

Hemochromatosis 2009: When to Check, How to Confirm, and Treat

Bruce R. Bacon, M.D.
James F. King M.D. Endowed Chair in Gastroenterology
Professor of Internal Medicine
Director, Division of Gastroenterology and Hepatology
Saint Louis University Liver Center
St. Louis, Missouri

Classification of Inherited Iron Overload Syndromes

- Hereditary Hemochromatosis
 - *HFE*-related
 - C282Y/C282Y
 - C282Y/H63D
 - Other *HFE* mutations
 - Non-*HFE*-related
 - Hemojuvelin (*HJV*)
 - Transferrin receptor-2 (*TfR-2*)
 - Ferroportin (*SLC40A1*)
 - Heparin (*HAMP*)
 - African iron overload

Classification of Iron Overload Syndromes - 2

- Secondary Iron Overload
 - Iron-loading anemias
 - Thalassemia major
 - Sideroblastic
 - Chronic hemolytic anemia
 - Aplastic anemia
 - Pyruvate kinase deficiency
 - Pyridoxine-responsive anemia
 - Parenteral iron overload
 - Red blood cell transfusions
 - Iron-dextran injections
 - Long-term hemodialysis
 - Chronic liver disease
 - Porphyria cutanea tarda
 - Hepatitis C
 - Hepatitis B
 - Alcoholic liver disease
 - Nonalcoholic steatohepatitis
 - Following portocaval shunt
 - Dysmetabolic iron overload syndrome
- Miscellaneous
 - Neonatal iron overload
 - Aceruloplasminemia
 - Congenital atransferrinemia

When to Check

Hereditary Hemochromatosis - Diagnosis

Requirements of Diagnosis

- Suspicion, serum iron studies
- Liver biopsy
- Use of HII
- Differential diagnosis
 - Alcoholic liver disease
 - Chronic viral hepatitis
 - Nonalcoholic steatohepatitis
- Genetic test

Typical Symptoms in Patients with HH

	%
• 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

Hemochromatosis 2009: When to Check, How to Confirm and Treat

Common Physical Findings in HH

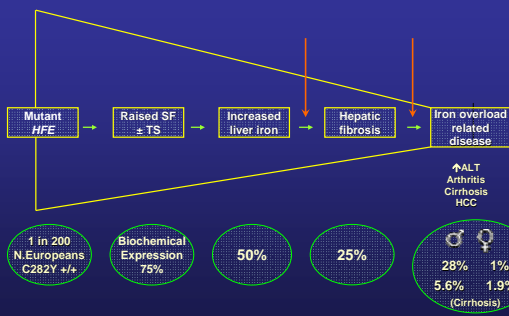
- | | % |
|---|-------|
| • Hepatomegaly | 60-85 |
| • Cirrhosis | 50-95 |
| • Skin pigmentation | 40-80 |
| • Arthritis (second, third metacarpophalaneal joints) | 40-60 |
| • Clinical diabetes | 10-60 |
| • Splenomegaly | 10-40 |
| • Loss of body hair | 10-30 |
| • Testicular atrophy | 10-30 |
| • Dilated cardiomyopathy | 0-30 |

Principal Clinical Features in Hereditary Hemochromatosis

Features	Milder et al. 1980	Edwards et al. 1980	Niederau et al. 1985	Adams et al. 1991	Bacon & Sadiq 1997
Number of subjects	341	35*	163*	371	40
Symptoms (#)					
Weakness, lethargy	73	20	83	19	25
Abdominal pain	50	23	58	3	0
Arthralgias	47	57	43	40	13
Loss of libido, impotence	56	29	38	32	12
Cardiac failure symptoms	35	0	15	3	0
Physical and Diagnostic Findings (%)					
Cirrhosis (biopsy)	94	57	69	3	13
Hepatomegaly	76	54	83	3	13
Splenomegaly	38	40	13	-	-
Loss of body hair	32	6	20	-	-
Gynecomastia	12	-	8	-	-
Testicular atrophy	50	14	-	-	-
Skin pigmentation	82	43	75	9	5
Clinical diabetes	53	6	55	11	-

* Patient selection occurred by both clinical features and family screening.
 † Only symptomatic index cases were studied.
 ‡ Discovered by family studies.
 Zakim Boyer, 1996:1453.

The natural history and disease burden of HH



(from Beutler et al 2002, Pietrangolo, NEJM 2004;350:2383; Whitlock et al, Ann Intern Med 2006;145:209; Powell et al, Arch Intern Med 2006;166:294; Allen et al, NEJM)

Allen et al.
Powell et al.

How to Confirm

Evaluation of Iron Stores

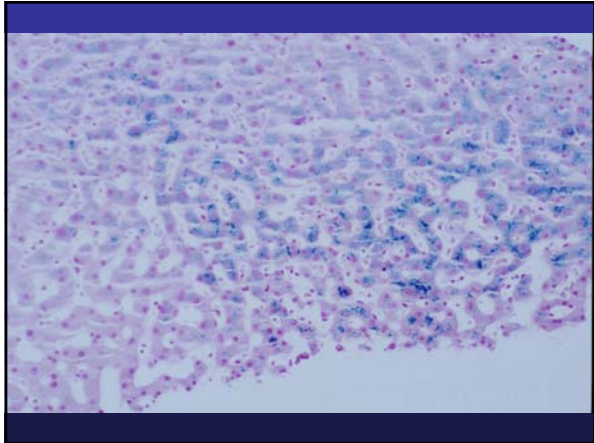
- Serum iron, TF saturation and ferritin
- Liver biopsy for stainable iron, biochemical determination of iron
- Noninvasive imaging modalities
 - Computed tomography
 - Magnetic resonance imaging
 - Magnetic susceptibility
- Iron removed by phlebotomy (1 U=250 mg)
- Genetic testing

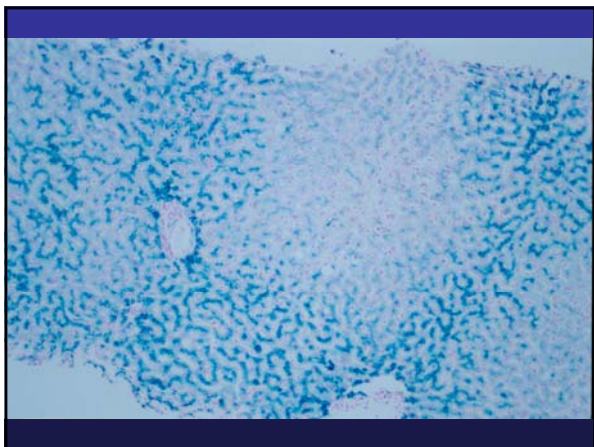
Blood Iron Studies in HH

	Normal	HH
• Serum iron (µg/dl)	50-150	180-300
• Transferrin (mg/dl)	250-370	200-300
• Transferrin saturation (%)	20-50	80-100
• Serum ferritin (ng/ml)		
Males	20-300	500-6,000
Females	15-250	500-6,000

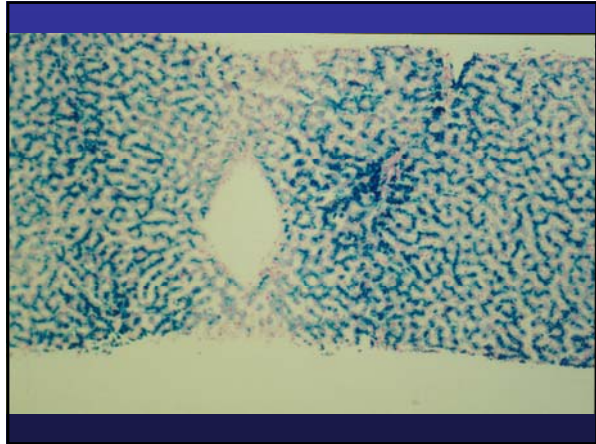
Hemochromatosis – Role of Liver Biopsy

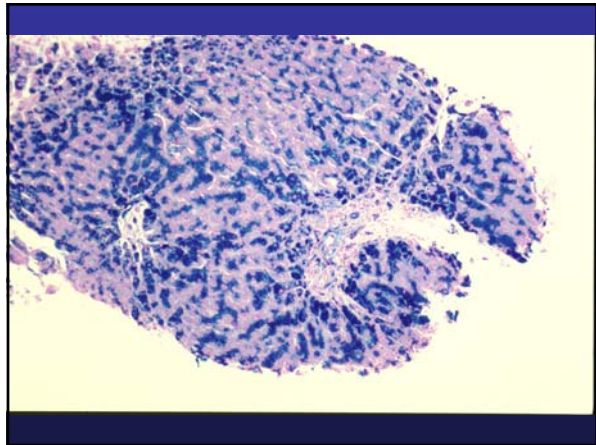
- In the past – establish diagnosis
- Determine degree of fibrosis, cirrhosis
- Determine other abnormalities
- Phenotypic variability
- Recommended if:
 - Ferritin > 1000 ng/mL
 - ALT, AST elevated
 - Hepatomegaly
 - Age > 40 years

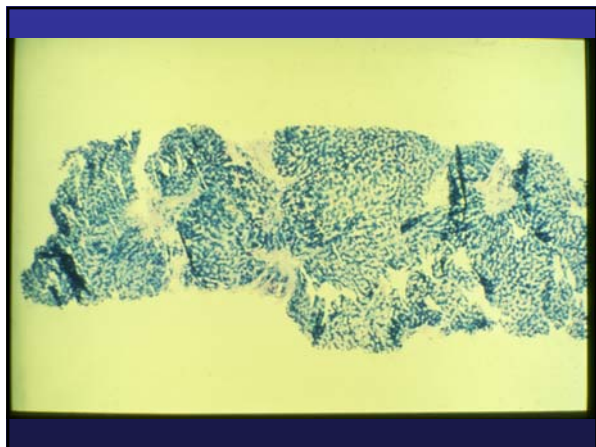


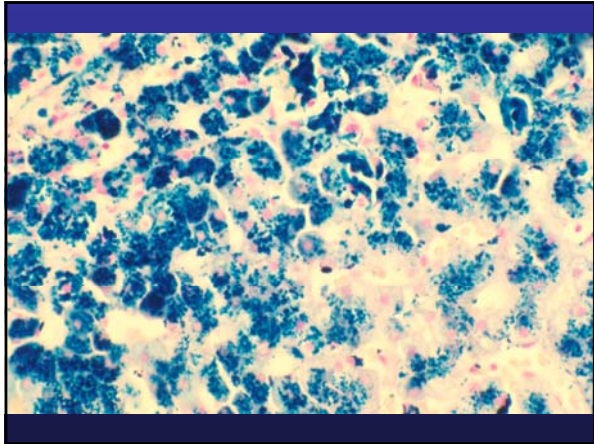


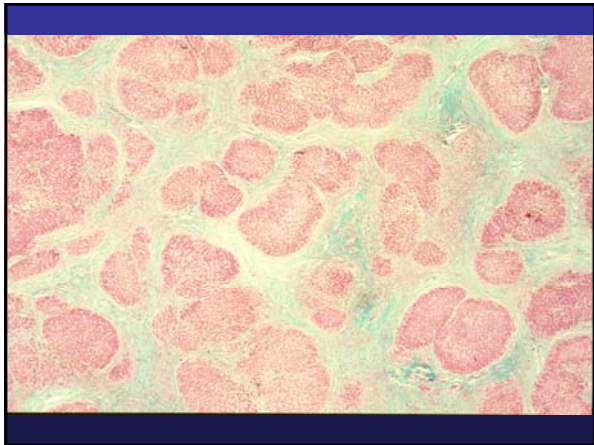
Hemochromatosis 2009: When to Check, How to Confirm and Treat











How to Treat

Therapeutic Phlebotomy for HH

- Clearly improves survival
- Prepare patients for up to 6 – 12 months
- Iron burden in men greater than in women despite initial HIC
- Difficult to predict phlebotomy requirements
- Each unit of blood – approximately 30 ng/mL ferritin

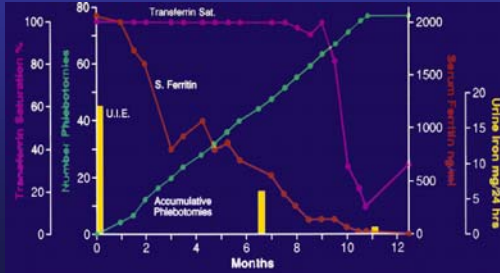
Therapeutic Phlebotomy for HH

- Weekly phlebotomy
- Hct. > 35% before each one
- Ferritin to 20 to 50 ng/ml
- Transferrin saturation to < 50%

Maintenance Phlebotomy for HH

- Most patients – one unit Q 2-3 months
- TS < 50%; ferritin < 50 ng/mL
- One unit of whole blood = 250 mg iron
- Most patients absorb 2 to 3 mg/day, more than needed
- Some patients – no re-accumulation

Hereditary Hemochromatosis Response to Therapy

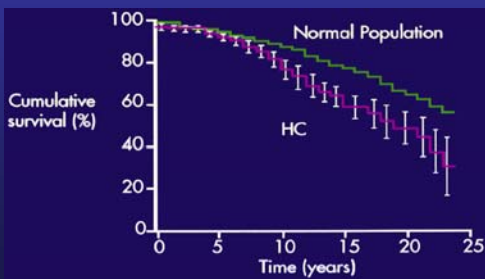


Edwards et al. *Ann Int Med* 93:519-525, 1980

Results of Therapy

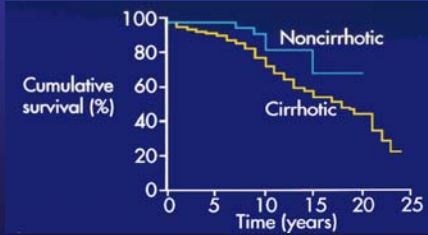
- Reduction to normal tissue iron stores.
- Improved survival if diagnosis and treatment before development of cirrhosis and diabetes.
- Improved sense of well-being, energy level.
- Improved cardiac function.
- Improved control of diabetes.
- Reduction in abdominal pain.
- Reduction in skin pigmentation.
- Normalization of elevated liver enzymes.
- Reversal of hepatic fibrosis (approximately 30% of cases).
- No reversal of established cirrhosis.
- Reduction in portal hypertension in cirrhotics.
- No (or minimal) improvement in arthropathy.
- No reversal of testicular atrophy.

Hereditary Hemochromatosis: Survival



N Engl J Med 313:1256-1262, 1985

Hereditary Hemochromatosis: Survival with Cirrhosis



N Engl J Med 313:1256-1262, 1985

HH – Family Screening

- *HFE* mutation analysis has replaced HLA-typing
- Practically – *HFE* mutation analysis, TS, and ferritin all at once

HH – Family Screening

- For analysis of risk in children – perform mutation analysis in spouse (or other parent) first
- May be able to avoid testing in children

Adams, Clin Genet 53:176-178, 1998

Population Screening for Hemochromatosis

- 41,038 adults screened in San Diego
- Health appraisal unit
- CBC, transferrin saturation, ferritin level, *HFE* genotype
- Questionnaire

Beutler et al., *Lancet* 359:211-218, 2002

Population Screening for Hemochromatosis

- 152 C282Y/C282Y
- 616 C282Y/H63D
- 67% of C282Y/C282Y had elevated ferritin
- No difference in symptoms from controls
- 1 of 152 with signs and symptoms of hemochromatosis

Beutler et al., *Lancet* 359:211-218, 2002

Population Screening for Hemochromatosis

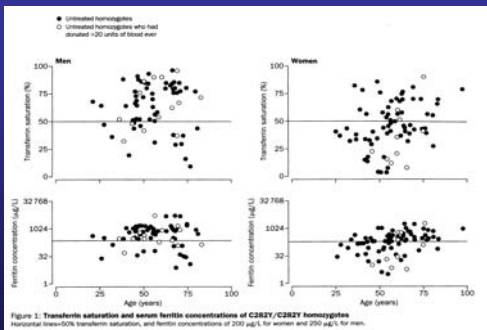


Figure 1: Transferrin saturation and serum ferritin concentrations of C282Y/C282Y homozygotes. Horizontal lines: 50% transferrin saturation, and ferritin concentrations of 200 µg/L for women and 200 µg/L for men.

Beutler et al., *Lancet* 359:211-218, 2002

Prevalence of C282Y Homozygotes Without Iron Overload in Screening Studies

Population sample	Country	n	Prevalence of homozygotes	C282Y homozygotes with a normal ferritin (%)
Electoral roll	New Zealand	1,064	1 in 213	40
Primary care	USA	1,653	1 in 276	50
Epidemiological survey	Australia	3,011	1 in 188	25
Blood donors	Canada	4,211	1 in 327	81
General public	USA	41,038	1 in 270	33
Primary care	North America	44,082	1 in 227	25
General public	Australia	29,676	1 in 146	32
Total		124,636	1 in 240	41

Hereditary Hemochromatosis

Summary

- In 2009...
 - Most patients with hemochromatosis do not need a liver biopsy
 - Only about 60% of C282Y homozygous patients have phenotypic expression
 - About 25% of C282Y homozygous men have signs or symptoms of hemochromatosis
