

GUIDELINES & PROTOCOLS

ADVISORY COMMITTEE

Iron Overload – Investigation and Management

Effective Date: December 15, 2006

Scope

This guideline provides recommendations for the investigation of iron overload and management of hemochromatosis. It applies to patients of all ages.

Iron overload refers to all conditions where excessive amounts of iron accumulate in tissues resulting in parenchymal damage and organ dysfunction. The various forms of iron overload may be classified as:

- a) INHERITED
 - *HFE*-related (occurs predominantly in people of European descent)
 - Non-*HFE*-related (can occur in other ethnic groups but is uncommon)
- b) ACQUIRED
 - Iron loading anemias, transfusion iron overload, etc.

Note: The terminology varies in the literature. More recent references reserve the terms ‘hereditary hemochromatosis’ and ‘genetic hemochromatosis’ for *HFE*-related iron overload. The symbol ‘*HFE*’ has been used for many years to designate the gene for hemochromatosis.

RECOMMENDATION 1

Who should be tested for iron overload

- a) Patients who have symptoms or signs that might be caused by iron overload. These include patients with (unexplained):
 - arthritis (including premature osteoarthritis)
 - congestive heart failure or cardiomyopathy
 - adult-onset diabetes
 - persistent elevation of liver enzymes or cirrhosis
 - secondary hypogonadism
 - increased skin pigmentation
- b) Patients with persistently elevated serum ferritin not explained by an underlying inflammatory/systemic disease.

Notes:

- Serum ferritin typically has a wide reference range and may vary with age and gender: consult your laboratory.
- First degree relatives of a known case of *HFE*-related hemochromatosis should be offered DNA testing as the first step. Refer to Recommendation 3.
- Other groups at risk of iron overload include patients receiving long-term red cell transfusion support for chronic anemia and patients with porphyria cutanea tarda. Management of these patients should be discussed with a specialist.
- Serum ferritin levels may be elevated out of proportion to total body iron stores in patients with infection, inflammation, or cancer.

RECOMMENDATION 2 **How to test for iron overload**

Patients who meet any of the criteria in Recommendation 1 should receive testing for iron overload on a fasting blood sample. Depending on the laboratory, the test can either be transferrin saturation or saturation of total iron binding capacity. For practical purposes, the two tests are equivalent. In the discussion to follow, we will use the term 'fasting transferrin saturation' (fTS).

- a) If fTS \leq 0.45, no further testing is required.
- b) If fTS is between 0.45 and 0.60, repeat test within a month.
 - If repeat test is \leq 0.45, no further hemochromatosis testing is required.
 - If repeat test is $>$ 0.45, DNA testing for *HFE* mutations should be considered in light of the patient's clinical history.
- c) If fTS $>$ 0.60, DNA testing for *HFE* mutations is indicated.

Note: Serum ferritin is not a reliable screening test for iron overload because it may be nonspecifically elevated as an acute-phase reactant. It is useful only for monitoring response to phlebotomy.

Refer to algorithm in Appendix 1: Investigation of Iron Overload

RECOMMENDATION 3 **Who should be offered DNA testing**

Persons of European descent who:

- a) Fulfill criteria b) or c) in Recommendation 2.

OR
- b) Have one or more first-degree relatives with a confirmed or presumptive diagnosis of hereditary hemochromatosis.

OR
- c) Have previously been diagnosed with hemochromatosis, but have not had DNA testing.

Note: DNA testing for the common *HFE* mutations is not informative for persons of non-European descent. Non-European patients with evidence of iron overload should be evaluated by a specialist.

Refer to algorithm in Appendix 1: Investigation of Iron Overload

RECOMMENDATION 4 **Follow-up based on DNA testing**

- a) If DNA testing confirms the presence of one or more C282Y mutations on the *HFE* gene, DNA testing should be offered to all first-degree relatives.

- b) If DNA testing confirms the presence of two *HFE* mutations, at least one of which is C282Y*, further management requires a serum ferritin level. If serum ferritin is elevated, proceed to Recommendation 5. If serum ferritin is normal, then manage as follows:
- C282Y/C282Y - homozygotes: Monitor serum ferritin every two years. If ferritin becomes elevated, proceed to Recommendation 5.
 - C282Y/H63D - compound heterozygotes: Less than three per cent will develop iron overload. Monitor ferritin every five years.
 - C282Y/Norm - simple heterozygotes: Low risk of developing iron overload. Further ferritin testing is not required.
- c) If iron overload is present, but DNA testing does not reveal the cause, then referral to a specialist is appropriate.

* Subjects with H63D/H63D or H63D/Norm are at very low risk of developing iron overload. Ferritin testing is not required and DNA testing of family members is not recommended.

RECOMMENDATION 5 Management of hemochromatosis

Therapeutic phlebotomy is the treatment of choice for *HFE*-related hereditary hemochromatosis and for non-*HFE*-related hemochromatosis. Serum ferritin is the preferred method for monitoring response to therapy. Prior to initiating a phlebotomy program, the patient should be thoroughly assessed for possible end organ damage, e.g. arthritis, liver dysfunction, diabetes, heart disease, etc. Patients with ferritins greater than 1000µg/L should have liver function tests because of the increased risk of cirrhosis and hepatoma.

- a) Volume and frequency of phlebotomy need to be individualized according to the patient's age and clinical circumstances. For severely iron overloaded patients, weekly phlebotomy of 500 ml of whole blood should be continued until serum ferritin is less than 50 µg/L. Fasting transferrin saturation (fTS) may be used to monitor response to therapy in patients who have elevation of their serum ferritin due to other causes. Patients with massive iron overload may require in excess of 100 phlebotomies.
- b) Phlebotomy technique is important for maintaining venous access. Refer to Appendix 2: Therapeutic Phlebotomy Using an 18 Gauge Cannula.
- c) Serum ferritin and hemoglobin should be monitored regularly (e.g. every 4th phlebotomy) to assess response to therapy. It is unusual for iron overloaded patients to develop anemia early in the course of phlebotomy therapy. If this occurs, clearly, the frequency of phlebotomy needs to be reduced.
- d) Once patients have been successfully depleted of excess iron stores, a program of maintenance therapy should be established. Removal of 500 ml every 2-3 months is usually sufficient. Serum ferritin should be monitored yearly to ensure that it is maintained within the normal range.
- e) Patients on maintenance therapy may be eligible to donate to the Canadian Blood Services.
- f) End organ damage should be reassessed periodically. If liver enzymes have been abnormal, they often improve once iron stores have been depleted. There may also be improvement in iron-induced cardiac dysfunction. Diabetic patients often note improvement in blood sugars with less dependency on insulin or oral hypoglycemic agents. Conditions that often do not improve with phlebotomy include arthropathy, cirrhosis and testicular atrophy.

Note: Phlebotomy results in formation of new red cells; therefore HbA1c may underestimate glycemia for up to three months after phlebotomy.

Rationale

Hereditary hemochromatosis is the most common autosomal recessive genetic disorder in persons of European descent, with an estimated prevalence of 2-5 per 1000,^{1,2} however, the clinical manifestations of hemochromatosis are observed in less than 10 per cent of those who carry the *HFE* gene.³

Iron overload occurs when iron accumulation exceeds physiological requirements leading to deposition of excess iron in tissues. Subsequent parenchymal damage results in organ dysfunction.⁶ Iron overload may result from inherited or acquired disorders. The most common form of inherited iron overload is hereditary hemochromatosis, which results from a mutation on the *HFE* gene on chromosome 6.⁴

Acquired iron overload includes a variety of clinically distinct syndromes that should be distinguished from hereditary hemochromatosis. A multiply transfused patient is a common example. An increase in absorption of intestinal iron may be promoted by underlying conditions such as anemia from ineffective erythropoiesis, various liver diseases, excessive ingestion of medicinal iron, and congenital atransferrinemia.⁵

The absorption of iron in the intestine is regulated by the body's iron requirements. A typical diet contains 15 mg iron per day, and in the normal situation, only 1-2 mg is absorbed. In hemochromatosis, regulation of iron absorption is defective, and iron absorption is typically 3-6 mg per day. This equates to excess absorption of about 1 gram per year; consequently it may take three decades or more to accumulate the 20-40 grams of total-body iron needed to cause organ damage. Iron loading is even slower in women because of the "protective" effect of menstruation and pregnancy. End organ damage occurs more rapidly in juvenile hemochromatosis which is known to be caused by a mutation in the *HJV* (hemojuvelin) gene on chromosome 1.²

Target organ dysfunction may manifest as diabetes, complications of cirrhosis, cardiomyopathy, hypogonadism, arthropathy, or increased skin pigmentation. However, nonspecific symptoms such as arthralgias, fatigue, and abdominal pain may be noted years before organ dysfunction becomes apparent. A review of family-based screening studies reported that 52 per cent of family members in whom hereditary hemochromatosis had been diagnosed by DNA testing were asymptomatic.⁷ The other 48 per cent had at least one clinical manifestation of disease such as cirrhosis, skin bronzing, fatigue, weight loss, abdominal pain, or impotence.

The most common mutation associated with hereditary hemochromatosis is a change at amino acid 282 from cysteine to tyrosine (Cys282Tyr), however, another mutation at amino acid 63 from histidine to aspartate has also been described (His63Asp). In persons of European descent with hereditary hemochromatosis, 85 per cent are due to *HFE* mutations. It is clear that defects in other iron-transport proteins (e.g. hepcidin) can also cause hemochromatosis,² however, at present testing for mutations in these other genes is only available at research centres.

Because hemochromatosis can lead to numerous chronic conditions, its symptoms can be confused with those of more common diseases such as alcoholic liver disease, diabetes, and osteoarthritis. If untreated, hemochromatosis can cause serious disease and premature death. Presymptomatic detection and treatment can completely prevent clinical sequelae and, in symptomatic patients, phlebotomy effectively reduces morbidity and mortality.

The availability of biochemical and molecular tests that allow diagnosis of hereditary hemochromatosis in the early stages has increased awareness of the importance of early diagnosis.^{6,7} Although most reviews have concluded that there is insufficient evidence to warrant population screening at this point,^{8,9} there is widespread consensus that efforts to increase early detection and treatment of hemochromatosis are warranted.

Physicians and patients are encouraged to contact:

The Canadian Hemochromatosis Society
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Richmond, BC V6Y 3Z5

Toll-Free (Canada): 1 877 BAD-IRON (1 877 223-4766)
Phone: 604 279-7135
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References

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Sponsors

This guideline was developed by the Guidelines and Protocols Advisory Committee and supersedes the previous guideline developed in 2001. This guideline has been approved by the British Columbia Medical Association and adopted by the Medical Services Commission.

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This guideline is based on scientific evidence current as of the effective date.

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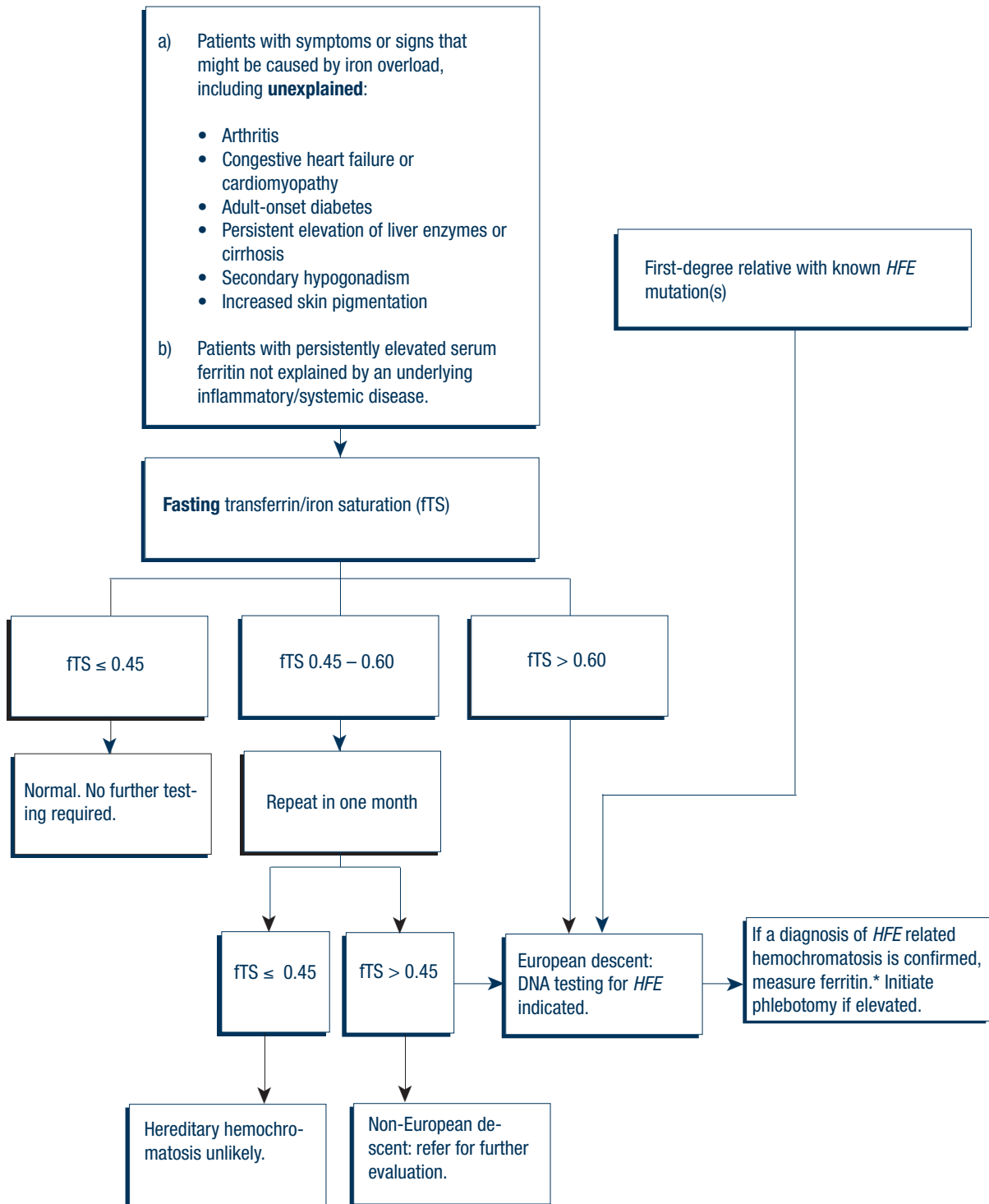
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The principles of the Guidelines and Protocols Advisory Committee are:

- to encourage appropriate responses to common medical situations
- to recommend actions that are sufficient and efficient, neither excessive nor deficient
- to permit exceptions when justified by clinical circumstances.

Appendix 1: Investigation of Iron Overload



*See Recommendation 5

Appendix 2: Therapeutic Phlebotomy Using an 18 Gauge Cannula

Purpose

The standard equipment provided for phlebotomy is a blood collection unit with a 15 gauge stainless steel needle attached to the unit. The large inflexible needle makes venipuncture difficult if the patient has poor or limited venous access.

The equipment and procedure used here are effective and yet:

- provide more choice of venous access
- patients report the procedure is more comfortable as the cannula is smaller and softer
- patients and nurses report less bleeding post cannula removal.

Equipment

1. 18 ga x 1^{1/4} inch teflon coated IV catheter
2. extension set, luer lock adapters, 38 cm
3. injection cap, 7/8 inch, male luer lock
4. single blood pack unit without anticoagulant
5. BP cuff
6. alcohol swabs
7. sterile 2 x 2 inch gauze
8. tape
9. clamps x 2
10. weigh scale
11. stretcher with adjustable height
12. clean gloves

Procedure

A. Prepare patient

1. provide explanation
2. lay patient down
3. baseline BP and pulse
4. apply heat to arms prn
5. provide a handgrip prn
6. sedation as ordered

B. Prepare equipment

1. open extension set, close clamp
2. attach injection cap to female end of extension unit
3. clean injection cap with alcohol swab
4. insert needle of blood collection unit into injection cap

C. Perform venipuncture

1. BP cuff to 90 mm Hg, clamp to prevent leakage
2. select and clean site
3. glove
4. perform venipuncture, advance cannula to hub
5. attach male adapter to IV device
6. release pressure
7. secure cannula: tape extension set to arm; gauze over venipuncture site

D. Perform phlebotomy

1. open clamp on extension set
2. apply pressure by pumping BP cuff to 60 mm Hg
3. lower collection unit to scale to measure volume
4. adjust flow by the height of bed and pressure of cuff
5. on completion, clamp extension set, release BP cuff and remove IV device
6. apply pressure, dress site
7. monitor patient and discharge per protocol