Hemochromatosis

Updated 2008 May 29 09:10 AM: N Engl J Med 2008 May 22 commentary (Possible risk factors)
brief "What you should do" review (BMJ 2008 Mar 1)
continued peer review

General Information (including ICD-9/-10 Codes)

Description:

- abnormal deposition of iron

ICD-9 Codes:

- 275.0 disorders of iron metabolism
- 713.0 arthropathy associated with other endocrine and metabolic disorders

ICD-10 Codes:

- E83.1 disorders of iron metabolism
    - ICD-10-CA modification in Canada: E83.1 subdivided to identify
        - E83.10 haemochromatosis
        - E83.18 other disorders of iron metabolism
        - E83.19 disorder of iron metabolism, unspecified
- M14.5 arthropathies in other endocrine, nutritional and metabolic disorders

Organs Involved:

- liver, heart, pancreas, testes, pituitary, joints (pseudogout), adrenal, thyroid, parathyroid, spleen, kidney, skin

Who is most affected:

- men:women 5-10:1
- age 40-60 (45-50), later in females thought to be due to menstrual blood loss
- genetic disease of Europeans, but similar disorder identified in African Americans known as African Iron Overload (AIO) (Am J Med 1996;101;5,9 in Hosp Pract 1996 Oct;31(10);168)
- neonatal hemochromatosis has been reported in > 100 cases, review can be found in Pediatrics 2001 Oct;108(4);960
    - gestational intravenous immunoglobulin (IVIG) reported to be associated with good pregnancy outcomes in 15 women with history of delivering infant with neonatal hemochromatosis (Lancet 2004 Nov 6;364(9446):1690), editorial can be found in Lancet 2004 Nov 6-12;364(9446):1644
    - case presentation of neonatal hemochromatosis can be found in N Engl J Med 2005 Jul 14;353(2):189
    - disparate clinical presentation reported in 2 sets of fraternal twins with neonatal hemochromatosis (Pediatrics 2005 Dec;116(6):e880 full-text)
    - retrospective series of 16 patients with acute liver failure due to neonatal hemochromatosis can be found in Pediatrics 2006 Nov;118(5):2060

Incidence/Prevalence:

- 8-9% heterozygotes in US, 1/220 homozygotes
- estimated 4.5 cases per 1,000 adults (Ann Intern Med 1998 Dec 1;129(11):954 in J Watch 1999 Jan 15;19(2);17)
- in population-based study of white adults of northern European ancestry (3,011 unrelated white adults in Busselton, Australia), 0.5% (16) were homozygous for C282Y mutation and 14.1% (424) were heterozygous; of 16 homozygous patients, only 8 (50%) had clinical features of hemochromatosis, 4 (25%) had serum ferritin levels that remained normal over 4 years, serum transferrin saturation was > 45% in 15 and 43% in 1 homozygous patient (N Engl J Med 1999 Sep 2;341(10):718), editorial can be found in N Engl J Med 1999 Sep 2;341(10):755, correction can be found in N Engl J Med 1999 Nov 25;341(22):1708
- estimated prevalence of hemochromatosis (HFE) gene mutations in US is 5.4% for C282Y mutation and 13.5% for H63D mutation; estimated 0.26% C282Y homozygosity, 1.89% H63D homozygosity, 1.97% compound heterozygosity; estimated C282Y heterozygosity in 9.54% non-Hispanic whites, 2.33% non-Hispanic blacks and 2.75% Mexican-Americans; based on genotyped blood samples from 5,171 persons (JAMA 2001 May 2;285(17):2216)
- prevalence of disease much lower than prevalence of homozygous gene mutations (i.e. penetrance of clinical disease < 1%); study of 41,038 patients in United States, 152 were homozygous for C282Y, only 1 of 152 persons with homozygous HFE mutations had signs and symptoms consistent with diagnosis of hemochromatosis (Lancet 2002 Jan 19;359(9302):211), commentary can be found in Lancet 2002 Aug 3;360(9330):411

 Causes and Risk Factors

Causes:

- genetic
  - autosomal recessive most common and severe form, leads to increased absorption of iron in intestine
  - hereditary hemochromatosis usually due to mutation of hemochromatosis (HFE) gene on short arm of chromosome 6
    - most patients have substitution of tyrosine for cysteine at position 282 (C282Y)
    - H63D mutation much less likely to cause disease
    - occasional disease in compound heterozygotes who have both H63D and C282Y
  - hereditary hemochromatosis described in an Italian family without HFE gene mutation, underlying mutation not identified (N Engl J Med 1999 Sep 2;341(10);725), editorial can be found in N Engl J Med 1999 Sep 2;341(10):755
- liver disease
- high iron intake
- transfusions
  - multiple blood transfusions 3 units/month for 1 year
  - thalassemia major, myeloproliferative or myelodysplastic disease, aplastic anemia

Pathogenesis:

- duodenal metal transporter (DMT-1, also known as NRAMP-2) expression upregulated but not mutated, based on biopsy specimens from 20 patients with hemochromatosis

homozygous for C282Y mutation and 10 controls; causes uncontrolled absorption of iron from the gut (Lancet 1999 Jun 19;353(9170):2120), editorial can be found in Lancet 1999 Jun 19;353(9170):2089
- parenchymal cell iron (Fe) deposition leads to organ injury

Possible risk factors:

- homozygous C282Y/C282Y genotype may or may not be associated with increased risk for symptoms associated with hemochromatosis
    - based on inconsistent results in 2 studies
    - **C282Y homozygotes might have higher risk of symptoms related to iron overload**
        - 29,676 men and women aged 27-75 years had genotyping of *HFE* gene, genotyping of H63D variant only done in persons heterozygous for C282Y variant
            - 203 (0.68%) were homozygous for C282Y mutation
            - 3,295 (11.1%) were heterozygous for C282Y mutation only
            - 719 (2.4%) were heterozygous for C282Y and H63D mutations
        - all 203 participants with C282Y homozygosity and 1,235 randomly selected participants with other genotypes were evaluated for iron overload and iron overload-related disease in HealthIron study
        - 1,054 (73%) HealthIron participants completed at least 2 of 4 components (questionnaire, confirmatory *HFE* genotyping, blood sampling, and physical exam)
        - C282Y homozygotes had statistically significantly higher rates of
            - fatigue (in men but not in women)
            - use of arthritis medication at baseline
            - elevated aminotransferase levels
            - history of liver disease (in men but not in women)
        - no significant association of HFE genotype with
            - abnormal metacarpophalangeal joints
            - hepatomegaly
            - diabetes
        - 28.4% men and 1.2% women with C282Y homozygosity developed documented disease related to iron overload, 22 total cases included
            - 12 cases of liver fibrosis or cirrhosis
            - 11 cases of previous diagnosis of hereditary hemochromatosis prompted by symptoms
            - 6 cases of elevated aminotransferase levels
            - 5 cases of abnormal metacarpophalangeal joints
            - 2 cases of hepatocellular carcinoma
        - Reference - HealthIron study (N Engl J Med 2008 Jan 17;358(3):221), editorial can be found in N Engl J Med 2008 Jan 17;358(3):291, commentary can be found in N Engl J Med 2008 May 22;358(21):2293
    - **C282Y homozygotes might not have higher risk of symptoms associated with hemochromatosis**
        - 2 different comparisons
            - 124 C282Y homozygotes and 22,429 wild-type controls filled out questionnaires
            - 17 C282Y homozygotes and 29 wild-type controls had physician

double-blind interview
    - no significant differences in rates of arthritis or joint pain, abdominal pain, arrhythmias, or darkening of skin
    - diagnosis of arthritis or chronic pain in any joints was more frequent in C282Y homozygotes based on interviews, but not statistically significant
    - only symptom statistically more frequent in C282Y homozygotes was loss of body hair
    - Reference - Mayo Clin Proc 2002 Jun;77(6):522 full-text
- higher serum ascorbic acid levels were associated with increased prevalence of elevated serum ferritin levels among women in cross-sectional study so, until further data available, women with genetic susceptibility to iron overload should consider moderating intake of ascorbic acid; serum ascorbic acid levels not related to serum ferritin levels in men (Arch Intern Med 1999 Mar 22;159(6):619)

 Complications and Associated Conditions

Complications:

- 65% diabetes mellitus (bronze diabetes)
    - late-onset diabetes mellitus type 1 associated with hereditary hemochromatosis; retrospective study of 716 Danish patients who developed type 1 diabetes mellitus after age 30 and 9,174 controls from Danish population, homozygous C282Y mutation identified in 9 (1.26%) persons with late-onset diabetes mellitus type 1 and 23 (0.25%) controls (Lancet 2001 Oct 27;358(9291):1405)
    - elevated transferrin saturation not associated with diabetes in retrospective cohort study of 9,274 persons aged 25-74 in 1971-1974 and followed up in 1992 (J Fam Pract 2002 Nov;51(11):933)
- increased risk for liver cancer
    - prospective study of 101 patients with primary hemochromatosis followed for 1-12 years, 4 had primary liver cancer (hepatocellular carcinoma or cholangiocarcinoma) > 1 year after diagnosis of hemochromatosis which is 93x higher than the expected incidence for the general population, liver cancer risk was associated with cirrhosis (Int J Cancer 1995 Jan 17;60(2):160)
    - combination of cirrhosis and hereditary hemochromatosis associated with 200-fold risk for hepatocellular carcinoma (Ann Intern Med 1998 Dec 1;129(11):932)
    - **hereditary hemochromatosis may increase risk of hepatocellular carcinoma**; 8 of 144 cases of hepatocellular carcinoma were homozygous for HFE C282Y mutation, 14x higher than expected rate among males (BMC Gastroenterology 2005 Jun 1;5:17)
- restrictive cardiomyopathy
- gonadotropin deficiency
- growth hormone deficiency is an unusual complication of hemochromatosis; iron accumulates primarily in gonadotroph cells of anterior pituitary, but can accumulate in somatotrophic cells (case report in Adv Stud Med 2003 Feb;3(2):112)
- increased susceptibility to Vibrio vulnificus infection (patients should avoid raw seafood)
- homozygous C282Y mutation may be associated with hepatic fibrosis and cirrhosis in asymptomatic patients
    - liver biopsies done on 672 essentially asymptomatic patients with homozygous C282Y mutation found by family screening or health checks
    - among men, 56% had hepatic iron overload (grades 2-4), 18.4% had hepatic fibrosis

and 5.6% had cirrhosis
    - among women, 34.5% had hepatic iron overload (grades 2-4), 5.4% had hepatic fibrosis and 1.9% had cirrhosis
    - Reference - Arch Intern Med 2006 Feb 13;166(3):294, editorial can be found in Arch Intern Med 2006 Feb 13;166(3):269
- hemochromatosis carrier state may also be associated with increased risks but not usually hemochromatosis
    - hemochromatosis carrier state (C282Y mutation) associated with increased risk for diabetes mellitus type 2; prospective cohort study of 508 non-diabetic men 54-60 followed 4 years, 11% of 35 carriers and 5% of 473 non-carriers developed diabetes as defined in the study, carriers had an odds ratio of over 3.5 (95% confidence interval 1.02-12.1, p = 0.047) for developing diabetes compared with non-carriers (BMJ 2000 Jun 24;320(7251):1706), commentary can be found in BMJ 2000 Nov 18;321(7271):1288
    - asymptomatic carriers of gene for hereditary hemochromatosis are at increased risk for myocardial infarction and cardiovascular death; carriers had 2.3-fold risk (95% CI 1.1-4.8, p = 0.03) for acute myocardial infarction compared with non-carriers (Circulation 1999;100;1268,1274 in BMJ 1999 Oct 2;319(7214):930)
    - 10% of the white population is heterozygous for HLA-linked hemochromatosis mutation but rarely have complications; study of 1,058 heterozygotes revealed differences in iron studies but clinical complications extremely rare; liver biopsy abnormalities generally associated with alcohol abuse, hepatitis, or porphyria cutanea tarda (N Engl J Med 1996 Dec 12;335(24):1799)

Associated conditions:

- calcium pyrophosphate deposition (CPPD) disease (pseudogout)
- may be associated with porphyria cutanea tarda (N Engl J Med 1997 May 1;336(18):1327), inheritance of hemochromatosis genes an important susceptibility factor for sporadic porphyria cutanea tarda (Lancet 1997 Feb 1;349(9048):321)

 History

Chief Concern (CC):

- weakness, lassitude, abdominal pain, weight loss, loss of libido, diabetic symptoms, infertility (with underandrogenization)
- discussion of hemochromatosis presenting as arthritis can be found in Hosp Pract 1998 Mar;33(3);81

Past Medical History (PMH):

- anemia, alcoholic cirrhosis, thalassemia major, sideroblastic anemia, portocaval anastomosis

 Physical

General Physical:

- hypogonadism (related to pituitary involvement), testicular atrophy

Skin:

- 90% hyperpigmentation (related to both melanin and hemosiderin)
- jaundice (related to liver disease)
- spider angiomas (related to cirrhosis)
- loss of body hair (related to hypogonadism)

HEENT:

- melanin deposits in perilimbal bulbar conjunctiva

Chest:

- gynecomastia (related to hypogonadism)

Cardiac:

- arrhythmia
- 10% congestive heart failure

Abdomen:

- 95% hepatomegaly
- 50% splenomegaly
- ascites (related to liver disease)

Extremities:

- palmar erythema
- 25-50% arthropathy

 Diagnosis

Making the diagnosis:

- liver biopsy or HFE gene testing necessary for definitive diagnosis

Rule out:

- alcoholic liver disease
    - hemochromatosis typically has hepatic iron values 200-800 mcmol/g dry weight (normal < 35) and hepatic iron index (hepatic iron content in mcmol/g divided by age in years) > 2 in homozygotes
    - alcoholic siderosis typically has hepatic iron values 40-100 mcmol/g and hepatic iron index < 2
    - Reference - Sci Am Med 1997;1,4,IX,2-11 in Cortlandt Forum 1997 Feb;10(2);29
- iron overload associated with combination of iron supplementation and large doses of

vitamin C in case report (Ann Intern Med 2003 Sep 16;139(6):532), commentary can be found in Ann Intern Med 2004 May 18;140(10):846
- hereditary hyperferritinemia-cataract syndrome, a rare autosomal dominant disorder with elevated ferritin levels without iron overload (Lancet 2005 May 14-20;365(9472):1744)

Testing to consider:

- transferrin saturation level = (serum iron/total iron binding capacity) x 100
  - various cutoff levels used
  - elevated levels (> 45%) should be repeated in fasting state for confirmation if initial transferrin saturation level was not done in fasting state
  - level > 45% is most sensitive but less specific, repeat testing in 1-2 years
  - levels > 45% in premenopausal women and > 55% in men and postmenopausal women warrant further testing
- serum ferritin levels useful for monitoring iron status
- hepatic enzyme levels (AST/ALT) since liver biopsy warranted if elevated
- HFE gene testing (for C282Y and H63D mutations) if hemochromatosis strongly suspected or if transferrin saturation is abnormal
  - heterozygous mutations or homozygous H63D/H63D mutations suggest that hereditary hemochromatosis is not the cause of iron overload, consider liver biopsy
  - compound heterozygotes (C282Y/H63D) and homozygous C282Y/C282Y have hereditary hemochromatosis, consider liver biopsy
  - **C282Y homozygosity more common in non-Hispanic whites than other ethnic groups**; study of 99,711 persons screened for C282Y mutations, 299 (0.3%) had homozygous mutation; estimated prevalence of C282Y homozygotes was 0.44% in non-Hispanic whites, 0.11% in Native Americans, 0.027% in Hispanics, 0.014% in blacks, 0.012% in Pacific Islanders and 0.000039% in Asians (N Engl J Med 2005 Apr 28;352(17):1769), editorial can be found in N Engl J Med 2005 Apr 28;352(17):1741
- liver biopsy
  - indicated if clinical liver disease, elevated hepatic enzymes, age > 40
  - useful for ruling out other causes of liver disease and for determining prognosis (cirrhosis increases risk for hepatocellular carcinoma)
  - therapeutic phlebotomy without liver biopsy is reasonable for patients < 40 years old with normal AST/ALT and homozygous C282Y/C282Y mutations
  - cirrhosis unlikely in hemochromatosis patients with serum ferritin < 1,000 mcg/L; study of 182 patients with hemochromatosis based on hepatic iron measures, 40 (22%) had cirrhosis defined as bridging fibrosis or unequivocal cirrhosis on biopsy, cirrhosis present in 35 of 147 (24%) C282Y homozygotes; only 1 of 93 patients with serum ferritin < 1,000 mcg/L and 39 of 89 (44%) patients with serum ferritin > 1,000 mcg/L had cirrhosis (Ann Intern Med 2003 Apr 15;138(8):627), correction can be found in Ann Intern Med 2003 Aug 5;139(3):235; all patients had liver biopsy for diagnosis, liver biopsy still useful for ruling out other causes of liver disease in patients with serum ferritin < 1,000 mcg/L, full-text article and commentary provides information on predicting risk of cirrhosis for individual patients instead of using single ferritin level as arbitrary cut-point (DynaMed commentary)
- MRI can assess liver iron content non-invasively
- algorithm for evaluating suspected hereditary hemochromatosis can be found in J Am Board Fam Pract 2001 Jul-Aug;14(4):266 PDF

Blood tests:

- in symptomatic patients
    - increased serum iron (Fe 200-300 mcg/dL)
    - slightly decreased total iron-binding capacity (TIBC 200-300 mcg/dL, > 80% saturated)
    - increased ferritin (often > 1,000 ng/mL)
    - Reference - N Engl J Med 1993 Jun 3;328(22):1616 in Cortlandt Forum 1997 Dec;10(12);134,118-40
- asymptomatic patients or carriers may have normal values except for mildly elevated ferritin (15-400 ng/mL)
- test characteristics for detecting hemochromatosis
    - serum iron > 180 mcg/dL (32 mcmol/L) has 68% sensitivity, 83% specificity, 61% positive predictive value and 87% negative predictive value
    - transferrin saturation > 50% has 82% sensitivity, 88% specificity, 74% positive predictive value and 93% negative predictive value
    - serum ferritin > 400 ng/mL has 88% sensitivity, 95% specificity, 88% positive predictive value and 94% negative predictive value
    - elevation of transferrin saturation or serum ferritin has 94% sensitivity, 86% specificity, 73% positive predictive value and 97% negative predictive value
    - Reference - Am Fam Physician 1996 Jun;53(8);2623
- increased transaminases
- decreased insulin
- genetic test can identify 90% homozygotes (Gut 1997;41;841 in BMJ 1998 Jan 3;316(7124):84)
- Asians and Pacific Islanders may have higher normal serum ferritin and transferrin saturation levels than whites, based on analysis of 42,720 persons in North America without common hemochromatosis genes (Arch Intern Med 2007 Apr 9;167(7):722)

Urine studies:

- increased 24-hour urinary Fe with deferoxamine 0.5 mg

Imaging studies:

- usually not necessary, but may be helpful for patients with contraindications for liver biopsy
- CT may show increased liver density
- MRI can assess liver iron content non-invasively; 174 patients undergoing liver biopsy for suspicion of hepatic iron overload or evaluation of hepatitis C had MRI with gradient-recalled-echo sequences, 139 patients used to determine optimal saturation sequences for MRI interpretation; in 35 patients in validation group, liver/muscle signal intensity ratio (L/M ratio) < 0.88 had 89% sensitivity and 80% specificity for iron overload > 60 mcmol/g, L/M ratio < 1 had specificity > 87% (Lancet 2004 Jan 31;363(9406):357), editorial can be found in Lancet 2004 Jan 31;363(9406):341
- MRI may show dark liver in severe hepatic iron overload but not in moderate (3-4 g) iron overload, quantification requires gradient-echo MRI (letter in N Engl J Med 1997 May 22;336(21):1531)

EKG:

- cardiac conduction abnormalities may be noted

Pathology tests:

- liver biopsy findings
  - chronic liver inflammation
  - micronodular "pigment" cirrhosis if untreated
  - iron in hepatic and Kuppfer cells
    - primary iron overload leads to diffuse deposition in hepatocytes
    - secondary iron overload leads to deposition in reticuloendothelial system
  - differentiation of hemochromatosis from other liver diseases
    - based on liver biopsy in study of 55 patients with homozygous hemochromatosis and 454 patients with other liver diseases
    - hepatic iron concentration (HIC) > 71 mcmol Fe/g dry weight had 98.1% sensitivity, 99.8% specificity, 98.1% positive predictive value and 99.8% negative predictive value as diagnostic criterion for hemochromatosis
    - hepatic iron index (HIC/age) at least 1.9 had 92.7% sensitivity, 100% specificity, 100% positive predictive value and 99.1% negative predictive value as diagnostic criterion for hemochromatosis
    - Reference - Gastroenterology 1997 Oct;113;1270 in J Watch 1997 Nov 15;17(22);179
  - review of liver biopsy can be found in N Engl J Med 2001 Feb 15;344(7):495, commentary can be found in N Engl J Med 2001 Jun 28;344(26):2030

 Prognosis

Prognosis:

- normal life span if treated before the onset of cirrhosis or diabetes
- 80% survival at 15 years if diagnosed before cirrhosis
- cirrhosis, diabetes and gonadal failure not reversed with treatment
- treatment may reverse congestive heart failure, fatigue and pre-cirrhotic liver disease
- untreated symptomatic hemochromatosis has a 5-year survival of 18%
- **cirrhosis associated with increased risk of hepatocellular carcinoma and mortality (level 2 [mid-level] evidence)**
  - retrospective study of 95 patients with hereditary hemochromatosis and cirrhosis, follow-up ranged from 0 to 30 years (median 9.2 years)
  - cumulative survival 88% at 1 year, 69% at 5 years, 56% at 20 years
  - 19 (20%) developed hepatocellular carcinoma
  - Reference - Can J Gastroenterol 2006 Apr;20(4):257
- **serum transferrin saturation > 55% associated with increased overall mortality, but not clearly related to hemochromatosis (level 2 [mid-level] evidence)**; retrospective cohort study of 10,714 persons aged 25-74 years in national US studies who had serum transferrin saturation measurements; comparing subjects with transferrin saturation > 55% vs. < 55%, relative risk 1.6 for mortality (95% CI 1.17-2.21); no subjects had hemochromatosis recorded on death certificates, but subjects with serum transferrin saturation > 55% were more likely to have diabetes and cirrhosis on death certificate (Ann Fam Med 2004 Mar-Apr;2(2):133 full-text)
  - **among subjects with serum transferrin saturation > 55%, increased dietary intake of iron or red meat associated with increased overall mortality (level 2 [mid-level] evidence)**; based on 12-year cohort study of 9,229 subjects aged 30-75

years; no association between iron or red meat intake and mortality in subjects with transferrin saturation < 55% (Ann Fam Med 2004 Mar-Apr;2(2):139 full-text)

- **glutathione S-transferase P1 (GSTP1) *Val/Val* genotype associated with increased risk of cirrhosis**; in 172 patients with hereditary hemochromatosis homozygous for C282Y mutation, GSTP1 *Val/Val* genotype was present in 14.8% with cirrhosis vs. 2.1% without cirrhosis (Arch Intern Med 2005 Sep 12;165(16):1835), editorial can be found in Arch Intern Med 2005 Sep 12;165(16):1815
- **post transplant survival of patients with hemochromatosis similar to other patients having liver transplants**
    - based on cohort study
    - 217 patients with hemochromatosis who had liver transplants during 1997-2006 were compared with other liver transplant patients
    - comparing patients with hemochromatosis vs. other transplant recipients
        - 86.1% vs. 88.4% survival at 1 year
        - 80.8% vs. 80.3% survival at 3 years
        - 77.3% vs. 74% survival at 5 years
        - differences not significant at all time periods
    - Reference - Gastroenterology 2007 Aug;133(2):489

 Treatment

Treatment overview:

- therapeutic phlebotomy as needed to remove excess iron
    - induction phase
        - repeated phlebotomy 1-2x/week based on presence of iron toxicity, hemoglobin level and response to phlebotomy, and overall health status
        - target hematocrit 35-40%
        - iron depletion achieved when ferritin 20-50 mcg/L and hematocrit < 33% for > 3 weeks after phlebotomy
    - maintenance phase
        - most patients require phlebotomy 2-4x/year
        - maintain serum ferritin level < 50 mcg/L
- blood donation from patients with hemochromatosis
    - Current FDA regulations for blood donation do not prohibit blood from hemochromatosis patients. However, unless the blood center has an FDA variance, all blood that is drawn during therapeutic phlebotomies must be labeled and the source indicated. It is then up to physicians and their patients to decide whether they want to use the blood. Schreiber and REDS study co-authors note that labeled blood is usually not well accepted and is often discarded.
    - In 1999, the FDA began granting variances to blood collection organizations that offer free phlebotomies to all patients with hemochromatosis. The variances allow blood to be collected from these patients without special labeling. However, to qualify for a variance, the blood collection organization must bear the cost of the free phlebotomies. Only a small percentage of licensed and registered blood collection facilities have requested and received variances
    - NHLBI News Release 2001 Sep 25

Diet:

- drinking tannin-rich tea may reduce frequency of regular phlebotomy, since tannates inhibit absorption of iron, controlled trial of 18 patients in Germany found that patients drinking tea absorbed less iron in a test meal than did control group (Gut 1998;43;699 in BMJ 1998 Nov 7;317(7168):1330)

Medications:

- medications for hemochromatosis complicated by anemia (limited therapeutic phlebotomy)
    - erythropoietin (ensure adequate B12 and folate intake)
    - iron chelation (e.g. deferoxamine) in severe cases

Surgery:

- American Association for the Study of Liver Disease practice guidelines on management on evaluation of patient for liver transplantation can be found in Hepatology 2005 Jun;41(6):1407 or at National Guideline Clearinghouse 2005 Oct 31:7271

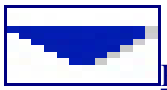
Prevention and Screening

Screening:

- fasting transferrin saturation > 60% in males or > 50% in females, and increased ferritin are suggestive of hemochromatosis and may warrant liver biopsy or genetic testing
- American College of Physicians guideline on screening for hereditary hemochromatosis
    - insufficient evidence to recommend for or against screening for hereditary hemochromatosis in general population
    - in case-finding for hereditary hemochromatosis, serum ferritin and transferrin saturation tests should be performed
    - physicians should discuss risks, benefits, and limitations of genetic testing in patients with positive family history or patients with elevated serum ferritin level or transferrin saturation
    - Reference - Ann Intern Med 2005 Oct 4;143(7):517, supporting systematic review can be found in Ann Intern Med 2005 Oct 4;143(7):522, summary can be found in National Guideline Clearinghouse 2006 Jan 3:8147, correction can be found in Ann Intern Med 2006 Mar 7;144(5):380
- **screening general population not recommended**; positive predictive value of abnormal screening transferrin saturation only 0.7% for abnormal liver tests, and 0.009% for cirrhosis due to hereditary hemochromatosis, based on pathway of confirming persistent transferrin saturation elevation, then increased serum ferritin, then liver testing; positive predictive value for homozygous C282Y mutation only 2% for abnormal liver tests, and 0.04% for cirrhosis due to hereditary hemochromatosis, based on same screening pathway (Arch Intern Med 2003 Nov 10;163(20):2421)
- conditions for screening not yet fulfilled (BMJ 1999 Aug 28;319(7209):531), commentary can be found in BMJ 2000 Jan 15;320(7228):183 (commentary can be found in BMJ 2000 Apr 22;320(7242):1146)
- prevalence rates up to 0.6% (or higher in patients with diabetes) have been reported with screening using transferrin saturation with or without ferritin levels
    - in study of 16,031 adults from 22 primary care practices, 311 were found to have transferrin saturation > 45% confirmed on fasting sample, 255 were further evaluated

for hemochromatosis with estimated combined prevalence 4.5 cases per 1,000 (Ann Intern Med 1998 Dec 1;129(11):940 in J Watch 1999 Jan 15;19(2);17)
    - in study of 15,839 nonpregnant adults from NHANES III, 1-6% had abnormal iron levels with serum transferrin saturation cutoff ranging from 62% to 45%, 0.2-0.7% had simultaneously abnormal transferrin saturation and ferritin levels (Ann Intern Med 1998 Dec 1;129(11):954 in J Watch 1999 Jan 15;19(2);17)
    - consider screening asymptomatic white men > 30 for iron overload (hereditary hemochromatosis); initially measure transferrin saturation, if saturation > 62% on repeat check, perform liver biopsy with iron weight determination; 3,977 eligible patients, 40 identified with elevated transferrin saturation levels, 14 still elevated on repeat testing, 8 had confirmed hemochromatosis on liver biopsy, 7 of 8 were white; based on this study prevalence of disease was 1/497 (and 1/282 in white patients); overall cost per case identified was $17,000 (halved by screening only whites) (Am J Med 1995 May;98(5):464 in QuickScan Reviews in Fam Pract 1995 Nov;8)
    - German researchers measuring serum ferritin and transferrin saturation in 6,039 persons found 42 with elevations in both, 33 had further evaluation and 28 eventually diagnosed with hemochromatosis, prevalence 0.3% women and 0.6% men (Ann Intern Med 1998 Mar 1;128(5):337 in J Watch 1998 Apr 1;18(7);59)
    - Italian researchers measured serum ferritin and transferrin saturation in 894 outpatients with diabetes and 467 controls without diabetes, 1.3% vs. 0.2% found to have hemochromatosis (Ann Intern Med 1998 Mar 1;128(5):370 in J Watch 1998 Apr 1;18(7);59)
- genetic screening not generally recommended
    - **United States Preventive Services Task Force (USPSTF) recommends against routine genetic screening for hereditary hemochromatosis in asymptomatic general population (D recommendation)**
        - fair evidence that disease due to hereditary hemochromatosis is rare in general population
        - fair evidence that low proportion of individuals with high-risk genotype (C2h82Y homozygote at the HFE locus) manifest the disease
        - poor evidence that early therapeutic phlebotomy improves morbidity and mortality in screening-detected versus clinically detected individuals
        - screening may identify large number of individuals who have high-risk genotype but may never manifest clinical disease resulting in unnecessary interventions and anxiety
        - USPSTF concludes potential harms of genetic screening outweigh potential benefits
        - Reference - Ann Intern Med 2006 Aug 1;145(3):204 or at National Guideline Clearinghouse 2006 Aug 7:9230, supporting systematic review can be found in Ann Intern Med 2006 Aug 1;145(3):209
    - genetic testing has been recommended instead of liver biopsy in patients < 40 years old with abnormal iron studies and no biochemical or clinical evidence of liver disease (Liver 1999 Apr;19(2):73)
    - genetic screening not recommended since many identified patients have no clinical manifestations of disease; 10,198 adults screened for 3 common mutations of HFE gene; heterozygous or homozygous HFE mutations identified in 40% whites, 29% Hispanics, 13% blacks, 7% Asians; 3% whites were homozygous for 1 of the 2 most common mutations; comparing untreated homozygous patients to other patients found no significant differences in hemochromatosis symptoms, diabetes or hepatic transaminase elevations (Ann Intern Med 2000 Sep 5;133(5):329 in J Watch 2000

Oct 15;20(20);157), commentary can be found in Ann Intern Med 2002 Oct 15;137(8):700, correction can be found in Ann Intern Med 2002 Oct 15;137(8):705
    - **community genetic screening reported to be acceptable (level 3 [lacking direct] evidence)**; 11,307 persons had painless cheek-brush screening for Cys282Tyr HFE mutation conducted at workplace, 47 homozygous individuals identified for yield of 0.4% (Lancet 2005 Jul 23;366(9482):314), editorial can be found in Lancet 2005 Jul 23-29;366(9482):269
    - genetic screening not recommended by CDC expert consensus panel convened in 1997 (JAMA 1998 Jul 8;280(2):172)
    - discussion of counseling patients regarding genetic testing can be found in Arch Intern Med 2001 Nov 12;161(20):2411, editorial can be found in Arch Intern Med 2001 Nov 12;161(20);2406, correction can be found in Arch Intern Med 2002 Jan 14:162(1)
- homozygous relatives of patients with hemochromatosis may have conditions related to hemochromatosis
    - study reports frequency of disease-related conditions among 184 hemochromatosis patients identified based on signs or symptoms ("clinical disease"), 107 hemochromatosis patients identified based on elevated transferrin saturation ("asymptomatic disease"), and 214 relatives of these 291 patients who were found to be "homozygous" as defined in the article through HLA genetic screening
    - not reported how many family members were screened to identify these 214 homozygous relatives
    - among men
        - cirrhosis identified in 40% patients with clinical disease, 4.5% patients with asymptomatic disease, and 12% homozygous relatives
        - any disease-related condition (including cirrhosis, fibrosis, aminotransferase elevation, or arthropathy) identified in 79% patients with clinical disease, 29% patients with asymptomatic disease, and 38% homozygous relatives
    - among women
        - cirrhosis identified in 21% patients with clinical disease, 4.9% patients with asymptomatic disease, and 2% homozygous relatives
        - any disease-related condition (including cirrhosis, fibrosis, aminotransferase elevation, or arthropathy) identified in 60% patients with clinical disease, 34% patients with asymptomatic disease, and 10% homozygous relatives
    - Reference - N Engl J Med 2000 Nov 23;343(21):1529, commentary can be found in N Engl J Med 2001 May 10;344(19):1477

 References including Reviews and Guidelines

General references used:

- Am Fam Physician 1996 Jun;53(8);2623 (correction in Am Fam Physician 1996 Nov 1;54(6);1896, commentary in Am Fam Physician 1997 Feb 1;55(2);440)
- review of hereditary hemochromatosis (J Am Board Fam Pract 2001 Jul-Aug;14(4):266 PDF)

Reviews:

- review can be found in Lancet 2007 Dec 1;370(9602):1855

- review can be found in Am Fam Physician 2002 Mar 1;65(5):853
- review can be found in Can Fam Physician 2002 Aug;48:1326 (Am Fam Physician 2003 Jan 15;67(2):402)
- review can be found in Ann Intern Med 1998 Dec 1;129(11):932
- review can be found in Can Fam Physician 2003 Jan;49:36
- review of hereditary hemochromatosis can be found in N Engl J Med 2004 Jun 3;350(23):2383, commentary can be found in N Engl J Med 2004 Sep 16;351(12):1263
- review with emphasis on genetics involved can be found in Hosp Pract 1999 Aug;34(8):55 and in Hosp Pract 2000 May;35(5);101
- review can be found in Mayo Clin Proc 1999 Sep;74(9):917
- review of hereditary hemochromatosis can be found in Liver 1999 Apr;19(2):73
- review can be found at GeneClinics 2000 Mar 31
- brief "What you should do" review can be found in BMJ 2008 Mar 1;336(7642):506
- case presentation can be found in N Engl J Med 2006 Oct 26;355(17):1812
- case reports of presentation with exercise-related joint pain and discussion can be found in BMJ 1999 Feb 13;318(7181):449 or in Am Fam Physician 1999 May 1;59(9):2587, commentary can be found in BMJ 1999 May 29;318(7196):1486
- review of hemochromatosis and hemochromatosis arthropathy can be found in J Musculoskel Med 2004 Apr;21(4):212
- review of disorders of iron metabolism can be found in N Engl J Med 1999 Dec 23;341(26):1986, correction can be found in N Engl J Med 2000 Feb 3;342(5):364, commentary can be found in N Engl J Med 2000 Apr 27;342(17):1293
- review of genetic liver disease in adults can be found in Postgrad Med 2000 Feb;107(2):147
- review of genetics of hemochromatosis can be found in Lancet 2002 Nov 23;360(9346):1673
- review of common hyperpigmentation disorders in adults can be found in Am Fam Physician 2003 Nov 15;68(10):1955
- review of screening for hereditary hemochromatosis from United States Preventive Services Task Force (USPSTF) can be found in Ann Intern Med 2006 Aug 1;145(3):209
- case presentation of herediatry hemochromatosis can be found in Lancet 2007 Sep 15;370(9591):1006
- case presentation of neonatal hemochromatosis can be found in N Engl J Med 2005 Jul 14;353(2):189

Guidelines:

- synthesis of 2 guidelines (ACP 2005, USPSTF 2006) for screening for hemochromatosis can be found at National Guideline Clearinghouse 2007 Jul 16:HEMOCHROMATOSIS1
- American Association for the Study of Liver Diseases guideline can be found in Hepatology 2001 May;33(5):1321 or at National Guideline Clearinghouse 2003 Jul 28:3448
- United States Preventive Services Task Force (USPSTF) recommendation statement on screening for hemochromatosis can be found in Ann Intern Med 2006 Aug 1;145(3):204 or at National Guideline Clearinghouse 2006 Aug 7:9230, summary can be found in Am Fam Physician 2007 Jun 1;75(11):1696 full-text

 Patient Information

Patient information:

- handout can be found in Am Fam Physician 2002 Mar 1;65(5):865

- handout from West Shore Endoscopy Center
- Hemochromatosis Foundation, Inc., P.O. Box 8569, Albany, NY 12208-0569, phone 518-489-0972

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