# Hemochromatosis Diagnosis Algorithm

## Clinical Evaluation & Management Protocol

Adults ≥ 18 years of age & ≥ 100 lbs

KEY ABBREVIATIONS:
HHC= hereditary hemochromatosis
HIC= hepatic iron content (or concentration)
HII=hepatic iron index
SF = serum ferritin
TIBC = total iron binding capacity
TS% = transferrin-iron saturation percentage

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

This algorithm is designed to be a general guideline only. Specific clinical circumstances may require modifications at the discretion of the clinician.

Fasting TS% > 45% and SF elevated:
adult male > 300 ng/mL
adult female > 200 ng/mL

NO → Explain dangers of elevated iron to patient

YES → Consider HFE gene test

Positive HFE gene test C282Y homozygote or C282Y/H63D compound heterozygote

YES → Diagnosis of classical hemochromatosis (HHC) established; consider liver biopsy to assess fibrosis if ALT or AST elevated or SF>1000 ng/mL

NO → Clinical Evaluation ALT or AST elevated or SF>1,000 ng/mL

NO to ALL → Consider trial 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 To Any → Advise liver biopsy with quantitative iron and iron stain.

Patient declines liver biopsy → Start iron reduction therapy* Do evaluation of the liver, heart, endocrine function

HIC ≥ 4500 mcg (80 mcmol) per gram of dry weight; HII≥ 2 or 3-4+ iron stain

YES → Non-classical HHC iron overload established → YES → Start iron reduction therapy* Do evaluation of the liver, heart, endocrine function

NO → Iron overload absent. Evaluate/Manage other clinical conditions.

### * Iron ReductionTherapy

Bi-weekly or weekly phlebotomy
Check hemoglobin/hematocrit prior to each phlebotomy.
Check SF and TS% periodically *(See back page: Management of Phlebotomy ).*
Hydrate patient orally prior to phlebotomy.
Avoid overbleeding: Do not perform phlebotomy if hemoglobin is <12.5 g/dL**

Serum Ferritin <50 ng/mL
NO → repeat phlebotomy
YES → Begin maintenance: 1 unit every 2-6 months. Maintain Ideal SF range 50-150 ng/mL and hemoglobin ≥12.5 g/dL

**Exceptions to 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 anemia. Serum ferritin should be maintained within normal limits. There is no known health benefit to below-normal SF.

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# Hemochromatosis Clinical Management

Adults ≥ 18 years of age & ≥ 100 lbs

## *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

*Non-specific, systemic symptoms or complaints by the patient:*

Weakness · Fatigue · Lethargy
Apathy · Weight loss

*Specific Organ-related symptoms or diseases:*

- Abdominal pain secondary to hepatomegaly
- Arthralgias (...especially reports of pain in the 2nd and 3rd metacarpophalangeal joints)
- Diabetes
- Amenorrhea
- Loss of libido, impotence
- Congestive heart failure, 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, knees, shoulders, and wrists)
  - Joint swelling
  - Osteoporosis
- Heart
  - Dilated cardiomyopathy
  - Congestive heart failure
- Skin
  - Increased pigmentation (bronze, ashen-gray)
- Endocrine
  - Testicular atrophy
  - Hypogonadism
  - Hypothyroidism

*Adapted with permission: Journal of Hepatology*
*Source: Harrison, S.A, B. R. Bacon. Hereditary hemochromatosis: Update for 2003. Journal of Hepatology 38 (2003): S14-S23.*

**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). Homozygosity (two copies) for C282Y is most likely to be associated with iron overload. Patients with other *HFe* combinations may be monitored periodically for possible iron loading.

## Management of Phlebotomy Therapy

| | induction | maintenance |
|---|---|---|
| Frequency (in weeks) | *1-2* | *8-20* |
| Threshold for bleed<br>*fingerstick hemoglobin (Hgb) (g/dL)* | *12.5** | *12.5* |
| Target values<br>—serum ferritin (ng/mL) | *50-75* | *50-150* |
| —TS% (transferrin-iron saturation percentage) | *<40%*** | *<40%*** |

***Monitor** serum ferritin (SF) and TS% monthly until SF is <200 ng/mL*
*Thereafter, monitor SF and TS% every two bleeds until SF is 75 ng/mL*
**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.*
*For iron avid patients (high TS% with normal or low normal SF), postpone phlebotomy until iron balance is restored. Some iron avid patients may require therapy to address iron deficiency.*

## Important Ferritin Reference Ranges

| ferritin | Adult Males | Adult Females |
|---|---|---|
| Ideal Range | 50-150 ng/mL | 50-150 ng/mL |
| Induction Phase* | 50-75 ng/mL | 50-75 ng/mL |

*Serum ferritin decreases ~30ng/mL per 500cc phlebotomy***

### Adolescents, Juveniles, Infants & Newborns
**of normal height and weight for their age and gender**

| | |
|---|---|
| Male ages 10-19 23-70 ng/mL | Infants 7-12 months 60-80 ng/mL |
| Female ages 10-19 6-40 ng/mL | Newborn 1-6 months 6-410 ng/mL |
| Children ages 6-9 10-55 ng/mL | Newborn 1-30 days 6-400 ng/mL |
| Children ages 1-5 6-24 ng/mL | |

*Induction applies only to patients with ihemochromatosis undergoing therapeutic phlebotomy—**Harrison, S.A, B. R. Bacon. Hereditary hemochromatosis: Update for 2003. Journal of Hepatology 38 (2003): S14-S23.*

**Diet:** *reduce consumption of red meat and while iron levels are elevated: avoid alcohol, raw shellfish and supplemental vitamin C at mealtime.*

## Comparing disorders of iron

| iron panel | IRON PANEL TESTS | | | | | |
|---|---|---|---|---|---|---|
| | Serum Iron | Serum Ferritin | Transferrin Iron Saturation Percentage | Total Iron Binding Capacity (TIBC) | Transferrin | Hemoglobin |
| Hemochromatosis | ↑ | ↑ | ↑ | ↓ | ↓ | NORMAL |
| Iron Deficiency Anemia | ↓ | ↓ | ↓ | ↑ | ↑ | ↓ |
| Sideroblastic Anemia | ↑ | ↑ | ↑ | ↓ | ↓ | ↓ |
| Thalassemia | ↑ | ↑ | ↑ | ↓ | ↓ | ↓ |
| Porphyria Cutanea Tarda (PCT) | ↑ | ↑ | ↑ | ↓ | ↓ | NORMAL |
| Anemia of Chronic Disease (ACD) | ↓ | ↑ OR NORMAL | ↓ | ↓ | ↓ | ↓ |
| African Siderosis (AS) | ↑ | ↑ | ↑ | ↓ | ↓ | NORMAL |
| Vitamin B12 Deficiency (pernicious anemia) | ↑ OR NORMAL | ↑ OR NORMAL | ↑ OR NORMAL | ↓ OR NORMAL | ↓ OR NORMAL | ↓ |

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