Hemochromatosis Diagnosis Algorithm

Clinical Evaluation & Management Protocol

Adults ≥ 18 years of age & ≥ 100 lbs

KEY ABBREVIATIONS:
HFe=high iron
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
MRI=magnetic resonance imaging
sMRI=MRI with T2* calculation for iron quantification
ALT=alanine transaminase
AST=aspartate aminotransferase
GGT=gamma-glutamyl transferase

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

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

NO → Explain dangers of elevated iron to patient

YES → Consider HFe gene test

Positive HFe gene test
C282Y homozygote or compound heterozygotes:
C282Y/H63D
C282Y/S65C

YES → Diagnosis of classical hemochromatosis (HHC) established; consider liver biopsy or non-invasive alternatives, such as, FibroScan®, or specialized MRI (sMRI) if ALT or AST are elevated or if 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. Consder assessment for other viral, autoimmune or metabolic cause of liver disease in patients with iron overload.

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*

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

Genetics: Patients who do not exhibit the classic form of genetic hemochromatosis may still be at risk of iron overload due to other causes. See Key References: Bacon, et al, for complete list of Iron Overload Syndromes. Consider referral to a genetic counselor for patients with non-HFE genetic iron overload, such as, juvenile hemochromatosis or for those with questions about inheritance patterns.

This algorithm is designed to be a general guideline only. Specific clinical circumstances may require modifications at the discretion of the clinician. Besides biochemical evidence, a positive family history of hemochromatosis can result in a complete diagnosis. Consider screening non-menstruating adult females or asymptomatic patients in the highest risk population (males >18yo) with northern European ancestry.

* Iron Reduction Therapy

Weekly or twice-monthly phlebotomy
Check hemoglobin/hematocrit prior to each phlebotomy.
Phlebotomize if hemoglobin is ≥12.5 g/dL** See exceptions
Check SF and TS% periodically (See back page: Management of Phlebotomy.) Hydrate patient orally prior to phlebotomy. Monitor progress every six months.

Serum Ferritin <50 ng/mL
NO → Phlebotomize
YES → Begin maintenance: 1 unit every 2-6 months. Maintain ideal SF range 50-100 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 (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.

Key References: Bacon BR, Adams PC, Kowdley KV, Powell LW, Tavill AS. Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology, 2011. 54(1): p. 328-43. • Kanwar P, Kowdley KV. Diagnosis and treatment of hereditary hemochromatosis: an update. Expert Review of Gastroenterolgy and Hepatology. 2013 7(6):517-30. • Crownover BK, Covey CJ. Hereditary hemochromatosis. American Family Physician. 2013 87(3):183-90.

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Hemochromatosis Clinical Management

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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

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
- Diabetes
- Amenorrhea; spontaneous abortion (miscarriage)
- Loss of libido, impotence
- Congestive heart failure, palpatations, 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, hips, and wrists.
  - Joint swelling
  - Osteoporosis, osteoarthritis
- Heart
  - Dilated cardiomyopathy
  - Congestive heart failure
- Skin
  - Increased pigmentation (bronze, ashen-gray)
- Endocrine: pituitary, thyroid, pancreas, parathyroid
  - Testicular atrophy; Hypogonadism; Hypothyroidism and possible symptoms of endocrine abnormalities: depression, mood swings, emotional outbursts.

Portions adapted with permission: 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). 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. All individuals with elevated iron levels are at risk for iron mediated organ damage due to ferrotoxicity.

Management of Phlebotomy Therapy

	induction	maintenance
Frequency (in weeks)	*1-2*	*8-20*
Threshold for bleed *fingerstick hemoglobin (Hgb) (g/dL)*	*12.5**	*12.5**
Target values —serum ferritin (ng/mL)	*50-75*	*50-100*
—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 50-75 ng/mL. Pre-bleed 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.*

Iron Avid: Bardou-Jacquet E, Lainé F, Guggenbuhl P, Morcet J, Jézéquel C, Guyader D, Moirand R, Deugnier Y. Worse Outcomes of Patients With HFE Hemochromatosis With Persistent Increases in Transferrin Saturation During Maintenance Therapy. *Clinical Gastroenterology and Hepatology.* 2017 Jan 19. pii: S1542-3565(17)30056-3. doi: 10.1016/j.cgh.2016.12.039.

Important Ferritin Reference Ranges

ferritin	Adult Males	Adult Females
Induction Phase***	50-75 ng/mL	50-75 ng/mL
Ideal Range****	50-100 ng/mL	50-100 ng/mL

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

Adolescents, Infants, & Newborns

HFe related hemochromatosis is an adult onset condition. Juvenile hemochromatosis is a non-HFe genetic condition with earlier onset and severe disease complications. Neonatal Hemochromatosis is a gestational alloimmune liver disease (GALD.) Iron overload in pediatric cases requires a specialist for a complete diagnosis and clinical management.

****Induction applies only to adult patients with hemochromatosis undergoing therapeutic phlebotomy* Bolan CD, Conry-Cantilena C, Mason G, Rouault TA, Leitman SF. MCV as a guide to phlebotomy therapy for hemochromatosis. *Transfusion.* 2001. 41(6):819-27.

*****Bacon BR, Adams PC, Kowdley KV, Powell LW, Tavill AS. Diagnosis and management of hemochromatosis: 2011 practice guidelines by the American Association for the Study of Liver Diseases. *Hepatology*, 2011. 54(1): p. 328-43.

Juvenile Hemochromatosis: Camaschella C, Roetto A, De Gobbi M. Juvenile hemochromatosis. *Seminars in Hematology.* 2002 39(4):242-8.

Neonatal Hemochromatosis Feldman AG, Whitington PF. Neonatal hemochromatosis. *Journal of Clinical and Experimental Hepatology.* 2013 3(4):313-20.

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 or certified iron educator for education on diet modifications which may minimize the need for maintenance phlebotomy.

iron panel

iron panel	SI	SF	TS%	TIBC	Trans	Hgb
hemochromatosis	↑	↑	↑	↓	↓	normal
iron deficiency	↓	↓	↓	↑	↑	↓
sideroblastic anemia	↑	↑	↑	↓	↓	↓
thalassemia	↑	↑	↑	↓	↓	↓
anemia of inflammatory response	↓	↑ ABNORMAL	↓	↓	↓	↓
dysmetabolic iron overload syndrome	↑	↑	normal	↓	↓	normal

SI=serum iron; SF=serum ferritin; TS%= transferrin-iron saturation percentage; TIBC= total iron-binding capacity; trans= transferrin; Hgb=hemoglobin

Individuals with genetic hemochromatosis can also have combinations of conditions listed above.

Dysmetabolic iron overload syndrome (DIOS):Jézéquel C, Lainé F, Laviolle B, Kiani A, Bardou-Jacquet E, Deugnier Y. Both hepatic and body iron stores are increased in dysmetabolic iron overload syndrome. A case-control study. Public Library of Science (PLoS) One. 2015 Jun 1;10(6):e0128530. doi: 10.1371/journal.pone.0128530. eCollection 2015.

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