# ACG Clinical Guideline: Hereditary Hemochromatosis

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**Hereditary hemochromatosis (HH) is one of the most common genetic disorders among persons of northern European descent. There have been recent advances in the diagnosis, management, and treatment of HH. The availability of molecular diagnostic testing for HH has made possible confirmation of the diagnosis for most patients. Several genotype-phenotype correlation studies have clarified the differences in clinical features between patients with the C282Y homozygous genotypes and other *HFE* mutation patterns. The increasing use of noninvasive tests such as MRI T2* has made quantification of hepatic iron deposition easier and eliminated the need for liver biopsy in most patients. Serum ferritin of <1,000 ng/mL at diagnosis remains an important diagnostic test to identify patients with a low risk of advanced hepatic fibrosis and should be used routinely as part of the initial diagnostic evaluation. Genetic testing for other types of HH is available but is expensive and generally not useful in most clinical settings. Serum ferritin may be elevated among patients with nonalcoholic fatty liver disease and in those with alcoholic liver disease. These diagnoses are more common than HH among patients with elevated serum ferritin who are not C282Y homozygotes or C282Y/H63D compound heterozygotes. A secondary cause for liver disease should be excluded among patients with suspected iron overload who are not C282Y homozygotes. Phlebotomy remains the mainstay of therapy, but emerging novel therapies such as new chelating agents may have a role for selected patients.**

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## PREAMBLE

The guideline is structured in the format of key concepts, recommendations, and summaries of the evidence. Key concepts are statements that are not amenable to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) process, due to either the structure of the statement or the available evidence. In some instances, key concepts are based on the extrapolation of evidence and/or expert opinion. Each recommendation statement has an associated assessment of the quality of evidence and strength of recommendation based on the GRADE process (Table 1). Finally, the evidence summary for each section provides important definitions and data supporting the recommendations.

To best characterize the evidence cited in support of the recommendations, the ACG clinical guidelines have implemented GRADE. The strength of recommendations in the GRADE system is classified as strong or weak. The quality of evidence supporting strong or weak recommendations is designated by one of 3 levels: high, moderate, or low quality.

### Grading of Recommendations, Assessment, Development, and Evaluation

***Strength of recommendation.*** Strong: Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost.

Weak: Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, or higher cost or resource consumption.

***Quality of evidence.*** High: Further research is unlikely to change the confidence in the estimate of the clinical effect.

Moderate: Further research may change the confidence in the estimate of the clinical effect.

Low: Further research is very likely to affect the confidence on the estimate of clinical effect.

Very low: Any estimate of the effect is very uncertain.

Throughout the guidelines, patient, intervention, comparison, outcome (PICO) questions will also be used to guide patient management.

## INTRODUCTION

Hereditary hemochromatosis (HH) is defined as an inherited iron overload disorder characterized by excessive absorption of iron, due to deficiency of hepcidin (1). (For definitions of commonly used terms in this ACG Clinical Guideline, please see Box 1.) von Recklinghausen, a German pathologist, was the first to coin the term "hemochromatosis," based on his belief that abnormal pigmentation ("chrom") in the tissues of patients with this disorder was related to factors circulating in the blood ("hemo") (2). Subsequent discoveries have established the role of iron deposition in the affected organs as the cause of this disease's clinical manifestations, the genetic basis for the disorder, and the identification of mutations in the genes regulating iron metabolism (3).

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**Box 1. Definitions of commonly used terms**

- Hepcidin: A hormone synthesized and secreted by the liver in response to circulating iron levels, which inhibits iron absorption from the intestinal mucosal cells by degradation of ferroportin-1.
- Ferroportin-1: A transmembrane protein found predominantly in the intestinal epithelial cells, hepatocytes, and macrophages, which facilitates iron export from the cells.
- Transferrin: A glycoprotein synthesized by the liver which exists in 3 forms (apo, monoferric, and diferric); it carries iron in the circulation.
- Unsaturated iron-binding capacity: The portion of iron-binding sites on transferrin that are not occupied by iron. A low unsaturated iron-binding capacity raises the suspicion for hemochromatosis.
- Total iron-binding capacity: The sum of the serum iron and unsaturated iron-binding capacity.
- Transferrin-iron saturation: The percentage of iron bound to transferrin. Calculated by dividing serum iron by total iron-binding capacity.
- Ferritin: Intracellular protein that stores and releases intracellular iron.

Body iron stores are regulated at the level of intestinal iron absorption, as there are no physiologic processes for the excretion of excess iron other than blood loss via menses or sloughing of senescent intestinal mucosal or epidermal cells (4). Hepcidin, a 25-amino acid peptide produced mainly in the liver, is considered the key regulator of iron stores by inhibiting of iron absorption (5,6). Primary iron overload disorders are defined as inherited conditions with either abnormally low levels of hepcidin (7) or decreased binding of hepcidin to ferroportin (FPN), the transmembrane protein that exports iron outside the cell (1). Secondary iron overload may be considered as any condition of acquired hepcidin deficiency from disorders of erythropoiesis or increased red blood cell (RBC) turnover or due to other chronic liver disease or excess alcohol intake (8). Over time, iron deposition can lead to dysfunction and failure in multiple organs including the liver, pancreas, heart, joints, and pituitary gland. The primary goal in the management of HH is to identify patients before end-organ injury and initiate treatment via iron depletion before irreversible end-organ damage.

## REVIEW OF IRON ABSORPTION AND ITS CONTROL

Iron absorption occurs primarily in the second portion of the duodenum in the form of heme and non-heme iron. Heme iron is absorbed via mechanisms that are not yet fully understood (9). Non-heme or inorganic iron absorption follows a coordinated process that begins with the reduction of Fe from 3+ to 2+ via the ferric reductase duodenal cytochrome b and follows with intracellular transport across the intestinal cell via divalent-metal transporter 1 located on the apical surface. Subsequently, iron is exported via the basolateral iron transporter FPN1 which is

**Table 1. Summary and strength of recommendations**

| |
|---|
| Screening for HH |
| 1. We recommend that family members, particularly first-degree relatives, of patients diagnosed with HH should be screened for HH (strong recommendation, moderate quality of evidence). |
| Clinical features |
| 2. We suggest against the routine surveillance for HCC among patients with HH with stage 3 fibrosis or less (conditional recommendation, very low quality of evidence). |
| Diagnostic testing |
| 3. We recommend that individuals with the H63D or S65C mutation in the absence of C282Y mutation should be counseled that they are not at increased risk of iron overload (conditional recommendation, very low quality of evidence). |
| 4. We suggest against further genetic testing among patients with iron overload who tested negative for the C282Y and H63D alleles (conditional recommendation, very low quality of evidence). |
| 5. We suggest a non–contrast-enhanced MRI (in conjunction with software used for the estimation of HIC (i.e., MRI T2*) be used to noninvasively measure liver iron concentration, in the non-C282Y homozygote with suspected HH. If there is a concomitant need to stage hepatic fibrosis or evaluate for alternate liver diseases, then liver biopsy is the preferred method to determine HIC (conditional recommendation, low quality of evidence). |
| Treatment |
| 6. We recommend that phlebotomy be used as the first-line treatment in patients diagnosed with HH, as determined by C282Y homozygosity or C282Y/H63D compound heterozygosity (strong recommendation, moderate quality of evidence). |
| 7. We recommend against chelation as the first-line therapy for HH, given the effectiveness of phlebotomy, the associated side effects of chelation including hepatic and renal toxicity, and the relatively small sample size of clinical trials supporting chelation (strong recommendation, low quality of evidence). |
| 8. We recommend the use of iron chelation for the treatment of HH in the patient who is intolerant or refractory to phlebotomy or when phlebotomy has the potential for harm, such as in patients with severe anemia or congestive heart failure (strong recommendation, low quality of evidence). |
| 9. We recommend against the routine use of PPIs as the primary treatment of HH (strong recommendation, low quality of evidence). |
| Liver transplantation for HH |
| 10. We recommend that liver transplantation be considered in patients with HH who have decompensated cirrhosis or HCC (strong recommendation, low quality of evidence). |

HCC, hepatocellular carcinoma; HH, hereditary hemochromatosis; HIC, hepatic iron concentration; PPI, proton pump inhibitor.

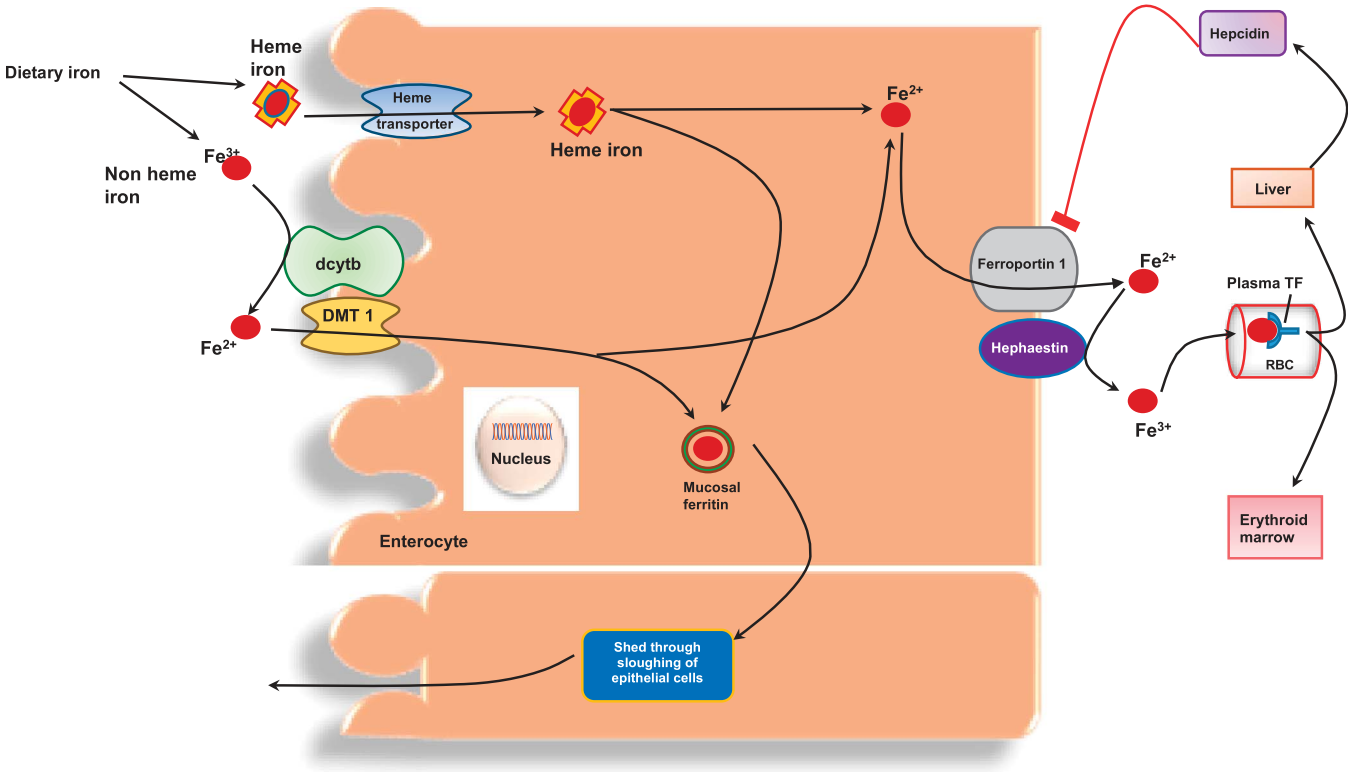


**Figure 1.** Overview of intestinal iron absorption. Dietary iron is taken up by enterocytes in the proximal small intestine. The primary types of iron in the diet are heme iron, which is readily absorbed by mechanisms that are poorly understood at present, and non-heme iron, which is predominantly ferric iron. To facilitate the transport of insoluble ferric iron across the luminal surface of the enterocyte, ferric iron ($Fe^{3+}$) is reduced by the ferric reductase duodenal cytochrome B (dcytb) to ferrous iron ($Fe^{2+}$), which is then transported into the enterocyte by DMT1. Once inside the cell, the iron may be stored bound to ferritin or can be transferred across the basolateral surface of the enterocyte by means of the transport protein FPN. The export process also involves a ferroxidase, hephaestin, which converts ferrous iron back to ferric iron. This step is necessary for iron to bind to TF. Diferric transferrin is the form in which iron is delivered to sites of iron utilization, such as the bone marrow. The transfer of iron across the enterocyte is regulated by hepcidin by means of its effect on FPN. Binding of hepcidin to FPN causes the latter protein to be internalized and degraded within the enterocyte. The elimination of the transporter prevents egress of iron from the cell. Iron retained within the enterocyte is then eliminated when the epithelial cell is sloughed at the end of its lifespan. DMT1, divalent metal transporter 1; FPN, ferroportin; RBC, red blood cell; TF, transferrin.

co-localized to hephaestin, a ferroxidase that oxidizes Fe from the 2+ state back to 3+ state (1,4) (Figure 1).

Hepcidin, produced in the liver in response to circulating iron levels, binds to FPN1 on macrophages, intestinal absorptive cells, and other tissues, after which FPN1 is internalized and degraded; this results in reduced iron release from the cells, diminished transfer of iron across the enterocyte, and reduced iron mobilization from the macrophages (9). Under conditions of low hepcidin, these effects on both macrophages and enterocytes are attenuated, leading to enhanced release of iron from the macrophages as well as increased intestinal iron uptake (10).

The physiologic response to iron deficiency is decreased hepcidin production at the level of transcription (1). Hepcidin production can also be induced by inflammatory cytokines. As such, chronic inflammation can lead to anemia secondary to increased hepcidin levels, sometimes referred to as anemia of chronic disease. By contrast, most cases of HH are due to inappropriately low expression of hepcidin relative to circulating iron and body iron stores (11–14).

## CLASSIFICATION OF HEMOCHROMATOSIS

There are 4 main types of HH (Table 2) that have been categorized based on which proteins involved in iron homeostasis are affected (1). Type 1 HH is the most frequent inherited form of iron overload. The most common mutation is a G to A transition at nucleotide 845 of the *HFE* gene, resulting in a cysteine to tyrosine substitution at amino acid 282 (C282Y), referred to as type 1a (15,16). Another known genetic subtype is the H63D mutation, which does not cause significant iron overload but may act as a cofactor for phenotypic expression of iron overload, primarily in combination with C282Y (17). This genotype of C282Y/H63D is classified as HH type 1b or compound heterozygote. The prevalence of this mutation is approximately 2%–4% among patients of northern European origin (18–20). Compound heterozygotes may have increased iron indices including transferrin-iron saturation (TS) and serum ferritin (SF) levels (21–23); however, the penetrance for developing clinically significant iron overload is rare among patients with this genotype (0.5%–2%) (24), unless cofactors such as alcohol or hepatitis C virus (HCV) are involved (23,25). Patients who are homozygous or heterozygous for the H63D substitution are not at increased risk of developing clinical iron overload compared with those without this mutation, though they may still present with an elevation in TS and SF levels (26). A third *HFE* genotype, known as type 1c, is related to the mutation S65C. The S65C mutation may lead to increased serum iron and ferritin levels but has not been

**Table 2. Categories of HH**

| Classification | Genes involved and location | Inheritance | Protein function | Clinical manifestations |
|---|---|---|---|---|
| Type 1A HH (homozygote) | *HFE* on 6p21.3<br>Mutations in *HFE*:<br>1. C282Y | AR | Involved in hepcidin synthesis via BMP6, interaction with TFR1. | Arthropathy, skin pigmentation, liver damage, diabetes mellitus, endocrine dysfunction, cardiomyopathy, hypogonadism. |
| Type 1B HH (compound heterozygote) | *HFE* on 6p21.3<br>Mutations in *HFE*:<br>1. C282Y<br>2. H63D | AR | Involved in hepcidin synthesis via BMP6, interaction with TFR1. | Arthropathy, skin pigmentation, liver damage, diabetes mellitus, endocrine dysfunction, cardiomyopathy, hypogonadism. |
| Type 1C HH | *HFE* on 6p21.3<br>Mutations in *HFE*:<br>1. S65C | AR | | Possible elevations in serum iron/ferritin, no evidence of tissue iron deposition. |
| Type 2A juvenile HH | *HJV* (hemojuvelin) on 1p21 | AR | Involved in hepcidin synthesis, BMP co-receptor. | Earlier onset, <30 years old, hypogonadism and cardiomyopathy are prevalent. |
| Type 2B juvenile HH | *HAMP* (hepcidin) on 19q13 | AR | Downregulation of iron efflux from erythrocytes. | Earlier onset, <30 years old, hypogonadism and cardiomyopathy are prevalent. |
| Type 3 HH | *TFR2* (transferrin receptor 2) on 7q22 | AR | Involved in hepcidin synthesis, interaction with transferrin. | Arthropathy, skin pigmentation, liver damage, diabetes mellitus, endocrine dysfunction, cardiomyopathy, hypogonadism. |
| Type 4A HH (FPN disease) | *SLC40A1* (FPN) on 2q32<br>Loss of function for FPN excretion | AD | Duodenal iron export. | Iron deposition in the spleen is very common, lower tolerance to phlebotomies and may have anemia. |
| Type 4B HH (nonclassical FPN disease) | *SLC40A1* (FPN) on 2q32<br>Gain of function, FPN cannot be internalized after hepcidin binding | AD | Resistance to hepcidin. | Fatigue, joint pain. |

AD, automosomal dominant; AR, autosomal recessive; FPN, ferroportin; *HAMP, hepatic antimicrobial protein*; HH, hereditary hemochromatosis.



associated with excess tissue iron stores and can, therefore, be considered a polymorphism without clinical significance (27,28).

The other HH genotypes are unrelated to the *HFE* gene and have a significantly lower prevalence. Type 2 HH, also called juvenile hemochromatosis, is associated with mutations in the *HJV* gene (type 2A) or the *hepatic antimicrobial protein* (*HAMP*) gene (type 2B), respectively, leading to hepcidin deficiency (29). This mutation tends to lead to the most severe form of primary iron overload, primarily occurring in younger individuals (30). Type 3 HH is associated with mutations in the *transferrin receptor 2* (*TFR2*) gene, also leading to hepcidin deficiency (31,32).

Type 4A HH, also known as FPN disease, is the only autosomal dominant form of hemochromatosis due to mutations in the *FPN1* gene (SLC40A1) (11,12). In this condition, the production of hepcidin is normal, but the export function of FPN1 is diminished, leading to intracellular iron retention with low levels of plasma iron and normal or low levels of TS but elevated SF levels (33). The spleen is the most affected organ in type 4A HH, because of high FPN1 activity at the level of macrophages (34). Type 4B HH is a form or iron overload due to resistance of FPN1 to hepcidin (35).

Another rare but serious iron overload disorder is aceruloplasminemia, caused by the absence of the ferroxidase enzyme ceruloplasmin (36). This condition leads to iron accumulation in most organs, including the central nervous system (7).

## EPIDEMIOLOGY

The prevalence of *HFE*-related HH has been observed to be similar in the United States, Europe, and Australia, of approximately 1 case in 200–400 persons (15). The highest prevalence exists in people of Irish and Scandinavian origin, whereas the lowest is among those of African descent (37,38). Additionally, the prevalence of *HFE*-related HH is lower among whites who are not of northern European descent, such as those of eastern European or Mediterranean origin (37,38). The prevalence among non-Hispanic whites in the United States is 1 in 300 (39). The incidence of HH varies from 1.5 to 3 cases per 1,000 persons up to 1 case per 200–400 persons, although the true incidence is difficult to determine as it can only be assessed in newborn screening studies (15).

According to a meta-analysis using a pooled cohort of 127,613 individuals across Europe, the allelic frequency of C282Y in the general population approaches 6.2% (40). The percentage of patients with phenotypic HH attributed to C282Y homozygosity, however, approaches 80.6%, according to a meta-analysis of 2,802 patients (40). The homozygous C282Y mutation is significantly more prevalent among non-Hispanic whites (0.44%) compared with Native Americans (0.11%), Hispanics (0.027%), African-Americans (0.014%), Pacific Islanders (0.012%), or Asians (0.000039%) (18).

The penetrance of C282Y homozygosity is incomplete and variable across studies and between genders. Biochemical penetrance, as determined by increased TS with or without elevation in SF, has been estimated to be 75% in men and 50% in women, based on 2 large studies done in the United States and Australia (18,19). Male C282Y homozygotes manifest symptoms related to tissue iron deposition more commonly than female individuals (18,19,21). The Melbourne Collaborative Cohort Study of 31,192 patients (19) showed that 28.4% of men had documented iron overload–related disease compared with only 1.2% of women. A French Mediterranean registry found the biochemical and clinical penetrance to be higher in men (19%) than in women (13%) (41).

## SCREENING FOR HH

General population screening for HH is not indicated (40,42,43). The recommendation against screening in the general population is based on both the variable prevalence of the *C282Y* gene across different ethnicities (18) and the incomplete penetrance of this mutation (19).

**PICO question: Should screening or no screening be offered for HH in first-degree relatives of patients with HH?**

Selective screening of first-degree relatives of patients affected with type 1 HH is suggested. Studies of patients with HH and their families have demonstrated that most homozygous relatives of probands demonstrate biochemical and clinical expression of the disease, not only due to the presence of the genetic mutation but also shared environmental factors that may increase the penetrance of the disease (44,45).

For children of an identified proband, *HFE* testing of the other parent is generally recommended, and if results are normal, the child is an obligate heterozygote and need not undergo further testing (46). One study estimated that the cost of screening children of C282Y homozygous patients with HH could be reduced by 39% by genotyping the spouses of the probands (46). A separate study found that screening the siblings of patients was cost saving, and the use of *HFE* gene testing was generally more cost effective than serum iron studies (47). Cost savings were realized by avoiding repeat testing among individuals not genetically at risk of iron overload. If the other parent cannot be tested, then the child need not be tested until age 18 years, because clinical manifestations of HH rarely present beforehand (48).

***Recommendations.***

1. We recommend that family members, particularly first-degree relatives, of patients diagnosed with HH should be screened for HH (strong recommendation, moderate quality of evidence).

## SECONDARY IRON OVERLOAD

Secondary iron overload is a phenomenon of excess absorption and organ deposition of iron, which is unrelated to one of the genetic mutations leading to type 1–4 HH (Table 3) (49). Most commonly, this is due to iron-loading anemias, such as thalassemia or sickle cell anemia, parenteral iron administration, or other liver diseases (49–52). Additional conditions that may lead to secondary iron overload include malignancy and chronic inflammatory states (53). Below, we briefly describe secondary iron overload related to other underlying liver diseases, which may be mistaken for HH (50–52,54).

**Table 3. Causes of secondary iron overload**

| |
|---|
| Iron-loading anemias |
| Thalassemia major |
| Hemoglobin H |
| Chronic hemolytic anemia |
| Sickle cell anemia |
| Aplastic anemia |
| Pyruvate kinase deficiency |
| Hereditary spherocytosis |
| Parenteral iron overload |
| RBC transfusions |
| Iron-dextran injections |
| Long-term hemodialysis |
| Chronic liver disease |
| Porphyria cutanea tarda |
| Hepatitis C |
| Hepatitis B |
| Alcoholic liver disease |
| NAFLD |
| Dysmetabolic iron overload syndrome |
| Miscellaneous |
| Malignancy (HCC, breast cancer, hematologic malignancies) |
| Chronic inflammatory states (systemic lupus erythematosus, rheumatoid arthritis) |

HCC, hepatocellular carcinoma; NAFLD, nonalcoholic fatty liver disease; RBC, red blood cell.

### Alcohol use disorder

Chronic alcohol consumption is associated with an elevation in SF level and TS and can result in increased hepatic iron stores from increased intestinal iron absorption in patients with alcohol use disorder (AUD) (51,55,56). Additionally, low hepcidin levels are also noted in AUD, due to ethanol-induced downregulation of the transcription factor regulating hepcidin expression (57). This downregulation of hepcidin synthesis in the liver may be one of the dominant underlying mechanisms of iron overload in alcoholic liver disease (58).

### Nonalcoholic fatty liver disease

Patients with nonalcoholic fatty liver disease (NAFLD) frequently have elevated serum TS, SF, or both, and elevated serum iron markers may be a reason for suspicion of iron overload (59). The term "dysmetabolic" or "insulin-resistance hepatic iron overload syndrome" (DIOS or IR-HIO, respectively) has been used in cases of unexplained hepatic iron overload characterized by high SF levels and normal serum iron, related to hepcidin downregulation from insulin resistance (60,61).

### Hepatitis C virus

Iron accumulation in the liver and iron overload have been found in HCV; 30%–40% of HCV-infected patients have elevated serum iron, SF, and TS (62). Iron can accumulate in either the

**Table 4. Clinical manifestations of HH**

| Organ | Manifestations |
|---|---|
| Liver | Elevated liver enzymes<br>Hepatomegaly<br>Fibrosis<br>Cirrhosis<br>HCC |
| Endocrine | Hyperglycemia<br>Diabetes mellitus<br>Hypogonadism<br>Testicular atrophy<br>Amenorrhea<br>Loss of libido<br>Hypopituitarism |
| Skin | Hypermelanotic pigmentation (bronze skin) |
| Joints | Arthralgia<br>Arthritis<br>Chondrocalcinosis |
| Heart | Cardiomyopathies<br>Arrhythmias<br>Heart failure |

HCC, hepatocellular carcinoma; HH, hereditary hemochromatosis.

reticuloendothelial system, mainly localized in the Kupffer cells, or the hepatocytes (63). Chronic hepatitis C may lead to an elevation in serum TS and hepatic iron concentration among patients heterozygous for *HFE* mutations (64).

## CLINICAL FEATURES

The difficulty in diagnosing a patient with HH lies in the broad way it can present clinically (Table 4). Fatigue and arthralgias are the most common symptoms encountered early in the disease (65,66). However, up to 18% of men and 5% of women may have hepatic iron overload in the absence of clinical symptoms (67). Disease manifestations usually occur earlier in men than in women, most commonly in the fourth to fifth decades of life (67). In women, clinical symptoms usually appear after postmenopause, due to iron loss during menstruation, pregnancy, and lactation offsetting the increased absorption of iron during this time (68). Given the lack of cardinal symptoms, clinical suspicion for HH relies primarily on an awareness of the disease. We review below the clinical features of the disease that the clinician should be aware of, to suspect and ultimately diagnose HH.

### Hepatic

The liver is the most commonly affected organ in type 1 HH. The clinical presentation can be variable, including asymptomatic elevation of serum aminotransferases, nonspecific right upper quadrant pain, or complications of end-stage liver disease (69,70). The risk of developing cirrhosis rises significantly with SF levels of >1,000 ng/mL at diagnosis (71). Increased alcohol consumption of more than 60 g/d can increase the risk of developing cirrhosis in HH by 9-fold (72), and excess of 80 g of daily alcohol consumption can significantly reduce survival (73). The key mechanism of iron-related tissue injury has been suggested to be oxidative injury that overwhelms cellular antioxidant mechanisms with the hepatocytes (15). Recent studies have revealed information regarding the natural history of HH and the risk of developing liver disease. According to one analysis, the lifetime incidence of cirrhosis approaches 10% among untreated men with HH (74). A separate study of 2,050 patients over 30 years demonstrated that iron overload may be worsened by both tobacco smoking and alcohol consumption; reduction of alcohol consumption over time has led to a reduction in phenotypic expression of the disease (75).

In the setting of cirrhosis, patients with HH are also at risk of developing hepatocellular carcinoma (HCC), which accounts for as much as 45% of deaths in this population (76–78). The relative risk of tumor formation in HH has been estimated to be between 20 and 200 (76,78,79), and a SF level above 2000 ng/mL indicates particularly high risk (80). The 10-year incidence of HCC in patients with cirrhosis secondary HH is approximately 6%–10% in most studies, with men at higher risk than women (76,79–81). Recommendations for HCC screening and surveillance for patients with cirrhosis due to HH are the same as those for patients with cirrhosis from other causes of chronic liver disease, specifically ultrasound with or without alpha-fetoprotein levels performed every 6 months (82). However, HCC surveillance in patients with HH with cirrhosis should continue after iron removal is completed, because HCC can develop years after successful iron depletion (83).

#### PICO question: Should HCC surveillance vs no surveillance be used to diagnose HCC in patients with HH and stage 3 or less fibrosis?

There are no data addressing the efficacy of HCC screening in patients with HH without cirrhosis, and the data regarding HCC occurrence among individuals without cirrhosis are limited to a small number of cases (84–86). Therefore, it is unknown whether patients with HH with stage 3 fibrosis are at increased risk of HCC.

#### *Recommendations*

2. We suggest against the routine surveillance for HCC among patients with HH with stage 3 fibrosis or less (conditional recommendation, very low quality of evidence).

### Cardiac

Although cardiac manifestations resulting from iron deposition do not occur commonly in type 1 HH, cardiomyopathy remains the second leading cause of mortality in this patient population (87). Accumulation of iron in the heart can result in cardiomyopathy, both restrictive and dilated, arrhythmias including sick sinus syndrome and atrial fibrillation, and heart failure (88). Iron overload is associated with impaired endothelial function and increased carotid intima-media thickness, resulting in increased oxidative stress (89). Patients may initially present with dyspnea on exertion from diastolic dysfunction, leading to restrictive hemodynamics and elevated filling pressures, with later manifestations of left ventricular systolic dysfunction (89). Sudden death due to cardiac dysrhythmias and cardiomyopathies can occur among patients with advanced iron overload (44,90).

However, the overall prevalence of cardiac manifestations among patients with HH is relatively low. In a study of 3,531 patients with HH, only 30 subjects studied were found to have dilated cardiomyopathy (0.9%) (91). In a more recent study of

1,085 patients with HH, evaluated from 1996 to 2009, only 34 patients (3.1%) were diagnosed with cardiomyopathy and 5 had cardiovascular-related death, predominantly those with a SF above 1,000 ng/mL (80).

### Endocrine

The prevalence of diabetes among patients with HH is estimated at approximately 13%–23% (92). The presence of diabetes has been best established in patients with type 1 HH. A higher prevalence of glucose intolerance has been reported in patients with juvenile HH in comparison with type 1 or type 3 HH (92). Diabetes has been seen in up to 25% of patients with type 4 HH (92). The pathogenesis of diabetes in HH involves injury of pancreatic β-islet cells due to iron accumulation and development of hepatic insulin resistance from associated liver injury (93).

Hypogonadotropic hypogonadism is the most common nondiabetic endocrine disorder in HH, resulting from iron accumulation in the pituitary gland (94) and occurring most commonly in juvenile HH. In men, it presents as impotence, loss of libido, and osteoporosis, whereas in women, it causes amenorrhea or, less commonly, premature menopause (94,95). Hypothyroidism can also occur, and men are particularly affected, with a risk 80 times that of men in the general population (96). Additionally, up to 25% of patients with HH are affected with osteoporosis (97).

### Joints

Arthropathy develops in patients with HH (65), predominantly in the second and third metacarpophalangeal joints. Other joints that may be involved include proximal interphalangeal joints, wrist, elbows, shoulder, and hips. Arthropathy is generally symmetrical and can be mono- or polyarticular (98). The presentation of HH-associated arthritis is similar to that of osteoarthritis and calcium pyrophosphate deposition disease (CPPD) (99). HH-associated arthritis can be distinguished from CPPD disease radiographically by its specific involvement of the second and third metacarpophalangeal joints and the hook-shaped osteophyte of the metacarpal head (100).

### Skin

Hyperpigmentation may be one of the earlier signs of HH (101). Iron deposits in the skin lead to increased melanin production and deposition, giving rise to the characteristic metallic or slate gray hue commonly referred to as bronzing (101). Hypermelanotic skin pigmentation is usually generalized but frequently is deeper on the face, neck, extensor aspects of the lower forearms, dorsa of the hands, lower legs, and genital region (101,102). It is best identified by comparing the volar surface of the forearm with that of a healthy white subject (102).

### Other

Fatigue is a common symptom associated with HH (103). The severity of fatigue can vary from mild to debilitating, and improvement with treatment has been observed (103,104). Patients with HH may also have a compromised immune system as iron overload is associated with dysregulation of CD8+ T cells, which can facilitate the growth of certain bacteria including *Listeria monocytogenes*, *Yersinia enterocolitica*, *Escherichia coli*, and *Vibrio vulnificus* (105). Rarely, movement disorders can occur due to iron deposition in the brain in HH, including Parkinsonism, chorea, and tremor (106).

## DIAGNOSTIC TESTING

### Iron studies

The initial approach to the evaluation of patients with suspected iron overload disorders includes measurement of serum iron level, TS, SF, and unsaturated iron-binding capacity (UIBC). TS is the preferred initial screening test, and fasting is not required to accurately determine TS (107). A TS of greater than 45% identifies 97.9%–100% of C282Y homozygotes (108), although a small proportion of patients with HH such as younger individuals at an earlier stage may have TS of <45% (109). Iron overload may also be present with an elevated SF level and a normal TS level, particularly in non–*HFE*-related iron overload (110).

SF is an excellent predictor of advanced fibrosis but lacks specificity as a screening test (111), because hyperferritinemia can be present in other conditions including alcoholic liver disease, HCV, NAFLD, and neoplastic disease. In C282Y homozygotes, a SF of >1,000 ng/mL, in combination with elevated aminotransferase levels and a low platelet count, predicts cirrhosis in more than 80% of patients (112). A normal SF, defined as less than 200 ng/mL in premenopausal women or 300 ng/mL in men and postmenopausal women, in combination with a TS of <45%, has a negative predictive value of 97% for excluding iron overload (112).

The UIBC is the inverse of TS and can be obtained as a one-step automated test. In large-scale population screening studies, UIBC has been shown to be comparable in diagnostic accuracy with TS and may be used as an alternative screening test for detecting HH (110). A UIBC below 26 μmol/L has a sensitivity of 90% and specificity of 90% for detecting C282Y homozygosity (37).

### Genetic testing

In 1996, Feder et al. (3) reported the identification of a homozygous mutation in a novel MHC class I–like gene that was present in 83% of subjects with clinically defined HH. After this discovery, genotyping for *HFE* mutations (C282Y) is now a standard part of the evaluation of patients in whom HH is suspected on clinical grounds or based on the finding of elevated iron studies.

H63D and S65C are the 2 other commonly described *HFE* mutations, and commercial laboratories frequently report on all 3 mutations on clinical *HFE* testing (22). The H63D mutation is more common than C282Y and is found in most populations worldwide, with the highest prevalence among whites, of whom approximately 20% carry at least 1 copy of H63D (18,19,24). The S65C mutation is less common than either C282Y or H63D, with a heterozygote frequency of about 2% among whites (113,114). This mutation appears to have a modest effect on iron metabolism in the presence of the C282Y mutation, but iron overload–related disease has not been reported in C282Y/S65C compound heterozygotes. Neither the homozygous nor the heterozygous H63D or S65C mutation is a cause of pathologic iron overload.

***Recommendations.***

3. We recommend that individuals with the H63D or S65C mutation in the absence of C282Y mutation should be counseled that they are not at increased risk of iron overload (conditional recommendation, very low quality of evidence).

**PICO question: Should testing for non-*HFE* genes vs not testing be used to diagnose hemochromatosis in those who are negative for the C282Y or H63D alleles?**

The question of testing for non-*HFE* hemochromatosis sometimes arises in a patient who has phenotypic evidence of iron overload but

in whom *HFE* gene mutations are not identified. Case reports and small series have demonstrated links between mutations in the genes encoding hemojuvelin, hepcidin, TFR2, and FPN with uncommon forms of iron overload. However, these disorders are very rare, with an estimated frequency of iron overload caused by pathogenic variants of *HFE*2 (hemojuvelin) and TFR2 in 1 in 5–6 million people; pathogenic variants arising from mutations in the hepcidin gene are even less common (115). Before pursuing testing for non-*HFE* hemochromatosis, alternative explanations for elevated serum iron tests should be excluded, because abnormal iron studies due to conditions such as AUD or NAFLD are far more common than non-*HFE* hemochromatosis (59,116). Contrarily, sequencing of non-*HFE* genes may be considered in atypical cases of iron overload, such as a younger patient presenting with endocrine or cardiac involvement.

### *Recommendations*

4. We suggest against further genetic testing among patients with iron overload testing negative for the C282Y and H63D alleles (conditional recommendation, very low quality of evidence).

### Liver biopsy

Given the widespread availability of *HFE* gene testing to establish the diagnosis of HH, currently the primary utility of liver biopsy in HH is for staging of fibrosis, particularly among patients who are C282Y homozygotes and have a SF of >1,000 ng/mL (71,112). Among C282Y homozygotes with a SF of <1,000 ng/mL, liver biopsy is not indicated, unless there is a concurrent risk factor for cirrhosis (72,111). In the absence of such risk factors, less than 2% of C282Y homozygotes with a SF of <1,000 ng/mL have advanced fibrosis or cirrhosis (71,111,112). However, if the patient does have clinical features of advanced fibrosis based on physical examination, laboratory studies, or imaging, a liver biopsy can be considered.

Histochemical staining of the liver biopsy specimen is done using hematoxylin and eosin stain, Masson's trichrome stain to determine fibrosis staging, and Perls' Prussian blue stain to identify and characterize the distribution of stored iron (117). Liver biopsy also allows for hepatic iron staining and determination of hepatic iron concentration (HIC) or hepatic iron index (HII) to distinguish C282Y homozygotes from compound heterozygotes. Furthermore, given the variable penetrance of HH, HIC can help determine long-term risk of developing cirrhosis (118) and as a surrogate measure of total body iron stores in iron-loading anemias (119).

HII is determined by dividing HIC by the patient's age in years and was developed based on the concept that homozygotes would continue to absorb excess dietary iron throughout their lifetime, whereas heterozygotes would not (120). An HII of ≥1.9 and/or an HIC of 71 μmol/g dry weight can distinguish homozygous HH from compound heterozygous HH or those with secondary iron overload (118). For the purposes of fibrosis staging, however, SF level is considered to be a more accurate predictor of fibrosis than HIC (121).

Diagnostic features of liver histology in type 1 HH include (118)

1. grade 4 stainable iron in hepatocytes with a periportal distribution and lack of stainable iron in Kupffer cells
2. an HIC of >71 μmol/g dry weight
3. an HII of >1.9.

Iron stores in *HFE*-related HH, juvenile HH, and type 3 HH typically are found in periportal hepatocytes, with little or no iron in Kupffer cells. As iron accumulation continues, midzonal and centrilobular hepatocytes along with the biliary epithelium accumulate iron (122). By contrast, in type 4 HH, iron is preferentially found in Kupffer cells (117). In secondary iron overload, a pattern of iron distribution similar to type 4 HH is observed, whereby iron deposition is primarily in Kupffer cells and reticuloendothelial cells, with a sparsity of iron in hepatocytes and lack of a periportal to pericentral iron gradient (123) (Figure 2).

Regarding the use of transient elastography, this modality has not been validated to assess fibrosis stage in HH. A prospective study demonstrated that transient elastography readings did not correlate with SF levels (124). This study, additionally, did not compare transient elastography directly with liver biopsy.

### Magnetic resonance imaging

MRI, specifically T2-weighted imaging, is another modality that can be used to diagnose iron overload due to HH and to estimate HIC noninvasively (125–127). Hepatic iron causes loss of signal intensity in the liver, which increases proportionally to the amount of iron deposition (128). The hepatic iron is then quantified by measuring the ratio of the signal intensity of the liver with that of a reference tissue (e.g., paraspinous muscle) (125–127). MRI can also distinguish between *HFE*-related hemochromatosis and FPN disease or secondary iron overload, as splenic iron deposition is absent in HFE hemochromatosis but present in FPN disease or secondary iron overload (Figure 3).

A meta-analysis of 20 studies evaluating 819 patients with HH and secondary iron overload showed that T2 spin echo and T2* gradient-recalled echo MRI identified patients without iron overload accurately, with a negative predictive value of 0.83 and 0.88, respectively. However, MRI was less accurate in establishing a definite diagnosis of liver iron overload, with a positive predictive value of 0.81 for T2 spin echo and 0.74 for T2* gradient-recalled echo imaging (129). These findings indicate that measurements of HIC by MRI may be more useful in ruling out than diagnosing clinically significant iron overload.

### PICO question: In patients with hemochromatosis, should MRI vs liver biopsy be used to assess hepatic iron content?

Liver biopsy provides a direct assessment of HIC and can also be used in fibrosis staging and ruling out concurrent liver diseases. It does, however, carry a small but tangible risk of complications including bleeding and perforation as well as the possibility of sampling variability, leading to misinterpretations (130). With the use of specific software to quantify iron, an MRI can noninvasively estimate HIC and distinguish between primary and secondary iron overload based on iron uptake in the reticuloendothelial system.

### *Recommendations*

5. We suggest a non–contrast-enhanced MRI in conjunction with software used for the estimation of HIC (i.e., MRI T2*) be used to noninvasively measure liver iron concentration in the non-C282Y homozygote with suspected iron overload. If there is a concomitant need to stage hepatic fibrosis or evaluate for alternate liver diseases, then liver biopsy is the preferred method (conditional recommendation, low quality of evidence).

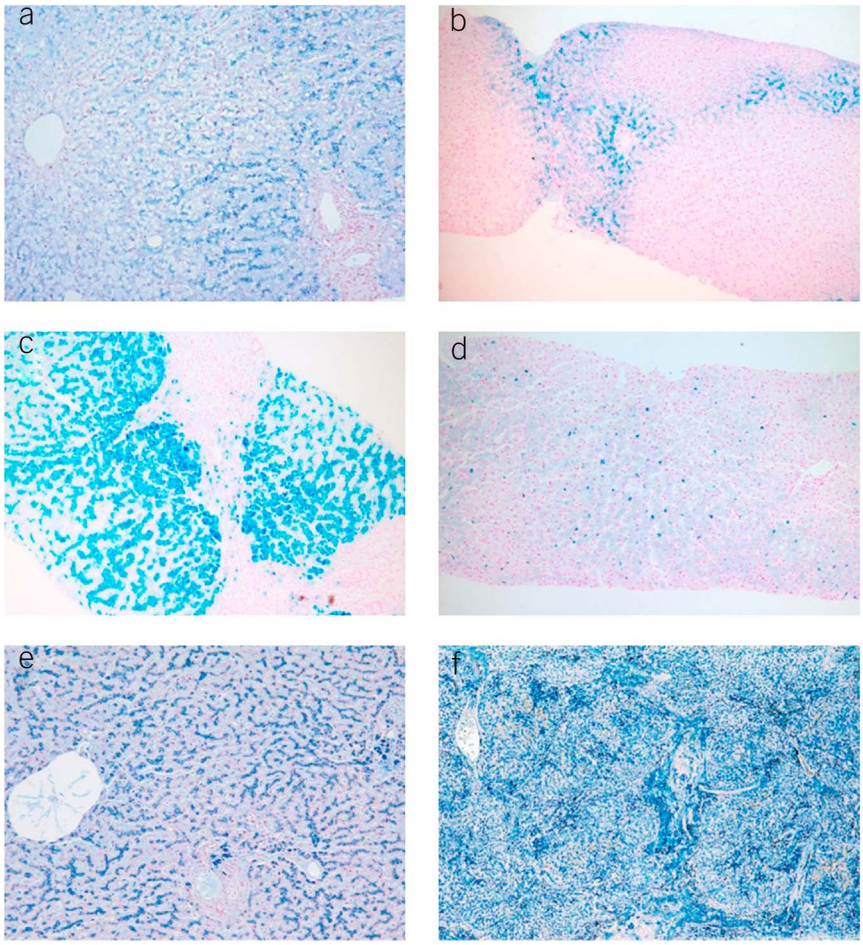


**Figure 2.** Pathologic findings in iron overload disorders. (**a**) HFE hemochromatosis (type 1): parenchymal iron overload with porto-central gradient; (**b**) Tfr2 hemochromatosis: parenchymal, periportal iron overload; (**c**) juvenile hemochromatosis: panlobular iron overload; (**d**) ferroportin disease: predominant Kupffer cell iron overload; (**e**) African siderosis: parenchymal cell iron overload; (**f**) thalassemia major: massive iron overload in the hepatocytes and Kupffer cells.

## TREATMENT

### When to initiate treatment

Treatment should be initiated in C282Y homozygotes with an elevated SF, defined as >300 ng/mL in men and >200 ng/mL in women, along with a TS of ≥ 45% (40,43). Homozygous patients with a SF within normal limits at diagnosis, however, are unlikely to develop clinically relevant iron overload later in life and therefore can be monitored with serial assessment of liver aminotransferase and SF levels (131,132). Although patients with a SF of <1,000 ng/mL at the time of diagnosis are unlikely to have end-organ damage from HH (133), we still suggest treatment in this population considering that between 13% and 35% of men and between 16% and 22% of women will progress to a SF of >1,000 ng/mL if left untreated (131). Benefits of treatment in this population extend beyond prevention of liver disease. One retrospective study reported a reduced mortality due to cardiovascular events and extrahepatic cancers, compared with the general population, among treated C282Y homozygotes, even with baseline SF levels below <1,000 ng/mL (80). Another randomized controlled trial comparing iron removal to sham treatment found an improvement in fatigue and quality of life in the treatment arm, thereby demonstrating the benefit of iron removal in these patients (134).

For compound heterozygotes (C282Y/H63D), the risk of developing clinically relevant iron overload is low based on *HFE* genotype mutation alone (22,23), although liver fibrosis may develop among heterozygotes with comorbidities such as NAFLD, diabetes, or excess alcohol consumption (23). Therefore, such risk factors need to be evaluated and treated before the consideration of iron removal. H63D homozygosity has also been reported to be associated with a phenotypic picture of hemochromatosis in rare cases, but this also is usually in association with other comorbidities (26). A liver biopsy can be considered in these patients to rule out secondary liver disorders or to evaluate HIC and fibrosis stage, particularly among individuals with a SF above 1,000 ng/mL (71). For compound heterozygotes or H63D homozygotes with evidence of elevated HIC on biopsy, iron removal can be considered (40,43).

Our suggested algorithm regarding when to initiate treatment is displayed in Figure 4.

### Phlebotomy

Phlebotomy as a means to treat hemochromatosis was first described over 70 years ago and remains the mainstay of treatment of HH (129). Once the decision is made to perform

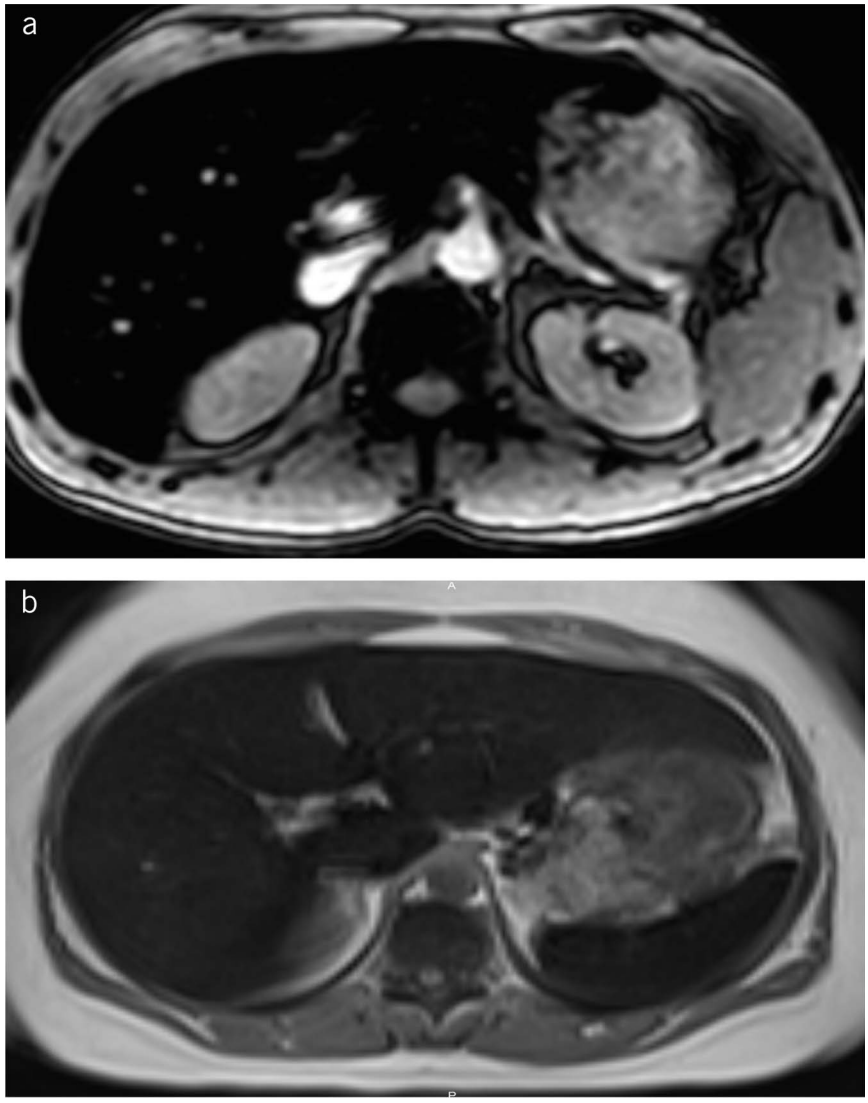


**Figure 3.** MRI of *HFE* iron overload and secondary iron overload. (**a**) Iron deposition in the liver from type 1 hereditary hemochromatosis; (**b**) iron deposition in the liver and spleen on the MRI, consistent with secondary iron overload.

phlebotomy, the initial phase typically is done with weekly removal of 500 mL of blood (40,43). Larger volumes of blood, usually 1,000 mL, can be removed if tolerated to expedite removal of excess iron; conversely, in patients who do not tolerate weekly phlebotomies, smaller volumes of blood can be removed or the interval between sessions can be increased, although this will lengthen the time required to mobilize the excess iron (135). It is important to check the hemoglobin level before and during treatment to ensure it is above 11 g/dL (136). SF level should be checked monthly during the course of phlebotomy until a goal SF level of 50–100 ng/mL is reached (40,43,135).

After the SF has reached its goal level, the initial induction phase of treatment is complete and the maintenance phase follows. The goal of this phase is to maintain SF levels near 50 ng/mL, and the frequency which phlebotomy occurs typically is 3–4 times per year (135,136).

Patients with HH should be advised to avoid vitamin C supplements because ascorbic acid increases iron absorption (137). (See Box 2 for additional information about counseling the patient who will undergo phlebotomy.) Elimination of red meat and other sources of dietary iron is not necessary in the patient undergoing phlebotomy, although a systematic review did suggest that dietary iron restriction may reduce the amount of blood needed to be phlebotomized by 0.5–1.5 L (138).

Blood removed by phlebotomy has been used for transfusion both from patients undergoing induction and maintenance treatment. However, there are no universal policies on the practice of using blood from patients with HH for donation. Many blood banks have a policy of not accepting blood from patients with HH, although others have done so without complications.

### Effects of phlebotomy on the manifestations of HH

***Liver fibrosis and portal hypertension.*** Several series comparing pre- and post-phlebotomy liver biopsies in patients with HH noted improvements in liver fibrosis after the removal of

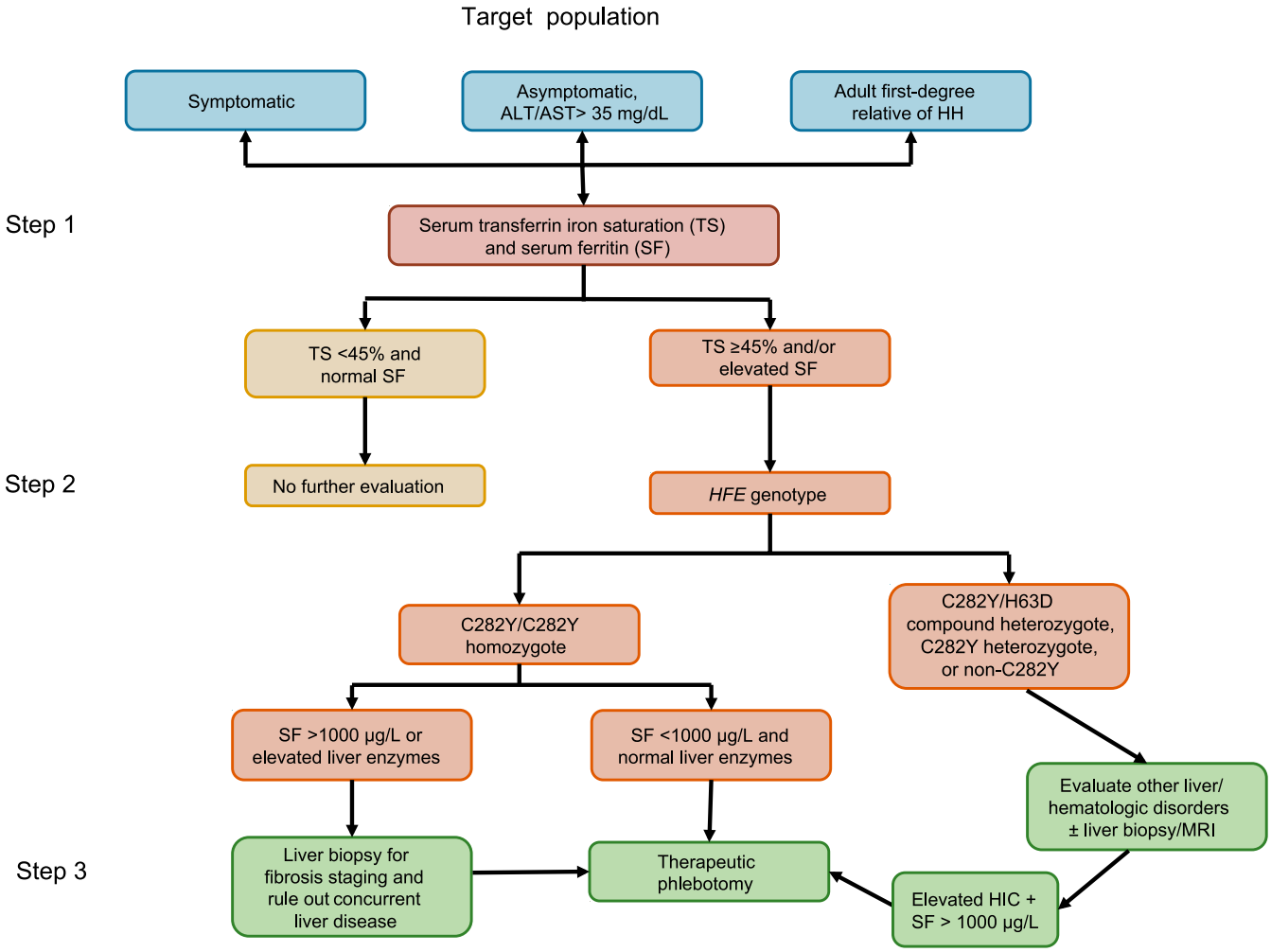


**Figure 4.** Algorithm regarding the diagnosis and treatment of HH. Step 1: In the patient with suspected HH based on symptoms, elevated liver enzymes, or family history, the suggested initial screening test should be TS and SF level. Step 2: If TS is <45% and SF is normal, further evaluation is not necessary. If TS is ≥45% and SF is elevated, *HFE* gene testing should be performed. Step 3: All patients who are C282Y homozygotes should proceed to phlebotomy. If SF is >1,000 µg/L, liver biopsy is suggested for fibrosis staging. Patients with cirrhosis should undergo screening for hepatocellular carcinoma. A liver biopsy can also be considered before initiating phlebotomy in C282Y homozygotes with elevated liver enzymes to rule out additional causes of liver disease. In the patient who is not a C282Y homozygote, evaluation for other causes of elevated iron indices should be performed, including liver and hematologic disorders. If other causes of iron overload have been ruled out, HIC should be assessed by liver biopsy or MRI. Patients with elevated HIC and SF of >1,000 µg/mL should proceed to therapeutic phlebotomy. ALT, alanine aminotransferase; AST, aspartate transaminase; HH, hereditary hemochromatosis; HIC, hepatic iron concentration; SF, serum ferritin; TS, transferrin-iron saturation.

excess iron. These improvements have been reported mainly in patients with mild to moderate fibrosis at baseline (67,70,139,140).

***Cardiomyopathy.*** Cardiomyopathy due to HH may improve with phlebotomy; however, information on treatment responses specific to patients with cardiac dysfunction secondary to proven type 1 HH is limited (141,142).

***Diabetes.*** Diabetes does not improve with iron depletion (143).

***Arthropathy.*** Phlebotomy does not reverse established joint disease, which may progress despite treatment; however, some patients report diminished arthralgias after iron removal (144,145).

***Hypogonadism.*** In most cases, hypogonadism does not improve with phlebotomy (94).

***Skin.*** Skin pigmentation slowly regresses after phlebotomy (146).

**PICO question: Should phlebotomy vs no phlebotomy be used as management in patients with HH defined as C282Y/C282Y or C282Y/H63D?**

***Recommendations***

6. We recommend that phlebotomy be used as the first-line treatment in patients diagnosed with HH, as determined by C282Y homozygosity or C282Y/H63D compound heterozygosity (strong recommendation, moderate quality of evidence).

***Key concept.***

1. The goal of phlebotomy is to achieve a SF level between 50 and 100 µg/dL.

Certain clinical manifestations do not improve with serial phlebotomy, including cirrhosis, arthropathy, diabetes, and hypogonadism.

**Box 2. Counseling the patient who will undergo phlebotomy**

- Phlebotomy is expected to occur weekly, removing around 500 mL of blood each session.
- The goal is to reduce your serum ferritin level to a goal of 50–100 ng/mL.
- In addition to monitoring your serum ferritin, we will monitor your hemoglobin so that it does not fall below 11 g/dL.
- Once the goal serum ferritin level is reached, we will reduce the frequency of phlebotomy to 3–4 times a year.
- You do not need to restrict dietary iron when undergoing phlebotomy.
- You should avoid iron and vitamin C supplements.
- Treatment with phlebotomy will reduce your risk of developing complications related to liver disease or liver cancer.
- The following complications may improve with phlebotomy: abnormal liver tests, heart dysfunction, fatigue.
- The following complications likely will not improve with phlebotomy: diabetes, arthralgias, hypogonadism.
- Treatment with phlebotomy does not medically prevent a patient from being a blood donor.

### Chelation

There are 3 chelating agents currently approved by the US Food and Drug Administration for the treatment of secondary iron overload: deferoxamine, deferiprone, and deferasirox. Deferoxamine has been approved for the treatment of secondary iron overload in thalassemia and is used as a subcutaneous or intravenous infusion, dosed at 20–60 mg/kg/d over 8–24 h and given 5–7 times weekly. Adverse effects include retinopathy and auditory toxicity (147). Deferiprone is an oral chelator, given at a dosage of 75–100 mg/kg/d 3 times daily, which is approved for the treatment in transfusion-dependent patients with thalassemia when chelation with deferoxamine is inadequate (147). Significant side effects of deferiprone include neutropenia and agranulocytosis. Deferasirox, the most recently approved oral chelator, has side effects including gastrointestinal upset, rash, aminotransferase elevation, and renal toxicity, which can occur in more than 10% of all patients (147).

### PICO question: Should chelation vs no chelation be used in patients with HH who are intolerant to serial phlebotomy?

Iron chelation has been shown to be effective in the treatment of HH in small clinical trials (148,149). In 1 study, 49 homozygotes with SF levels ranging from 300 to 2,000 ng/mL were randomized to receive deferasirox at doses ranging from 5 to 15 mg/kg/d. After 48 weeks of treatment, SF levels decreased by 63.5%, 74.8%, and 74.1% for the 5, 10, and 15 mg/kg/d doses, respectively. However, when receiving deferasirox at 15 mg/kg/d, side effects including elevated aminotransferases and creatinine were more prevalent (149). A more recent phase 2 study of 10 patients with HH, intolerant or refractory to phlebotomy, evaluated treatment with deferasirox at 10 mg/kg/d. After 12 months of treatment, deferasirox achieved reduction in median ferritin levels and HIC and was well tolerated (148).

We therefore recommend the use of iron chelation for the treatment of HH for the patient who is intolerant or refractory to phlebotomy or when phlebotomy has the potential for harm, such as in patients with severe anemia or congestive heart failure (150).

We do not recommend chelation as the first-line therapy for HH, given the effectiveness of phlebotomy, the associated side effects of chelation including hepatic and renal toxicity, and the relatively small sample size of clinical trials supporting chelation.

#### *Recommendations*

7. We recommend against chelation as the first-line therapy for HH, given the effectiveness of phlebotomy, the associated side effects of chelation including hepatic and renal toxicity, and the relatively small sample size of clinical trials supporting chelation (strong recommendation, low quality of evidence).
8. We recommend the use of iron chelation for the treatment of HH for the patient who is intolerant or refractory to phlebotomy or when phlebotomy has the potential for harm, such as in patients with severe anemia or congestive heart failure (strong recommendation, low quality of evidence).

### Erythrocytapheresis

An alternative to phlebotomy is erythrocytapheresis, a technique that selectively removes RBCs and returns the remaining components, such as plasma proteins, clotting factors, and platelets, to the patient (16). This intervention is particularly useful in patients suffering from hypoproteinemia or thrombocytopenia. Additionally, erythrocytapheresis can remove up to 1,000 mL of RBCs per procedure, compared with 200–250 mL with phlebotomy. Furthermore, erythrocytapheresis can be individualized for body weight, gender, hematocrit, and total blood volume (151,152), to increase its effectiveness, leading to a reduction in the number of treatment procedures needed.

The recommended frequency of erythrocytapheresis is once in every 2–3 weeks, depending on the patient's hemoglobin. The RBC volume to be removed is usually between 350 and 800 mL. The minimal targeted post-procedure hemoglobin must be at least 10 mg/dL. In patients without comorbidities and estimated removed RBC volume of $\leq$500 mL, volume expansion is not needed. For the removal of higher RBC volumes, it is recommended that 30% of the removed RBC volume should be replaced with isotonic saline during the first treatment procedure (16). The most frequently described but overall still rare adverse reactions during therapeutic apheresis procedures include reactions to the citrate used as anticoagulant, including muscle cramps, paraesthesias, and nausea.

Several studies have compared erythrocytapheresis with phlebotomy. One small series of 12 patients in the induction phase of treatment demonstrated erythrocytapheresis to yield a greater reduction in SF per treatment, although over time decreases in both SF and TS were similar (153). A larger trial of patients in the maintenance phase of treatment reported erythrocytapheresis equally effective as phlebotomy, with a significantly lower number of treatments annually (1.9 vs 3.3), although costs were still higher for erythrocytapheresis (154).

### Proton pump inhibitors

Gastric acid has an important role in the release of non-heme iron, the major form of iron in most food. Proton pump inhibitors (PPIs) inhibit the absorption of iron in patients with HH and therefore reduce the number of phlebotomies required to maintain SF below target levels (155–157). One small study of 7 homozygous patients found PPI administration to reduce the absorption of iron postprandially and further decreased the

volume of blood needed to remove by phlebotomy annually (155). A separate retrospective analysis demonstrated a reduction in the number of phlebotomies needed in patients taking PPIs for a minimum of 2 years (156).

In a recent randomized controlled trial, 30 C282Y homozygous patients were allocated to pantoprazole 40 mg/d or placebo for 12 months. Phlebotomies were performed when SF was >100 ng/mL. Phlebotomy need was significantly lower in patients taking PPI, with a median of 2.6 procedures among those receiving placebo and 1.3 among patients taking PPIs ($P$ = 0.005) (157).

The results of these studies imply that PPIs could have an additional role in the treatment of selected patients with HH to reduce the frequency of phlebotomies. Nonetheless, we do not recommend the routine use of PPIs as a treatment in HH. However, if they are otherwise needed for other primary indications, they may have the benefit of reducing the frequency of phlebotomies needed.

***Recommendations.***

9. We recommend against the routine use of PPIs as the primary treatment of HH (strong recommendation, low quality of evidence).

### Treatment of secondary iron overload

Both phlebotomy and chelation may have a therapeutic role in the treatment of iron-loading anemias, though chelation is the preferred treatment due to concerns regarding exacerbation of anemia from phlebotomy (158). In patients with secondary iron overload from excess transfusions, a correlation has been established between SF levels of >1,000 ng/mL and elevated HIC on liver biopsy (159,160). However, for patients with non–transfusion-dependent iron-loading anemias, such as the thalassemia intermedia, SF levels may underestimate HIC (160,161). As such, a SF threshold of >800 ng/mL should lead to initiation of treatment in such patients (162).

The indications for phlebotomy in other conditions such as AUD, HCV, and NAFLD remain controversial. We suggest that all patients should be screened for AUD before end counseled to abstain from alcohol in the appropriate setting, rather than proceeding with the treatment. In patients with HCV, phlebotomy and iron depletion have been shown to improve virologic response to interferon-based therapy (163), although these findings are less relevant given the excellent cure rates of direct acting antiviral therapy. Evidence has indicated that hyperferritinemia among patients with NAFLD increases the risk of progression to cirrhosis and HCC, which has led to exploratory studies to assess whether phlebotomy improves NAFLD (164,165). One randomized controlled trial comparing phlebotomy with the standard of care in patients with NAFLD demonstrated a greater reduction in SF in the treatment arm but no significant improvements in alanine aminotransferase levels, hepatic fat, or insulin resistance; further studies have corroborated these findings (164,166).

## LIVER TRANSPLANTATION FOR HH

### PICO question: Should liver transplantation vs no liver transplantation be used in patients with liver disease due to *HFE* hemochromatosis to improve the outcomes (mortality/survival)?

Referral for liver transplantation (LT) should be considered in patients with HH with end-stage liver disease or HCC. LT is curative not only in patients with decompensated cirrhosis and HCC but it also normalizes hepcidin levels and alterations in iron metabolism (167). Although several groups reported inferior outcomes of LT in patients with HH compared with patients transplanted for other etiologies of chronic liver disease (168), more recent series have demonstrated similar survival in these groups at 1- and 5-year posttransplant, compared with other etiologies of liver disease (168–173). Taken as a whole, these studies are limited by the small number of transplants performed in patients with proven HH, comprising ~1% of all transplants in most series. In the reports that found inferior outcomes in patients with HH, excess mortality was variably attributed to higher rates of infectious complications (174) or cardiovascular disease (172).

Treatment of iron overload should not be deferred in a patient with HH who is a potential transplant candidate and whose general health permits, but it may not be tolerated by patients with HH who present with advanced liver disease. In such cases, the inability to de-iron the patient preoperatively is not a contraindication to transplantation (168).

***Recommendations.***

10. We recommend that LT be used in patients with HH who have decompensated cirrhosis or HCC (strong recommendation, low quality of evidence).

## PROGNOSIS

A critical determinant of prognosis in HH is the presence of cirrhosis at the time of diagnosis. In a retrospective study, Strohmeyer and colleagues reported that the cumulative survival of patients with HH without cirrhosis did not differ from that of the general population, whereas survival of patients with HH and cirrhosis was significantly reduced (78). Bardou-Jacquet et al found that the mortality from liver disease including HCC for C282Y homozygotes with ferritin of >2,000 ng/mL at diagnosis was increased compared with the general population, with a standardized mortality ratio of nearly 24; the standardized mortality ratio for liver cancer in this group vs the general population was 49 (80).

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## CONFLICTS OF INTEREST

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