Clinical Standard Operating Procedure (SOP) for Adults and Children

DIAGNOSIS AND MANAGEMENT OF GENETIC HAEMOCHROMATOSIS

SETTING	Trust-wide
FOR STAFF	All multidisciplinary staff caring for patients with Haemochromatosis
PATIENTS	Adult patients

Investigation of a raised ferritin

Serum ferritin level is one of the most commonly requested investigations in both primary and secondary care. Whilst low serum ferritin levels invariably indicate reduced iron stores, raised serum ferritin levels can be due to multiple different aetiologies, including iron overload, inflammation, liver or renal disease, malignancy, alcohol excess and metabolic syndrome. A key test in the further investigation of an unexpected raised serum ferritin is the serum transferrin saturation. A raised fasting transferrin saturation suggests iron accumulation which can be inherited (Hereditary Haemochromatosis) or acquired (for example due to chronic haemolysis or anaemia or multiple red cell transfusions).

Initial assessment should include clinical review of any potentially secondary causes including alcohol consumption, infection, inflammation, neoplasm and enquiry of family history

First line investigations (e.g. in primary care) should include FBC, LFTs, Renal, CRP and fasting transferrin Saturation (TSAT)

If Ferritin is raised with normal TSAT then consider inflammation, DM, EtOH, liver dysfunction, metabolic syndrome. Check BP, BMI, CRP, GGT, Glucose, triglycerides, cholesterol and consider USS liver.

If ferritin is significantly raised with no obvious secondary cause and the patient has a family history (+/-) cataracts then consider the extended genetic testing (DNA sent to Oxford for causes of hereditary hyperferritinaemia).

If ferritin raised with raised TSAT (ideally twice) >50% male and >40% female then request HFE gene analysis: usually C282Y homozygote, though rarely due to compound heterozygosity for C282Y/H63D (or C282Y/S65C)

In iron-loaded patients without C282Y, consider Fe-loading anaemias (check FBC, retics, LDH, film and consider Hb electrophoresis or marrow), or primary liver pathology (e.g. NAFLD). If LFTs or USS liver abnormal then refer to hepatology. If there remains no obvious cause then further investigations may include extended genetic testing (DNA and form sent to Oxford) or MRI T2* to assess and quantitate liver and cardiac tissue iron (this can be requested on ice on the MRI for congenital cardiac anomaly tab and state for investigation of iron overload).

Extended genetic testing may also be appropriate in some patients with unexplained hyperferritinaemia (normal TSAT), particularly if a history of cataracts or family history.

Patients with confirmed Hereditary Haemochromatosis (HFE homozygote or compound heterozygote)
Take a detailed history to assess for iron related symptoms:

- Weakness/Tiredness
- Pigmentation
- Arthralgia/Arthritis
- Osteoporosis
- Diabetes
- Abdominal pain
- Cirrhosis
- Impotence (men)
- Heart Disease
- Loss of libido
- Thyroid

Give the patient an information leaflet
Assess suitability for future NHSBT blood donation
Advise to optimise lifestyle factors (alcohol, diet etc)
Advise to avoid over the counter supplements that contain iron
HFE H63D is a prevalent genotype in the general population and a weaker risk factor for mild iron overload. The clinical value of genotyping for this variant remains controversial. Therefore, other causes of a raised ferritin should be considered in patients who are HFE C282Y/H63D compound heterozygote or H63D homozygotes. If there is evidence of iron overload (fasting TSAT is also raised +/- MRI T2*) then these patients will be managed in the same way as C282Y homozygotes but the evidence for benefit is less clear.

Assess tissue damage
FBC, Ferritin, Transferrin Saturation
Liver function tests, including baseline alpha-Fetoprotein
Endocrine tests: Glucose, HbA1c, TFTs, Testosterone ( ).
Liver ultrasound if LFTs abnormal
Joint X-rays of any painful joints
ECG; consider echocardiogram if any cardiac symptoms/signs

Referral to hepatology indicated if
Ferritin >1000µg/L, or hepatomegaly, or raised ALT
They will arrange fibroscan and other investigations

Genetic/Family studies
Offer Ferritin, Tfn Sat & HFE gene studies to all siblings; document in notes and a clinic letter
If > 1 child, consider HFE testing other parent before suggesting testing child
Children should not generally be screened before age 18 yrs (i.e. to be done with their own consent)

Management of hereditary haemochromatosis

Venesection management should be individualised according to initial presenting iron loading, organ damage, age and comorbidity. For example, venesection may not be indicated in elderly frail patients or those with a short life expectancy. In addition, venesection strategy and aims will be gentler for patients picked up by family screening who have minimal iron loading compared to those presenting with end organ damage as a consequence of iron.

'Enhanced liver follow-up' for those with cirrhosis or advanced fibrosis at presentation
alpha-Fetoprotein and liver ultrasound, every 6/12 (screening for hepatocellular cancer)
These patients should be in liver clinic follow-up to arrange these tests

Initial Management of Fe overload (nurse-led service)

Venesect 500ml weekly if tolerated (↓ in elderly, CVS disease or treatment)
Contact Dr for advice if patient symptomatic post-venesection (may need IV fluid replacement or omission of antihypertensive)
Monitor FBC with each venesection: reduce frequency of venesection (e.g. to fortnightly) if Hb becomes < 110g/L or >20g/L less than baseline.
Measure Ferritin monthly; consider ↓ venesection frequency to monthly when Ferritin <150µg/L especially in elderly frail etc
When Ferritin <50µg/L start maintenance programme
If venesections are poorly tolerated or venous access difficulties are problematic then consider referral for haematology consultant review in clinic

Maintenance of normal Fe status (nurse-led service)

Start when patient is confirmed to have low/normal Fe status (Ferritin <50µg/L).
Consider whether patient is suitable for blood donations by NHSBT (a standard letter is available from NHSBT and email patient specific form [redacted]
Patients will require annual ferritin
Specialist nurse to estimate venesection frequency that will keep Ferritin 50-100µg/L.
Venesect every 2-4 months, checking FBC, LFTs & Ferritin at each visit for first year. At subsequent visits, check FBC at each visit, and ferritin and LFTs 6-12 monthly.
Check TSATs only in selected patients eg those where the ferritin is not dropping to the desired threshold.
For some patients more stringent targets may be chosen to maintain ferritin <50 and TSAT<50%
If Ferritin rises to > 150µg/L, consider ↑ frequency of venesection
If Ferritin falls to <50µg/L or Hb falls below normal recheck ferritin in 3-4 months before re-initiating and ↓ frequency venesection.
All patients will have an annual nurse-led review, ideally with recent ferritin.
Patients do not need regular follow up in the medical clinic but can be re-referred as needed.
If patient on 'enhanced liver follow-up', ensure from time to time that the patient is attending liver clinic and having AFP and ultrasound x2/year

Stopping/Pausing Venesection

At annual review a risk-benefit should be documented especially in elderly/frail patients. Any decision on stopping venesections can be discussed with the medical team.
Hold off venesections 3 months prior to major surgery and in pregnancy

FURTHER INFORMATION / QUERIES

Haemophilia Centre Consultants: [redacted] – Contact via switchboard

Haemophilia Specialist Nurses – Ext: [redacted] or Mobile: [redacted]

Haemophilia SpR – Bleep: [redacted]

Out of hours Haematology Unit – Ext: [redacted]

References

European Association for the Study of the Liver. EASL Clinical Practice Guidelines on haemochromatosis. J Hepatol. 2022 Aug;77(2):479-502. doi: 10.1016/j.jhep.2022.03.033. Epub 2022 Jun 1. PMID: 35662478.

BSH guideline: The investigation and management of a raised serum ferritin. BJH 2018, 181, 331–340

BSH guideline: Diagnosis and therapy of genetic haemochromatosis BJH 2018, 181, 293–303

Table A

REFERENCES	European Association for the Study of the Liver. EASL Clinical Practice Guidelines on haemochromatosis. J Hepatol. 2022 Aug;77(2):479-502. doi: 10.1016/j.jhep.2022.03.033. Epub 2022 Jun 1. PMID: 35662478. BSH guideline: The investigation and management of a raised serum ferritin. BJH 2018, 181, 331–340 BSH guideline: Diagnosis and therapy of genetic haemochromatosis BJH 2018, 181, 293–303
RELATED DOCUMENTS AND PAGES	Haemochromatosis Venesection SOP
AUTHORISING BODY	
SAFETY	Safe monitoring of high and low ferritin levels
QUERIES AND CONTACT	Bristol Haemophilia Centre [redacted]
AUDIT REQUIREMNTS	

Plan Elements	**Plan Details**
The Dissemination Lead is:	[redacted]
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Date of Version	Version Number	Lead for Revisions	Type of Revision	Description of Revision
15/02/2023	0.00	[redacted]	-	New SOP