

ACG Clinical Guideline: Hereditary Hemochromatosis

Kris V. Kowdley, MD, FACP¹, Kyle E. Brown, MD, MSc^{2,3,4}, Joseph Ahn, MD, MS, MBA, FACP (GRADE Methodologist)⁵ and Vinay Sundaram, MD, MSc⁶

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.

Am J Gastroenterol 2019;114:1202–1218. <https://doi.org/10.14309/ajg.0000000000000315>; published online July 22, 2019

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).

¹Organ Care Research and Liver Care Network, Swedish Medical Center, Seattle, Washington; ²Iowa City Veterans Administration Medical Center, Iowa City, Iowa; ³Department of Internal Medicine, Division of Gastroenterology-Hepatology, University of Iowa, Iowa City, Iowa; ⁴Free Radical and Radiation Biology Program, Roy J. and Lucille A. Carver College of Medicine, University of Iowa, Iowa City, Iowa; ⁵Division of Gastroenterology and Hepatology, Oregon Health and Sciences University, Portland, Oregon; ⁶Department of Medicine and Comprehensive Transplant Center, Cedars-Sinai Medical Center, Los Angeles, California.

Correspondence: Kris V. Kowdley, MD, FACP. E-mail: kris.kowdley@swedish.org.

Received December 11, 2018; accepted June 4, 2019

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.

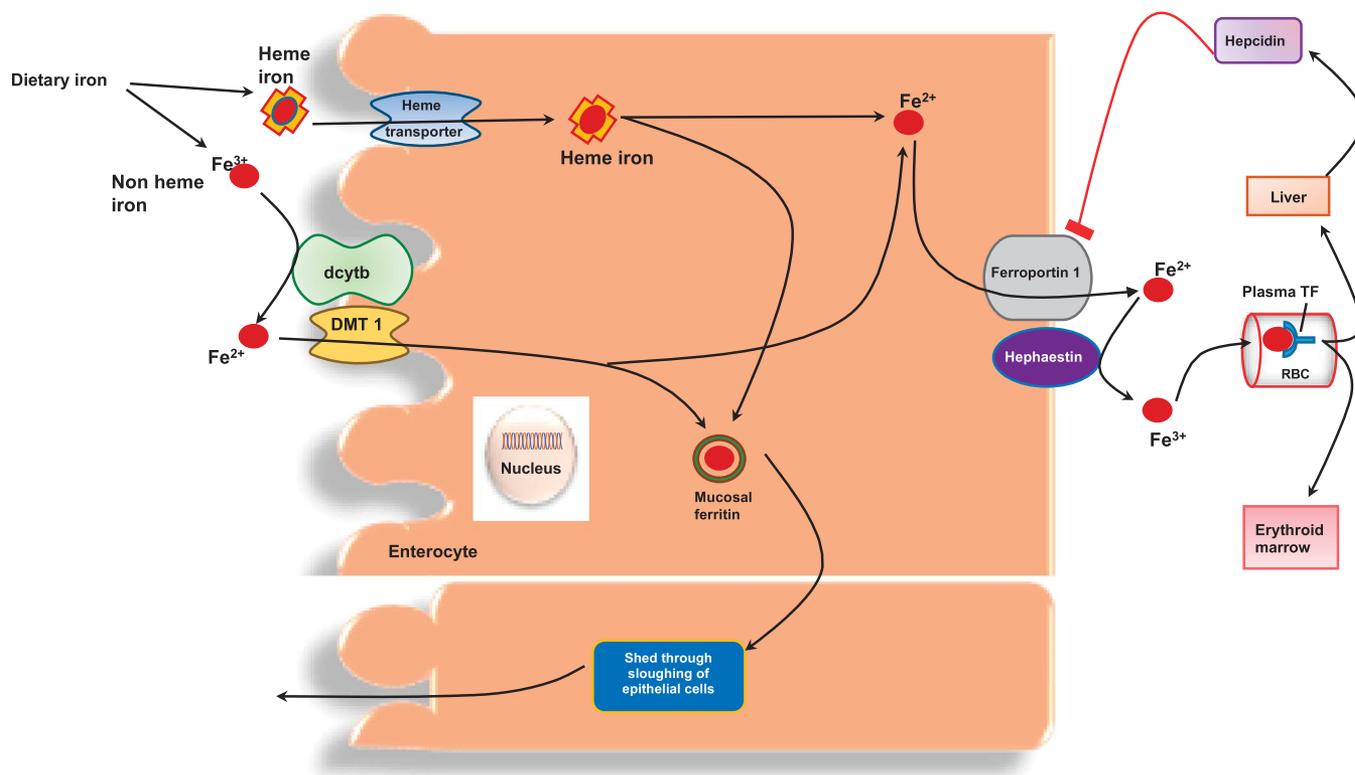


Figure 1. Overview of intestinal iron absorption. Dietary iron is taken up by enterocytes in the proximal small intestine. The primary types of iron in the diet are heme iron, which is readily absorbed by mechanisms that are poorly understood at present, and non-heme iron, which is predominantly ferric 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 (dctyb) 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)	<i>HFE</i> on 6p21.3 Mutations in <i>HFE</i> : 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)	<i>HFE</i> on 6p21.3 Mutations in <i>HFE</i> : 1. C282Y 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	<i>HFE</i> on 6p21.3 Mutations in <i>HFE</i> : 1. S65C	AR		Possible elevations in serum iron/ferritin, no evidence of tissue iron deposition.
Type 2A juvenile HH	<i>HJV</i> (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	<i>HAMP</i> (hepcidin) on 19q13	AR	Downregulation of iron efflux from erythrocytes.	Earlier onset, <30 years old, hypogonadism and cardiomyopathy are prevalent.
Type 3 HH	<i>TFR2</i> (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)	<i>SLC40A1</i> (FPN) on 2q32 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)	<i>SLC40A1</i> (FPN) on 2q32 Gain of function, FPN cannot be internalized after hepcidin binding	AD	Resistance to hepcidin.	Fatigue, joint pain.

AD, autosomal 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 (0.00039%) (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 Hepatomegaly Fibrosis Cirrhosis HCC
Endocrine	Hyperglycemia Diabetes mellitus Hypogonadism Testicular atrophy Amenorrhea Loss of libido Hypopituitarism
Skin	Hypermelanotic pigmentation (bronze skin)
Joints	Arthralgia Arthritis Chondrocalcinosis
Heart	Cardiomyopathies Arrhythmias 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

- 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 μ mol/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 *HFE2* (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 $71 \mu\text{mol/g}$ 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 $>71 \mu\text{mol/g}$ 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).

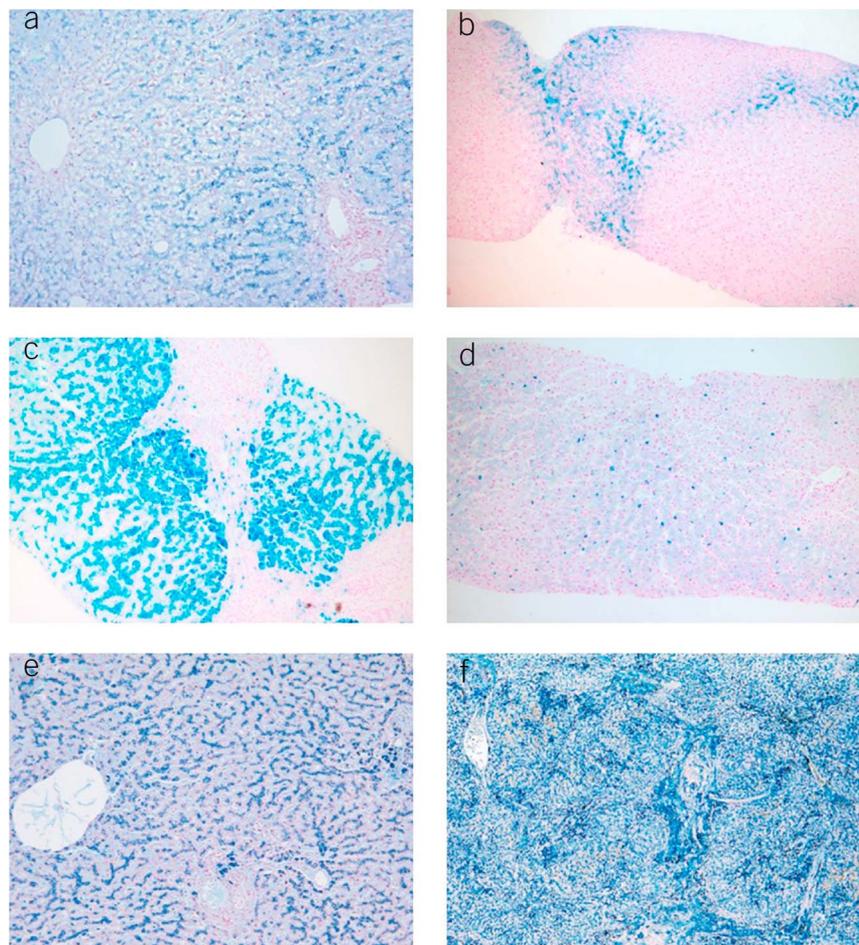


Figure 2. Pathologic findings in iron overload disorders. (a) HFE hemochromatosis (type 1): parenchymal iron overload with porto-central gradient; (b) Tfr2 hemochromatosis: parenchymal, periportal iron overload; (c) juvenile hemochromatosis: panlobular iron overload; (d) ferroportin disease: predominant 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 $\geq 45\%$ (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

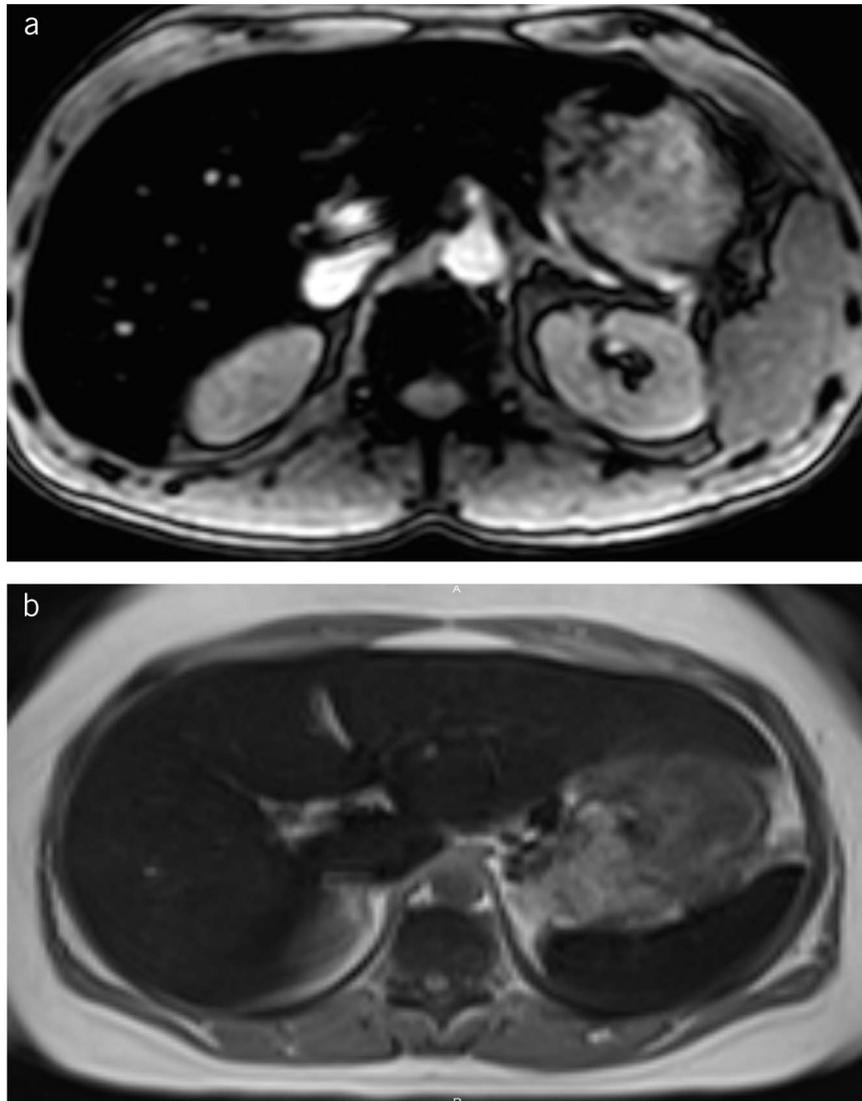


Figure 3. MRI of *HFE* iron overload and secondary iron overload. (a) Iron deposition in the liver from type 1 hereditary hemochromatosis; (b) iron deposition in the liver and spleen on the MRI, consistent with secondary iron overload.

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

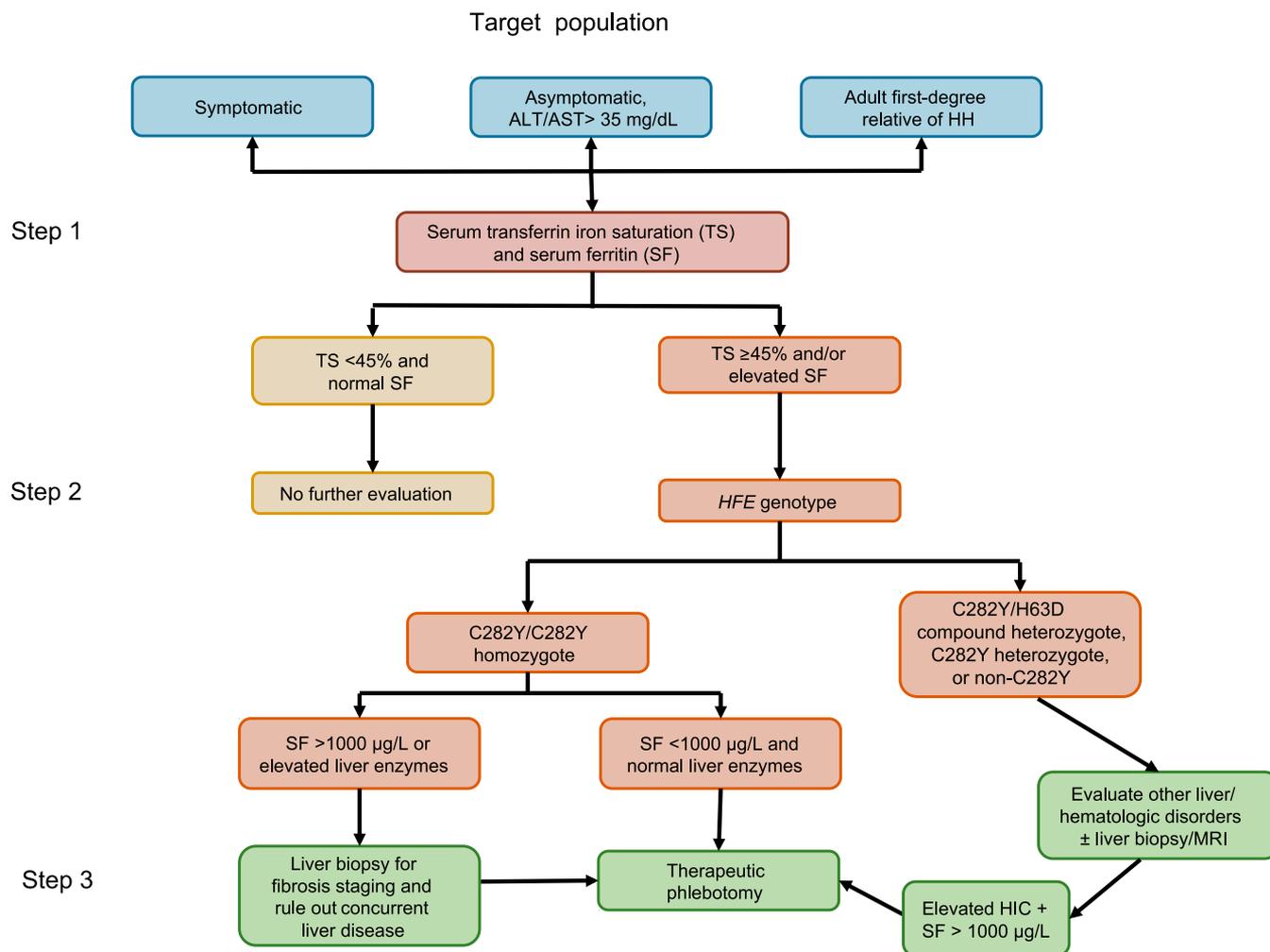


Figure 4. Algorithm regarding the diagnosis and treatment of HH. Step 1: In the patient with suspected HH based on symptoms, elevated liver enzymes, or family history, the suggested initial screening test should be TS and SF level. Step 2: If TS is $<45\%$ and SF is normal, further evaluation is not necessary. If TS is $\geq 45\%$ 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 $>1,000 \mu\text{g/L}$, 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 $>1,000 \mu\text{g/mL}$ 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

- 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.

- The goal of phlebotomy is to achieve a SF level between 50 and $100 \mu\text{g/dL}$.

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 ≤ 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, paresthesias, 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, Strohmeier 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).

ACKNOWLEDGEMENTS

This guideline was produced in collaboration with the Practice Parameters Committee of the American College of Gastroenterology. The Committee gives special thanks to Janice Jou, MD, who served as guideline monitor for this article, and to Bryan G. Sauer, MD, MSc (Clin Res), FACP, and Robert J. Wong, MD, MSD, FACP, who assisted with the GRADE methodologic process.

CONFLICTS OF INTEREST

Guarantor of the article: Vinay Sundaram, MD, MSc.

Specific author contributions: All authors contributed to the writing and review of the guideline.

Financial support: None.

Potential competing interests: K.V.K.: advisory boards: Abbvie, Gilead, Intercept, Merck, Novartis, Trio Health, Verlyx; consultant: Enanta, Gilead, Intercept, NGM Biopharma; speaking bureau: Gilead, Intercept; grant/research support: Abbvie, Evidera, Galectin, Gilead, Immuron, Intercept, Merck, NGM Biopharma, Novartis, Tobira, Trio Health. K.E.B.: no disclosures. J.A.: advisory board: Gilead. V.S.: speaker's bureau and advisory board: Gilead, AbbVie, Intercept, Salix.

REFERENCES

- Brissot P, Pietrangelo A, Adams PC, et al. Nature reviews. Dis Primers 2018;4:18016.
- von Recklinghausen FD. Über hamochromatose. Tagebl Versamml Natur Ärzte Heidelberg 1889;62:324.
- Feder JN, Gnirke A, Thomas W, et al. A novel MHC class I-like gene is mutated in patients with hereditary haemochromatosis. *Nat Genet* 1996; 13(4):399–408.
- Andrews NC. Disorders of iron metabolism. *N Engl J Med* 1999;341(26): 1986–95.
- Park CH, Valore EV, Waring AJ, et al. Hepcidin, a urinary antimicrobial peptide synthesized in the liver. *J Biol Chem* 2001;276(11): 7806–10.
- Pigeon C, Ilyin G, Courselaud B, et al. A new mouse liver-specific gene, encoding a protein homologous to human antimicrobial peptide hepcidin, is overexpressed during iron overload. *J Biol Chem* 2001;276(11):7811–9.
- Siddique A, Kowdley KV. Review article: The iron overload syndromes. *Aliment Pharmacol Ther*. 2012;35(8):876–93.
- Milic S, Mikolasevic I, Orlic L, et al. The role of iron and iron overload in chronic liver disease: Medical science monitor. *Int Med J Exp Clin Res* 2016;22:2144–51.
- Anderson GJ, Frazer DM. Current understanding of iron homeostasis. *Am J Clin Nutr* 2017;106(Suppl 6):1559S–66S.
- Daher R, Manceau H, Karim Z. Iron metabolism and the role of the iron-regulating hormone hepcidin in health and disease. *Presse Med* 2017; 46(12 Pt 2):e272–8.
- Abboud S, Haile DJ. A novel mammalian iron-regulated protein involved in intracellular iron metabolism. *J Biol Chem* 2000;275(26):19906–12.
- Donovan A, Brownlie A, Zhou Y, et al. Positional cloning of zebrafish ferroportin1 identifies a conserved vertebrate iron exporter. *Nature* 2000;403(6771):776–81.
- McKie AT, Marciani P, Rolfs A, et al. A novel duodenal iron-regulated transporter, IREG1, implicated in the basolateral transfer of iron to the circulation. *Mol Cell* 2000;5(2):299–309.
- Nemeth E, Tuttle MS, Powelson J, et al. Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization. *Science* 2004;306(5704):2090–3.
- Powell LW, Seckington RC, Deugnier Y. Haemochromatosis. *Lancet* 2016;388(10045):706–16.
- Rombout-Sestrienkova E, van Kraaij MG, Koek GH. How we manage patients with hereditary haemochromatosis. *Br J Haematol* 2016;175(5): 759–70.
- Moirand R, Jouanolle AM, Brissot P, et al. Phenotypic expression of HFE mutations: A French study of 1110 unrelated iron-overloaded patients and relatives. *Gastroenterology* 1999;116(2):372–7.
- Adams PC, Reboussin DM, Barton JC, et al. Hemochromatosis and iron-overload screening in a racially diverse population. *N Engl J Med* 2005; 352(17):1769–78.
- Allen KJ, Gurrin LC, Constantine CC, et al. Iron-overload-related disease in HFE hereditary hemochromatosis. *N Engl J Med* 2008;358(3): 221–30.
- Girouard J, Giguere Y, Delage R, et al. Prevalence of HFE gene C282Y and H63D mutations in a French-Canadian population of neonates and in referred patients. *Hum Mol Genet* 2002;11(2):185–9.
- Beutler E, Felitti VJ, Koziol JA, et al. Penetrance of 845G→A (C282Y) HFE hereditary haemochromatosis mutation in the USA. *Lancet* 2002; 359(9302):211–8.
- Gurrin LC, Bertalli NA, Dalton GW, et al. HFE C282Y/H63D compound heterozygotes are at low risk of hemochromatosis-related morbidity. *Hepatology* 2009;50(1):94–101.
- Walsh A, Dixon JL, Ramm GA, et al. The clinical relevance of compound heterozygosity for the C282Y and H63D substitutions in hemochromatosis. *Clin Gastroenterol Hepatol* 2006;4(11):1403–10.
- Gallego CJ, Burt A, Sundaresan AS, et al. Penetrance of hemochromatosis in HFE genotypes resulting in p.Cys282Tyr and p.[Cys282Tyr];[His63Asp] in the eMERGE Network. *Am J Hum Genet* 2015;97(4):512–20.
- Cheng R, Barton JC, Morrison ED, et al. Differences in hepatic phenotype between hemochromatosis patients with HFE C282Y homozygosity and other HFE genotypes. *J Clin Gastroenterol* 2009; 43(6):569–73.
- Gochee PA, Powell LW, Cullen DJ, et al. A population-based study of the biochemical and clinical expression of the H63D hemochromatosis mutation. *Gastroenterology* 2002;122(3):646–51.
- Aranda N, Viteri FE, Montserrat C, et al. Effects of C282Y, H63D, and S65C HFE gene mutations, diet, and life-style factors on iron status in a general Mediterranean population from Tarragona, Spain. *Ann Hematol* 2010;89(8):767–73.
- Asberg A, Thorstensen K, Hveem K, et al. Hereditary hemochromatosis: The clinical significance of the S65C mutation. *Genet Test* 2002;6(1):59–62.
- Papanikolaou G, Samuels ME, Ludwig EH, et al. Mutations in HFE2 cause iron overload in chromosome 1q-linked juvenile hemochromatosis. *Nat Genet* 2004;36(1):77–82.
- Porto G, Brissot P, Swinkels DW, et al. EMQN best practice guidelines for the molecular genetic diagnosis of hereditary hemochromatosis (HH). *Eur J Hum Genet* 2016;24(4):479–95.
- Camaschella C, Roetto A, Cali A, et al. The gene TFR2 is mutated in a new type of haemochromatosis mapping to 7q22. *Nat Genet* 2000; 25(1):14–5.
- Kawabata H, Fleming RE, Gui D, et al. Expression of hepcidin is down-regulated in Tfr2 mutant mice manifesting a phenotype of hereditary hemochromatosis. *Blood* 2005;105(1):376–81.
- Wallace DF, Clark RM, Harley HA, et al. Autosomal dominant iron overload due to a novel mutation of ferroportin1 associated with parenchymal iron loading and cirrhosis. *J Hepatol* 2004;40(4):710–3.
- Schimanski LM, Drakesmith H, Merryweather-Clarke AT, et al. In vitro functional analysis of human ferroportin (FPN) and hemochromatosis-associated FPN mutations. *Blood* 2005;105(10):4096–102.
- Drakesmith H, Schimanski LM, Ormerod E, et al. Resistance to hepcidin is conferred by hemochromatosis-associated mutations of ferroportin. *Blood* 2005;106(3):1092–7.
- Nittis T, Gitlin JD. The copper-iron connection: Hereditary aceruloplasminemia. *Semin Hematol* 2002;39(4):282–9.
- Adams PC. Epidemiology and diagnostic testing for hemochromatosis and iron overload. *Int J Lab Hematol* 2015;37(Suppl 1):25–30.
- Wood MJ, Skoien R, Powell LW. The global burden of iron overload. *Hepatol Int* 2009;3(3):434–44.
- Steinberg KK, Cogswell ME, Chang JC, et al. Prevalence of C282Y and H63D mutations in the hemochromatosis (HFE) gene in the United States. *JAMA* 2001;285(17):2216–22.
- European Association for the Study of the Liver. EASL clinical practice guidelines for HFE hemochromatosis. *J Hepatol* 2010;53:3–22.
- Aguilar-Martinez P, Bismuth M, Blanc F, et al. The Southern French registry of genetic hemochromatosis: A tool for determining clinical prevalence of the disorder and genotype penetrance. *Haematologica* 2010;95(4):551–6.
- U. S. Preventive Services Task Force. Screening for hemochromatosis: Recommendation statement. *Am Fam Physician* 2007;75(11):1696–8.
- Bacon BR, Adams PC, Kowdley KV, et al; American Association for the Study of Liver D. Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology* 2011;54(1):328–43.
- Buja LM, Roberts WC. Iron in the heart: Etiology and clinical significance. *Am J Med* 1971;51(2):209–21.
- Jacobs EM, Hendriks JC, Marx JJ, et al. Morbidity and mortality in first-degree relatives of C282Y homozygous probands with clinically detected hemochromatosis compared with the general population: The HEMochromatosis FAMily Study (HEFAS). *Neth J Med* 2007;65(11): 425–33.
- Adams PC. Implications of genotyping of spouses to limit investigation of children in genetic hemochromatosis. *Clin Genet* 1998;53(3):176–8.
- El-Serag HB, Inadomi JM, Kowdley KV. Screening for hereditary hemochromatosis in siblings and children of affected patients: A cost-effectiveness analysis. *Ann Intern Med* 2000;132(4):261–9.
- Delatycki MB, Powell LW, Allen KJ. Hereditary hemochromatosis genetic testing of at-risk children: What is the appropriate age? *Genet Test* 2004;8(2):98–103.
- Bottomley SS. Secondary iron overload disorders. *Semin Hematol* 1998; 35(1):77–86.
- Dostalíková-Cimburová M, Krátka K, Stranský J, et al. Iron overload and HFE gene mutations in Czech patients with chronic liver diseases. *Dis Markers* 2012;32(1):65–72.
- Mueller S, Rausch V. The role of iron in alcohol-mediated hepatocarcinogenesis. *Adv Exp Med Biol* 2015;815:89–112.
- Nelson JE, Brunt EM, Kowdley KV; Nonalcoholic Steatohepatitis Clinical Research Network. Lower serum hepcidin and greater parenchymal iron in nonalcoholic fatty liver disease patients with C282Y HFE mutations. *Hepatology* 2012;56(5):1730–40.

53. Cullis JO, Fitzsimons EJ, Griffiths WJ, et al; British Society for Haematology. Investigation and management of a raised serum ferritin. *Br J Haematol* 2018;181(3):331–40.
54. Anderson ER, Shah YM. Iron homeostasis in the liver. *Compr Physiol* 2013;3(1):315–30.
55. Costa Matos L, Batista P, Monteiro N, et al. Iron stores assessment in alcoholic liver disease. *Scand J Gastroenterol* 2013;48(6):712–8.
56. Costa-Matos L, Batista P, Monteiro N, et al. Hfe mutations and iron overload in patients with alcoholic liver disease. *Arq Gastroenterol* 2013;50(1):35–41.
57. Harrison-Findik DD, Schafer D, Klein E, et al. Alcohol metabolism-mediated oxidative stress down-regulates hepcidin transcription and leads to increased duodenal iron transporter expression. *J Biol Chem* 2006;281(32):22974–82.
58. Dostalikova-Cimbuova M, Balusikova K, Kratka K, et al. Role of duodenal iron transporters and hepcidin in patients with alcoholic liver disease. *J Cell Mol Med* 2014;18(9):1840–50.
59. Dever JB, Mallory MA, Mallory JE, et al. Phenotypic characteristics and diagnoses of patients referred to an iron overload clinic. *Dig Dis Sci* 2010;55(3):803–7.
60. Barisani D, Pelucchi S, Mariani R, et al. Hepcidin and iron-related gene expression in subjects with dysmetabolic hepatic iron overload. *J Hepatol* 2008;49(1):123–33.
61. Trombini P, Paolini V, Pelucchi S, et al. Hepcidin response to acute iron intake and chronic iron loading in dysmetabolic iron overload syndrome. *Liver Int* 2011;31(7):994–1000.
62. Rulyak SJ, Eng SC, Patel K, et al. Relationships between hepatic iron content and virologic response in chronic hepatitis C patients treated with interferon and ribavirin. *Am J Gastroenterol* 2005;100(2):332–7.
63. Bonkovsky HL, Banner BF, Rothman AL. Iron and chronic viral hepatitis. *Hepatology* 1997;25(3):759–68.
64. Tung BY, Emond MJ, Bronner MP, et al. Hepatitis C, iron status, and disease severity: Relationship with HFE mutations. *Gastroenterology* 2003;124(2):318–26.
65. Carroll GJ, Bredahl WH, Bulsara MK, et al. Hereditary hemochromatosis is characterized by a clinically definable arthropathy that correlates with iron load. *Arthritis Rheum* 2011;63(1):286–94.
66. Radford-Smith DE, Powell EE, Powell LW. Haemochromatosis: A clinical update for the practising physician. *Intern Med J* 2018;48(5):509–16.
67. Powell LW, Dixon JL, Ramm GA, et al. Screening for hemochromatosis in asymptomatic subjects with or without a family history. *Arch Intern Med* 2006;166(3):294–301.
68. Warne CD, Zaloumis SG, Bertalli NA, et al. HFE p.C282Y homozygosity predisposes to rapid serum ferritin rise after menopause: A genotype-stratified cohort study of hemochromatosis in Australian women. *J Gastroenterol Hepatol* 2017;32(4):797–802.
69. Adams PC, Speechley M, Kertesz AE. Long-term survival analysis in hereditary hemochromatosis. *Gastroenterology* 1991;101(2):368–72.
70. Niederau C, Fischer R, Purschel A, et al. Long-term survival in patients with hereditary hemochromatosis. *Gastroenterology* 1996;110(4):1107–19.
71. Morrison ED, Brandhagen DJ, Phatak PD, et al. Serum ferritin level predicts advanced hepatic fibrosis among U.S. patients with phenotypic hemochromatosis. *Ann Intern Med* 2003;138(8):627–33.
72. Fletcher LM, Dixon JL, Purdie DM, et al. Excess alcohol greatly increases the prevalence of cirrhosis in hereditary hemochromatosis. *Gastroenterology* 2002;122(2):281–9.
73. Adams PC, Agnew S. Alcoholism in hereditary hemochromatosis revisited: Prevalence and clinical consequences among homozygous siblings. *Hepatology* 1996;23(4):724–7.
74. Grosse SD, Gurrin LC, Bertalli NA, et al. Clinical penetrance in hereditary hemochromatosis: Estimates of the cumulative incidence of severe liver disease among HFE C282Y homozygotes. *Genet Med* 2018;20(4):383–9.
75. Laine JC, Martin BD, Novotny SA, et al. Role of advanced imaging in the diagnosis and management of active Legg-Calve-Perthes disease. *J Am Acad Orthop Surg* 2018;26(15):526–36.
76. Fracanzani AL, Conte D, Fraquelli M, et al. Increased cancer risk in a cohort of 230 patients with hereditary hemochromatosis in comparison to matched control patients with non-iron-related chronic liver disease. *Hepatology* 2001;33(3):647–51.
77. Kew MC. Hepatic iron overload and hepatocellular carcinoma. *Liver cancer* 2014;3(1):31–40.
78. Strohmeyer G, Niederau C, Stremmel W. Survival and causes of death in hemochromatosis: Observations in 163 patients. *Ann NY Acad Sci* 1988;526:245–57.
79. Elmberg M, Hultcrantz R, Ekbom A, et al. Cancer risk in patients with hereditary hemochromatosis and in their first-degree relatives. *Gastroenterology* 2003;125(6):1733–41.
80. Bardou-Jacquet E, Morcet J, Manet G, et al. Decreased cardiovascular and extrahepatic cancer-related mortality in treated patients with mild HFE hemochromatosis. *J Hepatol* 2015;62(3):682–9.
81. Haddow JE, Palomaki GE, McClain M, et al. Hereditary hemochromatosis and hepatocellular carcinoma in males: A strategy for estimating the potential for primary prevention. *J Med Screen* 2003;10(1):11–3.
82. Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases. *Hepatology* 2018;68(2):723–50.
83. Blumberg RS, Chopra S, Ibrahim R, et al. Primary hepatocellular carcinoma in idiopathic hemochromatosis after reversal of cirrhosis. *Gastroenterology* 1988;95(5):1399–402.
84. Blanc JF, De Ledinghen V, Bernard PH, et al. Increased incidence of HFE C282Y mutations in patients with iron overload and hepatocellular carcinoma developed in non-cirrhotic liver. *J Hepatol* 2000;32(5):805–11.
85. Bralet MP, Regimbeau JM, Pineau P, et al. Hepatocellular carcinoma occurring in nonfibrotic liver: Epidemiologic and histopathologic analysis of 80 French cases. *Hepatology* 2000;32(2):200–4.
86. Turlin B, Juguet F, Moirand R, et al. Increased liver iron stores in patients with hepatocellular carcinoma developed on a noncirrhotic liver. *Hepatology* 1995;22(2):446–50.
87. Queiroz-Andrade M, Blasbalg R, Ortega CD, et al. MR imaging findings of iron overload. *Radiographics* 2009;29(6):1575–89.
88. Demant AW, Schmiedel A, Buttner R, et al. Heart failure and malignant ventricular tachyarrhythmias due to hereditary hemochromatosis with iron overload cardiomyopathy. *Clin Res Cardiol* 2007;96(12):900–3.
89. Gulati V, Harikrishnan P, Palaniswamy C, et al. Cardiac involvement in hemochromatosis. *Cardiol Rev* 2014;22(2):56–68.
90. Adams PC, Deugnier Y, Moirand R, et al. The relationship between iron overload, clinical symptoms, and age in 410 patients with genetic hemochromatosis. *Hepatology* 1997;25(1):162–6.
91. Elmberg M, Hultcrantz R, Simard JF, et al. Risk of ischaemic heart disease and cardiomyopathy in patients with haemochromatosis and in their first-degree relatives: A nationwide, population-based study. *J Intern Med* 2012;272(1):45–54.
92. Pelusi C, Gasparini DI, Bianchi N, et al. Endocrine dysfunction in hereditary hemochromatosis. *J Endocrinol Invest* 2016;39(8):837–47.
93. Wood MJ, Powell LW, Dixon JL, et al. Clinical cofactors and hepatic fibrosis in hereditary hemochromatosis: The role of diabetes mellitus. *Hepatology* 2012;56(3):904–11.
94. McDermott JH, Walsh CH. Hypogonadism in hereditary hemochromatosis. *J Clin Endocrinol Metab* 2005;90(4):2451–5.
95. Siminoski K, D'Costa M, Walfish PG. Hypogonadotropic hypogonadism in idiopathic hemochromatosis: Evidence for combined hypothalamic and pituitary involvement. *J Endocrinol Invest* 1990;13(10):849–53.
96. el-Reshaid K, Seshadri MS, Hourani H, Qurtom M, Kamel H. Endocrine abnormalities in hemodialysis patients with iron overload: Reversal with iron depletion. *Nutrition* 1995;11(5 Suppl):521–6.
97. Valenti L, Varenna M, Fracanzani AL, et al. Association between iron overload and osteoporosis in patients with hereditary hemochromatosis. *Osteoporos Int* 2009;20(4):549–55.
98. Faraawi R, Harth M, Kertesz A, et al. Arthritis in hemochromatosis. *J Rheumatol* 1993;20(3):448–52.
99. Guggenbuhl P, Brissot P, Loreal O. Miscellaneous non-inflammatory musculoskeletal conditions. *Haemochromatosis: The bone and the joint. Best Pract Res Clin Rheumatol* 2011;25(5):649–64.
100. Frenzen K, Schafer C, Keysser G. Erosive and inflammatory joint changes in hereditary hemochromatosis arthropathy detected by low-field magnetic resonance imaging. *Rheumatol Int* 2013;33(8):2061–7.
101. Chevrand-Breton J, Simon M, Bourel M, et al. Cutaneous manifestations of idiopathic hemochromatosis: Study of 100 cases. *Arch Dermatol* 1977;113(2):161–5.

102. Hazin R, Abu-Rajab Tamimi TI, Abuzetun JY, et al. Recognizing and treating cutaneous signs of liver disease. *Cleveland Clinic J Med* 2009; 76(10):599–606.
103. Adams P, Brissot P, Powell LW. EASL International Consensus Conference on Haemochromatosis. *J Hepatol* 2000;33(3):485–504.
104. O'Neil J, Powell L. Clinical aspects of hemochromatosis. *Semin Liver Dis* 2005;25(4):381–91.
105. Porto G, De Sousa M. Iron overload and immunity. *World J Gastroenterol* 2007;13(35):4707–15.
106. Kumar N, Rizek P, Sadikovic B, et al. Movement disorders associated with hemochromatosis. *Can J Neurol Sci* 2016;43(6):801–8.
107. Adams PC, Reboussin DM, Press RD, et al. Biological variability of transferrin saturation and unsaturated iron-binding capacity. *Am J Med* 2007;120(11)(999):e991–7.
108. McLaren CE, McLachlan GJ, Halliday JW, et al. Distribution of transferrin saturation in an Australian population: Relevance to the early diagnosis of hemochromatosis. *Gastroenterology* 1998;114(3): 543–9.
109. Bassett ML, Halliday JW, Ferris RA, et al. Diagnosis of hemochromatosis in young subjects: Predictive accuracy of biochemical screening tests. *Gastroenterology* 1984;87(3):628–33.
110. Adams PC, Kertesz AE, McLaren CE, et al. Population screening for hemochromatosis: A comparison of unbound iron-binding capacity, transferrin saturation, and C282Y genotyping in 5,211 voluntary blood donors. *Hepatology* 2000;31(5):1160–4.
111. Guyader D, Jacquelinet C, Moirand R, et al. Noninvasive prediction of fibrosis in C282Y homozygous hemochromatosis. *Gastroenterology* 1998;115(4):929–36.
112. Beaton M, Guyader D, Deugnier Y, et al. Noninvasive prediction of cirrhosis in C282Y-linked hemochromatosis. *Hepatology* 2002;36(3): 673–8.
113. Arya N, Chakrabarti S, Hegele RA, et al. HFE S65C variant is not associated with increased transferrin saturation in voluntary blood donors. *Blood Cell Mol Dis*. 1999;25(5-6):354–7.
114. Mura C, Ragueneo O, Ferec C. HFE mutations analysis in 711 hemochromatosis probands: Evidence for S65C implication in mild form of hemochromatosis. *Blood* 1999;93(8):2502–5.
115. Wallace DF, Subramaniam VN. The global prevalence of HFE and non-HFE hemochromatosis estimated from analysis of next-generation sequencing data. *Genet Med* 2016;18(6):618–26.
116. George DK, Goldwurm S, MacDonald GA, et al. Increased hepatic iron concentration in nonalcoholic steatohepatitis is associated with increased fibrosis. *Gastroenterology* 1998;114(2):311–8.
117. Brunt EM. Pathology of hepatic iron overload. *Semin Liver Dis* 2005; 25(4):392–401.
118. Kowdley KV, Trainer TD, Saltzman JR, et al. Utility of hepatic iron index in American patients with hereditary hemochromatosis: A multicenter study. *Gastroenterology* 1997;113(4):1270–7.
119. Angelucci E, Brittenham GM, McLaren CE, et al. Hepatic iron concentration and total body iron stores in thalassemia major. *N Engl J Med* 2000;343(5):327–31.
120. Summers KM, Halliday JW, Powell LW. Identification of homozygous hemochromatosis subjects by measurement of hepatic iron index. *Hepatology* 1990;12(1):20–5.
121. Wood MJ, Crawford DHG, Wockner LF, et al. Serum ferritin concentration predicts hepatic fibrosis better than hepatic iron concentration in human HFE-Haemochromatosis. *Liver Int* 2017;37(9): 1382–8.
122. Pietrangelo A. Iron and the liver. *Liver Int* 2016;36(Suppl 1):116–23.
123. Pietrangelo A. Non-HFE hemochromatosis. *Hepatology* 2004;39(1): 21–9.
124. Adhoute X, Foucher J, Laharie D, et al. Diagnosis of liver fibrosis using FibroScan and other noninvasive methods in patients with hemochromatosis: A prospective study. *Gastroenterol Clin Biol* 2008; 32(2):180–7.
125. Gandon Y, Guyader D, Heautot JF, et al. Hemochromatosis: Diagnosis and quantification of liver iron with gradient-echo MR imaging. *Radiology* 1994;193(2):533–8.
126. St Pierre TG, Clark PR, Chua-Anusorn W. Measurement and mapping of liver iron concentrations using magnetic resonance imaging. *Ann NY Acad Sci* 2005;1054:379–85.
127. Westphalen AC, Qayyum A, Yeh BM, et al. Liver fat: Effect of hepatic iron deposition on evaluation with opposed-phase MR imaging. *Radiology* 2007;242(2):450–5.
128. Paisant A, d'Assignies G, Bannier E, Bardou-Jacquet E, Gandon Y. MRI for the measurement of liver iron content, and for the diagnosis and follow-up of iron overload disorders. *Presse Med* 2017;46(12 Pt 2): e279–87.
129. Sarigianni M, Liakos A, Vlachaki E, et al. Accuracy of magnetic resonance imaging in diagnosis of liver iron overload: A systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2015;13(1): 55–63.e5.
130. Rockey DC, Caldwell SH, Goodman ZD, et al; American Association for the Study of Liver Diseases. Liver biopsy. *Hepatology* 2009;49(3): 1017–44.
131. Gurrin LC, Osborne NJ, Constantine CC, et al. The natural history of serum iron indices for HFE C282Y homozygosity associated with hereditary hemochromatosis. *Gastroenterology* 2008;135(6): 1945–52.
132. Yamashita C, Adams PC. Natural history of the C282Y homozygote for the hemochromatosis gene (HFE) with a normal serum ferritin level. *Clin Gastroenterol Hepatol* 2003;1(5):388–91.
133. Allen KJ, Bertalli NA, Osborne NJ, et al. HFE Cys282Tyr homozygotes with serum ferritin concentrations below 1000 microg/L are at low risk of hemochromatosis. *Hepatology* 2010;52(3):925–33.
134. Ong SY, Dolling L, Dixon JL, et al. Should HFE p.C282Y homozygotes with moderately elevated serum ferritin be treated? A randomised controlled trial comparing iron reduction with sham treatment (Mi-iron). *BMJ open* 2015;5(8):e008938.
135. Adams P, Altes A, Brissot P, et al. Therapeutic recommendations in HFE hemochromatosis for p.Cys282Tyr (C282Y/C282Y) homozygous genotype. *Hepatol Int* 2018;12(2):83–6.
136. Brissot P. Optimizing the diagnosis and the treatment of iron overload diseases. *Expert Rev Gastroenterol Hepatol*. 2016;10(3):359–70.
137. Lynch SR, Cook JD. Interaction of vitamin C and iron. *Ann NY Acad Sci* 1980;355:32–44.
138. Moretti D, van Doorn GM, Swinkels DW, et al. Relevance of dietary iron intake and bioavailability in the management of HFE hemochromatosis: A systematic review. *Am J Clin Nutr* 2013;98(2):468–79.
139. Falize L, Guillygomarc'h A, Perrin M, et al. Reversibility of hepatic fibrosis in treated genetic hemochromatosis: A study of 36 cases. *Hepatology* 2006;44(2):472–7.
140. Fracanzani AL, Fargion S, Romano R, et al. Portal hypertension and iron depletion in patients with genetic hemochromatosis. *Hepatology* 1995; 22(4 Pt 1):1127–31.
141. Huijskes RV, Hoogenberg K, Wiesfeld AC, et al. Phlebotomies as a treatment of serious heart failure due to haemochromatosis: A case report. *Neth Heart J* 2009;17(11):438–41.
142. Kremastinos DT, Farmakis D. Iron overload cardiomyopathy in clinical practice. *Circulation* 2011;124(20):2253–63.
143. Utzschneider KM, Kowdley KV. Hereditary hemochromatosis and diabetes mellitus: Implications for clinical practice. *Nat Rev Endocrinol* 2010;6(1):26–33.
144. Hamilton EB, Bomford AB, Laws JW, et al. The natural history of arthritis in idiopathic haemochromatosis: Progression of the clinical and radiological features over ten years. *Q J Med* 1981;50(199): 321–9.
145. Harty LC, Lai D, Connor S, et al. Prevalence and progress of joint symptoms in hereditary hemochromatosis and symptomatic response to venesection. *J Clin Rheumatol* 2011;17(4):220–2.
146. Chevrant-Breton J. Cutaneous manifestations of hemochromatosis. In: Barton JC, Edwards CQ, eds. *Hemochromatosis: Genetics, Pathophysiology, Diagnosis and Treatment*. Cambridge University Press: Cambridge, 2000, pp 290–6.
147. Aydinok Y. Iron chelation therapy as a modality of management. *Hematol Oncol Clin North Am* 2018;32(2):261–75.
148. Cancado R, Melo MR, de Moraes Bastos R, et al. Deferasirox in patients with iron overload secondary to hereditary hemochromatosis: Results of a 1-yr phase 2 study. *Eur J Haematol* 2015;95(6):545–50.
149. Phatak P, Brissot P, Wurster M, et al. A phase 1/2, dose-escalation trial of deferasirox for the treatment of iron overload in HFE-related hereditary hemochromatosis. *Hepatology* 2010;52(5):1671–779.
150. Nagler M, Gregor M, Wuillemin WA. Iron chelation with deferasirox in two patients with HFE hemochromatosis and chronic anemia. *Acta Haematol* 2011;126(2):119–21.
151. Rehacek V, Blaha M, Jirousova H, et al. Therapeutic erythrocytapheresis in the initial treatment of hereditary hemochromatosis. *Acta Med* 2012; 55(4):180–5.

152. Rombout-Sestrienkova E, van Noord PA, van Deursen CT, et al. Therapeutic erythrocytapheresis versus phlebotomy in the initial treatment of hereditary hemochromatosis A pilot study. *Transfus Apher Sci* 2007;36(3):261–7.
153. Rombout-Sestrienkova E, Koek GH, Neslo R, et al. Course of iron parameters in HFE-hemochromatosis patients during initial treatment with erythrocytapheresis compared to phlebotomy. *J Clin Apher* 2016; 31(6):564–70.
154. Rombout-Sestrienkova E, Winkens B, Essers BA, et al. Erythrocytapheresis versus phlebotomy in the maintenance treatment of HFE hemochromatosis patients: Results from a randomized crossover trial. *Transfusion* 2016;56(1):261–70.
155. Hutchinson C, Geissler CA, Powell JJ, et al. Proton pump inhibitors suppress absorption of dietary non-haem iron in hereditary haemochromatosis. *Gut* 2007;56(9):1291–5.
156. van Aerts RM, van Deursen CT, Koek GH. Proton pump inhibitors reduce the frequency of phlebotomy in patients with hereditary hemochromatosis. *Clin Gastroenterol Hepatol* 2016;14(1):147–52.
157. Vanclooster A, van Deursen C, Jaspers R, et al. Proton pump inhibitors decrease phlebotomy need in HFE hemochromatosis: Double-blind randomized placebo-controlled trial. *Gastroenterology* 2017;153(3): 678–80.e2.
158. Olivieri NF. The beta-thalassemsias. *N Engl J Med* 1999;341(2):99–109.
159. Brittenham GM, Cohen AR, McLaren CE, et al. Hepatic iron stores and plasma ferritin concentration in patients with sickle cell anemia and thalassemia major. *Am J Hematol* 1993;42(1):81–5.
160. Pakbaz Z, Fischer R, Fung E, et al. Serum ferritin underestimates liver iron concentration in transfusion independent thalassemia patients as compared to regularly transfused thalassemia and sickle cell patients. *Pediatr Blood Cancer* 2007;49(3):329–32.
161. Ang AL, Le TT, Tan RS. HbH Constant Spring disease has lower serum ferritin relative to liver iron concentration (LIC): Importance of LIC measurement and potential impact on serum ferritin thresholds for iron chelation. *Br J Haematol* 2017;176(6):986–8.
162. Taher AT, Porter JB, Viprakasit V, et al. Defining serum ferritin thresholds to predict clinically relevant liver iron concentrations for guiding deferasirox therapy when MRI is unavailable in patients with non-transfusion-dependent thalassaemia. *Br J Haematol* 2015;168(2): 284–90.
163. Desai TK, Jamil LH, Balasubramaniam M, et al. Phlebotomy improves therapeutic response to interferon in patients with chronic hepatitis C: A meta-analysis of six prospective randomized controlled trials. *Dig Dis Sci* 2008;53(3):815–22.
164. Adams LA, Crawford DH, Stuart K, et al. The impact of phlebotomy in nonalcoholic fatty liver disease: A prospective, randomized, controlled trial. *Hepatology* 2015;61(5):1555–64.
165. Beaton MD, Chakrabarti S, Levstik M, et al. Phase II clinical trial of phlebotomy for non-alcoholic fatty liver disease. *Aliment Pharmacol Ther.* 2013;37(7):720–9.
166. Murali AR, Gupta A, Brown K. Systematic review and meta-analysis to determine the impact of iron depletion in dysmetabolic iron overload syndrome and non-alcoholic fatty liver disease. *Hepatol Res* 2018;48(3): E30–41.
167. Bardou-Jacquet E, Philip J, Lorho R, et al. Liver transplantation normalizes serum hepcidin level and cures iron metabolism alterations in HFE hemochromatosis. *Hepatology* 2014;59(3):839–47.
168. Kowdley KV, Brandhagen DJ, Gish RG, et al. Survival after liver transplantation in patients with hepatic iron overload: The national hemochromatosis transplant registry. *Gastroenterology* 2005;129(2): 494–503.
169. Brandhagen DJ, Alvarez W, Therneau TM, et al. Iron overload in cirrhosis-HFE genotypes and outcome after liver transplantation. *Hepatology* 2000;31(2):456–60.
170. Crawford DH, Fletcher LM, Hubscher SG, et al. Patient and graft survival after liver transplantation for hereditary hemochromatosis: Implications for pathogenesis. *Hepatology* 2004;39(6):1655–62.
171. Dar FS, Faraj W, Zaman MB, et al. Outcome of liver transplantation in hereditary hemochromatosis. *Transpl Int* 2009;22(7):717–24.
172. Farrell FJ, Nguyen M, Woodley S, et al. Outcome of liver transplantation in patients with hemochromatosis. *Hepatology* 1994;20(2):404–10.
173. Yu L, Ioannou GN. Survival of liver transplant recipients with hemochromatosis in the United States. *Gastroenterology* 2007;133(2):489–95.
174. Ashrafiyan H. Hepcidin: The missing link between hemochromatosis and infections. *Infect Immun* 2003;71(12):6693–700.