Hemochromatosis Diagnosis Algorithm
Clinical Evaluation & Management Protocol

**NO to ALL**

**KEY ABBREVIATIONS:**
- HHC=hereditary hemochromatosis
- HIC=hepatic iron content (or concentration)
- HI=hepatic index
- SF=serum ferritin
- AST=aspartate aminotransferase
- ALT=alanine transaminase
- GGT=gamma-glutamyl transferase
- TIBC=total iron binding capacity
- MRI=magnetic resonance imaging
- sMRI=mRI with T2* calculation for iron quantification.
- ALT=alanine transaminase
- AST=aspartate aminotransferase
- TIBC=total iron binding capacity
- HHC=hereditary hemochromatosis
- HIC=hepatic iron content (or concentration)
- SF=serum ferritin

**Exception**
Pre-treatment hemoglobin of 12.5 g/dL include females, whose normal hemoglobin range begins at 12.0 g/dL. Other exceptions include patients with cirrhosis or other disorders such as sideroblastic anemia. The intent is to avoid unnecessary over-bleeding and symptoms of iron deficiency (with or without) anemia. Serum ferritin should be maintained within normal limits. There is no known health benefit to below-normal SF. There is no known benefit to the outdated practice of forced-sustained anemia as an approach for iron reduction.

**NO**

**Clinical Evaluation**
- ALT or AST elevated or SF>1,000 ng/mL

**YES To Any**

**NO**

**Feasibility of Phlebotomy**
- Removal of >2 grams of iron without producing iron deficiency is diagnostic of non-classical HHC. In those with suspicion for other liver pathology or hepatic cirrhosis, consider liver biopsy.

**YES**

**Advice Liver Biopsy with Quantitative Iron and Iron Stain**

**Non-classical HHC Iron Overload Established**

**YES**

**HIC ≥ 4500 mcg (80 mcmol) per gram of dry weight; HI ≥ 2 or 3+ iron stain**

**Start Iron Reduction Therapy**

- Do evaluation of the liver, heart, endocrine function. Consider assessment for other viral, autoimmune or metabolic cause of liver disease in patients with iron overload.

**YES**

**Iron Overload Absent. Evaluate/Manage Other Clinical Conditions**

**No**

**Serum Ferritin < 50 ng/mL**

**Begin Maintenance**
- 1 unit every 2-6 months.
- Maintain ideal SF range 50-100 ng/mL and hemoglobin ≥ 12.5 g/dL.

**YES**

**Initial T% > 45%**
- No iron supplements or vitamin C for at least one week. Retest fasting T% + SF

**Explanation of Dangers of Elevated Iron to Patient**

**Consider HFE Gene Test**

**Positive HFE Gene Test**
- C282Y homozygote or
- Compound heterozygotes: C282Y/H63D

**Consider Liver Biopsy or Non-invasive Alternatives**
- Such as, FibroScan®, or specialized MRI (sMRI)

**Diagnosis of Classical Hemochromatosis (HHC)**

- Established; consider liver biopsy or non-invasive alternatives, such as, FibroScan®, or specialized MRI (sMRI)

**NO**

**Check SF and TS% periodically**

**Initial TS% > 45% and/or SF elevated:**
- Adult male > 300 ng/mL
- Adult female > 200 ng/mL

**Check TS% + SF for at least one week.**

**Fasting T% > 45%**

**KEY REFERENCES:**
- Adult ≥ 18 years of age & ≥ 100 lbs
- Norris Cotton Cancer Center, Dartmouth-Hitchcock Medical Center.
- S. Tavill, M.D., Cleveland Clinic State Hershey Medical Group Hope Drive Pediatrics
- Florida John Longshore, Ph.D., Carolina Medical Center, Charlotte, NC • Patrick MacPhail MBBCh, Ph.D. FCP FRC, University of the Witwatersrand, Johannesburg South Africa
- Active Hematology/Oncology Section University of Oklahoma College of Medicine Oklahoma City, OK • Bruce Bacon, M.D., St. Louis University School of Medicine
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Iron Disorders Institute
Advancing cures for Iron-Out-of-Balance™

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Sample Phlebotomy Order:
“Phlebotomize 500 cc once a week if Hgb is ≥12.5g/dL” (Approximate hematocrit of 38%)
Period of time should reflect frequency desired

Clinical Features of Patients with Hemochromatosis

There is a broad spectrum of features, ranging from total lack of symptoms to advanced liver, heart, joint or endocrine disease.

Following is a list of possible ways of identifying hemochromatosis in the asymptomatic patient:

- Abnormal serum iron studies on routine screening chemistry panel
- Evaluation of abnormal liver tests
- Identified by family screening
- Identified by population screening

Specific Organ-related symptoms or diseases:

- Abdominal pain secondary to hepatomegaly
- Arthralgias
- Diabetes
- Amnorrhea
- Loss of libido, impotence
- Congestive heart failure, palpitations, arrhythmias

Signs in the asymptomatic patient:

- Hepatomegaly

Signs in the symptomatic patient by system:

- Liver/Spleen/Gastrointestinal
  - Hepatomegaly
  - Cutaneous stigmata of chronic liver disease
  - Splenomegaly
  - Portal hypertension
  - Ascites
  - Esophageal varices
- Brain
  - Encephalopathy
- Bone & Joint Disease
  - Arthritis: especially 2nd and 3rd metacarpophalangeal joints (Iron Fist), knees, shoulders, and wrists
  - Joint swelling
  - Osteoporosis, osteoarthritis
- Heart
  - Dilated cardiomyopathy
  - Congestive heart failure
- Skin
  - Increased pigmentation (bronze, ashen-gray)
- Endocrine
  - Testicular atrophy
  - Hypogonadism
  - Hypothyroidism

Diet: reduce consumption of red meat and while iron levels are elevated: avoid alcohol, raw shellfish, and supplemental vitamin C at mealtime. Consider referral to Nutritionist for education on diet modifications which may minimize the need for maintenance phlebotomy.

Hemochromatosis Clinical Management

Adults ≥ 18 years of age & ≥ 100 lbs

<table>
<thead>
<tr>
<th>Management of Phlebotomy Therapy</th>
<th>induction</th>
<th>maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency (in weeks)</td>
<td>1-2</td>
<td>8-20</td>
</tr>
<tr>
<td>Threshold for bleed</td>
<td>12.5*</td>
<td>12.5*</td>
</tr>
<tr>
<td>serum ferritin (ng/mL)</td>
<td>50-75</td>
<td>50-100</td>
</tr>
<tr>
<td>TS% (transferrin-iron saturation percentage)</td>
<td>&lt;40%**</td>
<td>&lt;40%**</td>
</tr>
</tbody>
</table>

Monitor serum ferritin (SF) and TS% monthly until SF is <200 ng/mL. Thereafter, monitor SF and TS% every two bleeds until SF is 50-75 ng/mL. Hemoglobin: *12.5g/dL for the majority of cases. Exceptions can include women or patients with liver disease. **TS% is normally 25-35%.

IMPORTANT NOTE: It is no longer necessary to produce iron deficiency with or without anemia in patients with hemochromatosis. Otherwise a condition called “Iron Avidity” may occur and joint pain can worsen. For iron avid patients (normal or low normal SF, normal TIBC with persistently elevated TS%) postpone phlebotomy until iron balance is restored. Some iron avid patients may require therapy to address iron deficiency (low serum ferritin). Elevated GGT levels can contribute to worse outcomes for an iron avid patient.


Important Ferritin Reference Ranges

<table>
<thead>
<tr>
<th>ferritin</th>
<th>Induction Phase***</th>
<th>Adult Males</th>
<th>Adult Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum ferritin decreases ~30ng/mL per 500cc phlebotomy****</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induction Phase***</td>
<td>50-75 ng/mL</td>
<td>50-75 ng/mL</td>
<td></td>
</tr>
<tr>
<td>Ideal Range****</td>
<td>50-100 ng/mL</td>
<td>50-100 ng/mL</td>
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Genetics:
Each person inherits two copies of HFE, the candidate gene for classic hemochromatosis. Testing for three mutations is commercially available (C282Y, H63D, and S65C). Homozygotes C282Y/C282Y or compound heterozygotes C282Y/H63D or C282Y/S65C are most at risk for iron overload. Carriers of any mutation of HFE should be monitored periodically for possible iron loading.

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