

Hereditary Haemochromatosis

– *Diagnosis & Management
from a GP Perspective*

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The Irish College of General Practitioners

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Whilst every effort has been made by the Quality in Practice Committee to ensure the accuracy of the information and material contained in this document, errors or omissions may occur in the content.

This guidance represents the views of the ICGP which was arrived at after careful consideration of the evidence available.

This guide does not however override the individual responsibility of healthcare professionals to make decisions appropriate to the care of individual patients in consultation with the patient and / or guardian or carer.

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Evidence-based medicine ⁽¹⁾

Evidence-based medicine is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients.

In this document you will see levels of evidence using the GRADE system.

Explanation of GRADE system.

Quality of Evidence			
High	Randomized trials that show consistent results, or observational studies with very large treatment effects	Further research is very unlikely to change our confidence in the estimate of effect	A
Moderate	Randomized trials with methodological limitations, or observational studies with large effect	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate	B
Low and very Low	Observational studies without exceptional strengths, or randomized trials with very serious limitations; unsystematic clinical observations (e.g., case reports and case series; expert opinions) as evidence of very-low-quality evidence	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any estimate of effect is very uncertain	C
Strength of recommendations*			
Strong	Defined as being 'confident that adherence to the recommendation will do more good than harm or that the net benefits are worth the costs'		1
Weak	Defined as being 'uncertain that adherence to the recommendation will do more good than harm OR that the net benefits are worth the costs.'	The uncertainty associated with weak recommendations follows either from poor-quality evidence, or from closely balanced benefits versus downsides.	2

***Factors that affect the strength of a recommendation are: (a) quality of evidence, (b) uncertainty about the balance between desirable and undesirable effect; (c) uncertainty or variability in values and preferences; (d) uncertainty about whether the intervention represents a wise use of resources. ⁽¹⁾**

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Key to levels of evidence and grades of recommendations

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How to use this document

This document has been produced for General Practitioners with a view to enhancing the diagnosis, treatment and management of patients with Haemochromatosis in the Primary Care Setting.

Hereditary Haemochromatosis (HH) can be classified into: ^{(2), (2a), 3)}

1. Haemochromatosis HFE related
 - an autosomal recessive disorder where the mutations in the H.F E. gene are found in the short arm of chromosome 6
 - C282Y/homozygous
 - C282Y/H63D compound heterozygous
 - Other mutations eg. S65C ⁽⁴⁾
2. Haemochromatosis non–HFE related
 - Juvenile Haemochromatosis
 - Autosomal Dominant Haemochromatosis

This document refers to Haemochromatosis HFE related only.

Introduction

The European Association for the Study of the Liver (EASL) define Haemochromatosis as follows: ^{(2),(2A)}

“Haemochromatosis is an inherited disorder resulting from an inborn error of iron metabolism, which leads to progressive iron loading of parenchymal cells in the liver, pancreas and heart. In its fully developed stage, organ structure and function are impaired.”

Incidence

Hereditary Haemochromatosis (HH) is the commonest genetic disorder in Caucasians particularly those of North European and Celtic descent. It is very common in Ireland where its prevalence exceeds that of Cystic Fibrosis, Phenylketonuria and Muscular Dystrophy combined. ⁽⁵⁾

Carrier frequency in individuals of North European descent is between 1 in 8 and 1 in 10 and the homozygous frequency varies between 1 in 200 and 1 in 400 for the C282Y mutation. ^{(6),(7)}

In Ireland, the carrier frequency is higher at 1 in 5, and the homozygous frequency is 1 in 83 for the C282Y mutation. Over 93% of Irish HH patients are homozygous for the HFE gene C282Y. ^{(5),8),(9),(10)}

Estimates suggest that 70,000 people in the U.K. have symptomatic HH, but only about 3000 cases are recognised. Whether this is due to under diagnosis, non penetrance or other factors is unknown. ⁽¹¹⁾

Not all patients homozygous for C282Y or compound heterozygous (C282Y / H63D) develop iron overload. Moreover some patients who are carriers for C282Y can develop iron overload. The factors that affect penetrance are sex, age, physiological and pathological blood loss, blood donation, dietary intake of iron, alcohol, hepatitis C and B, obesity and the use of dietary supplements, (iron and vitamin C). ^{(12),(4),(13-16), 16a, 16b 16c, (17)}

Clinical Presentation

HH is under-diagnosed, because of its late and multiple non specific clinical presentations. Premature death may occur secondary to Diabetes Mellitus, Cirrhosis, Cardiac failure, and Hepatocellular cancer. ^{(2),(2A),(18),(3)} Cirrhosis has not been observed in patients under the age of 40 years, in the absence of Hepatitis C or excess alcohol intake, therefore major morbidity from the disease can be prevented if treatment is initiated before this age. The life expectancy of patients free from cirrhosis or diabetes at diagnosis is indistinguishable from their peers. ^{(19),(20),(21)}

The American Association for the Study of Liver disease (AASLD) practice guidelines state that HH evolves in a series of stages: ⁽³⁾

1. Clinically insignificant iron accumulation at approximately 0-20 years of age which is associated with 0-5g parenchymal iron storage.
2. Iron overload without disease at approximately 20-40 years of age which is associated with 10-20g parenchymal iron storage.
3. Iron overload with organ damage at approximately 40 years of age which is associated with more than 20g parenchymal iron storage.

The clinical features are secondary to the build up of iron in various organs. This build up is gradual, and symptoms do not usually appear, until between 30 and 40 years of age. ^(2,2A) The majority of patients with clinical HH are men aged between 40 – 60 years. The proportion of C282Y homozygous women with definite disease manifestation is significantly lower than men 1% versus 25%. (16A)

The differential diagnosis of this condition is addressed in [\(Appendix 1\)](#).

General Presentations ⁽²⁾

- Fatigue
- Lethargy
- Sleep disturbance
- Weakness

Musculoskeletal Presentations ⁽²⁾

- Vague aches and pains
- Exercise induced joint pains ⁽²²⁾
- Osteoporosis
- Early onset Osteoarthritis
- Chondrocalcinosis (commonly affecting wrists, knees, hips & symphysis pubis, may present acutely as pseudogout) ^(22a)
- HH arthropathy: A characteristic feature of HH arthropathy is involvement of the 2nd and 3rd metacarpals, which are often stiff, painful and mildly tender. Small cysts and hooked osteophytes develop on the metacarpal heads. The arthropathy is degenerative rather than inflammatory and can lead to joint destruction.

Hepatic Presentations ^{(23),(24),(25),(25a)}

- Abnormal Liver Function Tests (especially increased transaminases)
- Hepatomegaly
- Cirrhosis
- Hepatoma

Cardiac Presentations ⁽²⁾

- Arrhythmia ^(26a)
- Congestive Cardiac Failure
- Cardiomyopathy ⁽²⁶⁾

Endocrine Presentations ⁽²⁾

- Amenorrhoea
- Diabetes Mellitus type 1&2
- Decrease in libido
- Infertility ⁽²⁸⁾
- Impotence

Skin Presentations ⁽²⁾

- Pigmentation
- Porphyria cutanea tarda ^{(28A) (28B)}

Infectious Presentations

A theoretical increased incidence of Yersinia infections (patients with HH should not eat raw oysters). ⁽²⁹⁾

Other Presentations

- Abdominal pain
- Thyroid & Parathyroid abnormalities ^{(30),(31),(32)}
- Amyotrophic lateral sclerosis – There is a reported association in patients with H63D/H63Db ⁽³²⁾

Investigations

1. The EASL Guidelines 2011, suggest that ferritin levels should be checked as a first step in the diagnosis of HH. If elevated greater than 300Ng/ml for men and post-menopausal women, and greater than 200Ng/ml for pre-menopausal women, then proceed to measurement of Transferrin saturation.^(2a) (GRADE 1B) Fasting levels of transferrin saturation and ferritin are recommended at present.⁽³⁾

Taken together, elevated transferrin saturation and Ferritin have a strong positive predictive value, and their absence give an even stronger negative predictive value of HFE Haemochromatosis.^{(3)(2A)} (GRADE 1B)

Normal serum Ferritin is a sufficient screen to exclude current iron overload but does not exclude a diagnosis of HH in patients who have not had the genetic test.

Moderate iron overload is defined as greater or equal to 500ng/ml and severe overload as greater than or equal to 750ng/ml.⁽²⁾⁽³⁾⁽³³⁾

See [Appendix 1 and 2](#) for other causes of raised ferritin.

Transferrin Saturation levels more than 45% are strongly suggestive of hereditary haemochromatosis but do not necessarily indicate a need for treatment unless the ferritin threshold is exceeded. If there has been recent blood loss for any reason, this result may be normal.

2. If iron studies are positive then genetic testing should be performed for C282Y and H63D mutations, following appropriate counselling and discussion re the implication of the result of the genetic test;⁽³⁴⁾

HH is diagnosed in terms of phenotype (iron overload) not genotype therefore the diagnosis is not made by identification of mutated genes alone. Patients with abnormal iron studies and no mutation in the HFE gene may also have HH or other iron overload conditions and should be referred for further investigations. If a patient is found to be homozygous but has normal iron studies, pathological or physiological blood loss should be considered. Having ruled out blood loss, iron studies should be repeated every year.^{(2)(2a)} (GRADE 2C)

3. Having made the diagnosis a general work-up is undertaken as follows:- ^{(2a)*}

- Urea and Electrolytes
- Liver Function Tests
- Blood Sugar, Urinalysis, HbA1c (in most cases is sufficient to diagnose DM), Oral Glucose Tolerance Test, where HbA1c is not suitable, e.g. hemolytic anemia, chronic malaria, major blood loss, or blood transfusions, all symptomatic children and young people, symptoms suggesting Type 1 diabetes (any age), short duration of diabetes symptoms, patients at high risk of diabetes who are acutely ill, taking medication that may cause rapid glucose rise e.g. corticosteroids, antipsychotics, acute pancreatic damage/pancreatic surgery.⁽⁴⁵⁾⁽⁴⁶⁾
- Lipid profile
- ECG, Chest X-ray and X-ray of affected joints, and other biochemical tests may also be considered, depending on the clinical presentation, prior to referral.

*(GRADE 2C based on 2a reference).

Referral

Patients should be referred for further assessment to ascertain organ damage and to access hospital based phlebotomy services if necessary. Liver biopsy is no longer necessary to diagnose HH. It is used to assess cirrhosis/ fibrosis. It is also used to clarify a situation where there are other co factors involved, e.g. alcohol, hepatitis.^(2a)

Liver biopsy is recommended for those who are likely to have significant liver damage i.e. those who have one or more of the following;^{(2)(2a)(3)(48)(49)}

- Abnormal transaminases
- Ferritin>1000
- Alcohol abuse

Where cirrhosis is present, the patient needs to be monitored for the development of hepatocellular cancer by liver ultrasound and estimation of serum alpha feta protein levels 6-monthly.⁽²⁾⁽³⁵⁾ If cirrhosis is not present, this is not necessary.

MRI is presently being investigated as a way of assessing hepatic iron concentration, but is not at present widely available, and few patients with HH have been studied yet.^(2a)

Management

Dietary advice

A strict iron deficient diet is not recommended, but iron rich or iron fortified processed foods (iron supplemented cereals and bread), should be avoided or eaten in moderation. Iron and Vitamin C supplements should be avoided - See [Appendix 5](#) for a list of Iron rich foods. Tea drinking in large amounts is beneficial and should accompany meals.⁽³⁶⁾ Alcohol should only be drunk in moderation (max 14 units/ week for women, 21 units / week for men) or avoided altogether, according to the severity of the clinical picture.⁽³⁵⁾

Venesection

Venesection is commenced when there is evidence of iron overload rather than waiting for symptoms - 400-500 ml. of blood is removed on each occasion.^{(3)(2a)} (GRADE 1C) When serum Ferritin is greater than normal, venesection is performed twice weekly to twice monthly (depending on the patients health status), until Ferritin is between 25-50ng/ml. Published guidance and expert practice varies as to the ideal maintenance level of serum ferritin. Traditionally, expert guidance advised maintenance ferritin levels of 25 – 50 ng/ml but in more recent years maintenance levels ranging from 20 – 100 ng / ml are considered acceptable.

When normal levels are reached venesection is tailored to the individual's requirements. In most cases serum Ferritin levels of 50-100 ng/ml can be maintained by about four venesections per year.⁽³⁾ The frequency of venesection and corresponding maintenance ferritin levels must also consider individual patients circumstances.

Venesection in the GP surgery

Venesection can be performed in the GP surgery (please see [Appendix 3](#) for the protocol) but the following need to be taken into consideration in the provision of this service:

- It requires at least thirty minutes to undertake a venesection. This does not include supervised resting time afterwards. Thus, time and room space, may need to be allocated on a weekly basis (at least in the initial stages) for a year or more.

- Blood bags and associated collecting sets are the main equipment required. In some instances these combined sets are available from the HSE through local hospitals. Some sets are fitted with a sampling portal, enabling Ferritin levels to be taken without the need for additional needle access.
- Supply arrangements of blood bags and associated collecting sets differ around the country therefore enquiries will be required at local HSE level.
- The blood bag should be placed in a yellow hazard bag and placed in a placenta bucket (also supplied by HSE). These are collected by Initial Medical Services at:

Hazel House, Millennium Park, Naas, Co Kildare.

Tel: 059 913 4811. Fax 059 913 4812.

Email: info@initialmedical.ie

This is a nationwide service. Certificates of collection and disposal will be issued to the GP Practice.

- The amount of blood removed must be recorded accurately at each visit (**Appendix 4**). The Irish HH Association provides record cards for patients which they should present at each visit.
- Maintenance venesection is tailored for the individual patient on an ongoing basis by 6-monthly monitoring of Ferritin levels aiming for a level of less than 50 ng/ml.⁽²⁾⁽³⁾⁽³³⁾
- Liver Function Test's and Blood Sugar should be performed on a regular basis.
- A DEXA scan needs to be performed and repeated at regular intervals as determined by the findings of the DEXA scan and the future risk of Osteoporosis as HH is a known risk factor for Osteoporosis.
- There is no STC Coding for venesection for GMS patients with HH, thus venesection is not covered under the GMS contract. (The IMO intends to raise this issue in the context of the review of the GMS contract). Laya Healthcare, VHI and Hibernian Health Insurers, will pay the GP for venesection, provided the patient meets their policy criteria.

Blood Donation

The present policy of the Irish Blood Transfusion Service (IBTS):-

(1) Any person picked up by family screening, or other health check, and who fulfil IBTS criteria, can donate blood, provided venesection is not required and the person does not have any complication of HH, other than joint complications.

(2) If a person becomes diagnosed with HH, and is already a donor, and had donated within the last two years, (termed a regular donor), they may continue to be a blood donor, provided venesection is required no more than four times a year, and the person does not have complications from HH, other than joint complications.

(3). The IBTS is running a clinic in Stillorgan Co. Dublin, specifically for patients with HH, who are attending hospital for venesections. This service is currently at capacity.

There are plans for future countrywide expansion of this programme which are available at

<http://www.giveblood.ie>

Screening

Case Finding

At present case finding as opposed to population screening is recommended. ^{(2)(2a)(33a)(39)(40)(41)(42)}

Patients with the following conditions are at increased risk and should be screened ^{(2a)*}:

- Chronic parenchymal liver disease (GRADE 1C)
 - Hepatocellular cancer (GRADE 2C)
 - Diabetes Mellitus, Type 1 (Type 2 is no longer included for screening) ^{(2A)(32A)(45)(46)} (GRADE 2C)
 - Well defined chondrocalcinosis ^(22a) (GRADE 2C)
 - Porphryria Cutanea Tarda (GRADE 1B)
- (* Levels of Evidence based on 2a reference).

Carriers

A small percentage of carriers have iron overload, and go on to develop organ damage. ⁽⁴²⁾⁽⁴³⁾ Therefore they should be monitored for symptoms on an ongoing basis. A study of male heterozygotes for C282Y amongst the Finnish population showed that their risk of Myocardial Infarction was double that of their non carrying controls. ⁽⁴³⁾ In another study heterozygosity for HH was associated with cardiovascular death in postmenopausal women especially if they already had classic risk factors. ⁽⁴⁴⁾

Screening of relatives

The patient should be advised that their first degree relatives should be screened i.e. parents and siblings. Consideration should also be given to screening aunts, uncles and cousins.

EASL recommends that children are not screened until they are of an age where they can understand the implications of the test, take responsibility for the result and can give informed consent.

In these circumstances, consideration should be given to screening the patient's partner. ^{(2)(2a)} (GRADE 1B)

If the patient's partner is found to have no mutations of the HFE genes, then the children will not absolutely require screening.

At present there are no guidelines, as to the minimum age for diagnosis and treatment, to prevent complications.

Screening should include fasting iron studies and genotyping. ^{(2)(2a)(33)}

Possible consequences of genetic testing in relation to life insurance should be explained. ^{(2)(3)(2a)}

Insurance

Under the Disability Act of 2005, the processing of genetic data from applicants for a variety of Life Insurances is prohibited. Therefore application or other forms which ask health related questions of an individual or his/ her doctor should not include any question concerning genetic tests. It should be made clear on any relevant form, that neither the applicant nor their doctor should disclose the result of a genetic test.

An Insurer may not require an applicant to undergo a genetic test. Should a genetic test result come into the possession of an Insurer, it must be ignored and not taken into account in any way.

See Also: The Society of Actuaries in Ireland Briefing Statement on Insurance Provisions in the Disability Bill 2004 (<http://www.actuaries.ie>).

Conclusion

HH is an inherited iron overload condition. It is the commonest genetic disease amongst Caucasians, especially those of Celtic origin and is particularly frequent in Ireland. Patients are predominantly men aged between 40 and 65. Early detection and treatment prevents organ damage and allows a normal life expectancy. HH is particularly amenable to diagnosis, treatment and ongoing follow-up in the Primary Care setting. Treatment is by venesection, which is feasible, if time consuming, in General Practice. Unfortunately venesection is not covered under the GMS contract.

References

- (1) GRADE Working Group. Grading quality of evidence and strength of recommendations. 2004; Available at: http://www.gradeworkinggroup.org/publications/Grading_evidence_and_recommendations_BMJ.pdf. Accessed 01/12, 2013.
- (2) Adams P, Brissot P, Powell LW. EASL International Consensus Conference on Haemochromatosis. *J.Hepatol.* 2000 Sep;33(3):485-504.
- (2a) European Association for the Study of the Liver (EASL). EASL Clinical practice guidelines for HFE Hemochromatosis. 2010; Available at: http://www.easl.eu/assets/application/files/03d32880931aac9_file.pdf. Accessed 12/01, 2013.
- (3) Bacon BR, Adams PC, Kowdley KV, Powell LW, Tavill AS, American Association for the Study of Liver Diseases. Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology* 2011 Jul;54(1):328-343.
- (4) Rosmorduc O, Poupon R, Nion I, Wendum D, Feder J, Berezziat G, et al. Differential HFE allele expression in hemochromatosis heterozygotes. *Gastroenterology* 2000 Oct;119(4):1075-1086.
- (5) Merryweather-Clarke AT, Pointon JJ, Shearman JD, Robson KJ. Global prevalence of putative haemochromatosis mutations. *J.Med.Genet.* 1997 Apr;34(4):275-278.
- (6) Rochette J, Pointon JJ, Fisher CA, Perera G, Arambepola M, Arichchi DS, et al. Multicentric origin of hemochromatosis gene (HFE) mutations. *Am.J.Hum.Genet.* 1999 Apr;64(4):1056-1062.
- (7) Ropero P, Briceno O, Mateo M, Polo M, Mora A, Gonzalez FA, et al. Frequency of the C282Y and H63D mutations of the hemochromatosis gene (HFE) in a cohort of 1,000 neonates in Madrid (Spain). *Ann.Hematol.* 2006 May;85(5):323-326.
- (8) Ryan E, O'keane C, Crowe J. Hemochromatosis in Ireland and HFE. *Blood Cells Mol.Dis.* 1998 Dec;24(4):428-432.
- (9) Ryan F, Vaughan J. Haemochromatosis mutation analysis in a normal Irish population. *Br.J.Biomed.Sci.* 2000;57(4):315-316.
- (10) Lucotte G. Celtic origin of the C282Y mutation of hemochromatosis. *Blood Cells Mol.Dis.* 1998 Dec;24(4):433-438.
- (11) Rosenberg W, Howell M, Roderick P, Eccles D, Day I. Hereditary haemochromatosis should be more widely known about. *BMJ* 1999 May 29;318(7196):1486-1487.
- (12) 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 Apr 28;352(17):1769-1778.
- (13) Aguilar-Martinez P, Bismuth M, Picot MC, Thelcide C, Pageaux GP, Blanc F, et al. Variable phenotypic presentation of iron overload in H63D homozygotes: are genetic modifiers the cause? *Gut* 2001 Jun;48(6):836-842.
- (14) Sham RL, Raubertas RF, Braggins C, Cappuccio J, Gallagher M, Phatak PD. Asymptomatic hemochromatosis subjects: genotypic and phenotypic profiles. *Blood* 2000 Dec 1;96(12):3707-3711.
- (15) Olynyk JK, Cullen DJ, Aquilia S, Rossi E, Summerville L, Powell LW. A population-based study of the clinical expression of the hemochromatosis gene. *N.Engl.J.Med.* 1999 Sep 2;341(10):718-724.

- (16) Crawford DH, Powell LW, Halliday JW. Factors influencing disease expression in hemochromatosis. *Annu.Rev.Nutr.* 1996;16:139-160.
- (16a) Allen KJ, Gurrin LC, Constantine CC, Osborne NJ, Delatycki MB, Nicoll AJ, et al. Iron-overload-related disease in HFE hereditary hemochromatosis. *N.Engl.J.Med.* 2008 Jan 17;358(3):221-230.
- (16b) Asberg A, Hveem K, Thorstensen K, Ellekjer E, Kannelonning K, Fjosne U, et al. Screening for hemochromatosis: high prevalence and low morbidity in an unselected population of 65,238 persons. *Scand.J.Gastroenterol.* 2001 Oct;36(10):1108-1115.
- (16c) Rossi E, Jeffrey GP. Clinical penetrance of C282Y homozygous HFE haemochromatosis. *Clin.Biochem.Rev.* 2004 Aug;25(3):183-190.
- (17) Burt MJ, George PM, Upton JD, Collett JA, Frampton CM, Chapman TM, et al. The significance of haemochromatosis gene mutations in the general population: implications for screening. *Gut* 1998 Dec;43(6):830-836.
- (18) McDonnell SM, Preston BL, Jewell SA, Barton JC, Edwards CQ, Adams PC, et al. A survey of 2,851 patients with hemochromatosis: symptoms and response to treatment. *Am.J.Med.* 1999 Jun;106(6):619-624.
- (19) Niederau C, Fischer R, Purschel A, Stremmel W, Haussinger D, Strohmeyer G. Long-term survival in patients with hereditary hemochromatosis. *Gastroenterology* 1996 Apr;110(4):1107-1119.
- (20) Ajioka RS, Kushner JP. Clinical consequences of iron overload in hemochromatosis homozygotes. *Blood* 2003 May 1;101(9):3351-3; discussion 3354-8.
- (21) Scotet V, Le Gac G, Merour MC, Mercier AY, Chanu B, Ka C, et al. Impact of HFE genetic testing on clinical presentation of hereditary hemochromatosis: new epidemiological data. *BMC Med.Genet.* 2005 Jun 1;6:24.
- (22) McCurdie I, Perry JD. Haemochromatosis and exercise related joint pains. *BMJ* 1999 Feb 13;318(7181):449-451.
- (22a) Timms AE, Sathananthan R, Bradbury L, Athanasou NA, Wordsworth BP, Brown MA. Genetic testing for haemochromatosis in patients with chondrocalcinosis. *Ann.Rheum.Dis.* 2002 Aug;61(8):745-747.
- (23) Morrison ED, Kowdley KV. Genetic liver disease in adults. Early recognition of the three most common causes. *Postgrad.Med.* 2000 Feb;107(2):147-52, 155, 158-9.
- (24) Willis G, Bardsley V, Fellows IW, Lonsdale R, Wimperis JZ, Jennings BA. Hepatocellular carcinoma and the penetrance of HFE C282Y mutations: a cross sectional study. *BMC Gastroenterol.* 2005 Jun 1;5:17.
- (25) Willis G, Wimperis JZ, Lonsdale R, Fellows IW, Watson MA, Skipper LM, et al. Incidence of liver disease in people with HFE mutations. *Gut* 2000 Mar;46(3):401-404.
- (25a) Gleeson F, Ryan E, Barrett S, Crowe J. Clinical expression of haemochromatosis in Irish C282Y homozygotes identified through family screening. *Eur.J.Gastroenterol.Hepatol.* 2004 Sep;16(9):859-863.
- (26) Pereira AC, Cuoco MA, Mota GF, da Silva FF, Freitas HF, Bocchi EA, et al. Hemochromatosis gene variants in patients with cardiomyopathy. *Am.J.Cardiol.* 2001 Aug 15;88(4):388-391.
- (26a) Rosenqvist M, Hultcrantz R. Prevalence of a haemochromatosis among men with clinically significant bradyarrhythmias. *Eur.Heart J.* 1989 May;10(5):473-478.

- (27) Salonen JT, Tuomainen TP, Kontula K. Role of C282Y mutation in haemochromatosis gene in development of type 2 diabetes in healthy men: prospective cohort study. *BMJ* 2000 Jun 24;320(7251):1706-1707.
- (28) Tweed MJ, Roland JM. Haemochromatosis as an endocrine cause of subfertility. *BMJ* 1998 Mar 21;316(7135):915-916.
- (28a) Egger NG, Goeger DE, Payne DA, Miskovsky EP, Weinman SA, Anderson KE. Porphyria cutanea tarda: multiplicity of risk factors including HFE mutations, hepatitis C, and inherited uroporphyrinogen decarboxylase deficiency. *Dig.Dis.Sci.* 2002 Feb;47(2):419-426.
- (28b) Ellervik C, Birgens H, Tybjaerg-Hansen A, Nordestgaard BG. Hemochromatosis genotypes and risk of 31 disease endpoints: meta-analyses including 66,000 cases and 226,000 controls. *Hepatology* 2007 Oct;46(4):1071-1080.
- (29) Ashrafian H. Hcpidin: the missing link between hemochromatosis and infections. *Infect.Immun.* 2003 Dec;71(12):6693-6700.
- (30) Edwards CQ, Kelly TM, Ellwein G, Kushner JP. Thyroid disease in hemochromatosis. Increased incidence in homozygous men. *Arch.Intern.Med.* 1983 Oct;143(10):1890-1893.
- (31) Murphy MS, Walsh CH. Thyroid disease in patients with genetic haemochromatosis: a prospective study. *Endocrine Abstracts* 2002;3:308.
- (32) Pawlotsky Y, Le Dantec P, Moirand R, Guggenbuhl P, Jouanolle AM, Catheline M, et al. Elevated parathyroid hormone 44-68 and osteoarticular changes in patients with genetic hemochromatosis. *Arthritis Rheum.* 1999 Apr;42(4):799-806.
- (32a) Allaby M. Screening for Heamochromatosis: A report for the UK National Screening Committee. 2009; Available at: www.screening.nhs.uk/policydb_download.php?doc=71. Accessed 12/01, 2013.
- (33) Dooley JD, Worwood MP, British Society for Haematology. Genetic Haemochromatosis. British Committee for Standards in Haematology: Guidelines for diagnosis & therapy. Version 1.0 ed. Oxfordshire: Darwin Medical Communications Ltd; 2000. p. 38.
- (34) The UK Haemochromatosis Consortium. A simple genetic test identifies 90% of UK patients with haemochromatosis. The UK Haemochromatosis Consortium. *Gut* 1997 Dec;41(6):841-844.
- (35) Scotet V, Merour MC, Mercier AY, Chanu B, Le Faou T, Ragueneas O, et al. Hereditary hemochromatosis: effect of excessive alcohol consumption on disease expression in patients homozygous for the C282Y mutation. *Am.J.Epidemiol.* 2003 Jul 15;158(2):129-134.
- (35a) Fletcher LM, Dixon JL, Purdie DM, Powell LW, Crawford DH. Excess alcohol greatly increases the prevalence of cirrhosis in hereditary hemochromatosis. *Gastroenterology* 2002 Feb;122(2):281-289.
- (36) Kaltwasser JP, Werner E, Schalk K, Hansen C, Gottschalk R, Seidl C. Clinical trial on the effect of regular tea drinking on iron accumulation in genetic haemochromatosis. *Gut* 1998 Nov;43(5):699-704.
- (37) Sanchez AM, Schreiber GB, Bethel J, McCurdy PR, Glynn SA, Williams AE, et al. Prevalence, donation practices, and risk assessment of blood donors with hemochromatosis. *JAMA* 2001 Sep 26;286(12):1475-1481.
- (38) Pennings G. Demanding pure motives for donation: the moral acceptability of blood donations by haemochromatosis patients. *J.Med.Ethics* 2005 Feb;31(2):69-72.

- (39) Emery J, Rose P, Harcourt J, Livesey K, Merryweather-Clarke A, Pointon JJ, et al. Pilot study of early diagnosis of hereditary haemochromatosis through systematic case finding in primary care. *Community Genet.* 2002;5(4):262-265.
- (39a) Davis TM, Beilby J, Davis WA, Olynyk JK, Jeffrey GP, Rossi E, et al. Prevalence, characteristics, and prognostic significance of HFE gene mutations in type 2 diabetes: the Fremantle Diabetes Study. *Diabetes Care* 2008 Sep;31(9):1795-1801.
- (39b) Njajou OT, Alizadeh BZ, Vaessen N, Vergeer J, Houwing-Duistermaat J, Hofman A, et al. The role of hemochromatosis C282Y and H63D gene mutations in type 2 diabetes: findings from the Rotterdam Study and meta-analysis. *Diabetes Care* 2002 Nov;25(11):2112-2113.
- (39c) Acton RT, Barton JC, Passmore LV, Adams PC, Speechley MR, Dawkins FW, et al. Relationships of serum ferritin, transferrin saturation, and HFE mutations and self-reported diabetes in the Hemochromatosis and Iron Overload Screening (HEIRS) study. *Diabetes Care* 2006 Sep;29(9):2084-2089.
- (39d) Halsall DJ, McFarlane I, Luan J, Cox TM, Wareham NJ. Typical type 2 diabetes mellitus and HFE gene mutations: a population-based case - control study. *Hum.Mol.Genet.* 2003 Jun 15;12(12):1361-1365.
- (40) Seamark CJ, Hutchinson M. Should asymptomatic haemochromatosis be treated? Update from Seamark and Hutchinson. *BMJ* 2000 Oct 14;321(7266):956.
- (41) Byrnes V, Ryan E, Barrett S, Kenny P, Mayne P, Crowe J. Genetic hemochromatosis, a Celtic disease: is it now time for population screening? *Genet.Test.* 2001 Summer;5(2):127-130.
- (42) Bulaj ZJ, Ajioka RS, Phillips JD, LaSalle BA, Jorde LB, Griffen LM, et al. Disease-related conditions in relatives of patients with hemochromatosis. *N.Engl.J.Med.* 2000 Nov 23;343(21):1529-1535.
- (43) Tuomainen TP, Kontula K, Nyyssönen K, Lakka TA, Helio T, Salonen JT. Increased risk of acute myocardial infarction in carriers of the hemochromatosis gene Cys282Tyr mutation : a prospective cohort study in men in eastern Finland. *Circulation* 1999 Sep 21;100(12):1274-1279.
- (44) Roest M, van der Schouw YT, de Valk B, Marx JJ, Tempelman MJ, de Groot PG, et al. Heterozygosity for a hereditary hemochromatosis gene is associated with cardiovascular death in women. *Circulation* 1999 Sep 21;100(12):1268-1273.
- (45) World Health Organisation (WHO). Use of glycated HbA1c in diagnosis of diabetes mellitus, WHO 2011. http://www.who.int/diabetes/publications/report-hba1c_2011.pdf. Accessed 12/02, 2013.
- (46) John WG. Use of haemoglobin (HbA1c) in the diagnosis of diabetes mellitus:The implementation of World Health Organisation guidance 2011. 2011; Available at: <http://onlinelibrary.wiley.com/doi/10.1111/j.1464-5491.2012.03762.x/pdf>. Accessed 12/01, 2013.
- (47) Beaton MD, Adams PC. Treatment of hyperferritinemia. *Ann.Hepatol.* 2012 May-Jun;11(3):294-300.

Appendix 1: Differential Diagnosis of Haemochromatosis ⁽²⁾

Acquired iron overload:

- Fatty liver
- Iron loading anaemias
- Thallassaemia major
- Sideroblastic anaemia
- Chronic haemolytic anaemia's
- Transfusional and parenteral iron overload
- Dietary iron overload
- Chronic liver disease
- Hepatitis C
- Alcoholic cirrhosis
- Non alcoholic steatohepatitis
- Porphyria Cutanea Tarda
- Dysmetabolic iron overload syndromes
- Post porta caval shunting

Miscellaneous conditions:

- Iron overload in sub Sahara Africa
- Neonatal iron overload – a congenital alloimmune hepatitis
- Aceruloplasminaemia
- Congenital Atransferrinaemia

Table 1. Causes and spectrum of hyperferritinemia.

<ul style="list-style-type: none"> Serum ferritin 300-1,000 µg/L. Metabolic syndrome/NAFLD. Daily alcohol consumption. Systemic inflammation. Early hemochromatosis. Malignancy. Unknown.
<ul style="list-style-type: none"> Serum ferritin 1,000-5,000 µg/L. Hemochromatosis. Aceruloplasminemia. Ferroportin mutations. Hereditary-hyperferritinemia cataract syndrome (HHCS). Alcoholic liver disease. Viral hepatitis. Secondary iron overload. <ul style="list-style-type: none"> Transfusion related. Ineffective erythropoiesis.
<ul style="list-style-type: none"> Serum ferritin > 10,000 µg/L. Still's disease. Histiocytosis. Fulminant hepatic failure.

Table 2. Mechanisms of hyperferritinemia in various disorders.

<ul style="list-style-type: none"> Increased ferritin synthesis: <ul style="list-style-type: none"> HFE and other types of hemochromatosis. Anemias (heritable and acquired) associated with ineffective erythropoiesis. Aceruloplasminemia. Iron overload secondary to blood transfusion or parenteral iron administration.
<ul style="list-style-type: none"> Increased ferritin release from injured cells: <ul style="list-style-type: none"> Hepatic steatosis and steatohepatitis (alcoholic and nonalcoholic). Chronic viral hepatitis. Massive liver necrosis (ie. due to sepsis, acute hepatitis or toxic injury). Autoimmune and rheumatologic disorders. Acute and chronic infections. Splenic infarction.
<ul style="list-style-type: none"> Increased apoferitin (or L ferritin) synthesis or secretion: <ul style="list-style-type: none"> Chronic ethanol ingestion. Malignancy (malignant histiocytosis, carcinomas of lung, breast, ovary, kidney; lymphoma, liposarcoma). Gaucher disease. Reactive histiocytosis. Hereditary hyperferritinemia-cataract syndrome (HHCS).

In the majority of cases, Hyperferritinaemia does not represent true iron overload.

Appendix 3: Protocol for Venesection

Venesection should be tailored to the individuals requirements**. Patients should be instructed to rest immediately before the Venesection for 15 minutes, and drink 500 ml of fluid.

Full blood count and Ferritin are taken during alternate Venesections, until approaching target values, then take on each occasion. Venesection should take place weekly until the Ferritin is less than 250 ng/ml, and then monthly until Ferritin has reduced to less than 50 ng/ml. As the target figure is approached, Ferritin needs to be repeated more frequently to prevent development of iron deficiency anaemia. Levels less than 25 ng/ml indicate iron deficiency and require a temporary hold on venesection. Transferrin Saturation usually remains elevated until iron stores are depleted.

*** Special precautions may need to be taken for patients on Beta-blockers, as they may be susceptible to syncope.*

Protocol

1. Lie Patient semi prone or prone, with arm extended and resting comfortably.
2. Wash hands.
3. Record resting Blood Pressure and pulse.
4. Locate vein and apply tourniquet above site.
5. Glove up, clean site skin with Alcohol Swab, introduce Collecting Set needle, secure with Tape, hang blood-bag below bedside for good flow.
6. Draw required amount, (usually 450 to 500 ml). Remove tourniquet.
7. Take Serum Ferritin and Transferrin Saturation if indicated.
Take via the separate portal on the Venesection Bag, if available.
8. Apply gauze to site, tape in position, and remove needle. Press until bleeding stops.
9. Clip blood-bag tube firmly. Cut off needle (if attached) and dispose in Sharps Bin.
10. Place blood- bag into Placenta Bin and dispose.
11. Check Blood pressure and pulse.
12. After treatment the patient should stand up slowly and sit in a chair for 15 minutes, keeping pressure on the arm where the needle was sited . Offer a glass of water, to offset the hypovolemia.
13. Fill in patient record card, with quantity drawn, etc.
14. Instruct patient to monitor the dressing for bleeding or swelling, and not to lift heavy objects for 24 hours.
15. Advise the patient is to avoid strenuous exercise for 24 hours.

Appendix 4: Continuation Sheet for Patients with HH

NAME: _____ DOB: _____

ADDRESS: _____

FAMILY: Parents: _____ Partner: _____

Siblings: _____ Children: _____

GENETIC PROFILE: _____ Year of diagnosis: _____ Venesection: _____

C2 H5OH _____ Cigs _____

Current symptoms

Fatigue

Skin

Arthralgia

Diabetes Mellitus

CVS disease

Liver Disease

Sexual dysfunction:

BP

Pulse

Results date						
Haemoglobin						
Haematocrit						
Transferrin saturation						
Ferritin						
Blood Sugar						
LFT's						
Lipid Profile						
Liver Biopsy						
ECG						
X-ray						

Appendix 5: Iron Rich Foods⁽²⁾

Offal	Liver, Kidney, Heart.
Meat	Black Pudding, Liver sausages, Liver Pate, 100% Beef Burgers.
Red Meats	Beef, Corned Beef, Lamb, Pork, Mutton.
Fish	Sardines, Salmon, Tuna, Crab, Pilchards.

Lesser sources of iron include:

Eggs

Wholemeal bread especially fortified wholemeal bread

Fortified wholegrain breakfast cereal: eg. Branflakes, All-Bran.

Dark green leafy vegetables e.g. Cabbage, Brussels Sprouts, Spinach, Kale, Broccoli.

Wholegrain rice/pasta

Pulses: Peas, Beans, Lentils.

Dried Fruit,

Bovril

Cocoa

Vegetarian Marmite

The absorption of iron from these foods is increased by including a Vitamin C source in the same meal.

Rich Vitamin C sources are as follows:-

- Fortified Fruit Juices
- Orange, Grapefruit, Lemon
- Tomatoes
- Vegetables such as Green Peppers
- Salads

As can be seen from the above, advising an Iron Deficient Diet would be almost impossible and indeed unwise.

Appendix 6: Glossary of Terms and Abbreviations

HH	Hereditary Haemochromatosis
EASL	European Association for the study of the Liver
AASDL	American Association for the study of Liver diseases
IBTS	Irish Blood Transfusion Service
HSE	Health Service Executive



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