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DIGESTIVE DISEASES: NEW ADVANCES

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Hemochromatosis: Is It the Liver's Heavy Metal?

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Disclosures

- **Nancy Reau, MD**
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  - **Consultant:**
    - Gilead, Salix, AbbVie, Intercept

Agenda:

1. Review current Guidelines
2. Presentation
3. Diagnosis
4. Family Screening
5. Treatment

Hereditary Hemochromatosis (HC)

- Disorder of iron homeostasis characterized by increased intestinal iron absorption and iron release from macrophages, leading to an expanded circulating iron pool
- Autosomal recessive condition

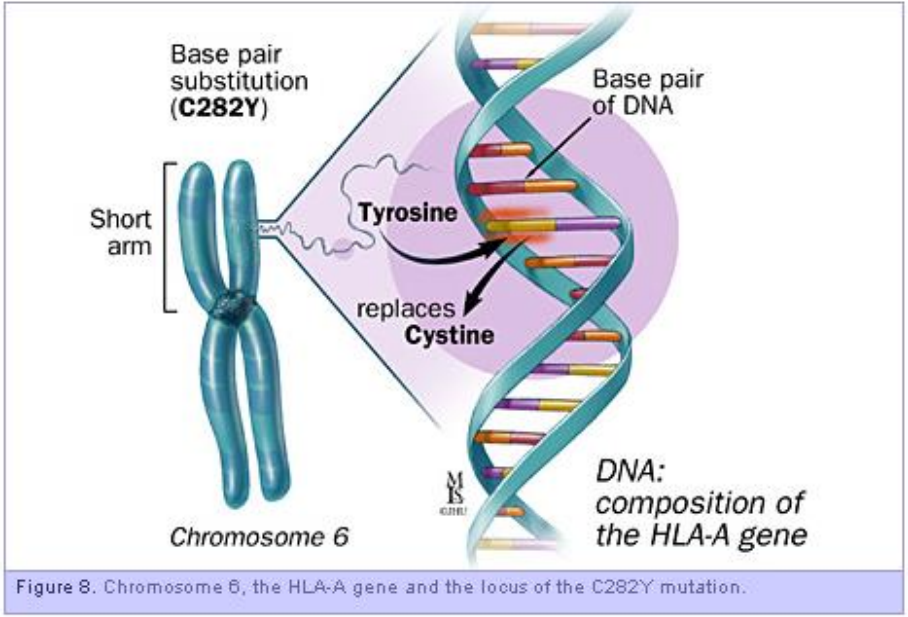


Figure 8. Chromosome 6, the HLA-A gene and the locus of the C282Y mutation.

1 Guidelines

1. EASL 2022 (in Press)
2. ACG 2019
3. AASLD 2011

ARTICLE IN PRESS

Clinical Practice Guidelines

JOURNAL OF HEPATOLOGY

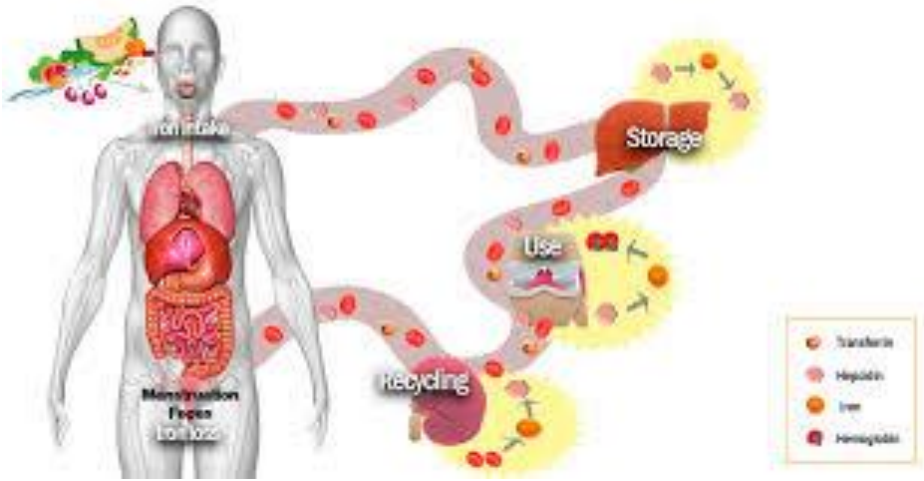
EASL Clinical Practice Guidelines on haemochromatosis☆

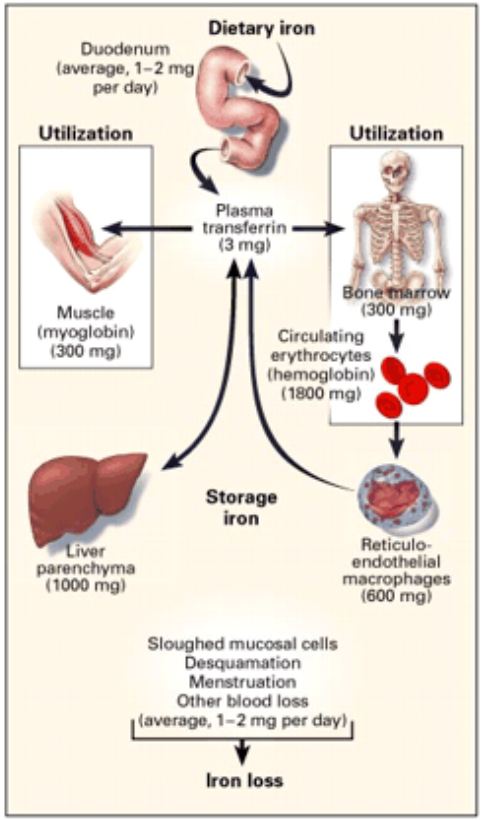
European Association for the Study of the Liver*

https://easl.eu/wp-content/uploads/2022/06/PIIS01688278220021121.pdf.

Iron Absorption

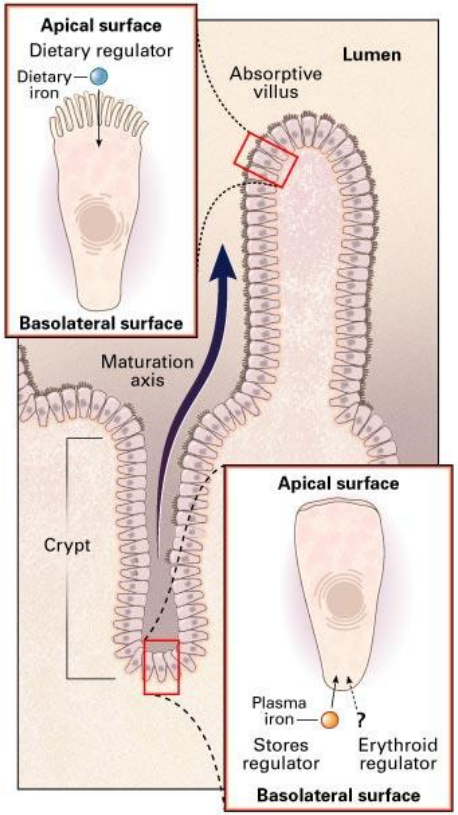
- Duodenal crypt cells sense iron needs
- Enterocytes close to gastroduodenal junction absorb all iron

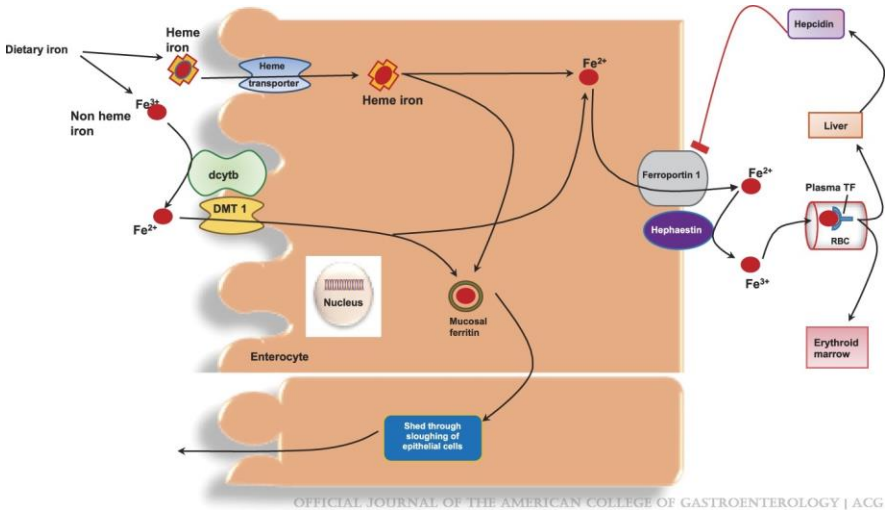




Regulation of Intestinal Iron

- Dietary regulator
- Stores regulator
- Erythropoietic regulator
- Anemic states
- Hypoxia





- **Hepcidin**: A hormone synthesized and secreted by the liver in response to circulating iron levels, which inhibits iron absorption from the intestinal mucosal cells by degradation of ferroportin-1.
- **Ferroportin-1**: A transmembrane protein found predominantly in the intestinal epithelial cells, hepatocytes, and macrophages, which facilitates iron export from the cells.
- **Transferrin:** A glycoprotein synthesized by the liver which exists in 3 forms (apo, monoferric, and diferric); it carries iron in the circulation.
- **Unsaturated iron-binding capacity:** The portion of iron-binding sites on transferrin that are not occupied by iron. A low unsaturated iron-binding capacity raises the suspicion for hemochromatosis.
- **Total iron-binding capacity:** The sum of the serum iron and unsaturated iron-binding capacity.
- **Transferrin-iron saturation:** The percentage of iron bound to transferrin. Calculated by dividing serum iron by total iron-binding capacity.
- Ferritin: Intracellular protein that stores and releases intracellular iron.

Wolters Kluwer

ACG Clinical Guideline: Hereditary Hemochromatosis.
Kowdley, Kris V.; Brown, Kyle E.; Ahn, Joseph; Sundaram, Vinay.
Official journal of the American College of Gastroenterology | ACG114(8):1202-1218, August 2019.

2 Presentation

1. Disease penetrance is dependent on age and sex
2. 203 p.C282Y homozygotes between 40 and 69 yo monitored for mean 12 years
   - Penetrance of iron overload-related disease was 28% in men and 1.2% in women
   - 81.8% of men and 55.4% of women had increased serum ferritin at baseline, suggesting higher rates of biochemical penetrance
3. HC penetrance → end- organ damage w/ p.C282Y homozygosity 50%
4. H63D is common in the population
   - Compound heterozygote and homozygote H63D does not cause iron overload without other environmental factors **(look for other causes!)**

Clinical Manifestations

Early Stages:

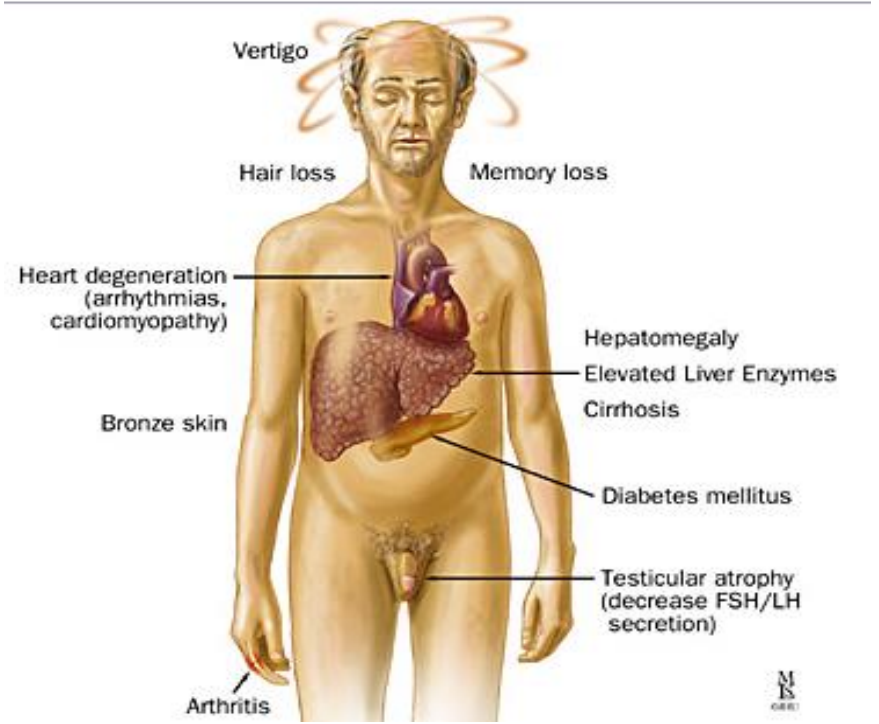
- Asymptomatic

Common:

- Fatigue
- Joint Pain

Advanced

- Cardiac arrhythmia
- Impotence
- Skin pigmentation
- Diabetes
- Liver disease
- Liver Cancer



Parenchymal Deposition

- Liver: Transaminases, HSM
- Heart: CHF, arrhythmias, pericarditis
- Endocrine glands
  - Pancreatic -diabetes mellitus
  - Pituitary-primary testicular failure
  - Hypothyroidism
  - Hypoparathyroidism
- Skin: bronzed from melanin
  - Gray: iron deposits in basal layers of epidermis
- Joints

Patients with severe iron overload should be evaluated for arrhythmia and cardiac dysfunction (electrocardio-gram [ECG] and echocardiography) (LoE 4, strong recommendation, strong consensus).

Patients with severe haemochromatosis and signs or symptoms of heart disease (conduction disease and/or contractile dysfunction) should be investigated with cardiac MRI for iron quantification without delaying treatment (LoE 4, strong recommendation, strong consensus).

3 Diagnosis

1. Test anyone presenting with clinical manifestations
   - Cardiomyopathy and hypogonadotrophic hypogonadism are more common in juvenile haemochromatosis
2. Iron Overload: transferrin saturation (TS) >50% and ferritin >300 lg/L in men and >45% and ferritin >200 lg/L in women
3. Genotyping for p.C282Y in HFE with biochemical evidence of iron overload or otherwise unexplained persistently elevated transferrin saturation with or without clinical signs or symptoms suggestive of haemochromatosis

Abnormal TS and increased ferritin → 93% sensitive for HHC
Normal TS and ferritin → 97% neg predicative value

- Elevated TS not homozygous for p.C282Y→ quantification of hepatic iron with MRI is recommended
- Identification of the specific disease-causing genetic variant is neither required with adult-onset HC nor sufficient for the diagnosis of haemochromatosis, which is based on **phenotypic criteria**

In whom should non-invasive tests for quantification of iron overload be performed?

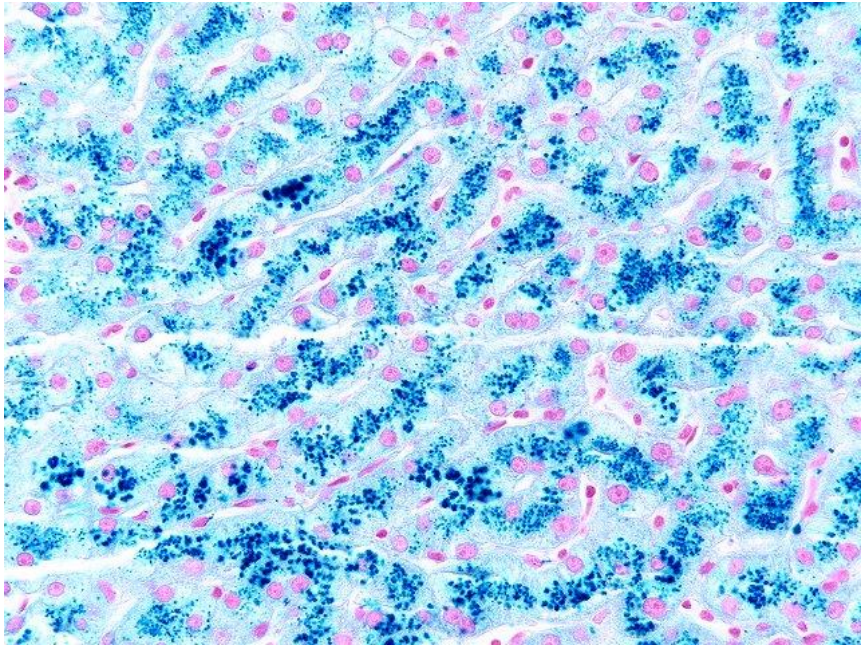
Recommendations

In patients with an unclear cause of hyperferritinemia, biochemical iron overload (increased transferrin saturation and ferritin) or positive liver iron staining, MRI should be used to quantify hepatic iron concentrations and to assess extrahepatic organ involvement **(LoE 4, strong recommendation, strong consensus).**

Cardiac MRI can be performed in patients with haemochromatosis and signs of heart disease, and in juvenile forms of haemochromatosis **(LoE 5, strong recommendation, strong consensus).**

Liver biopsy is not recommended for the diagnosis of hepatic iron overload

- Liver Bx
  - Perls' Prussion blue
  - Iron concentration >80 umol/gm dry
  - Iron index >1.9 mmol/kg/yr
- Iron
  - Periportal distribution
  - None in Kupffer cells
  - Becomes panlobular with kupffer cell involvement



1. Differential Diagnosis

- Several genetic defects are associated with HC

Young individuals with biochemical evidence and clinical manifestations of haemochromatosis (liver disease, amenorrhea, hypogonadism, cardiomyopathy) should be tested for rare haemochromatosis gene variants **(LoE 4, strong recommendation, strong consensus).**

Patients with evidence of significant, unexplained iron overload should be referred for assessment by a specialist in iron disorders **(LoE 5, strong recommendation, strong consensus).**

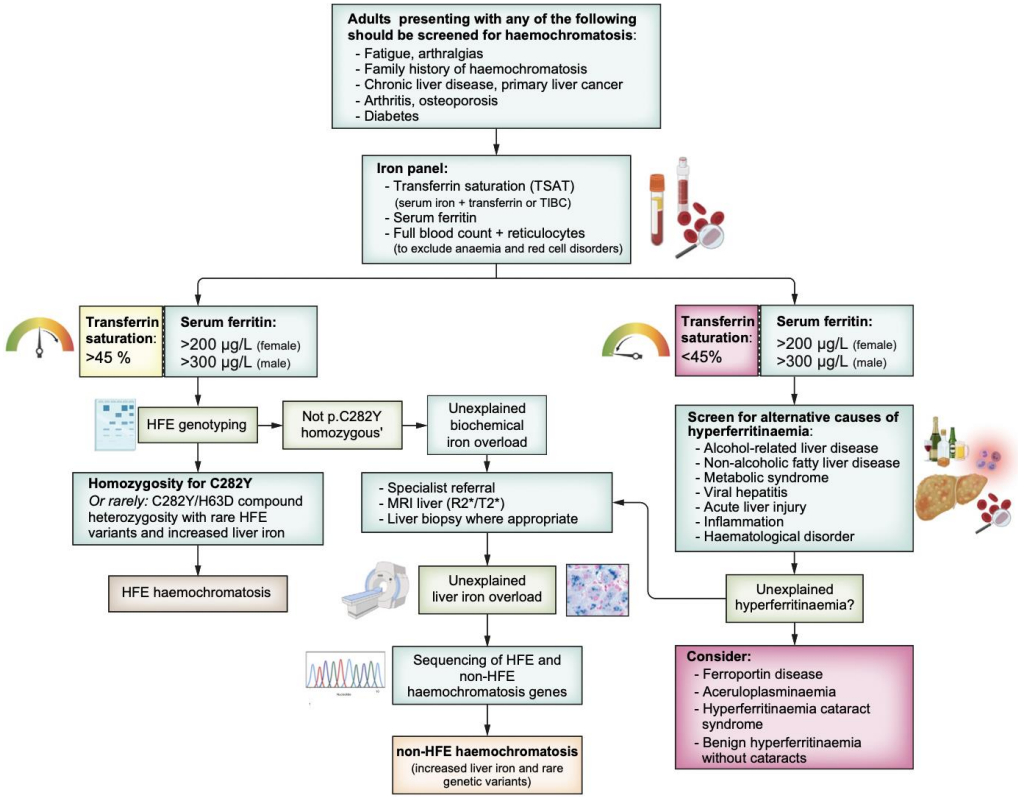
Adult first-degree relatives of patients with rare variants in haemochromatosis genes should be tested for these variants; particular focus should be given to siblings as they are at the highest risk of haemochromatosis **(LoE 5, strong recommendation, strong consensus).**

Ferritin

- Acute phase reactant
- Tumor marker
- Increased angiogenesis
- Released from necrotic or lysed cells
- Elevated with fatty liver disease
  - Excess alcohol consumption
  - Metabolic syndrome

- Gene-set for the assessment of HC should include: HFE, HAMP, HJV, TFR2, TF, CP, BMP6, SCL40A1.
- HFE p.C282Y/p.H63D and p.H63/p.H63 are not sufficient to induce significant iron overload without additional factors;
- **Rare HC gene variants should be tested in patients with these genotypes and confirmed severe iron overload, in the absence of other obvious causes of excess iron.**

Diagnostic Approach for Hyperferritinemia and Suspected Hemochromatosis



4 Staging

Staging and Liver Cancer Screening

- Historically ferritin > 1,000 ug/L high risk for cirrhosis
- HHC with cirrhosis requires screening with imaging +/- AFP at q6 months

Transient elastography can be used to rule out advanced fibrosis in patients with haemochromatosis if liver stiffness is ≤6.4 kPa **(LoE 4, weak recommendation, consensus).**

In patients with ferritin <1,000 μg/L, normal transaminases and no liver enlargement, the risk of advanced liver fibrosis is very low **(consensus).**

Fibrosis Staging With HC

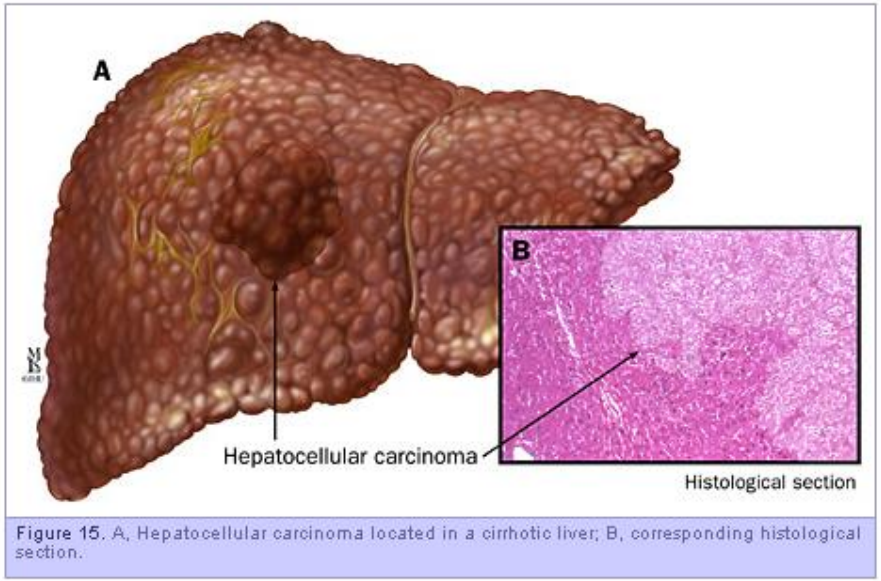
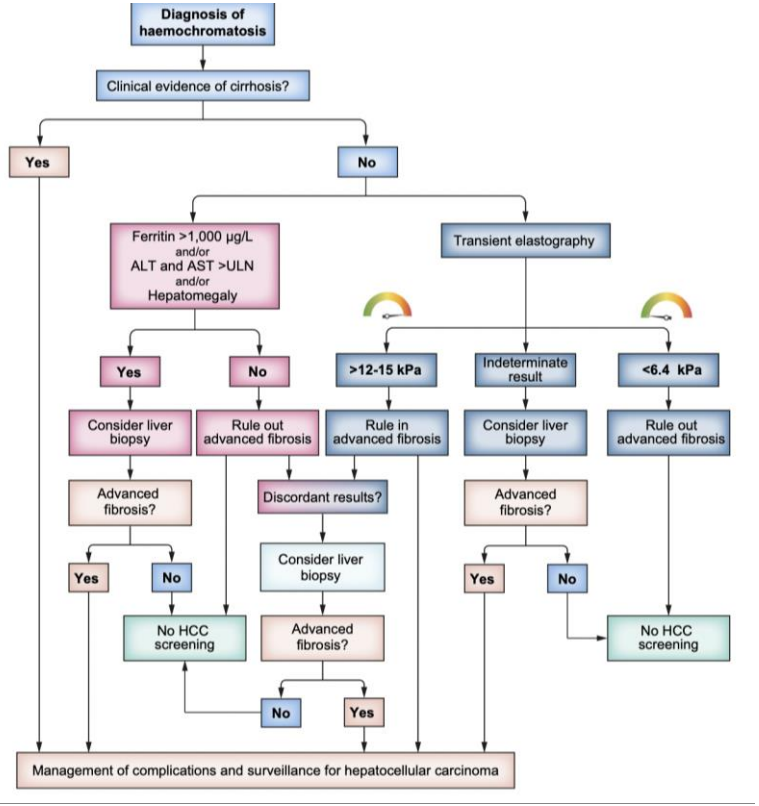


Figure 15. A, Hepatocellular carcinoma located in a cirrhotic liver; B, corresponding histological section.

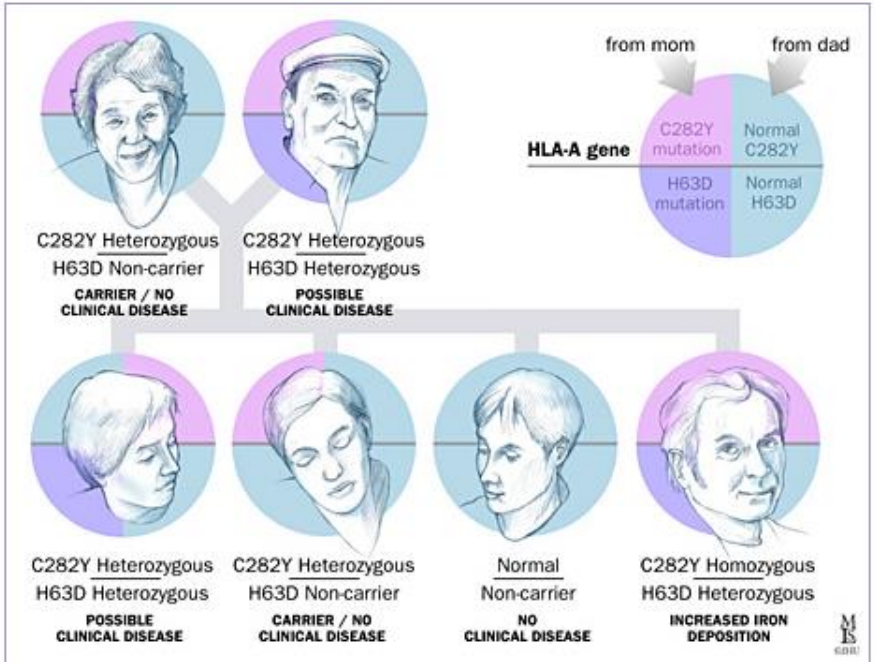


4 Family Screening

1. Adult individuals with a positive family history of first-degree relatives with haemochromatosis should be genetically tested for haemochromatosis
2. Adult (>18 years of age) first-degree relatives of patients with p.C282Y homozygous haemochromatosis should be tested for the p.C282Y variant in HFE

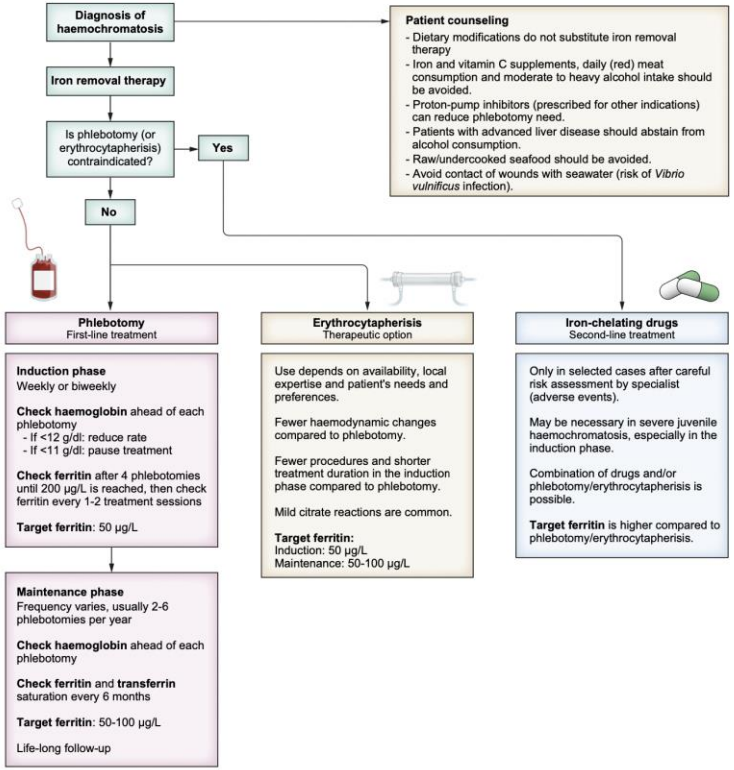
Family Screening

- Evaluate all first and second degree relatives of proband
  - TS and Ferritin
    - **usually abnormal by age 40**
  - Considered genetic testing



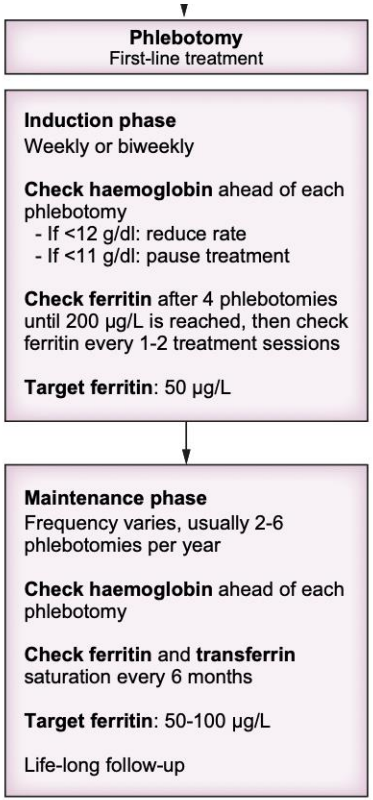
5 Treatment

Treatment


Diagnosis of haemochromatosis
Iron removal therapy
Is phlebotomy (or erythrocytapherisis) contraindicated?
Yes
No
Patient counseling
- Dietary modifications do not substitute iron removal therapy
- Iron and vitamin C supplements, daily (red) meat consumption and moderate to heavy alcohol intake should be avoided.
- Proton-pump inhibitors (prescribed for other indications) can reduce phlebotomy need.
- Patients with advanced liver disease should abstain from alcohol consumption.
- Raw/undercooked seafood should be avoided.
- Avoid contact of wounds with seawater (risk of Vibrio vulnificus infection).
Phlebotomy
First-line treatment
Induction phase
Weekly or biweekly
Check haemoglobin ahead of each phlebotomy
- If <12 g/dl: reduce rate
- If <11 g/dl: pause treatment
Check ferritin after 4 phlebotomies until 200 µg/L is reached, then check ferritin every 1-2 treatment sessions
Target ferritin: 50 µg/L
Maintenance phase
Frequency varies, usually 2-6 phlebotomies per year
Check haemoglobin ahead of each phlebotomy
Check ferritin and transferrin saturation every 6 months
Target ferritin: 50-100 µg/L
Life-long follow-up
Erythrocytapherisis
Therapeutic option
Use depends on availability, local expertise and patient's needs and preferences.
Fewer haemodynamic changes compared to phlebotomy.
Fewer procedures and shorter treatment duration in the induction phase compared to phlebotomy.
Mild citrate reactions are common.
Target ferritin:
Induction: 50 µg/L
Maintenance: 50-100 µg/L
Iron-chelating drugs
Second-line treatment
Only in selected cases after careful risk assessment by specialist (adverse events).
May be necessary in severe juvenile haemochromatosis, especially in the induction phase.
Combination of drugs and/or phlebotomy/erythrocytapherisis is possible.
Target ferritin is higher compared to phlebotomy/erythrocytapherisis.

1. Disease management is determined by organ involvement and liver disease stage
2. At early stages, therapeutic phlebotomy will improve fatigue in most patients, prevent or halt progres-sion of liver fibrosis and normalise life expectancy.[11,12] At advanced disease stages, phlebotomy can induce fibrosis regression and can even cause regression of early cirrhosis.[13] In contrast, phlebotomy has not been shown to be of benefit and is not recommended in patients with high ferritin or iron overload linked to metabolic-dysfunction associated liver dis-ease and not haemochromatosis

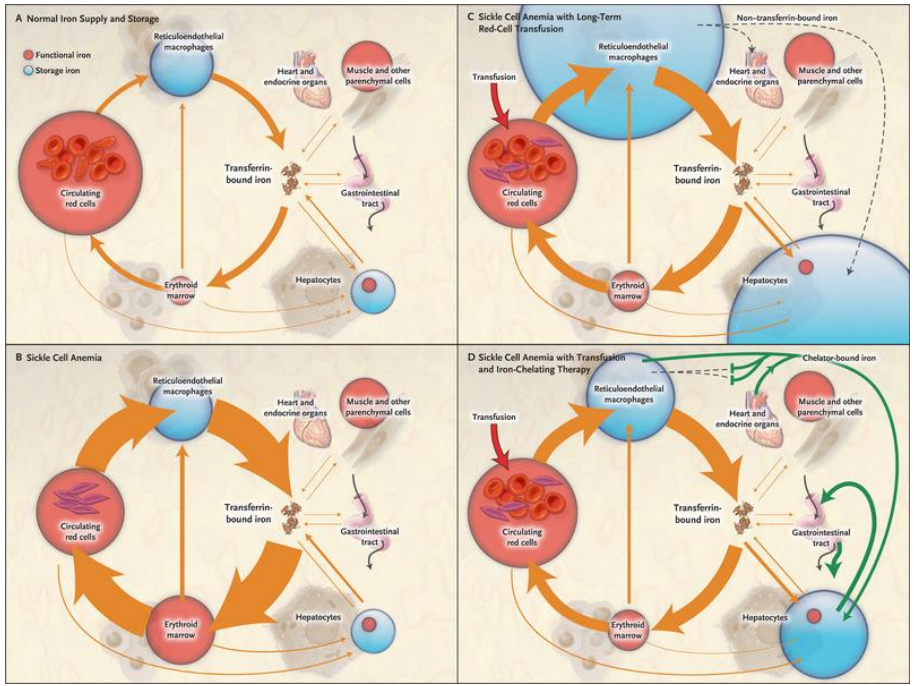
Hemochromatosis: Treatment



Erythrocytapheresis

- Apheresis procedure→ RBC separated from whole blood and remaining blood returned to the circulation
- Fewer hemodynamic changes compared to phlebotomy and returns valuable blood components

Chelation



- Inaccessible veins
- Needle phobia
- Anemia
- Cardiac iron overload

Recommendation

If phlebotomy is not possible, iron chelation therapy can be started after careful consideration of risk-benefit ratio **(LoE 4, weak recommendation, consensus).**

Conclusions

- Screen with TS and ferritin
- Confirm with HFE or MRI
- Treat with phlebotomy
- Expand the differential in those that are not C282Y