



## Complete Summary

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### GUIDELINE TITLE

Diagnosis and management of hemochromatosis.

### BIBLIOGRAPHIC SOURCE(S)

Tavill AS. Diagnosis and management of hemochromatosis. Hepatology 2001 May; 33(5):1321-8. [50 references] [PubMed](#)

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## SCOPE

### DISEASE/CONDITION(S)

- Hereditary hemochromatosis
- Secondary iron overload

### GUIDELINE CATEGORY

Diagnosis  
Management  
Treatment

### CLINICAL SPECIALTY

Gastroenterology  
Medical Genetics

### INTENDED USERS

Advanced Practice Nurses  
Allied Health Personnel  
Managed Care Organizations

Nurses  
Physician Assistants  
Physicians

## GUIDELINE OBJECTIVE(S)

To suggest preferable approaches to the diagnostic, therapeutic, and preventative aspects of care for hemochromatosis

## TARGET POPULATION

### Screening for Hereditary Hemochromatosis

- Symptomatic patients
  - Patients with unexplained manifestations of liver disease or a presumably known cause of liver disease with abnormality of one or more indirect serum iron markers
  - Patients with type 2 diabetes mellitus, particularly with hepatomegaly, elevated liver enzymes, atypical cardiac disease or early-onset sexual dysfunction
  - Patients with early-onset atypical arthropathy, cardiac disease, and male sexual dysfunction
- Asymptomatic patients
  - First-degree relatives of a confirmed case of hemochromatosis
  - Individuals with abnormal serum iron markers discovered during routine testing
  - Individuals with unexplained elevation of liver enzymes or the serendipitous finding of asymptomatic hepatomegaly or radiologic detection of enhanced computed tomography attenuation of the liver

### Treatment

- Individuals with confirmed hereditary hemochromatosis or secondary iron overload

## INTERVENTIONS AND PRACTICES CONSIDERED

### Diagnosis

1. Transferrin saturation after an overnight fast
2. Serum ferritin determination
3. Genotyping to detect HFE mutations
4. Liver biopsy
  - Histologic assessment
  - Qualitative hepatic iron determination by Perls' staining, and quantitative iron measurement

### Treatment/Management

#### Hereditary hemochromatosis

1. Phlebotomy, with prior checking of hematocrit and regular checking of serum ferritin levels
2. Avoidance of vitamin C and iron supplements
3. Regular screening for hepatocellular carcinoma
4. Liver transplantation may be an option when end-stage liver disease has occurred

#### Secondary iron overload

1. Phlebotomy
2. Iron chelation therapy (deferrioxamine mesylate [Desferal])
3. Follow-up liver biopsy to ascertain iron removal
4. Avoidance of vitamin C and iron supplements

#### MAJOR OUTCOMES CONSIDERED

- Sensitivity and specificity of diagnostic screening tests for iron overload
- Iron levels
- Progression and complications of liver disease (e.g., cirrhosis, hepatocellular carcinoma)
- Other major organ damage and dysfunction
- Mortality

## METHODOLOGY

#### METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)  
Searches of Electronic Databases

#### DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

A formal review and analysis of the recent published literature on hemochromatosis (Medline Search from 1990-2000) was performed.

#### NUMBER OF SOURCE DOCUMENTS

Hundreds of pieces of literature

#### METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

#### RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

In an attempt to standardize recommendations, the Practice Guidelines Committee of the American Association for the Study of Liver Diseases modified the categories of the Infectious Diseases Society of America's Quality Standards:

Grade I: Evidence from multiple well-designed randomized controlled trials each involving a number of participants to be of sufficient statistical power.

Grade II: Evidence from at least one large well-designed clinical trial with or without randomization, from cohort or case-control analytic studies, or well-designed meta-analysis.

Grade III: Evidence based on clinical experience, descriptive studies, or reports of expert committees.

Grade IV: Not rated

## METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

## DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

The authors and committee members reviewed the available literature from the time period stated and summarized the findings with recommendations made based on the most robust evidence in the literature.

## METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

## RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

## COST ANALYSIS

Evidence is accumulating to support the cost effectiveness of serologic strategies for screening the general population for iron overload. Most of these reports have only assessed the usefulness of standard serologic tests such as serum iron, transferrin saturation, or serum ferritin; only one study has included the recently discovered HFE gene mutation. This latter study compared screening of blood donors by phenotypic or genotypic methods. It was concluded that the most cost-effective strategy for identifying cases in the general population was phenotypic screening (standard iron markers) with genotypic confirmation of homozygosity in those with indirect markers of iron overload (\$2,700 per case). This strategy had a high predictive value for the detection of homozygotes with iron overload and remained cost effective even when it was assumed that as few as 20% of cases would ever develop life-threatening complications of the disease. In contrast, genotypic screening (by mutation analysis) of the general population would be prohibitively expensive (\$110,000 to detect one case) and the strategy would have specificity limitations in the light of accumulating evidence for the incomplete penetrance of the gene mutations.<sup>6</sup> These limitations may become less important as newer and less expensive techniques of mutation analysis are developed. At this time the guideline developers are supportive of a low-cost phenotypic approach for screening the general population.

## METHOD OF GUIDELINE VALIDATION

External Peer Review  
Internal Peer Review

## DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

This guideline was produced in collaboration with the Practice Guideline Committee of the American Association for the Study of Liver Diseases. This committee, in concert with additional external consultants, supplied extensive peer review of the document.

## RECOMMENDATIONS

### MAJOR RECOMMENDATIONS

Recommendations are followed by quality of evidence ratings (Grades I-IV) and categories reflecting the evidence to support the use of a recommendation (A-E), which are defined at the end of the "Major Recommendations" field.

#### Diagnosis

1. Initial screening of individuals with suspected iron overload and those over the age of 20 years who are first-degree relatives of known cases of hereditary hemochromatosis (HH) should be done by measurement of transferrin saturation after an overnight fast. Simultaneous serum ferritin determination increases the predictive accuracy for diagnosis of iron overload. Transferrin saturation (TS) is also the test of choice for screening the general adult population for iron overload states (refer to Figure 1 in the original guideline document) (rating: II A, B, C, D, and E).
2. Genotyping to detect HFE mutations should be performed for all individuals who have abnormal iron studies and on those who are first-degree relatives of identified homozygotes as detailed in step 1 of the diagnostic algorithm (refer to original guideline document). Liver biopsy is recommended in all homozygotes with clinical evidence of liver disease, serum ferritin greater than 1,000 ng/mL, and particularly in those greater than 40 years of age with other risk factors for liver disease. Liver biopsy should also be considered in compound or C282Y heterozygotes with elevated transferrin saturation, particularly those who have had abnormal liver enzyme levels or clinical evidence of liver disease (rating: II A, B, C, D, and E).
3. Liver biopsy is helpful in suspected HH to assess hepatic iron concentration (HIC) and the stage of fibrosis (see recommendation 2, above). In addition to routine histologic assessment, qualitative hepatic iron determination should be performed by Perls' staining. Due to the low sensitivity of this method, quantitative iron measurement should be obtained if HH is suspected (rating: II A, B, C, D, and E).

#### Treatment

#### Hereditary hemochromatosis

4. All patients with HH who have evidence of iron overload should be strongly encouraged to undergo regular phlebotomies until iron stores are depleted. These should be continued for life, gauging the frequency of maintenance therapy on the serum ferritin level. Vitamin C supplements should be avoided. HH patients with cirrhosis should undergo regular screening for hepatocellular carcinoma (HCC) (rating: II A, B, C, D, and E).

#### Secondary iron overload

5. Treatment of secondary iron overload should be tailored to the underlying cause. Phlebotomy using a regimen similar to HH (see recommendation 4, above) may be tolerated in some forms of secondary iron overload without preexisting anemia. Parenteral chelation therapy with deferoxamine is currently the treatment of choice in patients with chronic dyserythropoietic syndromes or chronic hemolytic anemia. Monitoring of the efficacy of therapy during chelation may require repeat liver biopsies to confirm adequate reduction of hepatic iron concentration (rating: II A, B, C, D, and E).

#### Definitions:

##### Quality of evidence

Grade I: Evidence from multiple well-designed randomized controlled trials each involving a number of participants to be of sufficient statistical power.

Grade II: Evidence from at least one large well-designed clinical trial with or without randomization, from cohort or case-control analytic studies, or well-designed meta-analysis.

Grade III: Evidence based on clinical experience, descriptive studies, or reports of expert committees.

Grade IV: Not rated

##### Evidence to support use

A: Survival benefit

B: Improved diagnosis

C: Improvement in quality of life

D: Relevant pathophysiologic parameters improved

E: Impacts cost of health care

#### CLINICAL ALGORITHM(S)

An algorithm is provided in the original guideline document for the management of hereditary hemochromatosis.

## EVIDENCE SUPPORTING THE RECOMMENDATIONS

### TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence is specifically stated for each recommendation (see the "Major Recommendations" field).

## BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

### POTENTIAL BENEFITS

#### Overall benefits

- Early diagnosis of hereditary hemochromatosis (HH) prevents organ damage and dysfunction due to tissue iron toxicity
- Screening and early detection of asymptomatic HH cases may reduce mortality
- Recognition and diagnosis of symptomatic cases of HH may minimize progression and complications of the disease
- Adequate treatment of HH may promote rapid, safe, and effective removal of iron

#### Specific benefit

- There is overwhelming evidence that institution of phlebotomy therapy before cirrhosis and/or diabetes develop will significantly reduce the morbidity and mortality of hereditary hemochromatosis.

### POTENTIAL HARMS

- Phlebotomy may cause or worsen anemia if performed too frequently.
- Cardiac dysrhythmias and cardiomyopathy are the most common causes of sudden death in iron overload states. Since the risk of these complications may increase during rapid mobilization of iron, certain additional precautions and therapy may be required.
- The application of deferoxamine therapy is limited by cost (particularly in developing countries), the need for a parenteral route of therapy, discomfort and inconvenience (a challenging prospect in young patients), and neurotoxicity.

#### Subgroups Most Likely to be Harmed:

Those with underlying cardiac disease are most at risk for arrhythmias. Individuals with anemia of any cause may be at risk of exacerbations due to phlebotomy.

## QUALIFYING STATEMENTS

### QUALIFYING STATEMENTS

- These guidelines are intended to be flexible, in contrast with "standards of care," which are inflexible policies to be followed in almost every case.
- Since the development of these practice guidelines was initiated by the American Association for the Study of Liver Diseases (AASLD), an International Consensus Conference on Haemochromatosis was conducted by the European Association for the Study of Liver (EASL), cosponsored by the World Health Organization (WHO), National Institutes of Health (NIH), and the Centers for Disease Control and Prevention (CDC), and was recently published as a conference report. Although many of the conclusions and recommendations of this conference accord with the AASLD Practice Guidelines on hemochromatosis, others remain tentative for the international group, particularly those relating to screening for iron overload. However, the guideline developers share with the international group an awareness of the need for information derived from well-designed screening programs that incorporate careful follow-up of identified hereditary hemochromatosis patients and matched controls.

## IMPLEMENTATION OF THE GUIDELINE

### DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

## INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

### IOM CARE NEED

Living with Illness  
Staying Healthy

### IOM DOMAIN

Effectiveness

## IDENTIFYING INFORMATION AND AVAILABILITY

### BIBLIOGRAPHIC SOURCE(S)

Tavill AS. Diagnosis and management of hemochromatosis. Hepatology 2001 May; 33(5):1321-8. [50 references] [PubMed](#)

### ADAPTATION

Not applicable: The guideline was not adapted from another source.

### DATE RELEASED

2001 May

#### GUIDELINE DEVELOPER(S)

American Association for the Study of Liver Diseases - Private Nonprofit Research Organization

#### SOURCE(S) OF FUNDING

American Association for the Study of Liver Diseases

#### GUIDELINE COMMITTEE

Practice Guidelines Committee

#### COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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#### FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

#### ENDORSER(S)

American College of Gastroenterology - Medical Specialty Society  
American Gastroenterological Association - Medical Specialty Society

#### GUIDELINE STATUS

This is the current release of the guideline.

#### GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the [American Association for the Study of Liver Diseases Web site](#).

Print copies: Available from the American Association for the Study of Liver Diseases, 1729 King Street, Suite 200; Alexandria, VA 22314; Phone: 703-299-9766; Web site: [www.aasld.org](http://www.aasld.org); e-mail: [aasld@aaasld.org](mailto:aasld@aaasld.org).

#### AVAILABILITY OF COMPANION DOCUMENTS

None available

#### PATIENT RESOURCES

None available

#### NGC STATUS

This NGC summary was completed by ECRI on May 9, 2003. The information was verified by the guideline developer as of June 12, 2003.

#### COPYRIGHT STATEMENT

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Date Modified: 11/15/2004

The logo for FIRST GOV, with "FIRST" in blue and "GOV" in red.

