Hereditary Hemochromatosis

Screening, clinical features, diagnostic testing, phlebotomy/chelation therapy, and liver transplantation for HFE-related iron overload.

2019 ACG Clinical Guideline
Hereditary Hemochromatosis
Kowdley, Brown, Ahn, Sundaram · Am J Gastroenterol
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STRENGTH Strong Conditional

1 Screening

STATEMENT	STRENGTH
R1 — First-degree relatives of patients diagnosed with HH should be screened for HH	Strong Moderate

2 Clinical Features

STATEMENT	STRENGTH
R2 — Against routine HCC surveillance in HH with stage 3 fibrosis or less	Conditional Very low

3 Diagnostic Testing

STATEMENT	STRENGTH
R3 — H63D or S65C mutation without C282Y: counsel patient as not at increased iron-overload risk	Conditional Very low
R4 — Iron overload, negative for both C282Y and H63D: against further genetic testing	Conditional Very low
R5 — Suspected HH, non-C282Y homozygote: non-contrast MRI (T2*) to noninvasively measure hepatic iron concentration; liver biopsy preferred if concurrent fibrosis staging or alternate liver disease evaluation needed	Conditional Low

4 Treatment

STATEMENT	STRENGTH
R6 — Phlebotomy as first-line treatment in C282Y homozygotes or C282Y/H63D compound heterozygotes	Strong Moderate
R7 — Against chelation as first-line therapy given phlebotomy efficacy and chelation toxicity risk	Strong Low
R8 — Iron chelation if intolerant/refractory to phlebotomy, or phlebotomy poses harm (e.g., severe anemia, CHF)	Strong Low
R9 — Against routine PPI use as primary treatment of HH	Strong Low

5 Liver Transplantation

STATEMENT	STRENGTH
R10 — Consider liver transplantation in HH patients with decompensated cirrhosis or HCC	Strong Low

6 Diagnostic & Treatment Algorithm at the Bedside

STEP	ACTION & THRESHOLDS
1	Suspected HH (symptoms, elevated LFTs, or family history) → screen with **transferrin saturation (TS)** and **serum ferritin (SF)**
2	TS <45% + normal SF → no further evaluation needed. TS ≥45% + elevated SF → proceed to **HFE genetic testing**
3	**C282Y homozygote** → phlebotomy. If SF >1,000 ng/mL, liver biopsy first to stage fibrosis; cirrhotic patients enter HCC surveillance
4	**Not C282Y homozygote** → evaluate alternate causes (liver/hematologic disease); if excluded, assess hepatic iron concentration (biopsy or MRI T2*)
Goal	Phlebotomy target: SF **50–100 ng/mL**. Cirrhosis, arthropathy, diabetes, and hypogonadism typically do not reverse with phlebotomy alone

Kowdley KV, Brown KE, Ahn J, Sundaram V. ACG Clinical Guideline: Hereditary Hemochromatosis. *Am J Gastroenterol.* 2019;114(8):1202–1218.