OPEN ACCESS

Venesection treatment in haemochromatosis – current best practice from the BSG/BASL Special Interest Group

Prabhsimran Singh ,[1,2] Gerri Mortimore,[3] Kim Hicks,[4] Natasha McDonald ,[5] Johnny Cash ,[6] Lisa Lowry,[7] William Griffiths,[8] Jeremy Shearman[9,10]

ABSTRACT

Haemochromatosis is the most common single gene disorder affecting the population of the UK, resulting in iron overload and organ damage. Venesection (therapeutic phlebotomy) has been the primary treatment offered to patients for more than half a century. Despite the prevalence of the condition in the UK, there has been little progress in new treatments being offered over this time. Moreover, there is a lack of robust research to guide the optimal frequency, timing and treatment targets for venesection treatment in haemochromatosis.

Retrospective cohort studies established a clear mortality benefit when treatment is commenced before the development of liver cirrhosis—assumed to be due to limiting the progression of liver disease and development of hepatocellular carcinoma. However, the benefit of venesection on symptoms of haemochromatosis lacks quality evidence.

In this best practice description, we review the currently available literature on the benefits and limitations of venesection treatment. We describe current practice as reflected by the experiences of a multidisciplinary team of professional members of the British Society of Gastroenterology/British Association for the Study of the Liver haemochromatosis Special Interest Group. We describe a framework and recommendations for treatment in addition to describing the management of treatment side effects and complications. Through this work and the establishment of consistency in treatment, patients will benefit from better evidence-based care and the profession will be better able to identify the potential value of future treatments.

KEY POINTS

⇒ Haemochromatosis refers to genetic iron overload most commonly seen in patients of Northern European heritage who are homozygous for pC282Y genetic variant.

⇒ Patients with haemochromatosis and evidence of biochemical iron overload (raised serum ferritin±transferrin saturation) should be commenced on treatment with venesection regardless of symptoms or organ dysfunction.

⇒ Treatment with venesection improves mortality and reduces morbidity from liver disease, but there is limited evidence regarding its benefit in the setting of symptoms and other organ damage.

⇒ Patients undergoing maintenance venesection can be directed to explore blood donation, depending on the individual eligibility criteria of the national blood transfusion service.

⇒ Patients undergoing venesection for haemochromatosis should be reviewed annually to assess their venesection requirement (ie, treatment frequency) and assess for potential disease complications.

⇒ Venesection can be paused during any significant intercurrent illness (such as surgery, cancer treatment, etc), with reassessment after a period to establish if or when treatment should be restarted.

⇒ Further research is required to establish optimal venesection treatment targets and frequencies, its impact on morbidity and quality of life and how newer molecular therapies will fit into current pathways considering their potential cost.

INTRODUCTION

Venesection (or therapeutic phlebotomy) refers to the removal of blood with the intention of altering the natural history of a disease. Although 'bloodletting' was

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/flgastro-2025-103172).

[1]Department of Hepatology, York and Scarborough Teaching Hospitals NHS Foundation Trust, York, UK
[2]Hull York Medical School, York, UK
[3]University of Derby, Derby, UK
[4]Royal Cornwall Hospitals NHS Trust, Truro, UK
[5]NHS Lanarkshire, Bothwell, UK
[6]Belfast Health and Social Care Trust, Belfast, UK
[7]Somerset NHS Foundation Trust, Taunton, UK
[8]Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK
[9]South Warwickshire University NHS Foundation Trust, Warwick, UK
[10]Warwick Medical School, Coventry, UK

Correspondence to
Dr Jeremy Shearman; Jeremy.Shearman@warwick.ac.uk

Received 23 March 2025
Accepted 21 May 2025

Check for updates

To cite: Singh P, Mortimore G, Hicks K, *et al*. *Frontline Gastroenterology* Epub ahead of print: [please include Day Month Year]. doi:10.1136/flgastro-2025-103172

widely practised for a range of maladies in the past, venesection now has a limited range of clinical indications—the most common of which is the treatment of haemochromatosis.

Since the identification of the *HFE* gene in 1996, great progress has been made in delineating the molecular intermediaries involved in mammalian iron metabolism and haemochromatosis has been confirmed as the most common single gene systemic disorder to affect Northern Europeans. Despite this, there has been limited progress in the treatments being offered for haemochromatosis, as well as a lack of research studies on current treatments to guide clinicians on optimal patient management.

This document will outline the established basis for venesection treatment and published evidence for its benefit. It will describe current treatment methodology and best practice as reflected by the experiences of medical and nursing members of the British Society of Gastroenterology (BSG)/British Association for the Study of the Liver (BASL)/British Society of Haematology (BSH) Haemochromatosis Special Interest Group, but the recommendations are applicable to the care of haemochromatosis in other countries. This document is approved by the BSG Liver Section, CSSC and the BASL team. We describe opportunities for research and the potential development of targeted molecular treatments that might one day augment, if not replace, one of the most ancient treatments practised by humans.

HAEMOCHROMATOSIS: CASE DEFINITION

Genetic predisposition

Haemochromatosis (previously referred to as genetic or hereditary haemochromatosis) is the most common genetic condition to affect people of a Northern European heritage. The hereditary nature of the condition was established in 1977[1] and the molecular basis was established with the identification of the pC282Y genetic variant in the *HFE* gene in 1996.[2] Homozygosity for pC282Y was strongly associated with haemochromatosis in the UK,[3] and the presence of this genotype now underpins the diagnosis of the condition.

Although the exact function of the *HFE* gene product remained obscure for a number of years, it is now clear that in haemochromatosis a defective *HFE* protein fails to engage with transferrin receptor 2. This in turn leads to a blunted production of hepcidin in response to high iron loads and a failure to inhibit release of iron from duodenal enterocytes and macrophages through ferroportin, effectively negating the feedback suppression of dietary iron absorption. In the absence of any physiological mechanism for iron excretion, unchecked absorption ultimately leads to iron overload and organ damage (figure 1).

Data from UK Biobank have confirmed the very high prevalence of pC282Y in the UK with homozygosity prevalence of 0.6%.[4] Therefore, roughly 1:156 or as many as 340–400 000 000 of the UK population have the genetic predisposition to accumulate iron. Iron accumulation is associated with significant harm. Historical descriptions of haemochromatosis

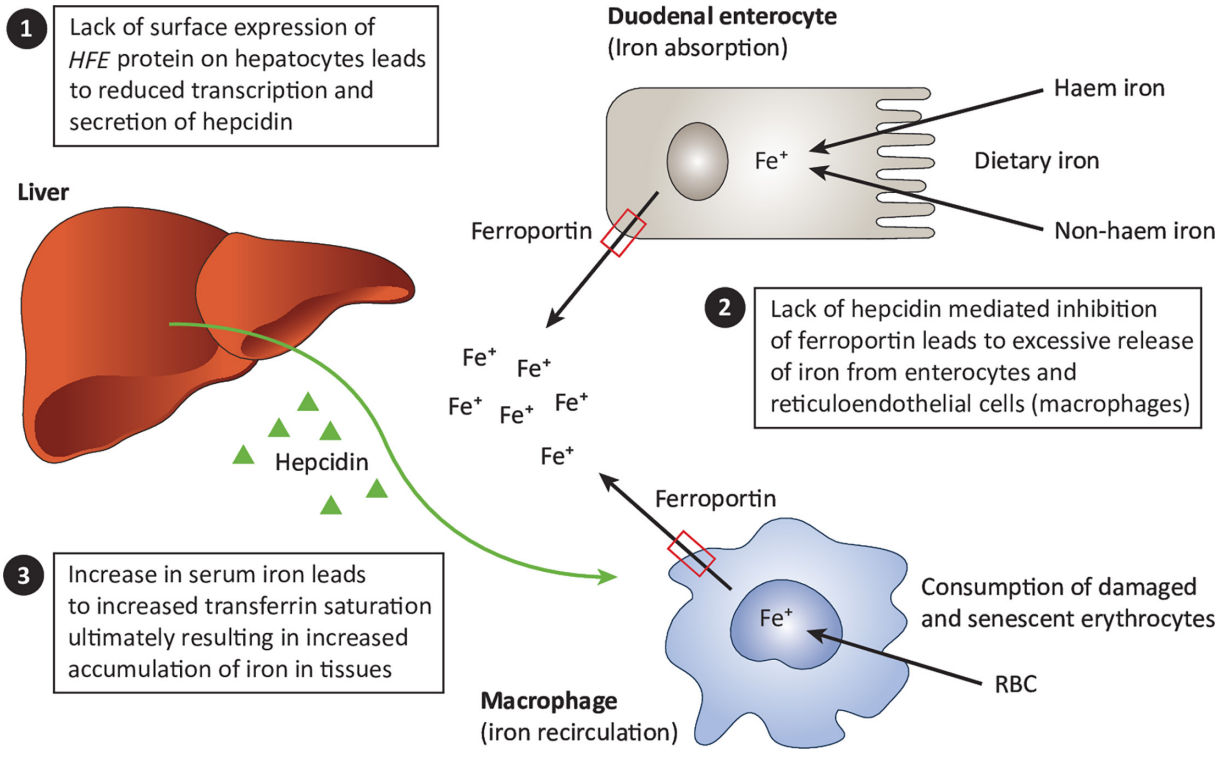

Figure 1 Schematic depicting the underlying pathophysiology of haemochromatosis. RBC, red blood cell.

described it as 'bronzed diabetes' and it was associated with a poor prognosis.[5] Over recent decades, the diagnosis of haemochromatosis has been made at an ever earlier stage in its natural history, which has led to a significant improvement in prognosis. However, the diagnosis is still an important one, as late diagnosis is associated with significant morbidity.[6]

In the original paper reporting the identification of the *HFE* gene, a second 'minor' mutation, pH63D, was described.[2] This variant was identified in association with pC282Y in a small number of the original cohort of patients with haemochromatosis (referred to as 'compound heterozygotes') from the USA. The contribution/significance of this variant to haemochromatosis and iron overload has been debated for a number of years, but clinical and scientific consensus now accepts that the pH63D variant is rarely clinically significant and most patients with compound heterozygosity and apparent iron overload often have minimal excess liver iron and frequently have other/additional factors accounting for a high serum ferritin (hyperferritinaemia).

This review and its recommendations are based principally on the management of *HFE*-associated haemochromatosis (ie, secondary to homozygosity of the pC282Y genetic variant). A description of rarer and atypical forms of genetic iron overload can be found in the report of Girelli *et al*[7]—their treatment is considered to be beyond the scope of this review.

Iron overload in haemochromatosis

Although pC282Y homozygosity now forms the basis of the diagnosis of haemochromatosis, the condition has variable clinical/biochemical penetrance, which will affect rates of iron loading and organ damage. Although not all pC282Y homozygotes will necessarily need treatment, iron accumulation and organ damage do increase over time, and by age 80 years, 56% of males and 40.5% of women will have a diagnosis of haemochromatosis.[6]

Indirect evidence of iron overload

The initial clinical evaluation of iron overload relies on blood tests.

Ferritin

Serum ferritin is an intracellular protein that stores iron. It is also present in very low concentration in serum where its function is largely unknown. Serum ferritin assays measure a soluble fraction of ferritin protein. This is a well-established and reliable method in the assessment of iron deficiency where serum ferritin levels are low, often <30 µg/L, but high levels of serum ferritin (hyperferritinaemia) are less specific and their interpretation requires additional considerations. Ferritin transcription increases in the presence of inflammation and through the translation of ferritin mRNA by inactivation of iron-response proteins. Non-iron drivers of ferritin transcription are diverse and include common clinical conditions such as acute and chronic inflammation, steatotic liver disease (metabolic hyperferritinaemia)[8] and alcohol use.[9] An important additional consideration is that a number of different assays, with differing reference ranges, are currently used by clinical diagnostic laboratories and ferritin measurements vary quite significantly at concentrations >500 µg/L.

Transferrin saturation

Iron absorbed from the gut and circulating in the bloodstream is predominantly bound to the transport molecule transferrin. Historically, diagnostic laboratories reported measurements of iron and total iron binding capacity, but more recently these have been reported as transferrin saturation (TSat)—the proportion of transferrin iron binding sites occupied by iron. As a laboratory assay, transferrin saturation is more reliable and consistent than the measurement of ferritin, but this result is subject to a number of biological influences including time of day and eating. Despite these influences being very well recognised, there is no consensus/standardisation of how samples should be taken (eg, morning, fasting, etc). A raised transferrin saturation is recognised as the biochemical hallmark of haemochromatosis, although its specificity is limited.

Homozygosity for the pC282Y variant in *HFE* represents a genetic risk of iron overload. A combination of a raised ferritin and a raised transferrin saturation strongly suggests the presence of iron overload with this genotype.

Direct evidence of iron overload

Liver biopsy

Historically, the diagnosis of haemochromatosis was based on liver biopsy. This practice predated current laboratory assays and reflected the fact that the liver is the dominant site of iron excess, and that severe liver disease was the most common clinical presentation. With the development of non-invasive technologies to assess liver fibrosis and iron overload, liver biopsy is now rarely performed. If these modalities are unavailable, liver biopsy can be used to determine the stage of liver fibrosis and directly measure liver iron concentration.

MRI measurement of liver iron concentration

For many years, it has been possible to measure liver iron concentration by MRI (MRLIC) and this correlates with liver iron concentration as established by liver biopsy.[10] Various methods have subsequently been described,[11] and expert consensus on best practices is provided by a recent radiology guideline.[12] The use of MRLIC measurement of liver iron concentration in patients with clinically suspected iron overload has shown that this approach was useful in determining

Table 1 Grading of liver iron concentration (after Henninger *et al*) with approximate correlates with excess iron ('mobilisable' iron) and the expected number of complete venesections needed to normalise stored iron

Grading	Liver iron concentration (established by biopsy or MRLIC)		'Mobilisable' iron	Approximate number of venesections
Normal	0–36 µmol/g	0–2 mg/g		
Borderline/Insignificant	36–75 µmol/g	2–4 mg/g	<2 g	<10
Mild	75–100 µmol/g	4–6 mg/g	2–3.5 g	Up to about 15
Moderate	100–150 µmol/g	6–8 mg/g	3.5–5 g	15–25
Moderate-severe	150 to <300 µmol/g	8–16 mg/g	5–10 g	>25
Extreme	>300 µmol/g	>16 mg/g	>10 g	>40/50

MRLIC, liver iron concentration by MRI.

which patients required venesection treatment.[13] Importantly, this approach was able to rule out serious liver iron overload in patients with significant hyperferritinaemia and low-risk *HFE* genotypes (ie, those without pC282Y homozygosity). Magnetic resonance elastography can also be used to assess liver fibrosis instead of liver biopsy if modalities such as transient elastography (FibroScan, 2D Shear Wave Elastography) are unavailable or provide unreliable results.

Quantitative phlebotomy

An alternative method for quantifying iron excess is quantitative phlebotomy. This approach is based on the principle that a patient's iron excess can be broadly calculated from the volume of blood removed to normalise their serum markers of iron stores, assuming that each unit of blood contains between 200 and 250 g of iron (table 1). If a patient is subjected to serial (ie, weekly) venesection until they achieve normal iron status (nominally a ferritin <50 µg/L), the total amount of 'mobilisable' iron can be calculated by the number of treatments the patient has received (ie, the total volume of blood removed). Although this approach effectively commits a patient to undergoing initial/induction treatment, it can prove useful in selected patients with low-risk *HFE* genotypes when considering the need for long-term/maintenance treatment.

For example, if a patient with low-risk *HFE* genotype and hyperferritinaemia requires <10 venesections to normalise their ferritin level, one can roughly calculate that their excess, or mobilisable, iron amounts to only 2.5 g of iron (10×250 mg).

The background to the use of venesection in haemochromatosis

Venesection evolved from the ancient practice of bloodletting and therefore has a long history dating back to ancient civilisations.

- Bloodletting was used by the ancient Egyptians, Greeks and Romans with early descriptive reports on its practice coming from Hippocrates (460–370 BC) and later Galen (129–216 AD).
- During the Middle Ages, bloodletting became a common medical treatment in Europe. It was performed by barber-surgeons who used a variety of tools, including lancets and leeches, to draw blood.
- This practice continued through the Renaissance and into the 18th century, despite a growing scepticism about its efficacy in light of a developing understanding of the circulation led by Vesalius and William Harvey.
- The 19th century saw an overall decline in the popularity of venesection as an improved understanding of diseases led to more evidence-based medical practices. Bloodletting was increasingly viewed as harmful, and its use diminished.
- Despite the overall decline in its use, venesection is only a treatment option for a limited number of conditions—specifically polycythaemia and iron overload.
- Venesection was first reported as a potential treatment for haemochromatosis in the 1950s and, after initial individual case reports, cohort studies showed this to be tolerated and beneficial.[14]

Venesection treatment has continued to this day and is regularly performed on tens of thousands of patients in the UK each year. The practice might be considered technically simple and of low immediate risk, but there is a significant lack of quality evidence to support its best use. An attempted Cochrane review of interventions for haemochromatosis performed in 2017 found insignificant evidence from randomised trials to make any formal recommendation.[15] A subsequent meta-analysis/systematic review of venesection found insufficient quality evidence to support anything beyond a narrative or descriptive analysis.[16]

The following review of published evidence in venesection will provide the basis for a pragmatic recommendation regarding how treatment should be best undertaken.

Benefits of treatment

The aims of treatment in haemochromatosis are to prevent premature death, reduce the morbidity associated with iron-associated organ damage and improve symptoms/quality of life.

Mortality

The impact of venesection therapy on improved mortality in haemochromatosis was first widely

reported in the 1970s from small retrospective studies comparing treated against untreated populations.[17 18] Studies from the mid-80s to early 90s with a larger patient population and longer duration of follow-up demonstrated that patients who were non-cirrhotic and underwent venesection had mortality comparable with the general population.[14 19] In 1996, Niederau *et al* reported their findings on 251 patients with haemochromatosis, which further showed the benefits of venesection in improving life expectancy and sequelae associated with iron overload including hepatocellular carcinoma (HCC).[20]

Many of these early studies assessing the impact of venesection on mortality were reported prior to the discovery of the *HFE* gene, and therefore many of the patients were diagnosed with more advanced disease, with one study showing 85% of their study cohort had cirrhosis and 45% of the group also consuming at least 50 g (six units) of alcohol/day.[17]

More recently, a study looking at mortality in the period between 1996 and 2009 and after the availability of genetic testing demonstrated that those with mild haemochromatosis (serum ferritin <1000 µg/L) who had been treated had improved mortality from cardiovascular disease and non-liver malignancies.[21]

Regardless of treatment with venesection, patients with haemochromatosis exhibiting cirrhosis had worse mortality compared with those without cirrhosis.[16] However, adequate venesection in the cirrhotic cohort has been shown to improve mortality even in the presence of irreversible liver damage.[22 23]

Morbidity

Review of the effects of venesection on haemochromatosis morbidity must accommodate the evolving clinical manifestations of the disease. Although early reports of the condition described skin, cardiac and pancreatic disease along with liver disease,[5] these issues are seen much less frequently in the 21st century due to multiple factors leading to much earlier diagnosis. More recent analyses of the natural history of pC282Y homozygosity highlight the risk of the long-term risks of liver disease (including liver cancer), joint disease and central nervous system (CNS) sequelae.[4 6]

Liver disease (fibrosis, cirrhosis and HCC)

Improvement in liver fibrosis has been demonstrated following treatment with venesection.[20 24–26] It has been inferred that this evidence of fibrosis regression is likely to reduce future risk of hepatocellular cancer.[24]

Improvement in portal hypertension has also been observed in patients with haemochromatosis exhibiting cirrhosis following treatment with venesection.[23] However, 26% of this study cohort had been labelled as having 'alcohol abuse' in addition to haemochromatosis and almost all stopped drinking after their haemochromatosis diagnosis.

The UK Biobank data investigated 1294 male pC282Y homozygotes and found greater risk of HCC compared with the rest of the population, but this did not reflect if these patients had been treated with venesection.[27] Data from a systematic review showed conflicting results when reviewing the effect of venesection on HCC risk, but all the studies were at high risk of bias.[16]

Joint disease

Joint pain (arthralgia) is one of the most common symptoms reported by patients with haemochromatosis.[28] Some patients develop a characteristic arthropathy typically affecting the second and third metacarpophalangeal joints and ankles in addition to other large joints commonly affected in osteoarthritis (knees, hips, etc). This has been reported to be associated with the presence of significant iron overload defined by a serum ferritin >1000 µg/L,[29 30] although not universally. The development of arthropathy is a key feature that adversely impacts the quality of life of patients.[31]

The mechanism by which iron overload leads to joint damage is not fully understood. This is further reflected by a lack of symptom improvement in patients with haemochromatosis even after venesection.[32] It has also been reported that some patients experience worsening of joint symptoms after treatment.[33] The pathophysiology of haemochromatosis arthropathy is hypothesised to be akin to osteoarthritis but in a much more aggressive form affecting patients at a younger age. Radiographic findings typically seen in patients with haemochromatosis arthropathy are similar to osteoarthritis, which includes osteophytes and joint space narrowing, but these are more prominent and additionally the presence of chondrocalcinosis.[33 34] Validated radiological scoring systems have been developed to help clinicians evaluate and categorise the severity of arthropathy in this group of patients.[35]

Treatment for haemochromatosis arthropathy at present is largely supportive with the use of analgesia, physiotherapy and joint replacement surgery in severe cases. There are no disease-modifying therapeutic options at present that prevent or reverse joint damage. As a result, joint replacements are not uncommon in this population,[4 36] who are 9 times more likely to require joint replacement surgery compared with the general population.[34] In a small prospective study, the key variables associated with joint replacement surgery were female gender, presence of chondrocalcinosis and metacarpophalangeal joint damage.[34]

CNS manifestations

Historically, it has been felt that the nervous system was largely unaffected in haemochromatosis as limited neuropsychiatric morbidity had been described.[5] This was in sharp distinction to aceruloplasminaemia, where CNS iron deposition dominates the clinical

presentation.[37] This view must now be challenged and may, in part, reflect the consequences of earlier diagnosis following discovery of the *HFE* gene, greater patient awareness and reduction in premature mortality.

Neurological morbidity with dementia, delirium and movement disorders was found to be more prevalent in older male pC282Y homozygotes.[6] This observation has been supported by the demonstration of excess brain iron on MRI.[38 39] This excess iron deposition affects areas similar to Alzheimer's disease such as the hippocampus and thalamus.[38] Given that these observations are relatively recent, there has been no evidence reported to date to suggest that venesection treatment improves these neurological morbidities or even that early diagnosis and treatment might prevent long-term iron-related brain damage.

Approximately 20%–38% of patients with haemochromatosis describe symptoms of depression.[28 32] Whether this reflects increased brain iron levels or the consequences of other disease manifestations, such as fatigue and arthropathy,[40] or even the impact of living with a chronic illness and associated stigma,[41] remains undetermined. In a patient survey, approximately 40% reported improvement in their depression following treatment, while about 10% reported worsening symptoms.[32] It is unwise to draw conclusions from these observations alone and prospective studies with long-term patient follow-up will need to consider careful assessment of neurological and psychological factors within the broader context of quality of life.

Cardiac disease

Although cardiac disease is seen more rarely than in the past, the most common manifestations of cardiac disease in the haemochromatosis population are heart failure and supraventricular arrhythmias.[42] Secondary haemochromatosis from transfusion-related iron overload more commonly causes cardiovascular dysfunction compared with primary haemochromatosis. Treatment with venesection and iron chelation in secondary iron overload has a better-established evidence base in improving cardiac function compared with primary haemochromatosis.[43 44] Case reports and smaller non-randomised studies have described improvement in angina and cardiac function following venesection in patients with haemochromatosis.[45–48] Despite the paucity of good evidence, clinically, patients with cardiac dysfunction from haemochromatosis are usually managed with venesection and/or iron chelation with the aim of improving their outcomes. Venesection is not advisable in those with severe heart failure, for example, New York Heart Association class IV.

Interestingly, patients with haemochromatosis treated with venesection were found to have a lower incidence of cardiac mortality compared with the general population, with the UK Biobank also showing that male pC282Y homozygotes were at lower risk of coronary artery disease.[4 21] Whether data from these studies indicate a random association or a clear pathophysiological relationship remains uncertain.

Endocrine dysfunction

Hypogonadism due to haemochromatosis can lead to erectile dysfunction and loss of libido.[49] The benefit of venesection in this aspect is uncertain due to conflicting study results.[16] One study reported that 27.8% of patients felt their symptoms of sexual dysfunction were worse following venesection compared with only 12.7% who felt it had improved.[32] Historical data from 1959 to 1983 among 51 patients indicated that 11 had improvement in sexual function compared with five in whom symptoms worsened (unchanged in 35).[19]

Diabetes forms part of the classical triad of haemochromatosis (along with liver cirrhosis and bronze skin pigmentation). Recent population data of pC282Y homozygotes in Europe have provided evidence that this genotype does infer a risk of diabetes,[4 50] although the effect is less pronounced than previously assumed.[51] The postulated mechanism of diabetes in haemochromatosis had previously assumed iron loading of the islet cells in the pancreas, although it is recognised that hepatocellular iron overload and/or established chronic liver disease will contribute to insulin resistance and the earlier diagnosis and treatment in recent years has resulted in lower prevalence of diabetes. The benefits of venesection on diabetes remain uncertain.[16 49] Small studies that have been done show improvement in glucose tolerance in only a small proportion of patients with diabetes or impaired fasting glucose.[49 52] The effect of venesection on glucose control seems to be highest during the early (induction) phase of treatment.

Symptoms

Patients with haemochromatosis report a range of symptoms, with fatigue and joint pain being the most common in most patient surveys.[32 53] Improvement in fatigue is the most widely reported symptom to benefit from venesection but can worsen in a small group of patients.[20 32 54] Patients with haemochromatosis treated with erythrocytapheresis had improved fatigue compared with the sham group, but this has never been investigated for venesection in a randomised trial setting.

Venesection has not shown to be of significant benefit in patients with arthralgia.[32 33] In addition, once arthritis/joint damage occurs, venesection does not result in recovery and joint damage may progress.[55 56] Several questions remain unanswered regarding the relationship between arthralgia and haemochromatosis, including why only a proportion of patients develop joint

disease and the occurrence or worsening of joint symptoms following treatment with venesection. Those without arthritis are unlikely to have advanced liver fibrosis.[57] Some association is noted between prolonged elevation in TSat (>50%) and more debilitating joint symptoms seen in a French longitudinal cohort study.[58] Taking this study into account, there is variation among various guidelines on the role of target TSat when undergoing venesection.[54 55 59 60]

VENESECTION TREATMENT IN HAEMOCHROMATOSIS

Indication for treatment

The decision to initiate venesection in haemochromatosis should be based on both clinical and laboratory findings. The frequency of venesections should be individualised, considering factors such as the severity of iron overload, extent of organ damage, patient age, comorbidities and tolerability of the procedure.

In men and postmenopausal women with haemochromatosis, venesection is usually started when the serum ferritin exceeds the upper limit of the laboratory reference range (>300 µg/L). For premenopausal women, a serum ferritin of >200 µg/L should prompt consideration of treatment.

Although venesection is recommended for all healthy patients exhibiting biochemical iron overload, regardless of the presence of clinical symptoms, venesection constitutes only one aspect of a patient's overall healthcare requirements. Therefore, all these factors must be considered when assessing each patient for venesection. In frail patients with minor iron loading and no evidence of advanced hepatic fibrosis, the risks of venesection may outweigh the potential benefits. There is currently no published data on frailty and venesection to guide specific recommendations on when to stop venesection and this should be decided by the treating clinician on a case-by-case basis. Additionally, there are no specific studies on the benefits of carrying out venesection in those aged >80 years. There are 2123 and 114 patients who are aged 70–79 years and >80 years, respectively with haemochromatosis who continue to donate blood as part of their treatment, highlighting that in the right patient, it can be carried out safely.[61]

Patients being referred for venesection should be informed that their treatment will be for an indefinite period of time or until a decision is made to cease the treatment based on clinical grounds or patient preference. The first phase of treatment is referred to as INDUCTION. This is an intense period of venesection, performed on a weekly basis, with the aim of effectively removing the body's excess iron stores. This is currently determined using serum ferritin as a surrogate biomarker for total body iron stores. The duration of the induction period will vary and will be followed by the MAINTENANCE phase. This second phase consists of much less frequent venesection treatment performed to prevent the re-accumulation of excess iron.

Referral for treatment

In most instances, the venesection treatment will be performed by a clinician other than that making the treatment recommendation. As such, a record of the request for venesection from the responsible clinician should be accessible in the patient record and forwarded to the appropriate department. This should include the following details:

- Diagnosis (including *HFE* genotype)
- Recommended initial frequency of venesection
- Volume of blood (mL) to be removed
- Replacement fluids and the volume to be infused (if applicable)
- Target level for ferritin
- Relevant clinical history such as:
  - Use of antihypertensives
  - History of vasovagal episodes
  - Cardiac history
  - Prescribed anticoagulants
  - Patient-specific characteristics such as needle phobia

Consent

Informed consent is the process by which a patient voluntarily agrees to a proposed medical procedure or treatment after understanding the risks, benefits, alternatives and potential consequences of that procedure/treatment. Consent for venesection can be provided orally or in writing using a standard consent form. It would be advisable that written informed consent is taken for the first venesection. Thereafter, verbal consent is accepted, but this must be acknowledged and recorded appropriately.

THE PROCEDURE

Venesection is a medical treatment and should be performed in a suitable healthcare setting by appropriately trained professional staff.

The patient should be seated or lying supine and should be observed/supervised throughout the duration of the procedure. Their identity and diagnosis must be checked, and they should confirm their consent for the procedure. After the placement of a suitable tourniquet device, the vascular access device is inserted into a suitably large vein in the antecubital fossa using an aseptic non-touch technique. Once blood is flowing, the needle should be secured with tape and the tourniquet released. The collection bag should be placed on a set of scales situated lower than the needle site to facilitate continuous flow. Blood is allowed to flow until the target weight of blood has been removed (most commonly about 478 g equating to a blood volume of 450 mL). Routine monitoring blood tests can be taken from the line during this period. Once the process is complete, the line can be removed, and pressure is

applied to the venepuncture site with gauze or cotton wool for at least 2 min. This may need to be longer in patients with cirrhosis and/or in those taking anticoagulant or antiplatelet medications.

Following the procedure, the patient should remain seated/reclined for a further 10–15 min. After confirmation of the next treatment or follow-up appointment, the patient can be discharged with a postprocedure advice sheet.

Vascular access device

A 16–18 Fr gauge cannula is usually recommended for venesection in transfusion donor services, although this size gauge is not strictly necessary for therapeutic venesections. Consideration should be given to the viscosity of the blood and the potential for blood clotting in smaller gauge devices and collection systems in addition to the patient's preference, their tolerance of needles, any previous scarring, and the planned insertion site.

Calculating the volume of blood to be removed

Generally, the recommended volume of blood removal for venesection is 450 mL.[59 62] However, smaller volumes should be considered individually based on the patient's tolerance, lower body mass or medical history. Where possible, the referring clinician should specify the amount to be removed. For example, some units might choose to restrict venesection volume to 350 mL in patients weighing <60 kg.

Healthcare services providing venesection treatment should weigh the amount of blood being removed and therefore weighing scales are key to the procedure. The mass of the full venesection bag can provide an approximation of the volume of blood removed.

- 1 mL of blood weighs 1.062 g.
- 450 mL of blood weighs 478 g

The empty collection bag should be weighed prior to venesection and the weight of the bag should be included during blood removal. For example, if the intended blood removal amount is 450 mL and the bag weighs 50 g, then the total mass of the bag filled with blood should not exceed 528 g (478 g blood (450 mL)+50 g bag=528 g).

Induction phase

The principle behind the induction or de-ironing stage of venesection treatment is to venesect the patient intensively. This removal of blood stimulates erythropoiesis, which in turn uses existing body iron stores. Traditionally, induction venesection is undertaken on a weekly basis. It can take several months and even over a year to achieve complete removal of excess iron, especially in patients who have significant iron loading at diagnosis.[26]

It is common practice during the induction phase to check haemoglobin on a weekly basis and to check ferritin and transferrin saturation monthly (figure 2). Treatment continues on a weekly basis, until ferritin measurements reach the preferred target level (see 'Discussion' section). If anaemia (haemoglobin <120 g/L) occurs during this period, the frequency of treatment should be adjusted accordingly. However, continued treatment is considered to be safe and without risk of excess treatment-associated complications.[63]

- Haemoglobin levels should be measured before every venesection.
- Serum ferritin levels should be checked monthly.

An early or disproportionate decrease in haemoglobin might require adjustment of venesection frequency and/or volume, but treatment should preferably continue until the intended serum ferritin target has been achieved (see 'Treatment targets' section).

If during regular and supervised treatment the ferritin level fails to fall (or appears to paradoxically increase), one should review the patient and consider whether other factors such as excess alcohol consumption or the co-existence of cardiometabolic risk factors (ie, metabolic hyperferritinaemia) might be present. Measurement of liver iron concentration by MRI could potentially guide treatment in atypical or exceptional cases.

The frequency of venesection can also be adjusted to longer intervals in the event of poor tolerance/side effects to the procedure. In some cases, a reduced volume of blood can be removed in patients who experience significant symptoms when the standard 450 mL blood is venesected. In these scenarios, it is important to have an open discussion with patients and agree on a personalised venesection plan.

Maintenance phase

Once excess iron has been removed and the induction venesection phase has been completed, iron would predictably re-accumulate without continuing treatment. The precise rate of re-accumulation is unpredictable, although it generally occurs more quickly in patients who initially had significant iron overload and/or presentation at a younger age. Patients should be offered reassessment of iron stores every 3–6 months, with additional phlebotomy performed as necessary (figure 2).

- Measure haemoglobin and ferritin before or at each treatment.
- Serum ferritin should be maintained at the agreed target level. While it is recognised that some patients feel better with a higher level of ferritin, treatment should be tailored to patient preference wherever possible and safe to do so.

During the maintenance phase of venesection, treatment for patients with haemochromatosis should be encouraged to explore the use of blood transfusion donor services. This will be subject to the individual donor service eligibility criteria and monitoring of

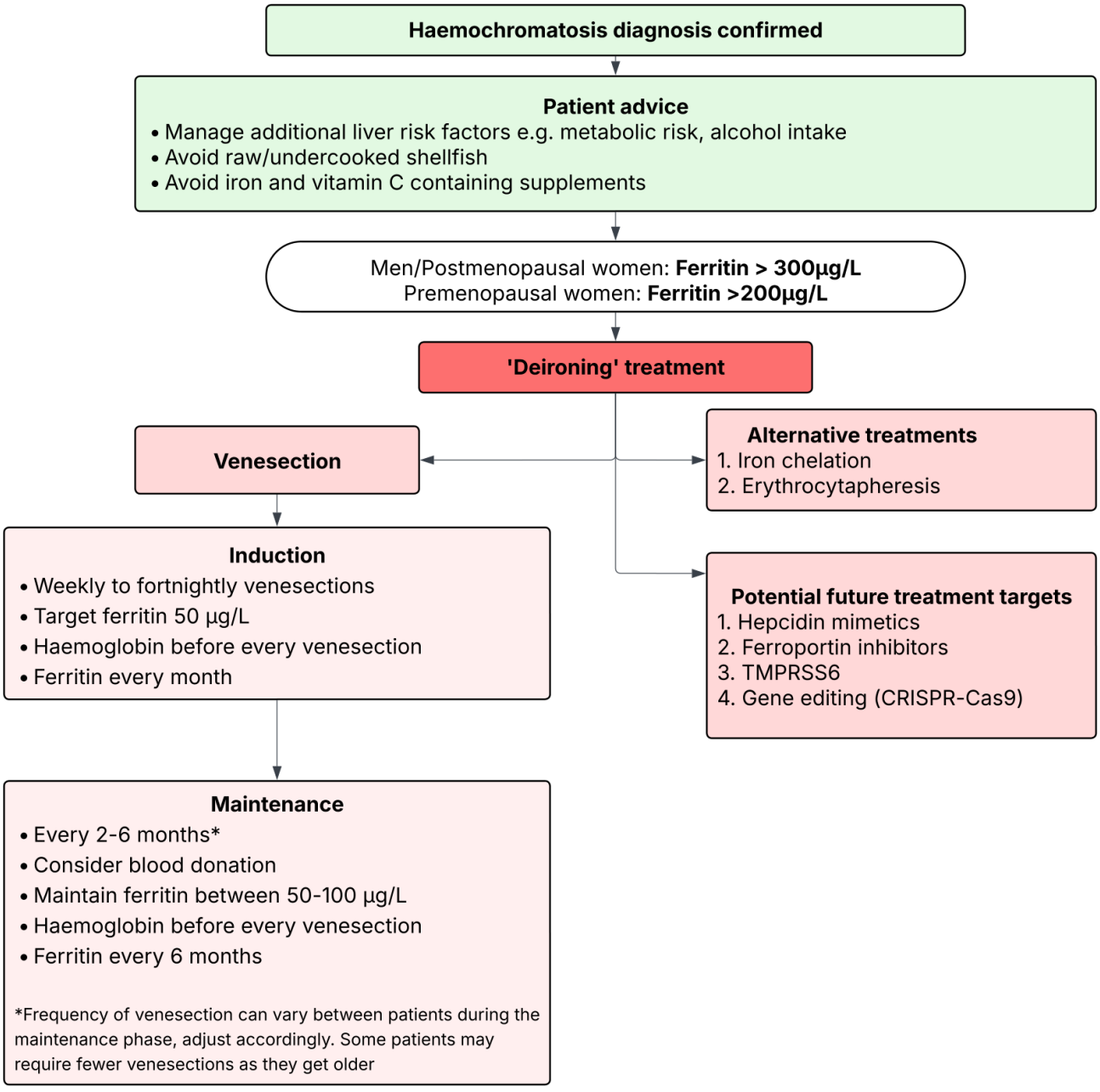

Figure 2 Haemochromatosis treatment pathway. CRISPR, clustered regularly interspaced short palindromic repeats; Cas-9, CRISPR-associated protein 9; TMPRSS6, transmembrane protease, serine 6.

treatment cannot be assumed (see section on use of blood transfusion donor services)

Dietary iron restriction

Patients may consider restricting their consumption of iron-rich foods in the expectation that this might reduce their venesection requirements. Whereas it is useful to consider a diagnosis of haemochromatosis as a useful opportunity to discuss additional co-factors for liver injury (ie, alcohol consumption and metabolic syndrome), there is no need to encourage patients to adopt a low iron diet. Patients should avoid nutritional supplements/multivitamins containing iron as well as vitamin C supplementation. Patients in the depletion phase should avoid raw/undercooked shellfish due to the risk of *Vibrio vulnificus* (bacterial food poisoning).

The effect of concurrent proton pump inhibitor treatment

Proton pump inhibitors (PPIs) inhibit dietary non-haem iron absorption[64] and can result in reduced venesection requirement.[65] The effect of PPI was investigated in a randomised placebo-controlled trial in patients with haemochromatosis demonstrating reduced need for venesection.[66] More recently, Dirweesh *et al*[67] carried out a systematic review and meta-analysis demonstrating the positive association between reduced frequency of venesection and PPI.[67] The relative safety of PPIs further adds to the case of

using them as adjunctive therapy to venesection in patients with haemochromatosis. However, the quantitative effect this has on venesection requirements has not been evaluated and the routine use of PPI therapy for this purpose is not currently recommended.[54 59]

TREATMENT TARGETS

In the absence of quality evidence, clinical guidelines published to date have been predominantly based on expert opinion. These have all adopted the use of serum ferritin for monitoring treatment, although they vary in their recommendations with some advocating more stringent treatment targets—requiring more frequent venesection. The American Association for the Study of Liver Disease recommended venesection to achieve and maintain a serum ferritin level of 50–100 µg/L,[68] figures endorsed in a subsequent American College of Gastroenterology guideline.[55] In 2018 the BSH guideline suggested stricter induction targets of serum ferritin target of 20–30 µg/L with an additional target of TSat <50%.[59] TSat is a measure of iron being transported in the blood (as opposed to stored iron) and results can be highly variable and often discordant with ferritin results. These BSH targets (including the maintenance targets of serum ferritin <50 µg/L and TSat <50%) were acknowledged to be more stringent than contemporary international guidelines but were justified on the indirect evidence of benefit on joint symptoms[58] and hypothetical concerns regarding potential harm from free or non-transferrin bound iron associated with high TSat. It is not known whether achieving strict control of TSat by venesection is feasible, tolerable or improves clinical outcomes.

The most recent European guidelines suggest an induction target ferritin of <50 µg/L and maintenance ferritin target 50–100 µg/L, with no formal recommendation for TSat targets in the absence of suitable high-quality evidence.[69] We therefore recommend a maintenance treatment ferritin target of 50–100 µg/L, although we accept that a more relaxed target can be entirely reasonable if suitably tailored to the individual clinical needs and experiences of the patient.

Although all published guidelines have recommended treatment targets for ferritin levels <100 µg/L, it is recognised that significant liver disease in haemochromatosis is unlikely when ferritin levels are <1000 µg/L.[70–72] No study published to date has used MRLIC to monitor treatment efficacy.

Clinical supervision and follow-up

All patients diagnosed with haemochromatosis should have an annual review by a member of their medical team—*preferably* one with an expressed interest in haemochromatosis.

In addition to adjusting venesection schedules, patients with severe fibrosis/cirrhosis (≥F3) require 6-monthly ultrasound surveillance for HCC (www.england.nhs.uk/long-read/hepatocellular-carcinoma-surveillance-minimum-standards/).

Side effects and complications of treatment

Venesection is well tolerated by most patients without significant side effects, but all patients should be aware of the risks and potential complications associated with the procedure.

The side effects can be broadly divided into procedure-related issues and the consequences of blood removal. Common side effects directly related to the procedure include pain at the cannulation site, bruising/haematoma, vasovagal syncope secondary to hypovolaemia, antecubital nerve injury and accidental arterial puncture.[73] Features of hypovolaemia may be abrogated by asking patients to ensure they are well hydrated prior to their procedure, but some patients might still require intravenous fluids infused alongside their venesection treatment.

Following the procedure, some patients may experience fatigue, syncope and poor appetite, with the former being the most common.[53 74] Repeated venesections, especially if appropriate monitoring is not undertaken, can lead to anaemia. This should prompt a pause in treatment with further assessment by the treating team. If there is iron deficiency anaemia that persists after stopping venesections, this should be investigated via the standard pathways.[75]

In the event of any significant complication or adverse reaction to the venesection procedure, an incident report should be completed, and the medical team must be notified.

Specific complications

Syncope/Vasovagal episode

A common acute complication of the venesection procedure, which can occur at any time before, during or after the procedure, is a vasovagal reaction. This can be triggered either by the volume of blood removed relative to the patient's total blood volume or by a psychological response mediated by the autonomic nervous system. Symptoms include discomfort, feeling hot, nausea, dizziness or light-headedness, weakness and anxiety. These symptoms may progress to loss of consciousness and collapse.

Venepuncture site haematoma

A haematoma is the most common complication of venesection, characterised by the accumulation of blood in the tissues. Clinical manifestations include bruising, discolouration, swelling and local discomfort. As the haematoma enlarges, the resultant swelling may exert pressure on surrounding tissues, potentially causing nerve irritation. This can present with neurological symptoms such as radiating pain down the forearm and hand, as well as paraesthesia and tingling. It is important to note that a haematoma may not always be visible, yet patients may still experience

significant nerve pain. Attending clinicians need to be vigilant to these symptoms and notify the medical team if they occur. It is also important to consider that patients taking anticoagulants will bruise more easily, making further attempts to cannulate surrounding veins more difficult.

Inadvertent arterial puncture

This involves the accidental penetration of the brachial artery or one of its branches by the venesection needle. The primary indication of this complication is the presence of bright red, pulsatile blood flow, resulting in the rapid filling of the collection bag due to the high arterial pressure. Other symptoms may include pain around the elbow and the formation of a haematoma. The occurrence of a haematoma in this context increases the risk of compartment syndrome as well as the rarer complications of brachial artery pseudoaneurysm and arteriovenous fistula. The needle should be removed immediately with firm pressure applied to the site for 5–10 min.

Compartment syndrome

This may develop if a haematoma is substantial and accumulates within the deep layers of the forearm, between the muscles and tendons. This condition can cause severe pain and potentially lead to nerve injury. The swelling associated with compartment syndrome may not be visible, making it challenging to recognise. Clinicians must be vigilant and respond promptly to the presenting symptoms. Patients must also be informed of this complication and signs to look out for once discharged home.

Calcification/Scarring of the vein

Patients who have undergone frequent venepunctures may experience increasing difficulty in accessing veins over time due to calcification that occurs during the healing process of the venous wall. With increasing age, veins become fragile due to loss of collagen.

Poor/Difficult to find veins

Venous anatomy is extremely variable and for some patients this can be a challenge—especially during the intense, induction phase of treatment. It is commonly recommended to alternate sites/arms in such situations and one can consider the use of ultrasound (if available) to locate veins. Using veins in the lower limbs is associated with a higher risk of phlebitis and venous thrombosis and should be considered only after all upper limb options have been exhausted.

Nerve injury/irritation

Nerve injury may occur during needle insertion or removal, resulting in severe radiating pain and associated paraesthesia. A haematoma, even if not visible, can cause nerve pain, presenting as paraesthesia, tingling or radiating pain. These symptoms should be explained to patients in case they occur postdischarge.

Other considerations

pC282Y homozygotes without evidence of iron accumulation

The widespread adoption of *HFE* genotyping in cascade screening has identified an increasing number of individuals identified as being at significant risk of iron loading but without evidence of iron accumulation (ie, pC282Y homozygotes). It is advisable to monitor serum ferritin and TSat annually to detect any onset of tissue iron accumulation. If or when serum ferritin levels are demonstrated to be progressively rising and reach a level beyond the laboratory reference range, the patient should be counselled about starting regular venesection. In such instances, the intensity of the induction period of treatment can be reduced and, in some instances, avoided altogether. This approach reduces the risk of developing organ dysfunction secondary to iron overload. It is unclear if arthralgia or arthropathy can be ameliorated when venesection is started early.

Low risk HFE genotypes with evidence of iron loading

Individuals with low-risk *HFE* genotypes (compound heterozygotes and pH63D homozygotes) may present with hyperferritinaemia (and even sometimes a borderline high TSat). In such circumstances, other factors that might cause hyperferritinaemia (alcohol use, metabolic syndrome) should be assessed and addressed. If it remains necessary to establish unequivocal iron overload, this can be done using MRLIC. If MRI is unavailable, or if induction venesection has already been completed, it is advisable to try and establish the true extent of iron overload using the principle of quantitative phlebotomy. Individuals with low-risk genotypes and with normal or even slightly elevated iron stores are unlikely to require maintenance venesection but may be suitable for regular blood donation to the transfusion service.

Use of blood transfusion donor services

Patients (aged 18–70 years) without significant comorbidity, diagnosed prior to the onset of end-organ damage and entering the maintenance phase should be encouraged to become regular blood donors. Access and eligibility criteria will vary between countries. The National Health Service, Blood and Transplant (NHS B&T) donor service has accepted UK haemochromatosis donors since 2020 (https://www.blood.co.uk/who-can-give-blood/haemochromatosis-and-blood-donation/). A dedicated phone line has now been set up for patients with haemochromatosis by the NHS B&T to provide smoother access to appointments. They will accept patients during the maintenance phase of treatment—provided the individual meets their own eligibility criteria. They can currently offer venesection at a frequency of up to every 6 weeks in England

and every 12 weeks in Scotland. The service is unable to offer treatment monitoring and patients require continued clinical review. Similar arrangements exist in other countries (eg, Lifeblood, Australia), although the offering is not universal.

In Wales, the Welsh Blood Donation Service currently offers fortnightly appointments for blood donations, thereby allowing some induction-phase venesection treatments to be conducted outside NHS settings, provided there is no evidence of organ dysfunction and all other standard eligibility criteria are met. For patients with haemochromatosis in Northern Ireland to donate blood, they must be referred by their secondary care physician to the Northern Ireland Blood Transfusion Service (NIBTS). The frequency offered by NIBTS is a minimum of 6 weekly. Those still in the induction phase are required to undergo donation at the NIBTS headquarters in Belfast, whereas those in maintenance are able to donate at local community centres as well.

The use of blood donor services may not be suitable for patients who encounter challenges during venesection, such as difficult venous access and syncopal episodes that might necessitate administration of intravenous fluids. Additionally, those that live remotely and have limited transportation options may not be able to access blood donation centres in the UK, which have 27 permanent locations in major cities, with the remaining being temporary community-based venues, which are open for donations only 2–3 times a year.

Pausing and stopping venesection

Although of undoubted clinical benefit, venesection may need to be paused or stopped in certain situations.

During induction phase

If a haemoglobin level <11 g/dL develops during induction or patients become symptomatic with anaemia, venesection should be paused to prevent further deterioration. Blood tests should then be repeated to ensure resolution of anaemia before recommencing venesection. The frequency of subsequent venesection or the volume of blood removed may need to be adjusted to prevent recurrence. Blood donation services tend to adopt a stricter haemoglobin cut-off prior to venesection/blood donation. However, the risk of adverse events peri-procedure is low in those donating below their specified threshold.[61]

In cases of significant intercurrent illness during the induction phase of venesection, the decision regarding the risks and benefits of continuing treatment needs to be evaluated on an individual basis.

During maintenance phase

Once excess iron stores have been corrected by the induction phase of treatment, maintenance can usually be adjusted to meet the patient's immediate healthcare priorities. As such, it is advisable to suspend venesection during any significant intercurrent illness (surgery, acute vascular event, cancer treatment, etc). In most instances, it would be appropriate for the patient to be offered formal clinical reassessment and re-balancing of risks and benefits before maintenance treatment is recommenced.

Increased fetal/placental iron demands experienced during pregnancy mean that in most cases, maintenance venesection can be suspended during pregnancy. Assessment and monitoring of iron stores post partum will help inform the decisions regarding the restitution of regular treatment.

Over time, some patients appear to lose their tendency for iron loading and maintain more normal iron balance, decreasing the need for venesection. In these situations, it is worth considering whether an additional, new medical problem might be contributing to blood loss.

Venesection can be considered in patients with cirrhosis but should be carried out cautiously and may require closer monitoring. While there are benefits to improving mortality and portal hypertension in this group, those with significant decompensated cirrhosis may not be appropriate to undergo venesection as the benefit of treatment in this setting would be extremely limited. Those who meet transplant listing criteria should be considered for referral to the liver transplant unit.

Patients with significant frailty, dementia or non-hepatic malignancies are unlikely to benefit significantly from venesection treatment and even in otherwise healthy patients the advantages gained by continuing maintenance venesection beyond the ninth decade of life are limited.

Alternatives to venesection

Erythrocytapheresis

Erythrocytapheresis is a procedure using a technique of extracorporeal blood separation to selectively remove erythrocytes while returning the rest of the blood to the patient. Although this has been demonstrated to be beneficial in patients with haemochromatosis,[76] the necessary equipment is not available in all centres and the capital costs will preclude it being made available in healthcare settings that do not have additional clinical requirements.

Iron chelation therapy

In principle, iron chelation therapies sequester and remove iron and thereby provide an alternative treatment option. In practice, these treatments are reserved for exceptional circumstances such as patients with rare juvenile haemochromatosis and associated severe heart failure where parenteral chelation with desferrioxamine may be lifesaving.

The oral iron chelator deferasirox (Exjade) in patients with pC282Y homozygous haemochromatosis and moderate iron loading (median serum ferritin 645 µg/L) was associated with significant reduction

in serum ferritin, although protracted compared with venesection.[77] Dose-dependent gastrointestinal, renal and hepatic toxicities occurred particularly above 10 mg/kg/day dosing. A follow-up study suggested deferasirox (10±5 mg/kg/day) was effective and well tolerated in patients with haemochromatosis.[78] This suggests that deferasirox, with careful monitoring, may be considered for pC282Y homozygous patients who are intolerant to therapeutic venesection, although it is not currently licensed for this indication.

Potential future treatments

A clearer understanding of the role of the *HFE* protein in iron metabolism led to the identification of potential targets for therapy.

Hepcidin mimetics/Ferroportin inhibitors

The hepcidin mimetic Rusfertide (Takeda) binds to and blocks the effect of ferroportin. This could conceivably redress the molecular pathology of haemochromatosis and reduce venesection requirements. This agent has been studied in polycythaemia rubra vera,[79] and a provisional proof-of-concept study suggests that it may be beneficial in haemochromatosis.[80] Larger, randomised controlled trials of this and agents with a similar mode of action (eg, Vamifeport, CSL Behring) will be necessary to prove their benefit and/or clarify their role in patient management.

Treatments targeting TMPRSS6

The TMPRSS6 gene codes for a transmembrane serine protease repressor of hepcidin production. Treatment directed towards silencing this gene's expression (eg, by the use of a specific antisense RNA) has been demonstrated to prevent iron overload in a mouse model of haemochromatosis,[81] and trials of such therapies in polycythaemia rubra vera are currently in progress.

Gene editing

In principle, gene editing technologies (eg, CRISPR-Cas9 genome editing) could be applied to correct the genetic transition that results in the pC282Y variant. In vivo adenine base editing has been demonstrated to improve iron metabolism in a mouse model of haemochromatosis,[82] but human trials of such therapy are awaited.

CONCLUSIONS/SUMMARY

Therapeutic venesection has a long history and is still practised widely in the treatment of haemochromatosis. It is generally well-tolerated and has been demonstrated to reduce many of the serious long-term consequences of the disease. More research is needed to refine its use, particularly in terms of identifying when it is beneficial versus when it is not, clarifying optimal treatment targets—especially during the maintenance phase—and exploring the role of novel molecular therapies, as well as their impact on clinical outcomes and quality of life.

Acknowledgements We are grateful to Howard Don and Phil Coathup who are patient representatives of the BASL/BSG/BSH Haemochromatosis Special Interest Group in reviewing and providing feedback to our manuscript.

Contributors JS developed the study concept and design. PS, GM and JS drafted the manuscripts. KH, NMcD, JC, LL, WG and JS critically reviewed and revised the manuscript. All authors approved the final manuscript. JS is the guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Disclaimer This BSG/BASL guidance represent a consensus of best practice based on the available evidence at the time of preparation. They may not apply in all situations and should be interpreted in the light of specific clinical situations and resource availability. Further controlled clinical studies may be needed to clarify aspects of these statements, and revision may be necessary as new data appear. Clinical consideration may justify a course of action at variance to these recommendations, but we suggest that reasons for this are documented in the medical record. BSG guidance is intended to be an educational device to provide information that may assist in providing care to patients. They are not rules and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring or discouraging any particular treatment.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Prabhsimran Singh http://orcid.org/0000-0002-9601-9480
Natasha McDonald http://orcid.org/0000-0002-9335-8495
Johnny Cash http://orcid.org/0000-0001-5874-6997

REFERENCES

1 Simon M, Bourel M, Genetet B, *et al*. Idiopathic hemochromatosis. Demonstration of recessive transmission and early detection by family HLA typing. *N Engl J Med* 1977;297:1017–21.
2 Feder JN, Gnirke A, Thomas W, *et al*. A novel MHC class I-like gene is mutated in patients with hereditary haemochromatosis. *Nat Genet* 1996;13:399–408.
3 Consortium tuh. A simple genetic test identifies 90% of UK patients with haemochromatosis. *Gut* 1997;41:841–4.

4 Pilling LC, Tamosauskaite J, Jones G, *et al*. Common conditions associated with hereditary haemochromatosis genetic variants: cohort study in UK Biobank. *BMJ* 2019;364:k5222.
5 Sheldon JH. Haemochromatosis. Oxford University Press; 1935.
6 Lucas MR, Atkins JL, Pilling LC, *et al*. *HFE* genotypes, haemochromatosis diagnosis and clinical outcomes at age 80 years: a prospective cohort study in the UK Biobank. *BMJ Open* 2024;14:e081926.
7 Girelli D, Busti F, Brissot P, *et al*. Hemochromatosis classification: update and recommendations by the BIOIRON Society. *Blood* 2022;139:3018–29.
8 Valenti L, Corradini E, Adams LA, *et al*. Consensus Statement on the definition and classification of metabolic hyperferritinaemia. *Nat Rev Endocrinol* 2023;19:299–310.
9 Stewart S, Evans W, Turnbull I, *et al*. Managing raised ferritin in primary care. *BMJ* 2023;382:e076750.
10 St. Pierre TG, Clark PR, Chua-anusorn W, *et al*. Noninvasive measurement and imaging of liver iron concentrations using proton magnetic resonance. *Blood* 2005;105:855–61.
11 Henninger B, Alustiza J, Garbowski M, *et al*. Practical guide to quantification of hepatic iron with MRI. *Eur Radiol* 2020;30:383–93.
12 Reeder SB, Yokoo T, França M, *et al*. Quantification of Liver Iron Overload with MRI: Review and Guidelines from the ESGAR and SAR. *Radiology* 2023;307:e221856.
13 Bhuva M, Patterson I, Godfrey EM, *et al*. Magnetic Resonance Liver Iron Concentration Can Guide Venesection Decision-Making in Hyperferritinemia. *Dig Dis Sci* 2023;68:2704–9.
14 Bomford A, Williams R. Long term results of venesection therapy in idiopathic haemochromatosis. *Q J Med* 1976;45:611–23.
15 Buzzetti E, Kalafateli M, Thorburn D, *et al*. Interventions for hereditary haemochromatosis: an attempted network meta-analysis. *Cochrane Database Syst Rev* 2017;3:CD011647.
16 Prabhu A, Cargill T, Roberts N, *et al*. Systematic Review of the Clinical Outcomes of Iron Reduction in Hereditary Hemochromatosis. *Hepatology* 2020;72:1469–82.
17 Conte D, Piperno A, Mandelli C, *et al*. Clinical, biochemical and histological features of primary haemochromatosis: a report of 67 cases. *Liver* 1986;6:310–5.
18 Powell LW. Changing concepts in haemochromatosis. *Postgrad Med J* 1970;46:200–9.
19 Niederau C, Fischer R, Sonnenberg A, *et al*. Survival and causes of death in cirrhotic and in noncirrhotic patients with primary hemochromatosis. *N Engl J Med* 1985;313:1256–62.
20 Niederau C, Fischer R, Pürschel A, *et al*. Long-term survival in patients with hereditary hemochromatosis. *Gastroenterology* 1996;110:1107–19.
21 Bardou-Jacquet E, Morcet J, Manet G, *et al*. Decreased cardiovascular and extrahepatic cancer-related mortality in treated patients with mild HFE hemochromatosis. *J Hepatol* 2015;62:682–9.
22 Milman N, Pedersen P, á Steig T, *et al*. 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.
23 Fracanzani AL, Fargion S, Romano R, *et al*. Portal hypertension and iron depletion in patients with genetic hemochromatosis. *Hepatology* 1995;22:1127–31.
24 Bardou-Jacquet E, Morandeau E, Anderson GJ, *et al*. Regression of Fibrosis Stage With Treatment Reduces Long-Term Risk of Liver Cancer in Patients With Hemochromatosis Caused by Mutation in HFE. *Clin Gastroenterol Hepatol* 2020;18:1851–7.
25 Falize L, Guillygomarc'h A, Perrin M, *et al*. Reversibility of hepatic fibrosis in treated genetic hemochromatosis: a study of 36 cases. *Hepatology* 2006;44:472–7.
26 Powell LW, Dixon JL, Ramm GA, *et al*. Screening for hemochromatosis in asymptomatic subjects with or without a family history. *Arch Intern Med* 2006;166:294–301.
27 Atkins JL, Pilling LC, Masoli JAH, *et al*. Association of Hemochromatosis HFE p.C282Y Homozygosity With Hepatic Malignancy. *JAMA* 2020;324:2048–57.
28 Smith KJ, Fife-Schaw C, Dibb B, *et al*. Living with the impact of iron overload. 2018. Available: https://www.haemochromatosis.org.uk/news/living-with-the-impact-of-iron-overload-a-summary
29 Carroll GJ, Breidahl WH, Bulsara MK, *et al*. Hereditary hemochromatosis is characterized by a clinically definable arthropathy that correlates with iron load. *Arthritis Rheum* 2011;63:286–94.
30 Richette P, Ottaviani S, Vicaut E, *et al*. Musculoskeletal complications of hereditary hemochromatosis: a case-control study. *J Rheumatol* 2010;37:2145–50.
31 Adams PC, Speechley M. The effect of arthritis on the quality of life in hereditary hemochromatosis. *J Rheumatol* 1996;23:707–10.
32 McDonnell SM, Preston BL, Jewell SA, *et al*. A survey of 2,851 patients with hemochromatosis: symptoms and response to treatment. *Am J Med* 1999;106:619–24.
33 Kiely PD. Haemochromatosis arthropathy - a conundrum of the Celtic curse. *J R Coll Physicians Edinb* 2018;48:233–8.
34 Sahinbegovic E, Dallos T, Aigner E, *et al*. Musculoskeletal disease burden of hereditary hemochromatosis. *Arthritis Rheum* 2010;62:3792–8.
35 Dallos T, Sahinbegovic E, Aigner E, *et al*. Validation of a radiographic scoring system for haemochromatosis arthropathy. *Ann Rheum Dis* 2010;69:2145–51.
36 Elmberg M, Hultcrantz R, Simard JF, *et al*. Increased risk of arthropathies and joint replacement surgery in patients with genetic hemochromatosis: a study of 3,531 patients and their 11,794 first-degree relatives. *Arthritis Care Res (Hoboken)* 2013;65:678–85.
37 Piperno A, Alessio M. Aceruloplasminemia: Waiting for an Efficient Therapy. *Front Neurosci* 2018;12:903.
38 Atkins JL, Pilling LC, Heales CJ, *et al*. Hemochromatosis Mutations, Brain Iron Imaging, and Dementia in the UK Biobank Cohort. *J Alzheimers Dis* 2021;79:1203–11.
39 Loughnan R, Ahern J, Tompkins C, *et al*. Association of Genetic Variant Linked to Hemochromatosis With Brain Magnetic Resonance Imaging Measures of Iron and Movement Disorders. *JAMA Neurol* 2022;79:919–28.
40 Stubbs B, Aluko Y, Myint PK, *et al*. Prevalence of depressive symptoms and anxiety in osteoarthritis: a systematic review and meta-analysis. *Age Ageing* 2016;45:228–35.
41 Manz U. Genetic explanations, discrimination and chronic illness: A qualitative study on hereditary haemochromatosis in Germany. *Chronic Illn* 2016;12:308–19.
42 Udani K, Chris-Olaiya A, Ohadugha C, *et al*. Cardiovascular manifestations in hospitalized patients with hemochromatosis in the United States. *Int J Cardiol* 2021;342:117–24.
43 Aronow WS. Management of cardiac hemochromatosis. *Arch Med Sci* 2018;14:560–8.
44 Mamtani M, Kulkarni H. Influence of iron chelators on myocardial iron and cardiac function in transfusion-dependent thalassaemia: a systematic review and meta-analysis. *Br J Haematol* 2008;141:882–90.
45 Feely J, Counihan TB. Haemochromatosis presenting as angina and responding to venesection. *Br Med J* 1977;2:681–2.
46 Skinner C, Kenmure AC. Haemochromatosis presenting as congestive cardiomyopathy and responding to venesection. *Br Heart J* 1973;35:466–8.

47 Carpenter JP, Grasso AE, Porter JB, *et al*. On myocardial siderosis and left ventricular dysfunction in hemochromatosis. *J Cardiovasc Magn Reson* 2013;15:24.
48 Byrne D, Walsh JP, Daly C, *et al*. Improvements in cardiac function detected using echocardiography in patients with hereditary haemochromatosis. *Ir J Med Sci* 2020;189:109–17.
49 Pelusi C, Gasparini DI, Bianchi N, *et al*. Endocrine dysfunction in hereditary hemochromatosis. *J Endocrinol Invest* 2016;39:837–47.
50 Mottelson M, Helby J, Nordestgaard BG, *et al*. Mortality and risk of diabetes, liver disease, and heart disease in individuals with haemochromatosis *HFE* C282Y homozygosity and normal concentrations of iron, transferrin saturation, or ferritin: prospective cohort study. *BMJ* 2024;387:e079147.
51 Adams PC. Non-expressing homozygous C282Y carriers and haemochromatosis. *BMJ* 2024;387:q2704.
52 Hatunic M, Finucane FM, Norris S, *et al*. Glucose metabolism after normalization of markers of iron overload by venesection in subjects with hereditary hemochromatosis. *Metab Clin Exp* 2010;59:1811–5.
53 Brissot P, Ball S, Rofail D, *et al*. Hereditary hemochromatosis: patient experiences of the disease and phlebotomy treatment. *Transfusion* 2011;51:1331–8.
54 Zoller H, Schaefer B, Vanclooster A, *et al*. EASL Clinical Practice Guidelines on haemochromatosis. *J Hepatol* 2022;77:479–502.
55 Kowdley KV, Brown KE, Ahn J, *et al*. ACG Clinical Guideline: Hereditary Hemochromatosis. *Am J Gastroenterol* 2019;114:1202–18.
56 Carroll GJ, Breidahl WH, Olynyk JK. Characteristics of the arthropathy described in hereditary hemochromatosis. *Arthritis Care Res (Hoboken)* 2012;64:9–14.
57 Andersson L, Powell LW, Ramm LE, *et al*. Arthritis Prediction of Advanced Hepatic Fibrosis in HFE Hemochromatosis. *Mayo Clin Proc* 2022;97:1649–55.
58 Bardou-Jacquet E, Lainé F, Guggenbuhl P, *et al*. Worse Outcomes of Patients With HFE Hemochromatosis With Persistent Increases in Transferrin Saturation During Maintenance Therapy. *Clin Gastroenterol Hepatol* 2017;15:1620–7.
59 Fitzsimons EJ, Cullis JO, Thomas DW, *et al*. Diagnosis and therapy of genetic haemochromatosis (review and 2017 update). *Br J Haematol* 2018;181:293–303.
60 Crawford DHG, Ramm GA, Bridle KR, *et al*. Clinical practice guidelines on hemochromatosis: Asian Pacific Association for the Study of the Liver. *Hepatol Int* 2023;17:522–41.
61 Thorpe R, Masser B, Gemelli CN, *et al*. Exploring the experiences of hemochromatosis (HHC) patients who undergo therapeutic venesection at a blood collection agency. *Transfusion* 2025;65:531–8.
62 McMullin MF, Harrison CN, Ali S, *et al*. A guideline for the diagnosis and management of polycythaemia vera. A British Society for Haematology Guideline. *Br J Haematol* 2019;184:176–91.
63 Lim Z, Bentley P, Olynyk JK. Ensuring donor safety: is venesecting therapeutic donors to haemoglobin levels below Blood Service guidelines safe? *Vox Sang* 2020;115:288–92.
64 Hutchinson C, Geissler CA, Powell JJ, *et al*. Proton pump inhibitors suppress absorption of dietary non-haem iron in hereditary haemochromatosis. *Gut* 2007;56:1291–5.
65 van Aerts RMM, van Deursen CTBM, Koek GH. Proton Pump Inhibitors Reduce the Frequency of Phlebotomy in Patients With Hereditary Hemochromatosis. *Clin Gastroenterol Hepatol* 2016;14:147–52.
66 Vanclooster A, van Deursen C, Jaspers R, *et al*. Proton Pump Inhibitors Decrease Phlebotomy Need in HFE Hemochromatosis: Double-Blind Randomized Placebo-Controlled Trial. *Gastroenterology* 2017;153:678–80.
67 Dirweesh A, Anugwom CM, Li Y, *et al*. Proton pump inhibitors reduce phlebotomy burden in patients with HFE-related hemochromatosis: a systematic review and meta-analysis. *Eur J Gastroenterol Hepatol* 2021;33:1327–31.
68 Bacon BR, Adams PC, Kowdley KV, *et al*. Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology* 2011;54:328–43.
69 European Association for the Study of the Liver. EASL Clinical Practice Guidelines on haemochromatosis. *J Hepatol* 2022;77:479–502.
70 Beaton M, Guyader D, Deugnier Y, *et al*. Noninvasive prediction of cirrhosis in C282Y-linked hemochromatosis. *Hepatology* 2002;36:673–8.
71 Morrison ED, Brandhagen DJ, Phatak PD, *et al*. Serum ferritin level predicts advanced hepatic fibrosis among U.S. patients with phenotypic hemochromatosis. *Ann Intern Med* 2003;138:627–33.
72 Bassett ML, Halliday JW, Powell LW. Value of hepatic iron measurements in early hemochromatosis and determination of the critical iron level associated with fibrosis. *Hepatology* 1986;6:24–9.
73 Newman BH. Blood donor complications after whole-blood donation. *Curr Opin Hematol* 2004;11:339–45.
74 Rombout-Sestrienkova E, van Kraaij MGJ, Koek GH. How we manage patients with hereditary haemochromatosis. *Br J Haematol* 2016;175:759–70.
75 Snook J, Bhala N, Beales ILP, *et al*. British Society of Gastroenterology guidelines for the management of iron deficiency anaemia in adults. *Gut* 2021;70:2030–51.
76 Ong SY, Gurrin LC, Dolling L, *et al*. Reduction of body iron in HFE-related haemochromatosis and moderate iron overload (Mi-Iron): a multicentre, participant-blinded, randomised controlled trial. *Lancet Haematol* 2017;4:e607–14.
77 Phatak P, Brissot P, Wurster M, *et al*. A phase 1/2, dose-escalation trial of deferasirox for the treatment of iron overload in HFE-related hereditary hemochromatosis. *Hepatology* 2010;52:1671–779.
78 Cançado R, Melo MR, de Moraes Bastos R, *et al*. Deferasirox in patients with iron overload secondary to hereditary hemochromatosis: results of a 1-yr Phase 2 study. *Eur J Haematol* 2015;95:545–50.
79 Kremyanskaya M, Kuykendall AT, Pemmaraju N, *et al*. Rusfertide, a Hepcidin Mimetic, for Control of Erythrocytosis in Polycythemia Vera. *N Engl J Med* 2024;390:723–35.
80 Kowdley KV, Modi NB, Peltekian K, *et al*. Rusfertide for the treatment of iron overload in HFE-related haemochromatosis: an open-label, multicentre, proof-of-concept phase 2 trial. *Lancet Gastroenterol Hepatol* 2023;8:1118–28.
81 Altamura S, Schaeper U, Dames S, *et al*. SLN124, a GalNAc-siRNA Conjugate Targeting TMPRSS6, Efficiently Prevents Iron Overload in Hereditary Haemochromatosis Type 1. *Hemasphere* 2019;3:e301.
82 Rovai A, Chung B, Hu Q, *et al*. In vivo adenine base editing reverts C282Y and improves iron metabolism in hemochromatosis mice. *Nat Commun* 2022;13:5215.