Annals of Internal Medicine | CLINICAL GUIDELINES

Screening for Hereditary Hemochromatosis: A Clinical Practice Guideline from the American College of Physicians

Amir Qaseem, MD, PhD, MHA; Mark Aronson, MD; Nick Fitterman, MD; Vincenza Snow, MD; Kevin B. Weiss, MD, MPH; and Douglas K. Owens, MD, MS, for the Clinical Efficacy Assessment Subcommittee of the American College of Physicians*

Hereditary hemochromatosis is a genetic disorder of iron metabolism. Diagnosis of hereditary hemochromatosis is usually based on a combination of various genetic or phenotypic criteria. Decisions regarding screening are difficult because of the variable penetrance of mutations of the *HFE* gene and the absence of any definitive trials addressing the benefits and risks of therapeutic phlebotomy in asymptomatic patients or those with only laboratory abnormalities. The purpose of this guideline is to increase physician awareness of hereditary hemochromatosis, particularly the variable penetrance of genetic mutations; aid in case finding; and explain the role of genetic testing. This guideline provides recommendations based on a review of evidence in the accompanying background paper by Schmitt and colleagues. The target audience for this guideline is internists and other primary care physicians. The target patient population is all persons who have a probability or susceptibility of developing hereditary hemochromatosis, including the relatives of individuals who already have the disease.

Ann Intern Med. 2005;143:517-521. www.annals.org
For author affiliations, see end of text.

RECOMMENDATIONS

Recommendation 1: There is insufficient evidence to recommend for or against screening for hereditary hemochromatosis in the general population.

There is currently insufficient evidence to determine whether the benefits of screening the general population outweigh the risks. The C282Y mutation is prevalent in certain populations, particularly white men, and treatment is not costly nor is it associated with any significant harm. Although patients homozygous for C282Y are more likely to have elevated serum ferritin level and transferrin saturation percentage, there currently is no way of predicting which patients will progress to overt disease. For clinicians who choose to screen, 1-time phenotypic screening of asymptomatic non-Hispanic white men with serum ferritin level and transferrin saturation would have the highest yield (1).

Recommendation 2: In case-finding for hereditary hemochromatosis, serum ferritin and transferrin saturation tests should be performed.

There is no information available on risk-stratifying in patients with an associated condition or conditions such as type 2 diabetes, cardiac arrhythmias and cardiomyopathies, liver failure, hepatomegaly, cirrhosis, elevated liver enzyme levels, hepatocellular carcinoma, arthritis, hypogonadism, or changes in skin pigmentation. The initial symptoms associated with iron overload might be nonspecific, and the decision to perform tests should be based on clinical judgment regarding what may cause such protean manifestations. If testing is performed for these patients, the cutoff values for serum ferritin level of more than 200 μg/L in women or more than 300 μg/L in men and transferrin saturation greater than 55% may be used as criteria for case-finding; however, there is no general agreement about diagnostic criteria. Case-finding may also be considered if there is a family history of hereditary hemochromatosis for an individual, as the risk for developing the disease may be higher than that of the general population.

Recommendation 3: Physicians should discuss the risks, benefits, and limitations of genetic testing in patients with a positive family history of hereditary hemochromatosis or those with elevated serum ferritin level or transferrin saturation.

Before genetic testing, individuals should be made aware of the benefits and risks of genetic testing. This should include discussing available treatment and its efficacy; costs involved (2); and social issues, such as impact of disease labeling, insurability and psychological well-being, and the possibility of as-yet-unknown genotypes associated with hereditary hemochromatosis.

Recommendation 4: Further research is needed to establish better diagnostic, therapeutic, and prognostic criteria for hereditary hemochromatosis.

The lack of information on the natural history of the disease makes it difficult to manage patients with heredi-

See also:

Print
Related article 522
Summary for Patients I-46

Web-Only
Conversion of table into slide

*This paper, written by Amir Qaseem, MD, PhD, MHA; Mark Aronson, MD; Nick Fitterman, MD; Vincenza Snow, MD; Kevin B. Weiss, MD, MPH; and Douglas K. Owens, MD, MS, was developed for the Clinical Efficacy Assessment Subcommittee of the American College of Physicians (ACP): Douglas K. Owens, MD, MS (*Chair*); Mark Aronson, MD; Patricia Barry, MD, MPH; Donald E. Casey Jr., MD, MPH, MBA; J. Thomas Cross Jr., MD, MPH; Nick Fitterman, MD; E. Rodney Hornbake, MD; Katherine D. Sherif, MD; and Kevin Weiss, MD, MPH (*Immediate Past Chair*). Approved by the ACP Board of Regents on 16 July 2005.

Annals of Internal Medicine encourages readers to copy and distribute this paper, providing such distribution is not for profit. Commercial distribution is not permitted without the express permission of the publisher.

Downloaded From: http://annals.org/ on 10/31/2016

tary hemochromatosis. There are no clearly defined criteria to risk-stratify patients into groups more or less likely to develop overt disease. Future developments in technology and genetic screening might help in the diagnosis and management of hereditary hemochromatosis. In addition, there is a need for more uniform diagnostic criteria.

Introduction

Hereditary hemochromatosis is a genetic disorder of iron metabolism and is characterized by tissue injury resulting from an abnormal accumulation of iron in various organs. This disease is usually a consequence of an increased absorption of iron from the gastrointestinal tract, which results in increased iron deposition in tissue, particularly in the liver, heart, and pancreas. If left untreated, it can lead to organ damage, such as cirrhosis, as well as hepatocellular cancer. However, early diagnosis of hereditary hemochromatosis is difficult because of variability in the case definition and diagnostic standard used.

Diagnosis of hereditary hemochromatosis is usually based on a combination of various genetic or phenotypic criteria. Genetically, it can be based on direct DNA testing for the 2 *HFE* gene mutations (C282Y and H63D) associated with hereditary hemochromatosis. The mutation of C282Y in the *HFE* gene on chromosome 6 is present in almost 90% of those affected. Most patients are homozygous, and mutation transmission is autosomal recessive. The H63D mutation may be associated with hereditary hemochromatosis, but the actual clinical effects of this mutation are uncertain (3). Although in a small proportion, compound heterozygotes (C282Y/H63D) can develop iron overload. Phenotypic markers of hereditary hemochromatosis may be used to identify the disease. Percentage of transferrin saturation and serum ferritin level have been used to confirm the diagnosis of hereditary hemochromatosis. Transferrin saturation determines how much iron is bound to the protein that carries iron in the blood. Serum ferritin level is elevated in patients with hereditary hemochromatosis and correlates with liver iron and development of cirrhosis. Liver biopsy to measure hepatic iron concentration by staining is considered the gold standard to test for hereditary hemochromatosis. However, with the advent of genetic testing, liver biopsy is not widely used to confirm the diagnosis. There is a consensus on the various diagnostic tests that could be used to diagnose hereditary hemochromatosis. However, the threshold levels that should be used to define the disease remain controversial. On the basis of the review of the background paper by Schmitt and colleagues (4), also in this issue, and considering that lower cutoffs are more sensitive and less specific, serum ferritin level greater than 200 μg/mL and transferrin saturation greater than 55% suggest an increased risk for hereditary hemochromatosis and the need for further investigation (5).

Hereditary hemochromatosis is the most common recessive genetic trait in white persons. However, estimating the prevalence of this disease is difficult. Genetic testing of populations originating in northern Europe showed that approximately 0.5% are homozygous for the C282Y mutation (6). The Hemochromatosis and Iron Overload Screening (HEIRS) Study showed that the prevalence of C282Y homozygotes was highest among non-Hispanic white persons (0.44% [95% CI, 0.42% to 0.47%]) (1). Phenotypic screening of the population in the United States demonstrated that 1% to 6% have elevated transferrin saturation and 11% to 22% of this group have an increased serum ferritin level (7). Hereditary hemochromatosis has been estimated to be present in 3 to 5 people per 1000 in the general population (8). Decisions regarding screening are difficult because of the variable penetrance of mutations of the *HFE* gene and the absence of any definitive trials addressing the benefits and risks of therapeutic phlebotomy in asymptomatic patients or those with only laboratory abnormalities.

The purpose of this guideline is to increase physician awareness of hereditary hemochromatosis, particularly the variable penetrance of genetic mutations; aid in case finding; and explain the role of genetic testing. The target audience for this guideline is internists and other primary care physicians. The target patient population is all persons who have a probability or susceptibility of developing hereditary hemochromatosis, including the relatives of individuals who already have the disease. This guideline is based on the systematic review of the evidence in the background paper (4).

This guideline attempts to answer the following questions: 1) What is the prevalence of hereditary hemochromatosis in the primary care setting? 2) In asymptomatic patients with hereditary hemochromatosis, what is the risk for end-organ damage or death? 3) How diagnostically useful are transferrin saturation and serum ferritin in identifying patients with hereditary hemochromatosis in the primary care setting? 4) Is phlebotomy efficacious in reducing morbidity or fatal complications in asymptomatic patients with hereditary hemochromatosis? 5) Do the benefits of screening primary care patients for hereditary hemochromatosis outweigh the risks?

Prevalence

Estimates of the prevalence of hereditary hemochromatosis in the general population vary widely because no set criteria define what constitutes hereditary hemochromatosis (5, 9, 10). Some argue that genotyping should be used as the gold standard and that the sensitivity and specificity of phenotyping should be calculated and compared with those of genotyping. Others support the use of persistently elevated serum ferritin level and percentage of transferrin saturation as the case definition of hereditary hemochromatosis. Studies of differing populations, using strict criteria recommended in the HEIRS Study (11), have esti-

Downloaded From: http://annals.org/ on 10/31/2016

Table. **Prevalence of Hereditary Hemochromatosis in Primary Care Settings***

Study, Year (Reference)	Setting	Sampling Approach	Sample Characteristics	Definitive Hereditary Hemochromatosis†	Reported Hereditary Hemochromatosis	Ceiling Estimate of Hereditary Hemochromatosis‡	Cirrhosis
Phatak et al., 1998 (5)	22 primary care practices in Rochester, New York	All adults ≥ 18 y of age	16 031 patients (19%–94% of eligible patients across practices); median age, 54 y in white patients and 43–45 y in nonwhite patients; 42% men	Overall: 29 of 16 031 (0.18%); white men: 20 of 5356 (0.37%); nonwhite men: 0 of 1349 (0%); white women: 9 of 7099 (0.13%); nonwhite women: 0 of 2227 (0%)	Overall: 47 of 16 031 (0.29%); white men: 28 of 5356 (0.52%); nonwhite men: 1 of 1349 (0.07%); white women: 18 of 7099 (0.25%); nonwhite women: 0 of 2227 (0%)	Overall: 59 of 16 031 (0.37%); white men: 41 of 5356 (0.77%); nonwhite men: 0 of 1349 (0%); white women: 18 of 7099 (0.25%); nonwhite women: 0 of 2227 (0%)	Overall: 3 of 16 031 (0.019%)
Baer et al., 1995 (9)	Oakland Kaiser Permanente	Consecutive men >age 30 y	3977 patients; median age, 54 y	Overall: 12 of 3977 (0.3%); white men: 9 of 1974 (0.46%) (mean age, 54.4 y); black men: 2 of 1148 (0.17%); other: 1 of 725 (0.14%)	Overall: 8 of 3977 (0.2%); white men: 7 of 1974 (0.35%); black men: 0 of 1148 (0%); other: 1 of 725 (0.14%)	Overall: 15 of 3977 (0.38%); white men: 11 of 1974 (0.56%); black men: 3 of 1148 (0.26%); other: 1 of 725 (0.14%)	Overall: 0 of 3977 (0%)
Niederau et al., 1998 (10)	9 primary care practices in the former West Germany	Every third primary care patient	3027 patients (95% eligible); age NA; 40.6% men	Overall: 18 of 3027 (0.59%) (mean age, 54.5 y); men: 13 (1.05%) (mean age, 55 y); women: 5 (0.28%) (mean age, 53 y)	Overall: 53.4 of 3027 (1.8%); men: 19.5 (1.6%); women: 33.9 (1.9%)	Overall: 24 of 3027 (0.79%); not designated by sex	Overall: 4 of 3027 (0.13%) (1 with hepatocellular cancer)

* NA = not available; ND = not determined.
† Definitive hereditary hemochromatosis requires liver biopsy with hepatic iron concentration > 30 μmol/g dry weight or >2000 mg iron stores by phlebotomy.
‡ Determined by application of hereditary hemochromatosis criteria to those with repeated elevations of transferrin saturation and serum ferritin level who did not undergo liver biopsy or phlebotomy.

mated that the prevalence of hereditary hemochromatosis ranges from 1 in 357 persons to 1 in 625 persons in the general population to rates almost as high as 1 in 135 persons among Norwegian men (4). The **Table** lists various studies showing the prevalence of hereditary hemochromatosis in primary care settings.

Risk for Complications in Asymptomatic Patients

Asymptomatic individuals are patients in the latent phase of hereditary hemochromatosis who were incidentally identified. These persons have not yet shown any signs or symptoms related to the disease. Although clinical manifestations associated with hereditary hemochromatosis are influenced by age, sex, diet, and other unknown factors, it is imperative to know the path of disease progression for treatment of the disease. Clinical outcomes that can be associated with hereditary hemochromatosis are cirrhosis, hepatocellular carcinoma, type 2 diabetes, congestive heart failure, arthritis, hypogonadism in males, and even death. However, most persons with the mutated gene remain asymptomatic.

The literature that discusses the relationship between biochemical primary iron overload (elevated serum ferritin level and transferrin saturation) and the development of hereditary hemochromatosis (or resulting disease or death) does not consistently identify increasing transferrin saturation and serum ferritin level over time in hereditary hemochromatosis (12–14). The studies that discuss the correlation between iron excess and cirrhosis indicate that a ferritin level less than 1000 μg/L was not associated with cirrhosis on liver biopsy (15–17). The National Health and Nutrition Examination Survey I (NHANES I) database (18) was used to analyze the association between transferrin saturation and all-cause mortality. The results showed that all-cause mortality significantly increased for persons whose transferrin saturation was above 55% compared with persons who had lower transferrin saturation (hazard ratio, 1.60 [CI, 1.17 to 2.21]).

Sensitivity and Specificity of Serum Ferritin Level and Transferrin Saturation

The variation in the case definition of hereditary hemochromatosis has an impact on calculating the sensitivity and specificity of a screening or diagnostic test. Some argue for comparing sensitivity and specificity of phenotyping with genotyping, while others use constant elevation of serum ferritin level and transferrin saturation as the case definition. Schmitt and colleagues (4) required that the gold standard be an independent demonstration of iron overload through iron deposition by liver biopsy or the amount of iron removed by phlebotomy. However, none

Downloaded From: http://annals.org/ on 10/31/2016

of 9 studies identified compared the screening tests for iron overload (transferrin saturation and serum ferritin) with the gold standard.

In a study by Phatak and associates (5) in the primary care setting, 311 of 747 patients had an elevated transferrin saturation greater than 45%. Liver biopsy was offered to 35 patients with transferrin saturation greater than 55% and a serum ferritin level greater than 200 μg/L. Hereditary hemochromatosis was diagnosed in 18 of 21 patients who underwent biopsy. Another study (10) included 3027 outpatients and used transferrin saturation values greater than 50% in men and greater than 60% in women, and serum ferritin values of 250 μg/L. The results showed that 235 of 3027 patients had an elevated serum ferritin level, 139 had elevated transferrin saturation, and 44 had both elevated serum ferritin level and elevated transferrin saturation. Hereditary hemochromatosis was diagnosed in 18 of 23 persons who were further evaluated. Baer and coworkers (9) showed that the diagnostic cutoff levels of 500 μg/L for serum ferritin and 62% for transferrin saturation identified a subgroup of patients in which all individuals had hereditary hemochromatosis.

Efficacy of Phlebotomy

The efficacy of phlebotomy for improving survival in patients without cirrhosis is based on the results of large uncontrolled case series and is accepted as the standard of care by a majority of hepatologists (19). None of the studies (19, 20) meets a standard of evidence that clearly establishes the efficacy of therapeutic phlebotomy; however, the studies do support the existing model of disease and suggest a benefit. In the presence of current opinion and lack of significant side effects, the prospect of having randomized, controlled trials is low and perhaps unethical.

Benefits versus Risks of Screening

No available data can definitively determine whether phlebotomy will delay or deter the development of cirrhosis over the lifetime of an asymptomatic patient. The value of detecting individuals who are homozygous for the mutation but do not develop iron overload is controversial. The psychological and social implications of identifying such individuals must be considered. Issues such as the impact on insurability and the anxiety of being labeled with a hereditary illness need to be considered when comparing the benefits and risks of screening (21). The recently published HEIRS Study indicates that C282Y mutation does not explain high transferrin saturation and serum ferritin level in nonwhite persons. The number of newly identified genes participating in the regulation of iron homeostasis has increased at a remarkable pace. Therefore, consideration of false reassurance in the setting of a negative genetic test result is not unreasonable.

Summary

The prevalence of hereditary hemochromatosis varies in the general population, depending on race, sex, age, and case definition of the disease. It is more commonly found in white men of northern European descent and older than 40 years of age. Some evidence shows that patients with a serum ferritin level greater than 1000 μg/L are more likely to develop cirrhosis.

The case definition has an impact on measuring the sensitivity and specificity of the tests. However, serum ferritin level and transferrin saturation have been useful in identifying patients who are prone to or already have hereditary hemochromatosis. The available literature supports the benefits of adequate phlebotomy. However, this benefit has not been proven for all end-organ damage, only for cirrhosis. Finally, there is insufficient evidence to support genetic testing because *HFE* mutations may not progress to overt disease.

From the American College of Physicians, Philadelphia, Pennsylvania; Beth Israel Deaconess Medical Center, Boston, Massachusetts; North Shore Medical Group, Huntington, New York; VA Palo Alto Health Care System and Stanford University, Stanford, California; and Hines VA Hospital and Northwestern University, Chicago, Illinois.

Note: Clinical practice guidelines are "guides" only and may not apply to all patients and all clinical situations. Thus, they are not intended to override clinicians' judgment. All ACP clinical practice guidelines are considered automatically withdrawn or invalid 5 years after publication, or once an update has been issued.

Grant Support: Financial support for the development of this guideline comes exclusively from the ACP operating budget.

Potential Financial Conflicts of Interest: None disclosed.

Requests for Single Reprints: Amir Qaseem, MD, PhD, MHA, American College of Physicians, 190 N. Independence Mall West Philadelphia, PA 19106; e-mail, aqaseem@acponline.org.

Current author addresses are available at www.annals.org.

References

1. **Adams PC, Reboussin DM, Barton JC, McLaren CE, Eckfeldt JH, McLaren GD, et al.** Hemochromatosis and iron-overload screening in a racially diverse population. N Engl J Med. 2005;352:1769-78. [PMID: 15858186]

2. **Beutler E, Felitti VJ, Koziol JA, Ho NJ, Gelbart T.** Penetrance of 845G—>A (C282Y) HFE hereditary haemochromatosis mutation in the USA. Lancet. 2002;359:211-8. [PMID: 11812557]

3. **Gochee PA, Powell LW, Cullen DJ, Du Sart D, Rossi E, Olynyk JK.** A population-based study of the biochemical and clinical expression of the H63D hemochromatosis mutation. Gastroenterology. 2002;122:646-51. [PMID: 11874997]

4. **Schmitt B, Golub R, Green R.** Screening primary care patients for hereditary hemochromatosis with transferrin saturation and serum ferritin level: systematic review for the American College of Physicians. Ann Intern Med. 2005;143:522-36.

5. **Phatak PD, Sham RL, Raubertas RF, Dunnigan K, O'Leary MT, Braggins C, et al.** Prevalence of hereditary hemochromatosis in 16031 primary care patients. Ann Intern Med. 1998;129:954-61. [PMID: 9867748]

6. **Olynyk JK, Cullen DJ, Aquilia S, Rossi E, Summerville L, Powell LW.**

Downloaded From: http://annals.org/ on 10/31/2016

A population-based study of the clinical expression of the hemochromatosis gene. N Engl J Med. 1999;341:718-24. [PMID: 10471457]
7. **Looker AC, Johnson CL.** Prevalence of elevated serum transferrin saturation in adults in the United States. Ann Intern Med. 1998;129:940-5. [PMID: 9867746]
8. **Powell LW, Subramaniam VN, Yapp TR.** Haemochromatosis in the new millennium. J Hepatol. 2000;32:48-62. [PMID: 10728794]
9. **Baer DM, Simons JL, Staples RL, Rumore GJ, Morton CJ.** Hemochromatosis screening in asymptomatic ambulatory men 30 years of age and older. Am J Med. 1995;98:464-8. [PMID: 7733125]
10. **Niederau C, Niederau CM, Lange S, Littauer A, Abdel-Jalil N, Maurer M, et al.** Screening for hemochromatosis and iron deficiency in employees and primary care patients in Western Germany. Ann Intern Med. 1998;128:337-45. [PMID: 9490593]
11. **McLaren CE, Barton JC, Adams PC, Harris EL, Acton RT, Press N, et al.** Hemochromatosis and Iron Overload Screening (HEIRS) study design for an evaluation of 100, 000 primary care-based adults. Am J Med Sci. 2003;325:53-62. [PMID: 12589228]
12. **Andersen RV, Tybjaerg-Hansen A, Appleyard M, Birgens H, Nordestgaard BG.** Hemochromatosis mutations in the general population: iron overload progression rate. Blood. 2004;103:2914-9. [PMID: 15070663]
13. **Yamashita C, Adams PC.** Natural history of the C282Y homozygote for the hemochromatosis gene (HFE) with a normal serum ferritin level. Clin Gastroenterol Hepatol. 2003;1:388-91. [PMID: 15017658]
14. **Olynyk JK, Hagan SE, Cullen DJ, Beilby J, Whittall DE.** Evolution of untreated hereditary hemochromatosis in the Busselton population: a 17-year study. Mayo Clin Proc. 2004;79:309-13. [PMID: 15008603]
15. **Guyader D, Jacquelinet C, Moirand R, Turlin B, Mendler MH, Chaperon J, et al.** Noninvasive prediction of fibrosis in C282Y homozygous hemochromatosis. Gastroenterology. 1998;115:929-36. [PMID: 9753496]
16. **Beaton M, Guyader D, Deugnier Y, Moirand R, Chakrabarti S, Adams P.** Noninvasive prediction of cirrhosis in C282Y-linked hemochromatosis. Hepatology. 2002;36:673-8. [PMID: 12198660]
17. **Morrison ED, Brandhagen DJ, Phatak PD, Barton JC, Krawitt EL, El-Serag HB, et al.** Serum ferritin level predicts advanced hepatic fibrosis among U.S. patients with phenotypic hemochromatosis. Ann Intern Med. 2003;138:627-33. [PMID: 12693884]
18. **Mainous AG 3rd, Gill JM, Carek PJ.** Elevated serum transferrin saturation and mortality. Ann Fam Med. 2004;2:133-8. [PMID: 15083853]
19. **Niederau C, Fischer R, Purschel A, Stremmel W, Haussinger D, Strohmeyer G.** Long-term survival in patients with hereditary hemochromatosis. Gastroenterology. 1996;110:1107-19. [PMID: 8613000]
20. **Milman N, Pedersen P, a Steig T, Byg KE, Graudal N, Fenger K.** Clinically overt hereditary hemochromatosis in Denmark 1948-1985: epidemiology, factors of significance for long-term survival, and causes of death in 179 patients. Ann Hematol. 2001;80:737-44. [PMID: 11797115]
21. **Shaheen NJ, Lawrence LB, Bacon BR, Barton JC, Barton NH, Galanko J, et al.** Insurance, employment, and psychosocial consequences of a diagnosis of hereditary hemochromatosis in subjects without end organ damage. Am J Gastroenterol. 2003;98:1175-80. [PMID: 12809845]

Downloaded From: http://annals.org/ on 10/31/2016

Current Author Addresses: Drs. Qaseem and Snow: American College of Physicians, 190 N. Independence Mall West, Philadelphia, PA 19106.
Dr. Aronson: 330 Brookline Avenue, Boston, MA 02215.
Dr. Fitterman: 120 New York Avenue, Huntington, NY 11743.
Dr. Weiss: 151H, PO Box 5000, Hines, IL 60141.
Dr. Owens: 117 Encina Commons, Stanford, CA 94305.

Downloaded From: http://annals.org/ on 10/31/2016