Iron Overload

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GI Grand Rounds

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Case

- 77 year-old white female
- Referred to Hepatology Clinic for asymptomatic elevation of transferrin saturation level

Case

- Past Medical Hx:
  - HLD
  - HTN
  - OA
  - Schatzki's ring s/p dilt for dysphagia
  - Bilateral Breast CA s/p bil mastectomy
  - s/p complete hysterectomy
  - cataracts

Case

- Medications:
  - Lipitor 10mg daily
  - Avalide 150/125mg daily
  - Calcium + D daily
  - Glucosamine/Chondroitin daily
  - Ibuprofen 400-800mg daily
- Allergies - PCN

Case

- Social Hx:
  - Retired secretary
  - Widowed
  - Three 12 oz cans of beer daily
  - Denies tobacco, IVDU, tattoos
- Family Hx:
  - M - Cerebral hemorrhage, deceased 67
  - F- CVA, deceased 72
  - B -Oat cell lung Ca, deceased 52

Case

- ROS:
  - Positives: moderate knee pain bilaterally
  - Denies: jaundice, diabetes, darkening of skin, dyspnea, orthopnea, swelling, abdominal pain

Case

- Physical Exam:
  - BP 173/86, P 77, R, 19, T 97.5, Ht 5'6", Wgt 178
  - ++Crepitis in knees bilaterally
  - Normal heart and lungs
  - No icterus, jaundice, spiders, hepatomegaly, splenomegaly or skin discoloration

Case

- Laboratories:
  - WBC 5.9
  - Hgb 13.8
  - MCV 97
  - Plt 203

  - AlkP 120
  - AST 27
  - ALT 33
  - TB 0.7
  - DB 0.17
  - TP 6.9
  - Alb 4.4

  - BUN 12
  - Cr 0.7
  - Glu 98

  - TG 77

  - IBC 226
  - Fe 187
  - % sat 83
  - Ferritin 380

Case

- A diagnostic test was performed…

Objectives

- Review the pathophysiology of iron overload and hemochromatosis
- Identify non-HFE iron overload mutations and causes of secondary iron overload
- Review AASLD Guidelines for Diagnosis and Management of Hereditary Hemochromatosis (HH)

What is normal anyway?

- Normal total body iron content is 3-4 grams
  - Hemoglobin 2.5 g
  - Ferritin and hemosiderin 1 g (men)
  - Proteins (myoglobin, cytochromes, catalase) 400 mg
  - Transferrin bound 3-7 mg

Pluses and Minuses

- Absorption
  - Dietary absorption is regulated so that it matches daily iron loss (Increased absorption in deficient states)
  - Mostly through the duodenum
  - Western diet 10-20mg/day
  - About 10% absorbed
- Losses
  - Sweat, shed skin cells, ?gi (1mg/day)
  - Premenopausal adult women (0.5 – 1.0mg/day)

Pathophysiology of Hemochromatosis

- Mechanisms
  - Alterations in HFE protein function
  - Increased intestinal absorption of dietary iron
  - Iron induced tissue injury and fibrosis

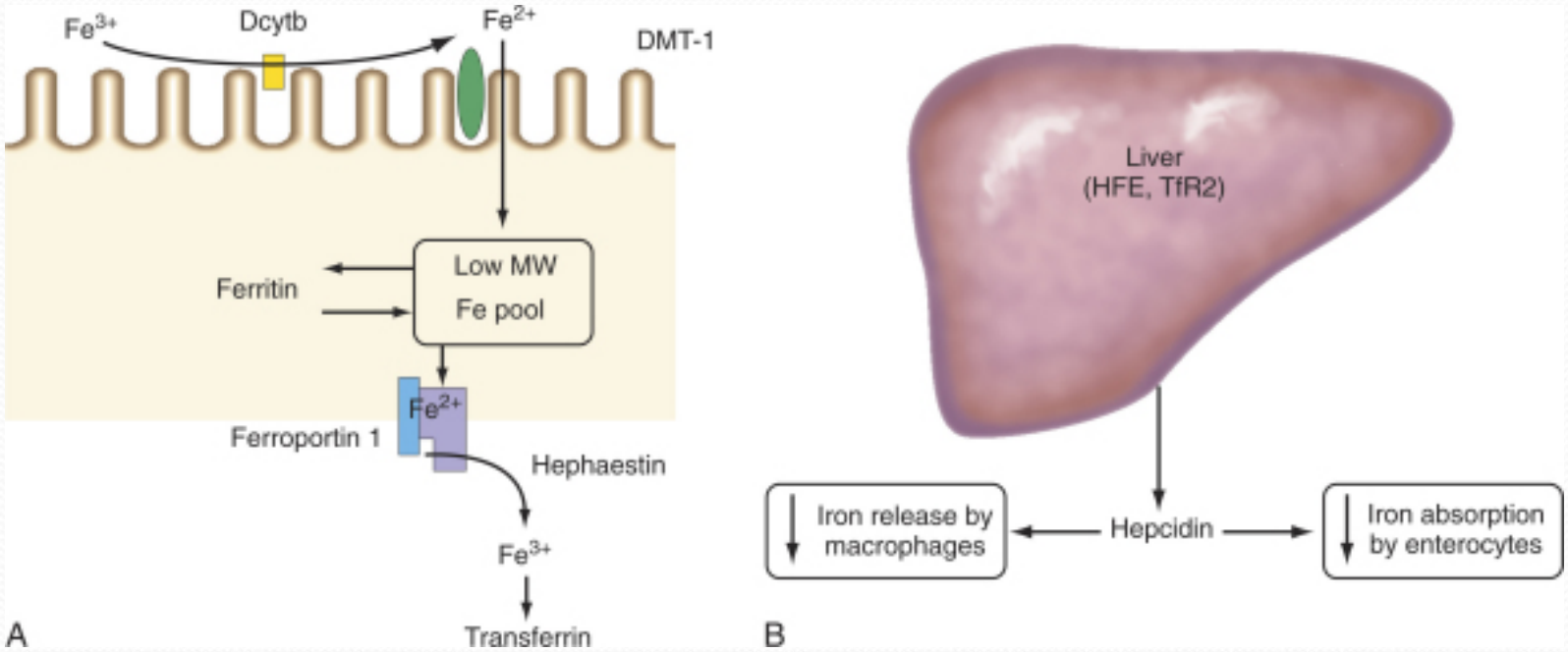
HFE protein

- Structure is similar to major histocompatibility complex (MHC) class I molecules but does not present antigen
- The HFE protein forms a complex with the transferrin receptor (TfR1) which effects cellular Fe uptake
- It may also participate with transferrin receptor (TfF2) to regulate hepcidin which acts to reduce dietary iron absorption and inhibit iron release by macrophages

Hepcidin

- Produced in the liver
- Possible iron storage regulator
- Inhibits iron absorption in the small intestine and prevents release of iron from macrophages
- Levels are low in HH
- Is an acute phase reactant and plays a central role in anemia of chronic disease (levels are high)

Duodenal absorption



Feldman: Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 8th ed

Duodenal iron absorption

- Regulated by:
  - Demands of erythropoesis independent of iron stores
  - Storage regulator (i.e. hepcidin) that prevents iron overload when needs are met

Iron Toxicity

- Increased iron causes saturation of circulating transferrin which leads to more “non-transferrin-bond” iron
- Iron tends to deposit in cells with high levels of transferrin receptors (i.e. heart, liver, thyroid, gonads, pancreatic islets)
- Reactive oxygen species attack lipids, proteins, RNA and DNA causing tissue damage and fibrosis

HH

Stages of iron overload	Years	Parenchymal iron storage (grams)
Insignificant	0-20	0-5
Iron overload without disease	20-40	10-20
Iron overload with organ damage	>40	>20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Causes of Iron Overload

- There is NO mechanism for increasing iron excretion, therefore, overload will ensue if there is excess absorption
  - Genetic (Increased iron absorption with normal intake)
  - Chronic liver diseases
  - Iatrogenic (Surely, it wasn't my fault?)

Secondary Iron overload (Acquired)

Iron-loading anemias

- Thalassemia major
- Sideroblastic anemia
- Chronic hemolytic anemia
- Aplastic anemia
- Pyruvate kinase deficiency
- Pyridoxine-responsive anemia

Parenteral Iron overload

- RBC transfusion
- IV iron
- Long-term hemodialysis

Secondary Iron overload (Acquired)

Chronic liver disease

- HCV
- HBV
- Alcoholic liver disease
- NASH
- Porphyria cutanea tarda
- Portacaval shunt

Other

- Dietary iron overload
- Dysmetabolic iron overload syndrome

Iron overload diseases affect 1.5 million people in the U.S.

Clinical Presentation

- Symptomatic iron overload usually occurs after the 5th decade
- Expression is influenced by age, sex, dietary iron, blood loss and unknown factors
- Women express the disease less frequently than men
- Alcohol and Hepatitis C may accelerate the disease expression

Symptoms	Occurrence, %
Weakness, lethargy, fatigue	40–85
Apathy, lack of interest	40–85
Abdominal pain	30–60
Weight loss	30–60
Arthralgias	40–60
Loss of libido, impotence	30–60
Amenorrhea	20–60
Congestive heart failure symptoms	0–40

Bacon BR, Powell LW, Adams PC, *et al.* Molecular medicine and hemochromatosis: at the crossroads. *Gastroenterology*. 1999. 116:193-207.
Edwards CQ, Cartwright GE, Skolnick MH, *et al.* Homozygosity for hemochromatosis: Clinical manifestations. *Ann Intern Med*. 1980. 93:511-525.

Hereditary Hemochromatosis

Hereditary Hemochromatosis (HH)

- **"Several inherited disorders of iron homeostasis characterized by increased intestinal iron absorption resulting in tissue iron deposition"**

Feldman: Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 8th ed.

HH

- HFE-related
  - C282Y homozygosity
  - C282Y/H63D compound heterozygosity
  - Other HFE mutations
- Non-HFE-related
  - Hemojuvelin (HJV) mutations
  - Hepcidin (HAMP) mutations
  - Transferrin receptor 2 (TfR2) mutations
  - Ferroportin 1 (SLC40A1) mutations

HH (alternate nomenclature)

- Type 1 (HFE)
- Type 2 (Hemojuvelin/Hepcidin)
- Type 3 (Transferrin Receptor 2)
- Type 4 (Ferroportin)

HFE-related HH

- The most common genetic disorder in the Caucasian population, especially northern European (Nordic, Celtic)
- Autosomal recessive
- Prevalence for homozygotic mutation in U.S. whites is 1:200-250
- 1:10 are heterozygous carriers

HFE Gene

- The clinically significant gene mutations are C282Y and H63D
- C282Y
  - Described in 1996
  - G to A missense mutation
  - Substitutes tyrosine for cysteine
- 60-93% of patients with iron overload are C282Y homozygous

HFE Gene

- Prevalence of compound heterozygotes (C282Y/H63D) is 1-2 %
- Only a small percentage of compound heterozygotes will develop iron overload
- A negative HFE gene test does not exclude iron overload

HFE-Gene

- All C282Y homozygotes had elevated transferrin saturation (100% positive predictive accuracy)
- C282Y homozygotes – full expression with progressive tissue iron overload in 58%
- The rate of iron accumulation is variable

Olynyk JK, et al. A population based study of the clinical expression of the hemochromatosis gene. N Engl J Med 1999;341:718-724.

Hemojuvelin and Hepcidin

- Hemojuvelin (HJV/1q) Mutation
- Hepcidin Antimicrobial Peptide (HAMP/19q13.1) Mutation
  - "Juvenile Hemochromatosis"
  - Autosomal recessive
  - HJV is a regulator of hepcidin
  - Very low hepcidin causes massive Fe influx.
  - High ferritin and transferrin saturation in 1st decade.
  - Hypogonadism before end of 2nd decade, cardiac disease & abdominal pain
  - Cirrhosis occurs later
  - Death during 3rd decade from heart failure

Transferrin Receptor 2 (TfR2)

- Located on hepatocytes
- Autosomal recessive mutation
- TfR2 is regulator of hepcidin -> Low hepcidin ->causes increased Fe influx.
- High transferrin saturation in 2nd to 3rd decades
- HHC may develop from 2nd to 4th decades
- Mild to severe Fe overload in periportal hepatocytes
- Hypochromic anemia

Ferroportin

- Missense mutation of ferroportin 1 gene
- Iron exporter located in enterocytes, macrophages, and hepatocytes
- Rare autosomal dominant mutations

Ferroportin

- Worldwide distribution
  - Decreased Fe efflux
  - High ferritin in 1st decade
  - Fe deposit in RES with very high ferritin but low or normal transferrin saturation; high saturation late in life.
  - Mild hypochromic anemia.
  - Mild liver injury with sinusoidal fibrosis
  - May cause cirrhosis
  - Treatment: Phlebotomy q 2-3 weeks (not weekly)

African Iron Overload

- Sub-Saharan Africa
- Non-HFE related genetic trait (? Ferroportin 1) exacerbated by dietary iron loading (maize beverage)
- Iron loaded Kupffer cells
- This contrasts HFE-related HH were Kupffer cells are spared

Aceruloplasminemia

- Autosomal recessive
  - Decreased Fe efflux
  - Lack of ceruloplasmin, which has ferroxidase activity needed to release Fe from cells
  - Causes deposit in the:
    - basal ganglia, dentate nucleus (ataxia and dementia)
    - Pancreas (diabetes mellitus)
    - RES (hypochromic microcytic anemia)
  - Liver disease is mild
  - Treatment: Chelation, Exjade® (deferasirox) & desferoxamine

Other

- Atransferrinemia/Hypotransferrinemia
  - Autosomal recessive
  - Increased Fe influx
  - Severe anemia
  - Onset in 1st & 2nd decade
- H-Ferritin associated hereditary Fe-Overload
  - Autosomal dominant
  - Increased Fe influx
  - Liver Fe overload in 4th-5th decade

AASLD Guidelines

Diagnosis and Management of Hereditary Hemochromatosis
2001

Management Objectives for HH

- Early diagnosis to prevent organ damage and dysfunction due to tissue iron toxicity
- Screening and early detection of asymptomatic HH cases to reduce mortality
- Recognition and diagnosis of symptomatic cases of HH, to minimize progression and complications of the disease
- Adequate treatment of HH to promote rapid, safe, and effective removal of iron
- Vigilant follow-up and maintenance treatment of all cases of HH

Tavill, A. Diagnosis and Management of Hemochromatosis. Hep May 2001.

Who gets screened?

- Symptomatic patients
  - Unexplained liver disease or known liver disease with abnormal serum iron studies
  - Type 2 DM especially with hepatomegaly, abnormal lft's, atypical cardiac disease, and/or early onset sexual dysfunction
  - Early-onset atypical arthropathy, cardiac disease, male sexual dysfunction

Tavill, A. Diagnosis and Management of Hemochromatosis. Hep May 2001.

Who gets screened?

- Asymptomatic patients
  - First-degree relatives
  - Abnormal iron studies on routine testing
  - Unexplained elevated liver enzymes or hepatomegaly or enhancing of liver on CT
- General Population???

Tavill, A. Diagnosis and Management of Hemochromatosis. Hep May 2001.

Screening

- Fasting Transferrin Saturation (TS)
  - Fasting Iron/Transferrin Iron Binding Capacity (TIBC)
  - Measured TIBC - repeat iron measurement after adding exogenous iron to saturate the serum transferrin followed by removal of the nontransferrin-bound iron
  - Calculated TIBC – (Fe +UIBC)
  - TS > 50% in women and >60% in men yield sensitivity of 92% and specificity of 93%
  - Cutoff of 45% increases the sensitivity for screening purposes (98% sensitive for homozygotes)[1]

1 McLaren CE, et al. Gastro1998;114:543-549.

Screening

- Elevated serum ferritin plus elevated TS has a NPV of 97%. 1
- With confirmed HH, a ferritin >1000 ng/mL predicts cirrhosis. 2

1 Bassett ML, et al. Gastro 1984;87:628-633.
2 Guyader D, et al. Gastro 1998;115:929-936.

Diagnosis

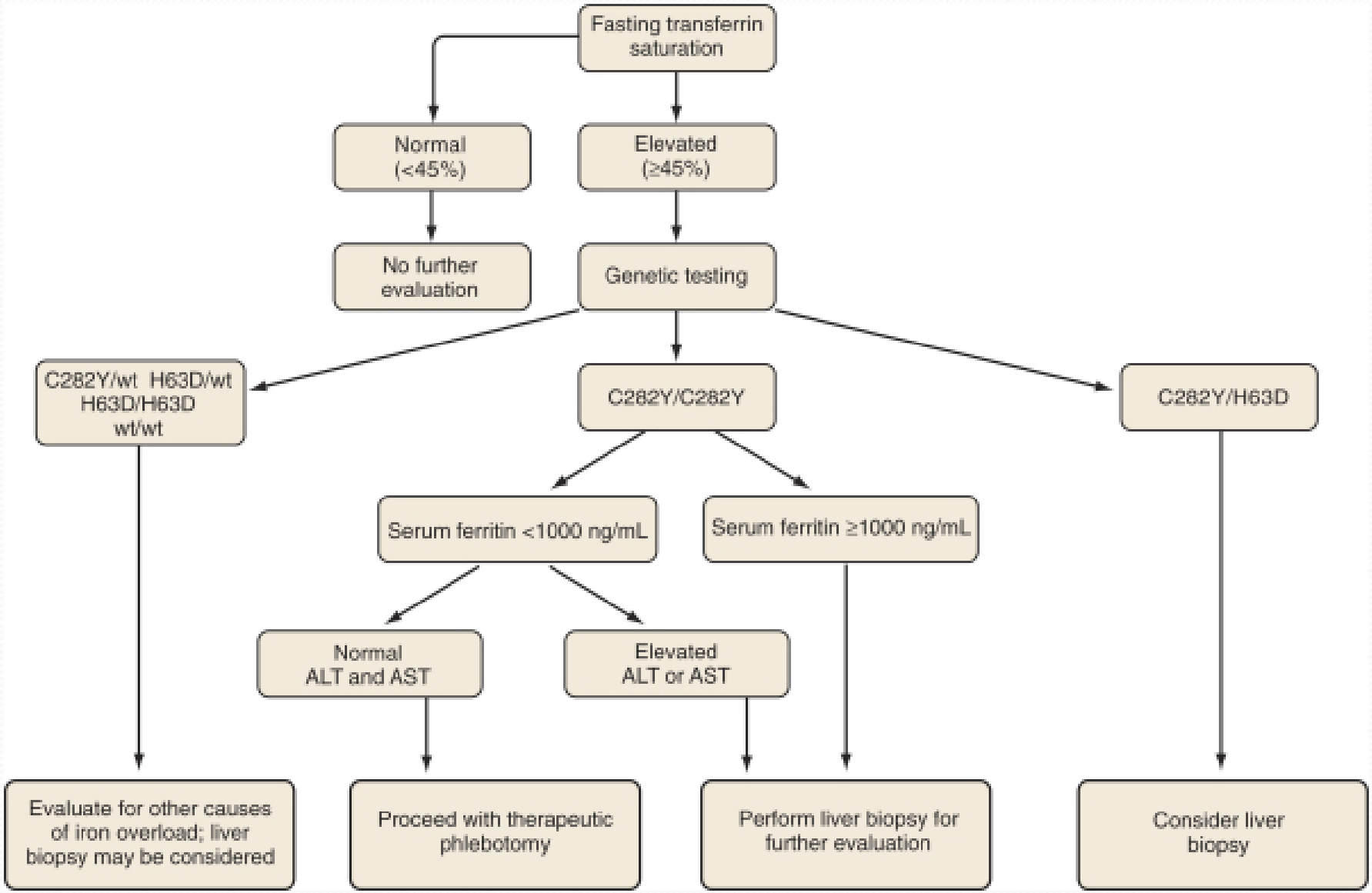
1. Liver Bx: Hepatic Iron Index (µmol/g ÷ age) > 1.9
2. Induced Fe deficiency (phlebotomy q week)
   a. > 20 g Fe after age 40
   b. > 10 gm for age 20-40
   c. (1 unit = 250 mg Fe)
3. HFE C282Y homozygote
4. C282Y/H63D + (1.) or (2.)

Who gets a Liver biopsy?

- All homozygotes with:
  - Age >/= 40
  - Ferritin > 1000 ng/mL
  - Elevated ALT or AST
  - Other risk factors for liver disease

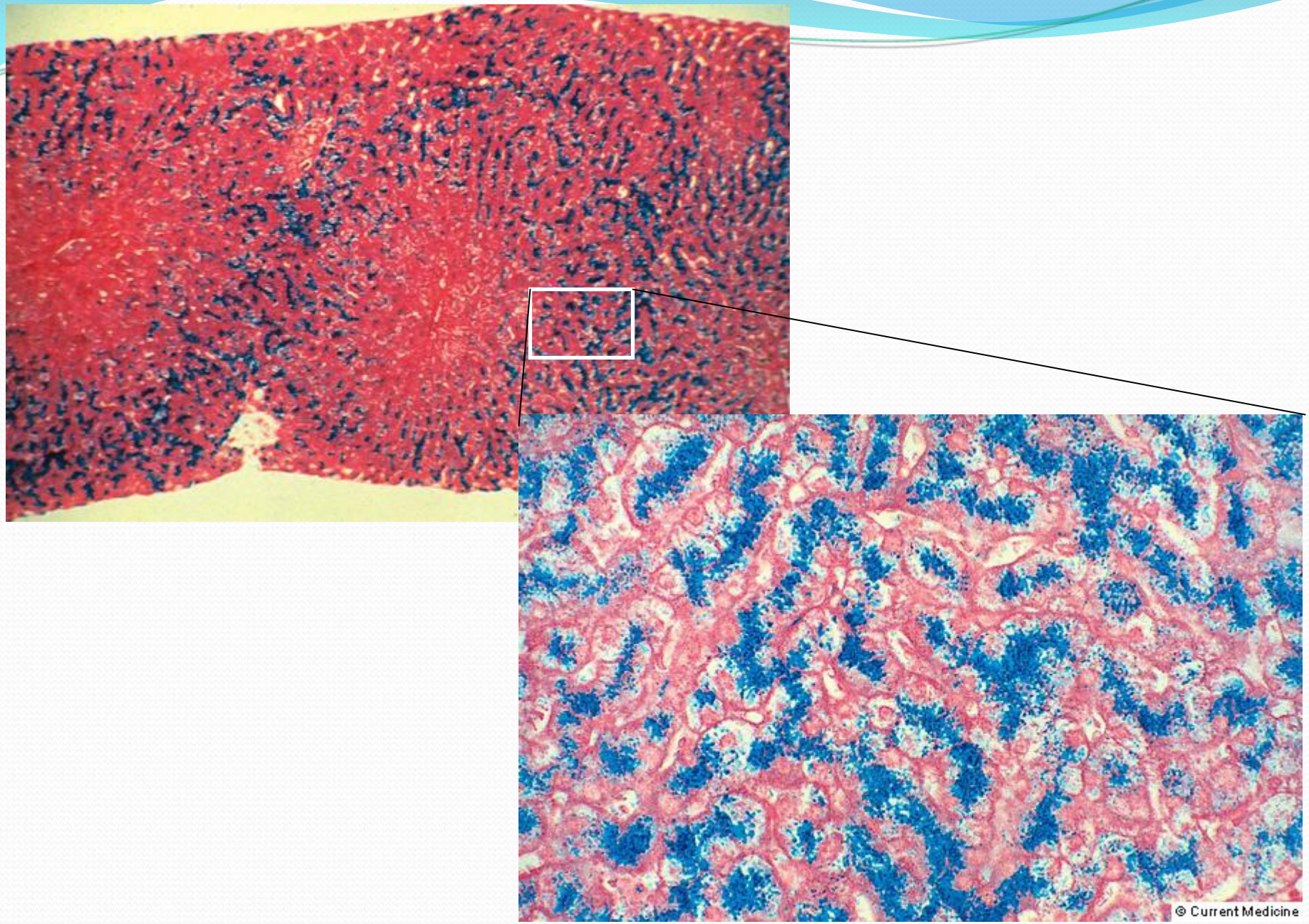
- Consider in compound heterozygotes with elevated TS and abnormal lft's

Diagnostic Algorithm



Liver Biopsy

- Prior to 1985 only qualitative measurements were used to assess the degree of iron deposition (Perl's Prussian blue stain)
  - Ludwig-Batts system (Grade 0-4)
  - Grades 2 and 3 correlate poorly with quantitative iron levels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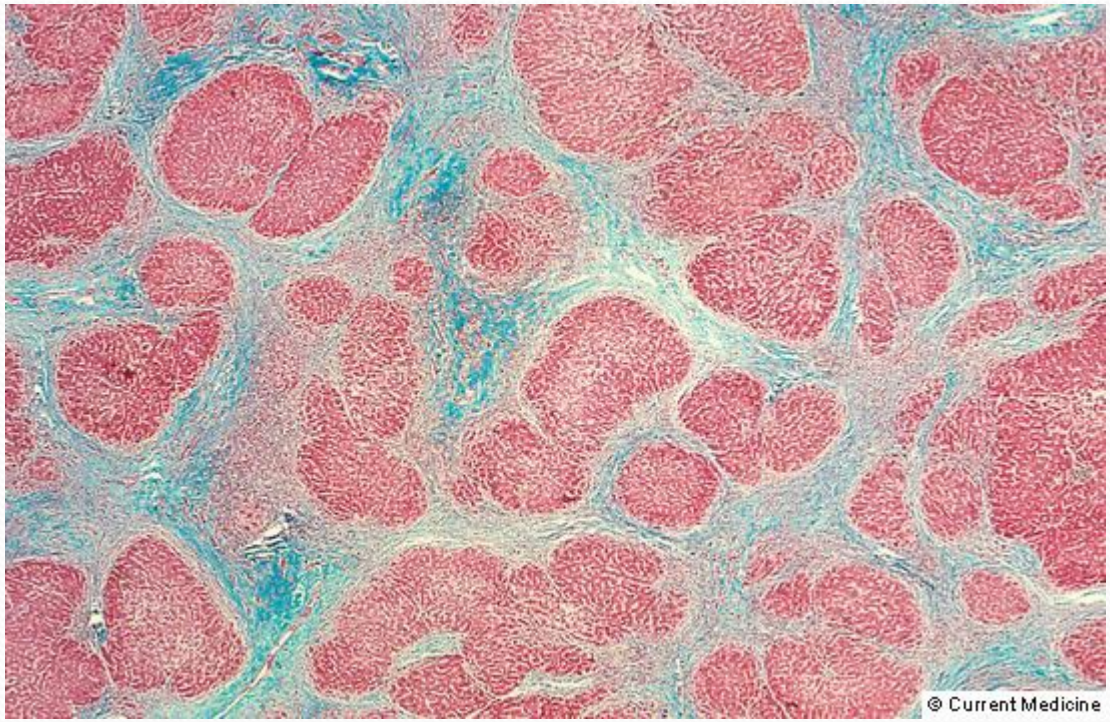
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Hepatic Iron Index (HII)

- Hepatic iron increases with age in most homozygotes
- HII - Hepatic Iron Concentration (μ moles per gram dry weight) divided by age in years
- A hepatic iron index (HII) in excess of 1.9 μmmol/g/yr was found to effectively distinguish homozygous hemochromatosis from heterozygotes and patients with alcohol-induced liver disease.
- 15% of homozygotes have an HII <1.9 μmol/g/yr (it is NOT required for diagnosis)

Treatment

- Hereditary hemochromatosis
  - One phlebotomy (removal of 500 mL of blood) weekly or biweekly
  - Check hematocrit prior to each phlebotomy; allow hematocrit to fall by no more than 20% of prior level
  - Check serum ferritin level every 10-12 phlebotomies
  - Stop frequent phlebotomy when serum ferritin falls below 50 ng/mL
  - Continue phlebotomy at intervals to keep serum ferritin to between 25 and 50 ng/mL
  - Avoid vitamin C supplements

Tavill, A. Diagnosis and Management of Hemochromatosis. Hep May 2001.

Treatment

- Secondary iron overload due to dyserythropoiesis
  - Deferoxamine (Desferal) at a dose of 20-40 mg/kg body weight per day
  - Consider follow-up liver biopsy to ascertain adequacy of iron removal
  - Avoid vitamin C supplements

Tavill, A. Diagnosis and Management of Hemochromatosis. Hep May 2001.

Am I going to feel better?

- YES! – malaise, fatigue, skin pigmentation, insulin requirements, abdominal pain
- NO! – arthropathy, hypogonadism, cirrhosis

Am I going to die?

- Patients with HH without evidence of cirrhosis have a normal life expectance if treated adequately

- Cirrhosis and HCC account for 50-75% of HH related deaths

Niederau C, et al. Gastro 1996;110:1107-1119.

Major Causes of HH-related Death

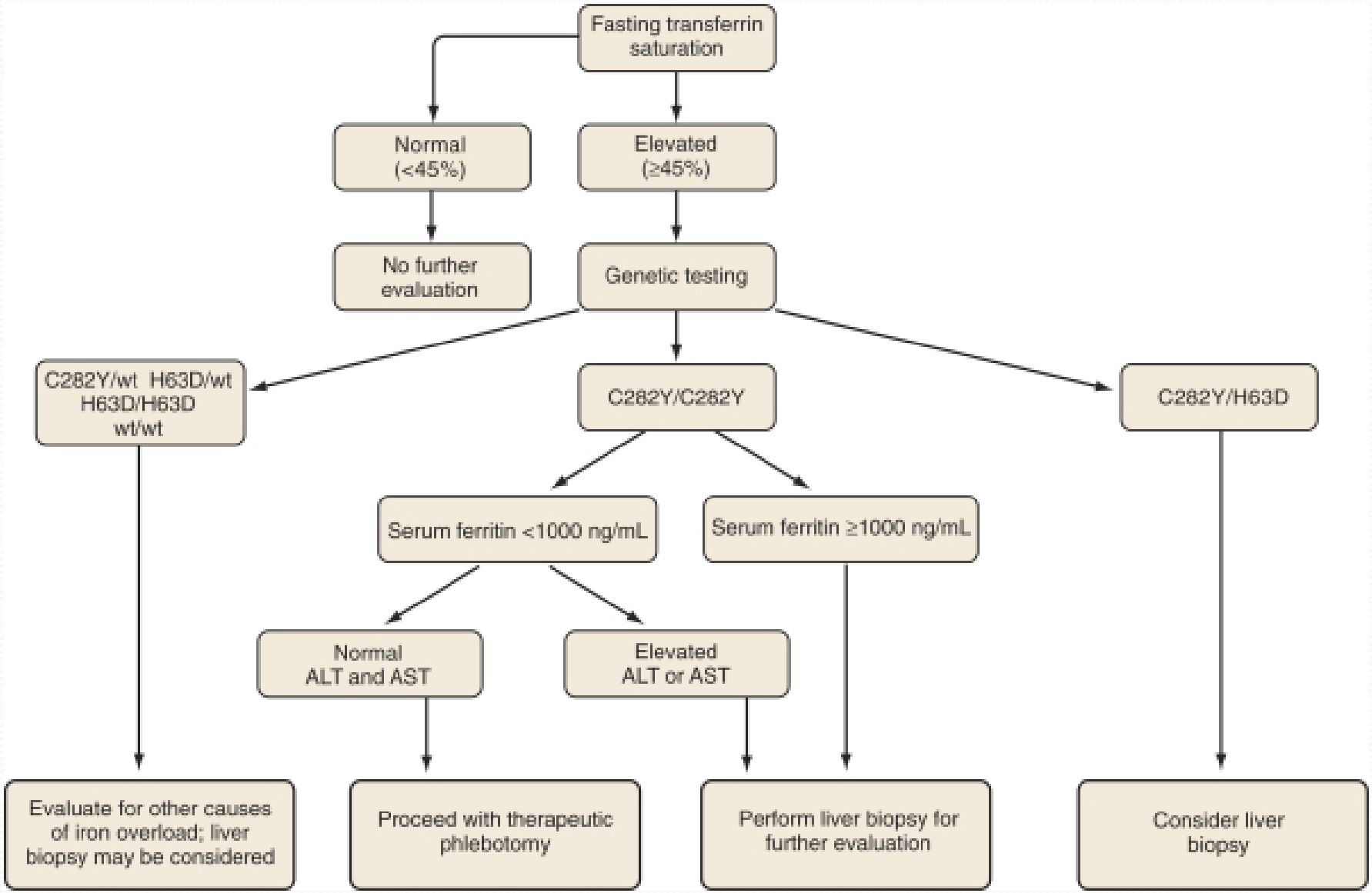
- Hepatocellular carcinoma (30%)
- Decompensated cirrhosis (20%)
- Diabetes mellitus
- Cardiomyopathy
- 10 – 119 fold increase over normal population

Niederau C, et al. Gastro 1996;110:1107-1119.

Are there things I should avoid?

- Official recommendation - avoid vitamin C
- Other things to consider
  - Limit red meat
  - Avoid iron skillets
  - Alcohol in moderation
  - Drink tea or coffee (tannins inhibit absorption)

Case Resolution



Summary

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02/12/2008