination of mobilizable iron, which can be a useful measure of iron overload and risk of organ damage. However, some of these individuals, especially those with a negative family history of HH, may reasonably choose expectant management with close monitoring and initiation of phlebotomy if iron stores continue to increase. (See 'Overview of management approach' above and 'Indications and contraindications' above and 'Evidence for efficacy' above.)

- **Heterozygous individuals** – Iron overload is extremely rare in individuals who are heterozygous for *HFE* C282Y or other *HFE* variants, although moderately increased ferritin is often seen. Often there is concomitant liver disease (alcoholic or nonalcoholic). Management is individualized according to clinical status and comorbidities. If we are unsure of the degree of iron overload, we often obtain a magnetic resonance imaging (MRI) study of the liver or ultrasound-based hepatic elastography to determine the presence of iron deposition and/or liver fibrosis, respectively. (See 'Heterozygous individuals' above.)

- **Phlebotomy** – Phlebotomy is the main intervention to remove excess iron. The procedure is essentially the same as donating blood; some individuals (lower weight, older, anemic) may have smaller volumes removed. The typical schedule is once weekly until the target ferritin level is reached, with modifications as needed for anemia and tolerance of the procedure. The number of phlebotomies can be estimated, but in practice, this is determined by the hemoglobin and ferritin levels, which are monitored periodically. Experts differ on the exact target ferritin, but most agree it should be between 50 and 100 ng/ml, and iron-deficiency should be avoided. Once the target is met, patients are monitored, with maintenance phlebotomies or expectant management guided by the ferritin. (See 'Procedure, schedule, and target ferritin level' above and 'Maintenance' above.)

- **Other interventions and counseling** – Other considerations include dietary advice, limiting alcohol, testing and counseling of first-degree relatives, and management of pregnancy. (See 'Other aspects of management' above.)

- **Prognosis** – Prognosis depends on the severity of iron overload at diagnosis and the extent of iron removal. Survival appears normal in those with ferritin <1000 ng/mL at diagnosis. Major causes of death include cirrhosis, hepatocellular cancer (HCC), and diabetes; alcohol use is associated with increased mortality. (See 'Prognosis' above.)

- **Diagnosis** – Clinical manifestations and diagnosis of HH, *HFE* variants and other genetic causes of iron overload, and general population screening are discussed separately. (See "Clinical manifestations and diagnosis of hereditary hemochromatosis" and "*HFE* and other hemochromatosis genes" and "Gene test interpretation: *HFE* (hereditary hemochromatosis gene)".)

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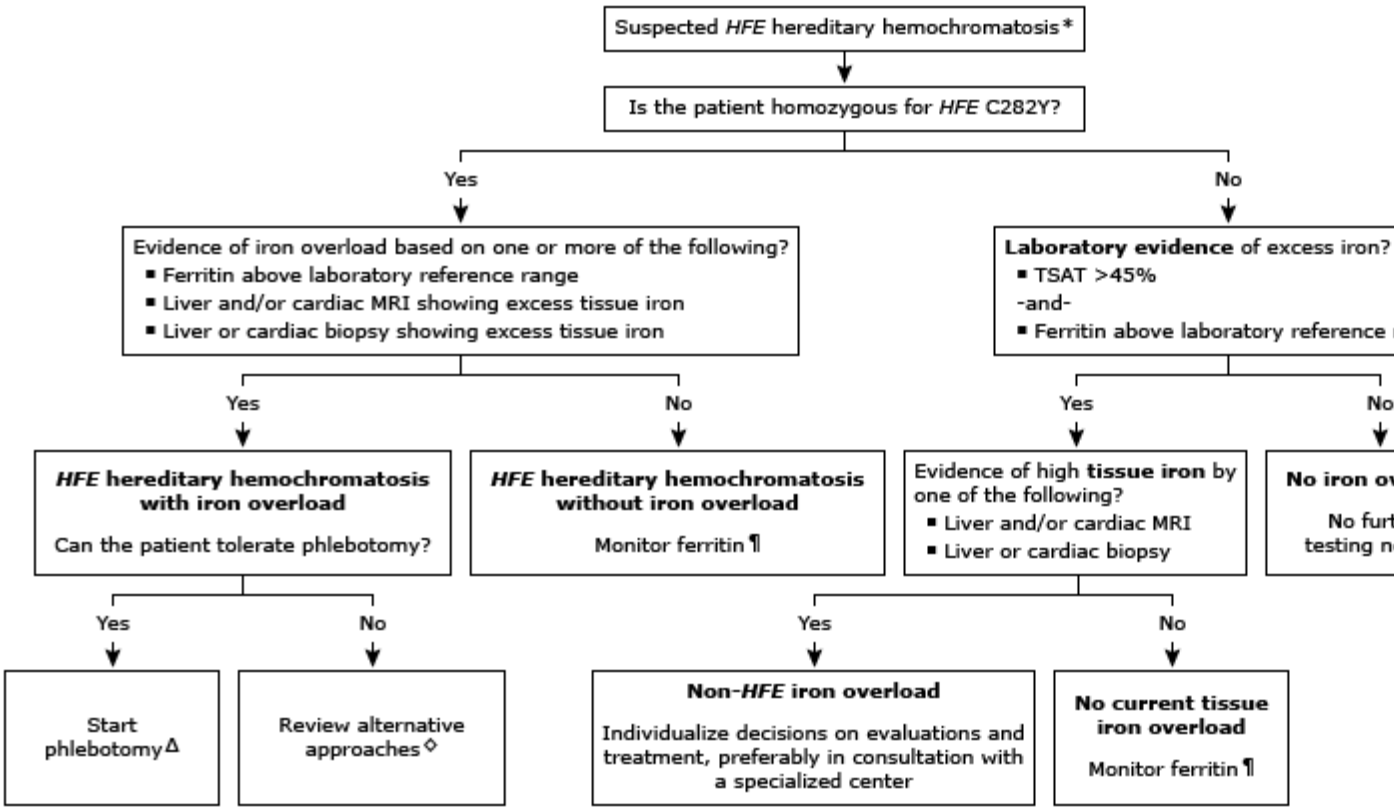
Topic 7136 Version 52.0

GRAPHICS

Management of *HFE* hereditary hemochromatosis (HH)



TSAT is nearly always increased in individuals with the *HFE* C282Y/C282Y genotype, but this does not necessa
Analysis of tissue iron by MRI or biopsy is generally reserved for individuals with ferritin >1000 ng/mL, eleva
failure, arrythmias, or other findings suggesting hepatic or cardiac involvement. Hematology consultation is
phlebotomy or for those with laboratory results that require further interpretation. Refer to UpToDate for de
hemochromatosis and management of patients for whom genetic testing is not available.

HH: hereditary hemochromatosis; TSAT: transferrin saturation; HCC: hepatocellular cancer.

* Reasons to suspect *HFE* HH:
- Positive family history of *HFE* HH or C282Y/C282Y genotype.
- Ferritin above laboratory reference range (females: >200 ng/mL; males: >300 ng/mL) and TSAT >45%, without symptoms of iron overload. Refer to UpToDate for a discussion of HH diagnosis.

¶ Typically done monthly or with each phlebotomy; refer to UpToDate for details and other testing.

Δ Urgency and frequency of phlebotomy depend on the severity of iron overload, hemoglobin, and tolerabil
individualized. Once the target ferritin is reached, maintenance phlebotomies are performed less frequently

◇ Iron chelation or erythrocytapheresis may be used in selected individuals. Consultation with an expert in i

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Graphic 141680 Version 1.0

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

Results of therapeutic phlebotomy in patients with hemochromatosis

Complications of iron overload	Expected treatment outcome
None	Prevention of complications of iron overload; normal life expectancy
Weakness, fatigue, lethargy	Improvement in majority of patients
Elevated serum concentrations of hepatic enzymes	Resolution or marked improvement
Hepatomegaly	Resolution often occurs
Hepatic cirrhosis	No change
Increased risk for primary liver cancer	No change*
Right upper quadrant pain	Resolution or marked improvement¶
Arthropathy	Improvement in arthralgias sometimes occurs; change in joint deformity is rare; progression is sometimes seen
Hypogonadotrophic hypogonadism	Resolution is rare
Diabetes mellitus	Occasional improvement, often temporary
Hypothyroidism, hypogonadism	Resolution is rare
Cardiomyopathy	Resolution sometimes occurs
Hyperpigmentation	Resolution usually occurs
Hyperferritinemia	Resolution
Excess absorption and storage of nonferrous metalsΔ	
Infection with *Vibrio vulnificus* or other bacteria	Little or no change

* Increased risk occurs only in persons with cirrhosis.

¶ Right upper quadrant pain in persons with hemochromatosis is often related to hepatic iron overload. In these cases, therapeutic phlebotomy usually results in marked improvement or resolution. However, right upper quadrant pain may also be caused by primary liver cancer, portal vein thrombosis, gallbladder disease, lesions in the hepatic flexure, or nephrolithiasis. Iron depletion alone will not alleviate right upper quadrant pain due to these causes.

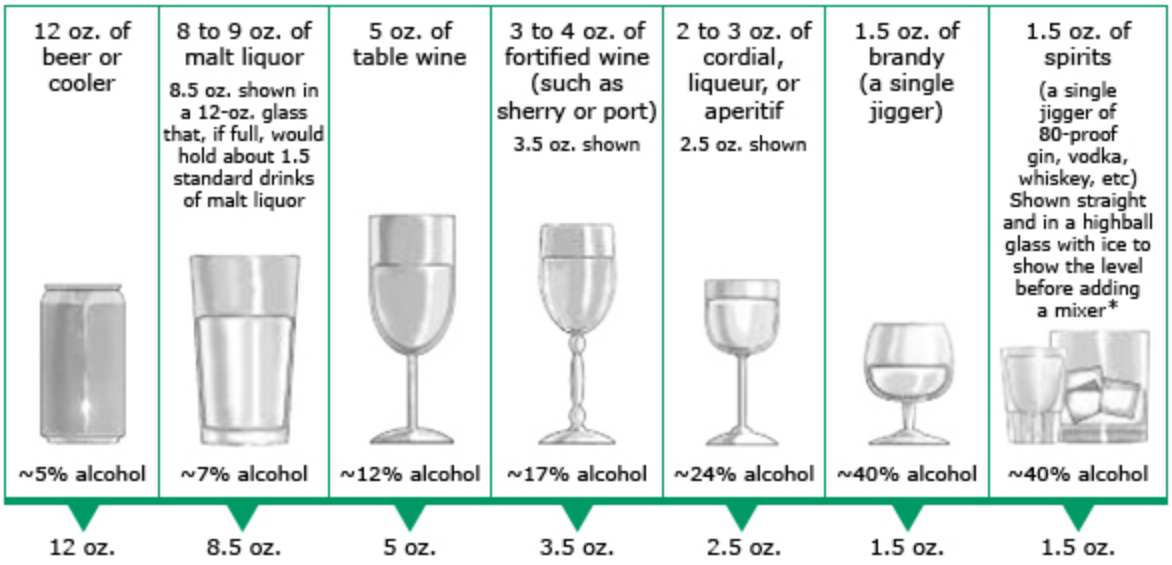
Δ Cobalt, manganese, zinc, and lead.

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

Graphic 68740 Version 8.0

What is a standard drink?

A standard drink in the United States is any drink that contains about 14 grams of pure alcohol (about 0.6 fluid ounces or 1.2 tablespoons). Below are US standard drink equivalents. These are approximate, since different brands and types of beverages vary in their actual alcohol content.



Many people don't know what counts as a standard drink and so they don't realize how many standard drinks are in the containers in which these drinks are often sold. Some examples:

- For **beer**, the approximate number of standard drinks in:
  - 12 oz. = 1
  - 16 oz. = 1.3
  - 22 oz. = 2
  - 40 oz. = 3.3
- For **malt liquor**, the approximate number of standard drinks in:
  - 12 oz. = 1.5
  - 16 oz. = 2
  - 22 oz. = 2.5
  - 40 oz. = 4.5
- For **table wine**, the approximate number of standard drinks in:
  - a standard 750-mL (25-oz.) bottle = 5
- For **80-proof spirits**, or "hard liquor," the approximate number of standard drinks in:
  - a mixed drink = 1 or more*
  - a pint (16 oz.) = 11
  - a fifth (25 oz.) = 17
  - 1.75 L (59 oz.) = 39

US: United States; oz.: ounces.

* It can be difficult to estimate the number of standard drinks in a single mixed drink made with hard liquor. Depending on factors such as the type of spirits and the recipe, a mixed drink can contain from 1 to 3 or more standard drinks.

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