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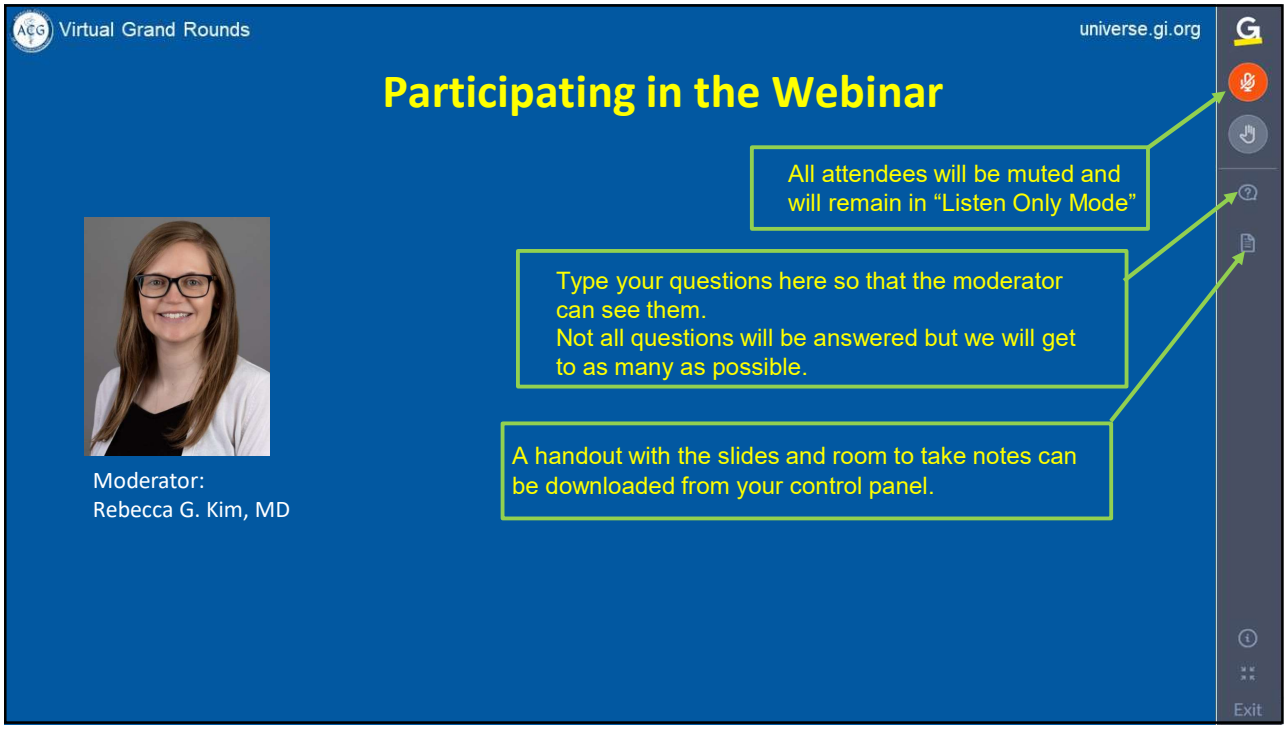

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ACG Virtual Grand Rounds

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There will be NO VGR on November 23 for Thanksgiving


Week 48 – Thursday, November 30, 2023
Management of Duodenal and Ampullary Polyps and Cancer
Faculty: Gregory B. Haber, MD, FACG
Moderator: Dhruv Mehta, MD
At Noon and 8pm Eastern


Week 49 – Thursday, December 7, 2023
An Update and Overview of the FTC's Rule on Non-Competition Employment Agreements
Faculty: Ann Bittinger, Esq.
Moderator: Louis Wilson, MD, FACG
At Noon and 8pm Eastern

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Disclosures

Manida Wungjiranirun, MD:
No disclosures with any ineligible company.

Rebecca G. Kim , MD:
No disclosures with any ineligible company.

**All of the relevant financial relationships listed for these individuals have been mitigated*

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Hereditary Hemochromatosis

Manida Wungjiranirun MD
Assistant Professor of Medicine
Oregon Health and Science University
ACG 2023

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Acknowledgements

- Thank you to Dr. Joseph Ahn for sharing his slides

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Hereditary Hemochromatosis (HH)

- Definition
- Physiology
- Pathophysiology
- Epidemiology
- Screening
- Presentation
- Diagnosis
- Management
- Prognosis

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History of Present Illness

- 40 year old white male referred to hepatology clinic for abnormal liver function tests
- No complaints

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History of Present Illness

- PMH
  - Appendectomy
  - Arthritis
- SH
  - Alcohol- occasional beer
- FMH
  - 2 Brothers alive and well
- NKDA
- Meds
  - None

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Evaluation

- **Physical Exam**
  - VSS
  - No stigmata of chronic liver disease
  - Normal skin color
  - No murmurs
  - No hepatomegaly
  - No splenomegaly

- Labs
  - Hg- 14.3
  - Plt- 157
  - Alb- 3.6
  - TB- 1
  - INR- 1.1
  - AST- 55
  - ALT- 60
- Fe/TIBC= Transferrin Saturation = 75%
- Ferritin- 2145
- Neg viral serologies, AIH, A1AT, ceruloplasmin

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Questions

- Is liver biopsy needed?
- What is the role of HFE genotyping?
- What is the optimal management

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Hereditary Hemochromatosis Definition

- Inherited iron overload disorder
- Excess absorption of iron due to a deficiency of Hepcidin
- Hepcidin: hormone synthesized and secreted by the liver in response to iron levels
  - Inhibits iron absorption by degrading ferroportin-1

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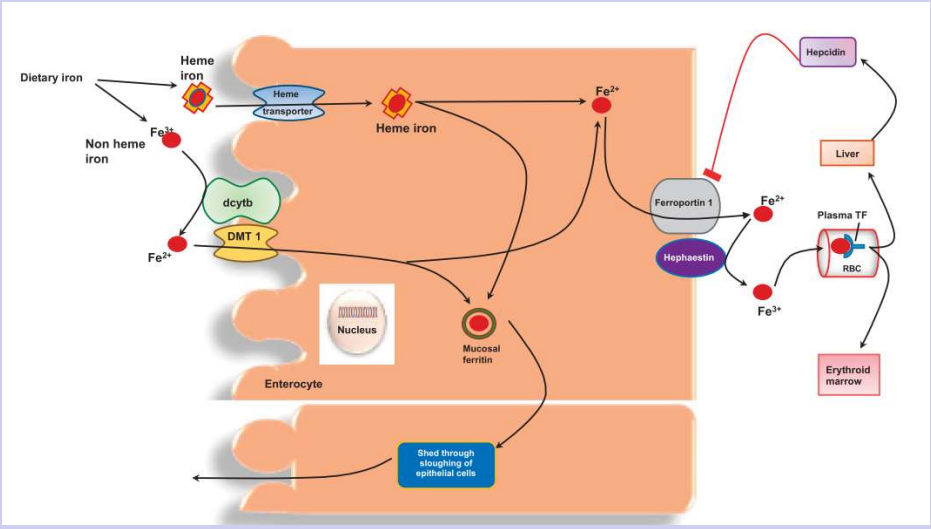
Physiology Iron Absorption



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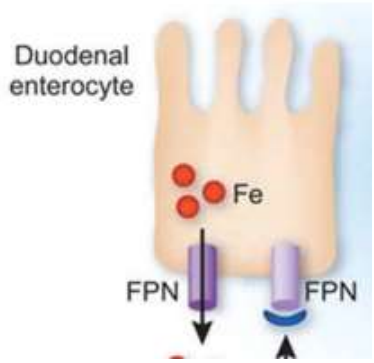
Physiology- Iron Absorption

- Fe absorption in villi of duodenum, jejunum
- Iron is transported via an iron transporter FPN1



Bacon et al, Hepatology Vol 54, No 1, 2011

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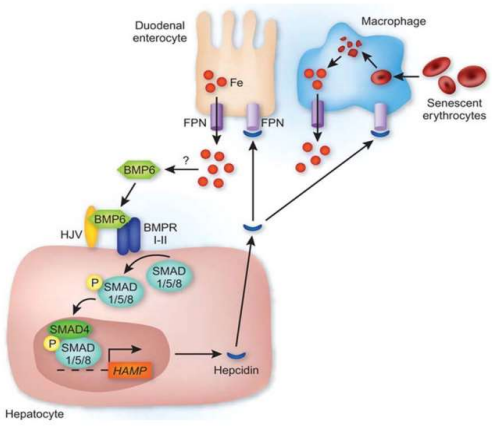
Physiology- Iron Absorption

- Hepcidin is made in the liver in response to iron levels
- Hepcidin binds to FPN1 on intestinal absorptive cells causing decreased absorption of Fe across the enterocyte



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Physiology Iron Absorption

- High Iron
  - Increased Hepcidin production
  - Increased binding of Hepcidin on enterocytes
  - Decreased intestinal uptake of iron
- Low iron
  - Decreased Hepcidin production
  - Decreased binding of Hepcidin on enterocytes
  - Increased intestinal absorption of iron

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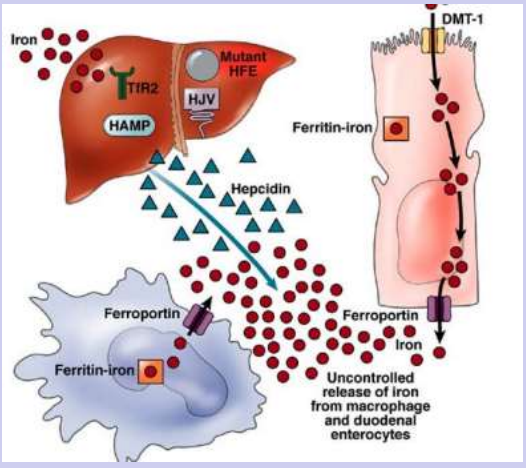
Pathophysiology of HH

- Hereditary Hemochromatosis
  - Inappropriately low expression of Hepcidin relative to circulating iron and body iron stores
  - Inappropriately increased iron absorption



Pietangello Gastroenterology 2010;139:393– 408
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HFE Mutations

- Autosomal recessive
- C282Y- Cys to Tyr substitution
- Homozygous= C282Y/C282Y → Type 1a HH
  - Most frequent inherited form of iron overload
- H63D- His to Asp substitution
  - Minimal effect on cell surface expression, transferrin receptor binding
- C282Y/H63D, Type 1b HH
  - Compound heterozygote
  - Prevalence of 2-4%

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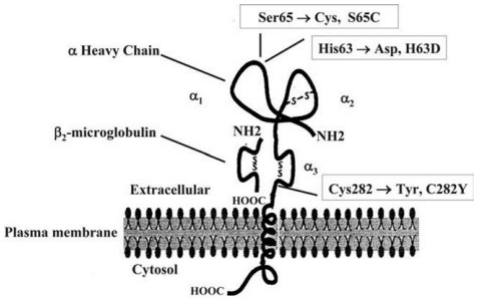
HFE Mutations

- S65C
  - Autosomal recessive
  - Increased iron and ferritin levels
  - No association with increased iron tissue stores
  - Polymorphism without clinical significance



Bacon et al, Hepatology Vol 54, No 1, 2011

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Hereditary Hemochromatosis Genotypes

- Type 2 Hereditary Hemochromatosis
  - Juvenile hemochromatosis
  - Mutation in HJV gene -> Hepcidin deficiency
- Type 3 Hereditary Hemochromatosis
  - Mutation in transferrin receptor 2 gene
  - Hepcidin deficiency
- Type 4A Hereditary Hemochromatosis
  - Autosomal dominant
  - Mutations in FPN1 gene
- Type 4B Hereditary Hemochromatosis
  - Resistance of FPN1 to Hepcidin
  - Increased iron

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Secondary Iron Overload

- Excess absorption and organ deposition of iron unrelated to hereditary hemochromatosis genetic mutations
  - Iron loading anemias (thalassemia, sickle cell anemia)
  - Parenteral iron
  - Liver disease
  - Malignancy
  - Chronic inflammatory state

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Secondary Iron Overload

Alcohol Use Disorder

- Elevation in ferritin and transferrin iron saturation levels
- Increased hepatic iron stores
- Low Hepcidin levels in AUD due to ethanol induced down-regulation of transcription

Metabolic Dysfunction Associated Steatotic Liver Disease

- Increased ferritin and/or transferrin iron saturation levels
- "dysmetabolic" or "insulin resistance hepatic iron overload syndrome"-> unexplained hepatic iron overload
  - High ferritin, normal serum iron levels, due to Hepcidin downregulation from insulin resistance

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Secondary Iron Overload

- Hepatitis C Virus
  - 30-40% of patients with HCV have elevated iron, ferritin, and transferrin saturation
  - Can lead to increased hepatic iron concentration in patients heterozygous for HFE genetic mutations

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Hereditary Hemochromatosis (HH)

- Definition
- Physiology
- Pathophysiology
- Epidemiology
- Screening
- Presentation
- Diagnosis
- Management
- Prognosis

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Epidemiology of HH

- Prevalence of 1 case in 200-400 persons
- Greatest incidence in northern European
  - Highest in Scandinavian and Irish origin
- Prevalence is lower in those of eastern European and Mediterranean origin
- Lowest incidence in African descent

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Penetrance

- Proportion of those with the genotype that express the phenotype
- Penetrance of C282Y/C282Y is incomplete, variable across studies and between genders
- Male C282Y/C282Y manifest symptoms more commonly than women

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Penetrance

- Multiple hit hypothesis
- Genetic modifiers
  - HFE- 37 allelic variants,9 other missense mutations besides C282Y,H63D
  - Other genes- i.e. Hepcidin, TFR2, FP/MTP
  - New genes being found
- Environmental factors
  - Diet → Fat, DM, Lipidemia → MASLD
  - Alcohol
  - Blood loss
- Sex modifiers
  - Men > Women (menstruation = auto-phlebotomy)
  - Women present later in life

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Screening

- Rationale
  - Asymptomatic, latent phase
  - Disease is common, fatal if untreated
  - Diagnosis- safe, reliable
  - Therapy- inexpensive, available
- Drawbacks
  - Uncertain penetrance
  - Discrimination
    - Insurance
    - Job
    - Reproductive
  - Cost
    - As penetrance decreases cost effectiveness decreases
  - Informed consent

Shaheen, Am J Gastroenterol; 2003; 98:1175

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Screening

- Should screening or no screening be offered for HH in first degree relatives of patients with HH?

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Screening

- First degree relatives of patients diagnosed with HH should be screened for HH
- In children of an identified proband, the other parent should be tested and if normal, no further testing needed
- Population screening→ Controversy regarding cost effectiveness, implementation

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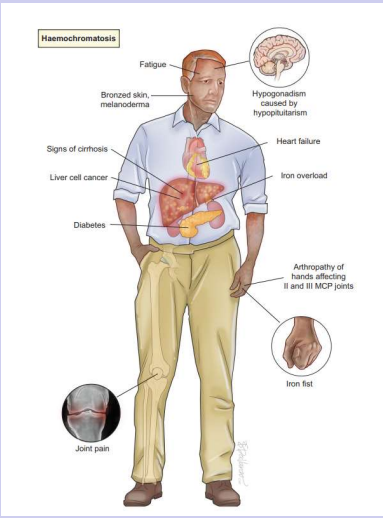
Clinical Manifestations



EASL Clinical Practice Guidelines Journal of Hepatology 2022 vol. 77 | 479–502

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Clinical Manifestations

Organ	Manifestation
Liver	Elevated liver enzymes, cirrhosis, hepatocellular carcinoma
Endocrine	Diabetes, hypogonadism, testicular atrophy, loss of libido, hypopituitarism
Skin	Hypermelanotic pigmentation
Joints	Arthralgia, arthritis, chondrocalcinosis
Heart	Cardiomyopathies, arrhythmias, heart failure

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Presentation Clues

- Early presentation:
  - Symptomatic > 40 to 50 years
  - Subtle, nonspecific symptoms ~ fatigue, malaise
  - LFT abnormalities
  - Arthropathy
- Late presentation:
  - Excessive skin melanin + Fe skin deposition in the skin→ bronzing
  - Dilated cardiomyopathy, CHF, conduction disturbances and arrhythmias
  - Cirrhosis → Hepatocellular carcinoma
  - Diabetes mellitus
  - Arthropathy ~ MCP & PIP, chondrocalcinosis

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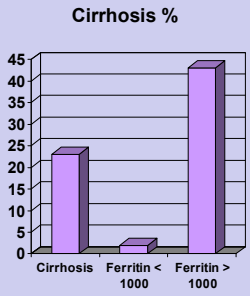
Serum Ferritin Level Predicts Advanced Hepatic Fibrosis among U.S. Patients with Phenotypic Hemochromatosis

- N=182 with HH
- Liver biopsy reviewed
- Found the following associated with cirrhosis:
  - Ferritin > 1000
  - ALT elevation



AIM 2003; 138:627

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Hepatic Manifestations

- Risk of developing cirrhosis increases significantly with ferritin level >1,000 ng/mL at diagnosis
- EtOH consumption of >60 g/day increases risk of developing cirrhosis by 9 fold
- Lifetime incidence of cirrhosis in untreated men with HH is ~10%
- Iron overload worsened by tobacco and EtOH
- High risk of liver cancer in persons with cirrhosis, even after phlebotomy – continue screen!

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How to Diagnose HH

- Transferrin saturation > 45%
- Ferritin > 200 in Women, > 300 in Men
- HFE gene testing

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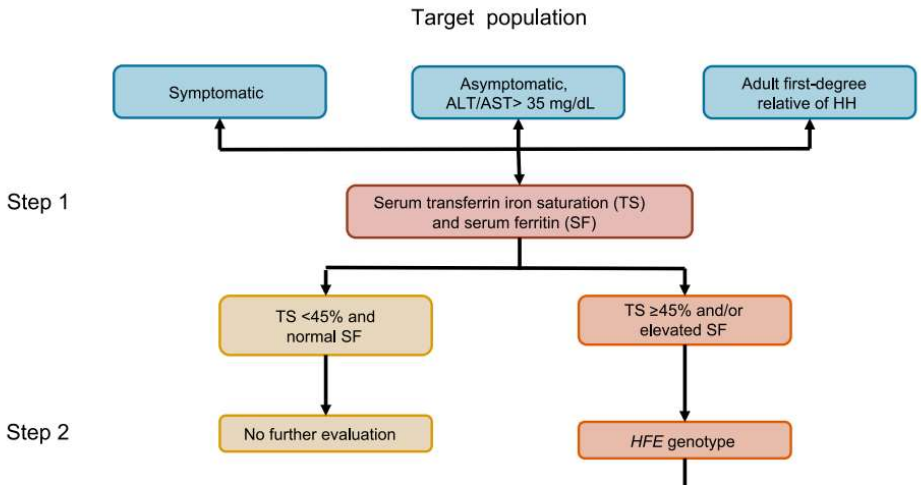
How to Diagnose HH



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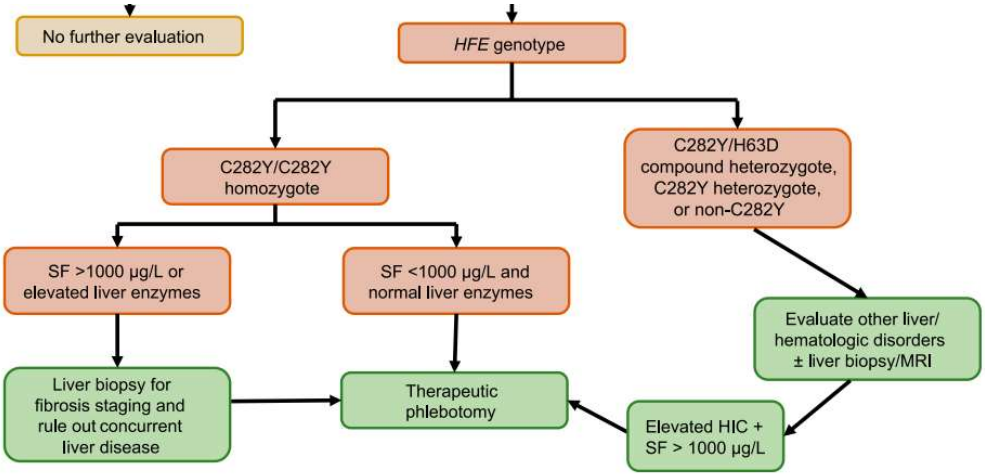
How to Diagnose HH



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HH Diagnosis: Liver biopsy vs MRI

- Liver Biopsy
  - Assessment of fibrosis
  - Evaluates for other diagnosis
- MRI
  - Distinguishes between HH and secondary iron overload
  - Hepatic iron quantification
- Transient elastography- Fibroscan
  - Limited data, not validated in hemochromatosis

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Diagnosis

- When should a liver biopsy be ordered?

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When to Obtain a Liver Biopsy

- HFE C282/C282Y with ferritin >1,000
  - Staging of fibrosis
- HFE C282Y/C282Y with ferritin <1,000 with concurrent risk factors for cirrhosis
  - ETOH
  - NAFLD
  - Viral hepatitis
- Consider biopsy if clinical features of advanced fibrosis are present
- Diagnostic & Prognostic
- Risk of complications and sampling variability

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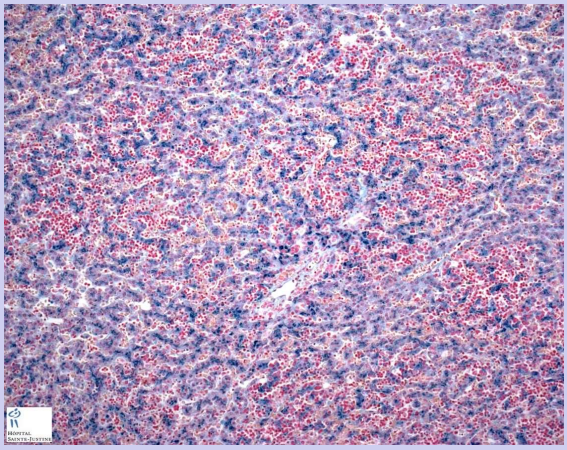
Liver Biopsy

- Diagnostic
- Evaluate for other liver diseases
- Best staging method



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Iron Deposition

- In primary iron overload, iron is primarily deposited in parenchymal cells, with reticuloendothelial cell accumulation occurring very late in the disease
- In secondary iron overload or in chronic disease (ESRD) iron deposition occurs first in the reticuloendothelial cells and then in parenchymal cells

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Hereditary Hemochromatosis (HH)

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Back to Case Presentation

- Genotyping= HFE C282Y/C282Y Homozygous
- Liver Biopsy
  - Grade 3 Hemosiderosis
  - Stage 1 Fibrosis
  - Hepatic iron index >2

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Management

- When to initiate treatment?
  - C282Y homozygotes with an elevated serum ferritin (300 ng/mL in men and 200 ng/mL in women) + with a transferrin saturation ≥ 45%
- C282Y homozygotes with ferritin <1,000 ng/mL should be treated to prevent progression of disease
- C282Y homozygotes with a normal ferritin should be monitored with serial aminotransferase levels and ferritin

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Management

- C282Y/H63D compound heterozygotes-> risk of clinically relevant iron overload is low
  - Liver fibrosis can develop if concurrent EtOH use, MASLD, or viral hepatitis
  - Treat risk factors before iron removal for HH
- For C282Y/H63D compound heterozygotes with evidence of elevated hepatic iron content on biopsy, iron removal can be considered

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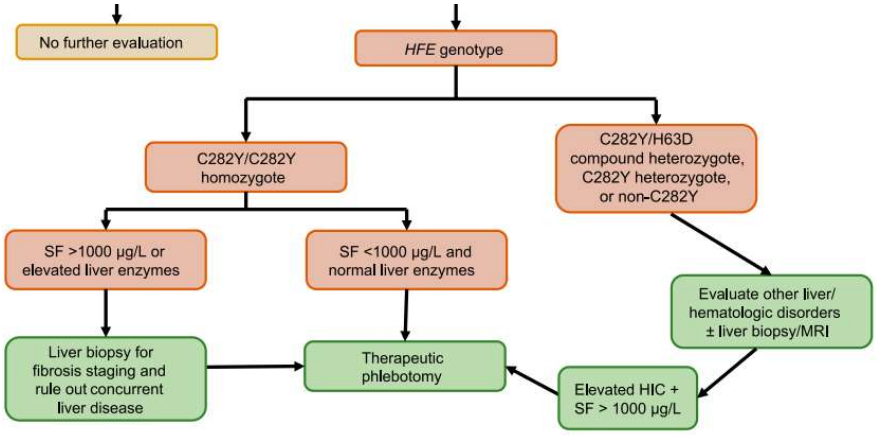
Management



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Practical Phlebotomy

- Induction Rx
  - Phlebotomize 500 cc weekly
- Monitor
  - Hg at each phlebotomy, ensure Hb > 11 g/dL
  - Monthly ferritin level
- Goals
  - Ferritin ~ 50-100
- Maintenance phase
  - Phlebotomy every 3-4x/year
  - Ferritin near 50 ng/mL

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Tavill Hepatology 2001; 33:1321

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Management

- Avoid vitamin C
  - Ascorbic acid increases iron absorption
- Elimination of red meat and dietary iron is not necessary if undergoing phlebotomy

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Management

- Chelation therapy can be used but is not first line therapy
  - Retinopathy, auditory toxicity
  - Neutropenia, agranulocytosis
  - Renal toxicity
- Use iron chelation when patients are intolerant or refractory to phlebotomy (severe anemia, cardiac dysfunction)

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Management

- Liver transplantation
  - ACG recommendation: Liver transplant should be used in patients with HH with decompensated cirrhosis or hepatocellular carcinoma
  - Normalizes hepcidin deficiency and alterations in iron metabolism

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Prognosis: good when caught early

- Phlebotomy initiated in asymptomatic patient can prevent all clinical manifestations of iron overload
- Phlebotomy in symptomatic patients can lead to improvement in hepatic fibrosis, cardiac dysfunction, skin pigmentation, and fatigue
- Phlebotomy is too late for cirrhosis, arthropathy, hypogonadism, and diabetes
- Phlebotomy does not reduce the risk of hepatocellular carcinoma

Niederau NEJM 1985; 313:1256

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Summary

- Subtle non specific symptoms
- Iron studies -> HFE genotyping
- Selective liver biopsy vs MRI
- Phlebotomy is effective particularly when started early
- HCC risk is high, continue screening with phlebotomy
- Screen first degree relatives

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Thank you!

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Questions

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