INTRODUCTION

Hereditary hemochromatosis (HH) is an autosomal recessive genetic disorder of iron metabolism. Without proper diagnosis and treatment, people with this disorder develop excessive iron overload and manifest symptoms related to abnormal iron accumulation in various body tissues. This can cause significant morbidity and mortality concerns—two issues of key interest to underwriters! To understand the risks involved with HH, it is first necessary to have a basic understanding of iron metabolism.

IRON ABSORPTION AND METABOLISM

All body cells need iron. Iron is used for oxygen transport, energy production, and cellular growth and proliferation. An average daily diet contains 10-20 mg of iron. Of this amount, only about 10% (1-2 mg) gets absorbed by the GI tract each day. Transferrin is the major transporter of iron throughout the body and transports the majority of absorbed iron (~75%) to the bone marrow for use in erythropoiesis and cellular production. Another 10-20% is transported to the liver and heart for storage as ferritin, the cellular storage protein for iron. The small remaining amount is used in other body processes or lost in sweat or shed cells from the skin or GI tract. There is typically a tight balance between iron absorption and iron storage/usage in the body. On average, the total body iron is approximately 3.5 grams.

PATHOPHYSIOLOGY AND PREVALENCE OF HEREDITARY HEMOCHROMATOSIS (HH)

Persons with HH continue to absorb iron even when their body already has enough. Once absorbed, there is no physiologic means of excreting iron from our bodies. (The only method to remove iron is via blood loss.) Without a physiological excretion mechanism, iron begins to accumulate, causing eventual iron overload with the excess iron being deposited in various body tissues (especially the liver, heart, pancreas, and pituitary).

Back in the 19th century, the classic presentation of HH was that of a bronze-skinned, diabetic, middle-aged man with hepatomegaly and cirrhosis. The disease was considered rare and most cases presented with advanced end-organ damage and a poor prognosis.

Fortunately, times have changed and the prognosis for HH has improved dramatically. Advances in genetics, routine laboratory testing and increased awareness have transformed HH to a common disease with many diagnosed much earlier in their disease process. The 21st century presentation is now that of a younger, asymptomatic person with mildly elevated liver function tests. Most cases present with no end-organ damage and have a very good prognosis.

Since the first genetic test for HH was developed in 1996, the prevalence has also increased.1,2,3 Population studies have shown HH to be the most common single-gene genetic disorder in the US. In the Caucasian population in the US and Western Europe, 10% are heterozygous for the mutation while 0.5% are homozygous for the genes.1

CLINICAL PRESENTATION

Most cases (75%) will be asymptomatic with a mild elevation of liver function tests (LFTs). If early symptoms do occur, they are non-specific fatigue
and weakness. Major clinical symptoms usually do not appear until a person reaches 40-50 years old, when significant iron accumulation has already occurred and organ damage has begun. The symptoms (in order of prevalence) will depend on where the iron is deposited.

- Liver - LFTs, hepatomegaly, cirrhosis
- Skin – bronze skin, hyperpigmentation
- Pancreas – diabetes
- Joints – arthritis/arthralgias
- Pituitary – impotence, early menopause
- Thyroid – hypothyroidism
- Heart – cardiomyopathy, arrhythmia

UNDERWRITING FOR HH

It is not uncommon for “clean” underwriting files to unveil mildly elevated liver function tests. Some of these cases might be undiagnosed HH. Let’s first review the differential diagnosis of increased LFTs:

- Drugs and alcohol
- Medications and supplements (e.g., acetaminophen, lipid-lowering drugs, antibiotics, seizure medication, herbal therapy)
- Liver disease (e.g., hepatitis, non-alcoholic fatty liver disease, hemochromatosis, Wilson’s disease, autoimmune hepatitis, alpha-1-antitrypsin deficiency)
- Other (e.g., muscle disorders, thyroid disorders, celiac disease, adrenal insufficiency)

Review of the medical history, medication lists, drug and alcohol questionnaires, and other lab tests may lead you toward one diagnosis over the others. If medical records are available, you should also look for any blood tests that may show a prior work-up for elevated LFTs. (See Figure 1 below)

Suspicion for HH occurs with abnormal iron studies. While an elevated serum iron and elevated ferritin both suggest iron overload, the best test for detecting iron overload is the transferrin saturation (TS), which indicates how much iron is bound to the carrier protein, transferrin. This will be the earliest lab abnormality in iron overload. Some labs will report this value, but if they do not, it is easily calculated by dividing the serum iron by the total iron binding capacity. Abnormally high TS is >50% in women and >60% in men.

Transferrin Saturation = \[\frac{\text{Serum Fe}}{\text{TIBC}}\]

I must provide you with a caution regarding ferritin. Ferritin is much less specific than TS for detecting iron overload and should NOT be used as a screening test. Ferritin is considered an acute phase reactant, which can increase up to 25% during inflammation, infection and tissue injury, and may not at all be increased due to iron overload. Never review the ferritin results by itself! You must ALWAYS look for (or calculate) the transferrin saturation in order to determine its significance. In general, ferritin > 600 ng/ml requires a work-up, while ferritin > 1000 ng/ml (despite a normal TS) may need a liver biopsy.

It is also important to point out that an abnormally high TS only indicates that an iron overload state is present. It is not diagnostic for HH. Other disorders can be associated with iron overload and must be ruled out also. (See Figure 2)

Once iron overload is diagnosed by an abnormally high transferrin saturation and other disorders associated with iron overload are considered, the next underwriting step is to see if genetic testing has been done.

GENETICS

Human DNA is composed of 46 chromosomes (structures that hold our genes) organized into 23 pairs (one copy from each parent); 22 pairs of autosomes and
one pair of sex chromosomes (XX, XY). The *locus* is the point on the chromosome where the gene is located. There are two *alleles* per locus. If a locus contains two copies of the same allele, it is considered *homozygote*. If a locus contains two different alleles, it is considered *heterozygote*. (See Figure 3)

Figure 3

In 1996, a mutation in the HFE gene (the gene that regulates iron absorption) was discovered on the short arm of chromosome 6 (6p21.3). To date, over 40 allelic variants of the HFE gene have been described, but only two mutations are significantly correlated with HH: C282Y (cysteine to tyrosine switch at position 282) and H63D (histidine to aspartate switch at position 63). The C282Y mutation has the stronger association with HH.

Since each chromosome has two alleles, with three possibilities for the HFE gene (C282Y, H63D, or normal), there are six possible HFE mutation combinations (*genotypes*) for chromosome 6. Homozygous C282Y/C282Y is the genetic combination of 69-100% of clinically diagnosed HH (average 83%) with a very high prevalence in Caucasians in North America. (See Figure 4 at bottom)

**DIAGNOSTIC CRITERIA FOR HH**

The minimum criteria for diagnosis of HH requires:

1. Increased iron stores (elevated transferrin saturation) plus
2. +HFE gene mutation (C282Y/C282Y or C282Y/H63D)

Liver biopsy is no longer essential for diagnosis but can be confirmatory in those with negative genetic testing. It is also valuable for prognostic reasons and should be performed on those over 40 years old with clinical evidence of liver disease, history of alcohol abuse, coexisting diabetes or ferritin levels > 1000 ng/mL, as these cases carry an increased risk for liver fibrosis. The development of liver fibrosis is often irreversible and can progress to liver cirrhosis with an increased risk for hepatocellular carcinoma.

A liver biopsy is not necessary for young (< 40 years old) C282Y homozygotes with no clinical evidence of liver disease (normal LFTs, ferritin < 1000 ng/ml). In these cases, clinicians often proceed directly to treatment.

**TREATMENT**

The mainstay of treatment for HH is *phlebotomy*, a simple, safe, effective way to remove excess iron. Initial treatment (the “de-ironing” phase) consists of removal of one unit of whole blood (450 ml contains about 250 mg of iron) weekly until ferritin < 50 ng/ml and TS < 50% (generally takes several months). Maintenance phlebotomies are then performed every 2-4 months for life, with optimal ferritin < 100 ng/ml with a normal hemoglobin.

<table>
<thead>
<tr>
<th><strong>Figure 4: HFE Mutation Combinations</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>C282Y/C282Y (homozygote)</td>
</tr>
<tr>
<td>C282Y/H63D (compound heterozygote)</td>
</tr>
<tr>
<td>H63D/H63D</td>
</tr>
<tr>
<td>C282Y/normal H63D/normal</td>
</tr>
<tr>
<td>normal/normal</td>
</tr>
</tbody>
</table>
In the rare case when phlebotomy is contraindicated (e.g. severe cardiac involvement), iron chelation can be performed. Chelation agents bind to iron, allowing iron to be excreted in either urine or bile. This is almost never necessary due to the ease and efficacy of phlebotomy.

Dietary management includes avoiding iron supplements, avoiding excess vitamin C (promotes iron absorption), avoiding uncooked seafood/raw oysters (increases the risk of Vibrio and Salmonella infections, bacteria that grow well in an iron-rich environment) and limiting alcohol consumption.

**HH AND MORBIDITY AND MORTALITY**

With treatment, non-specific symptoms can resolve, liver function can return to normal, endocrine changes may improve, and joint pain can resolve. Significant fibrosis in any organ, however, is irreversible. Liver disease (manifesting as cirrhosis and hepatocellular carcinoma) is the major cause (75%) of all HH-related deaths. Diabetes and cardiomyopathies round out the top three. Survival, however, is normal in HH patients in whom treatment was initiated before the development of cirrhosis or diabetes.

**SUMMARY/CONCLUSIONS**

Most people with HH will have a normal life expectancy. Early diagnosis and effective treatment are the key to preventing irreversible end-organ damage and fibrosis. While an elevated serum iron and elevated ferritin both suggest iron overload, the best test for detecting iron overload is the transferrin saturation. Phlebotomy therapy, if initiated early, can prevent cirrhosis, cardiac complications and diabetes. Best cases are asymptomatic individuals without end-organ damage who are compliant with treatment and have good clinical follow-up. Optimal ferritin level is <100 ng/mL with a transferrin sat <50%. Patients with evidence of iron overload, positive family history or other risk factors should be screened with a transferrin saturation blood test.

**GLOSSARY**

**Transferrin** – the major transporter of iron throughout the body.

**Ferritin** – the cellular storage protein for iron.

**Transferrin saturation** – the best test for detecting iron overload – indicates how much iron is bound to the carrier protein, transferrin, calculated by dividing the serum iron by the total iron binding capacity.

**Acute phase reactant** – a protein which can increase up to 25% during inflammation, infection and tissue injury.

**Chromosomes** – structures that hold our genes.

**Locus** – the point on the chromosome where the gene is located.

**Allele** – one of two versions of a gene at each locus.

**Homozygote** – a locus containing two copies of the same allele.

**Heterozygote** – a locus containing two different alleles.

**Genotype** – the genetic makeup of an individual.

**Phlebotomy** – the process of removing blood.

**REFERENCES**


**About the Author**

Gina C. Guzman, MD, DBIM, FALU, ALMI, is Second Vice President and Medical Director, Munich Re, where she has worked for over 12 years out of the Chicago branch office. She graduated from the University of Illinois at Chicago and Rush Medical College, then completed her residency training at Rush-Presbyterian-St. Lukes Medical Center in Chicago. Dr. Guzman is board-certified in both Internal Medicine and Insurance Medicine. She is the Past-President of the American Academy of Insurance Medicine (AAIM) and a Past-President of the Midwestern Medical Directors Association (MMDA). Dr. Guzman enjoys teaching and has presented many times over the years for both medical directors and underwriting groups.