

**Below is a partial translation of the French HAS-protocol on hemochromatosis.**

**This original protocol can be read on:**

**[http://www.has-sante.fr/portail/display.jsp?id=c\\_432802](http://www.has-sante.fr/portail/display.jsp?id=c_432802)**

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### **III.2. What are the therapeutic aims that depletion treatment is intended to achieve?**

*What are the aims?* Analysis of the literature shows that the reserve normalisation criterion has evolved over time: the earliest studies investigated anaemia caused by iron deficiency (39) or the normalisation of liver iron concentrations (which requires regular liver biopsies). Authors currently take the view that "reduction-normalisation" of iron reserves can be assessed by measuring ferritinaemia, which is sometimes carried out in conjunction with fasting T.S.% tests. No published study has been identified that was conducted with a view to determining the best approach or the best targets for reducing morbi-mortality.

**Ideal ferritinaemia level.** There is no real consensus, and individual teams have pursued different targets, ranging from  $< 50 \mu\text{g/l}$  to  $< 20 \mu\text{g/l}$ . The levels selected relate to normal or low iron reserve levels, and individuals who meet these levels should not suffer from deficiency-related anaemia.

No study has been analysed investigating whether normalising ferritinaemia is sufficient or whether it is preferable and more effective to aim for a level equating to hypoferritinaemia. The Sorrento consensus conference held in 1999 simply concluded that venesection should be conducted for life in order to keep ferritinaemia below 20 to 50  $\mu\text{g/l}$  (23). The British Committee for Standards in Haematology (BCSH) is of the opinion that venesection should be performed until ferritinaemia is  $< 20 \mu\text{g/l}$  (55). These two documents also draw a link with achieving a transferrin desaturation state (see below). In 2001, the AASLD's recommendations also set the therapeutic objective of reaching levels below 50  $\mu\text{g/l}$  (irrespective of the T.S.%) and stated that venesection should be performed at widely-spaced intervals in order to reach a level  $< 25 \mu\text{g/l}$  (54).

As a guide, and although what is regarded as a "normal" value depends on the normality thresholds supplied by laboratories, ferritinaemia values are usually between 30 and 300  $\mu\text{g/l}$  in men and between 20 and 200  $\mu\text{g/l}$  in women (3). These rates should be borne in mind when considering previously presented data which draws a link between morbi-mortality and the extent of iron overload (particularly elevated ferritinaemia).

**Aiming for "normalised" fasting T.S.%?** "Reduction-normalisation" of T.S.%, an objective mentioned and regarded as essential by some authors, is more difficult

to achieve. This parameter may be useful in monitoring treatment when there is a dissociation between ferritinaemia (which can rise in response to an inflammatory syndrome) and T.S.%. As a guide, two previously mentioned studies on the natural history of the condition suggest that T.S.% is a relatively stable indicative parameter, while ferritinaemia can be quite volatile as the disease progresses (27, 38).

Where T.S.% is regarded as a therapeutic objective, the benchmark thresholds referred to in the literature vary from 15% to < 40%. No study has been analysed investigating whether normalising T.S.% is necessary, whether it is sufficient, or whether it is preferable and more effective to aim for a below-normal level. In addition to the ferritinaemia objectives, the Sorrento consensus conference simply specified that T.S.% should be brought below 30% (23). The BCSH took the view that venesection should continue until T.S.% was below 16% (55). The AASLD did not take normalisation of T.S.% as a criterion in deciding whether or not to continue with venesection (54).

As a guideline, and although what is taken to be a "normal" value depends on the normality thresholds supplied by laboratories, T.S.% values are normally between 20% and 40% in adults and between 15% and 35% in sexually active women (4, 56, 57). In line with the results of the algorithm developed by the French Society for Clinical Biology and the French Haematology Society (57), the ANAES set an abnormality threshold at 45% in its 1999 and 2004 reports (3, 4).

Finally, data on the link between morbi-mortality and elevated T.S.% levels are patchy and not specific to haemochromatosis.

**Recommendation: rapid achievement of desaturation seems to have beneficial consequences in terms of the prognosis (evidence level 3). The recommended frequency of venesection in the induction stage of treatment is once a week. This should be adjusted in the light of:**

- the extent of ferritinaemia (desaturation can take place at a slower rate when hyperferritinaemia is not too severe [decision-making threshold limit values]);
- the patient's tolerance. **Induction treatment must continue until ferritinaemia is  $\leq 50 \mu\text{g/l}$ .** No consensus was achieved within the working group as to whether or not T.S.% should be normalised or on what target should be set.

### **III.3. What method of treatment (induction and maintenance) should be applied?**

#### **III.3.1. Induction treatment**

— *Principle*

The principle is to perform venesection to eliminate more iron than is contributed by the patient's diet, without causing any major side-effects to the patient. Treatment must be adjusted and declining levels of ferritinaemia (the decline should be steady and significant) must be monitored. Haemoglobin levels must be kept stable in order to adjust the volume of blood taken and the frequency of venesection for each individual patient.

In 1998, Adams (58) conducted a detailed examination of the treatment of 77 patients. Induction treatment involved weekly venesections in which 500 ml of blood were removed. The amount of iron removed each year was  $9.4 \pm 3.1$  g, equivalent to 25 to 50 venesections a year. Haemoglobinaemia was monitored during each venesection and if the level was below  $< 10$  g/dl, a smaller volume of blood was removed during each subsequent venesection. The criterion for stopping induction treatment was a blood ferritin level of  $< 50$   $\mu$ g/l. Few adverse effects were observed, mainly taking the form of local phlebitis. No cases of anaemia were diagnosed (haemoglobinaemia at the end of treatment:  $13.6 \pm 1.4$  g/dl).

— *Contraindications for venesection*

The normal contraindications for taking blood in the context of blood donation. An unpublished document produced by the French Blood Donation Institute (EFS) defining medical contraindications to homologous blood donation list the contraindications relating to risks to the donor. The working group accepted the following contraindications:

*Permanent contraindications:*

- **any pathology that might endanger the patient's health during venesection;**
- **sideroblastic anaemia and any other non-deficiency-related central anaemia;**
- **thalassaemia major;**
- **severe or decompensated cardiopathies that are not due to haemochromatosis: unstable or severe coronary disease, myocardial pathology that is regarded as severe, left heart valvulopathy, decompensated heart failure, poorly tolerated supraventricular or ventricular arrhythmia, etc. (A cardiologist should be consulted to assess the severity of the particular condition).**

**Patients who are in an unstable haemodynamic condition but where this condition is not related to haemochromatosis may undergo venesection under certain conditions (lying down with the head higher than the feet, specialist centre, etc.) and after a cardiologist's opinion has been sought.**

Temporary or transient contraindications requiring postponement of the venesection:

- **anaemia caused by significant iron deficiency (< 11 g/dl particularly where this might be the consequence of previous venesections; conjunctival pallor can indicate this condition<sup>1</sup>);**

<sup>1</sup>The WHO uses a haemoglobinaemia figure of < 11 g/dl to define cases of grade 1 or higher iatrogenic anaemia (59). Its thresholds for cases of anaemia caused by iron deficiency are 12 g/dl in non-pregnant women and 13 g/dl in men (60). These reference values should be used as a guideline. They approximate to the upper and lower limits of normality intervals for 95% of male and female subjects. The cases of anaemia discussed above do not relate to cases of anaemia that may be the result of repeated venesections in patients with haemochromatosis. The figures put forward can be used in the context of screening, but do not reflect the thresholds which are often reached in practice and tolerated in an interventional (medical treatment) or iatrogenic setting. The minimum reference values for venous blood used by the EFS in its document on medical contraindications to homologous blood donation are 12.5 g/dl in women and 13.5 g/dl in men, irrespective of the donor's haemochromatosis status. The preceding remarks on the fact that these figures are only a guideline also apply here.

- **arterial hypotension (BP < 100 mmHg);**
- **severe obliterative arteriopathy of the lower limbs, a past history of acute arterial ischaemia of thrombotic origin in a limb or recent stroke (within the past six months);**
- **a heart rate < 50 or > 100 bpm. ;**
- **pregnancy (the working group considers that there is no major risk requiring treatment to be suspended for nine months; the reference haemoglobinaemia threshold used by the EFS for blood donation in the six months following delivery is 12.5 g/dl);**
- **a very poor or inaccessible network of veins (upper limb);**
- **the development of intercurrent pathology leading to a decline in the patient's general state.**

The working group did not take on board the following contraindications listed by the EFS: neurological conditions (history of stroke or epilepsy), insulin-dependent diabetes, occasional fatigue, weight < 45 kg (limit for taking 13% of TBV between 45 and 50 kg).

— *Practical details: no consensus as to the practical details of treatment*

**Venesection volume.** Analysis of the literature did not reveal any studies looking at the impact of the rhythm and volume of venesections on the efficacy of treatment.

Most of the published studies referred to a volume of blood taken during venesection of 500 ml. This constant volume allows iron overload to be determined by means of a simple calculation (one venesection = 500 ml = 0.25 g of iron). The volume actually taken varied from 300 to 600 ml according to the studies. There were no references to adjustment for weight or sex. The 2004 Anaes report (4) gave an estimate of blood volume of 7 ml/kg, which is the usual figure.

The advantage of calculating the volume to be taken according to the patient's weight is to shorten the length of induction treatment for patients weighing over 70 kg, who can tolerate venesections in which over 500 ml of blood is taken, and to improve tolerance of the procedure for patients weighing under 70 kg: a 50-kg woman can only tolerate a venesection in which 350 ml of blood is taken.

***Recommendation:*** The recommended maximum volume of blood to be taken varies according to the patient's weight (7 ml/kg) but should not exceed 550 ml per venesection. The volume taken must be adjusted in the light of the patient's tolerance, age, and state of health (in particular, his or her cardiac function).

***Venesection frequency.*** The usual frequency referred to in the treatment protocols described in published studies is weekly, particularly for the BCSH (55), but bi-weekly or fortnightly intervals are sometimes mentioned. The weekly rhythm reflects the rate of erythroblast regeneration (the speed with which reticulocytes appear in the blood). Some authors (40, 54, 61) refer to a rhythm of 1 to 2 venesections a week. When this is well tolerated, it increases the iron mobilisation rate, especially when the overload is very high and in stage 4 patients (40). This shortens the duration of induction treatment. It seems important that the frequency of venesection be determined on the basis of the extent of iron overload and tolerance of treatment. The frequency can range from two to four venesections a month, with efficacy determined by the steady and significant decline in ferritinaemia.

***Treatment duration.*** As a guide, the BCSH has suggested that induction treatment should comprise 25 venesections (once a week) with a view to extracting a total of 4.5 g of iron from the body, based on a blood volume of 450 ml (or around 200 mg of iron according to their calculations) and assuming an average daily nutritional iron intake of 3 mg (55). A similar estimate presented in the 2004 Anaes report gave an iron mobilisation rate (amount of iron extracted each year) of 10 g (4). However, the working group notes that in addition to the intensity of treatment, its duration depends on the iron overload, the iron mobilisation rate and patients' willingness to attend venesection sessions.

- ***Iron overload.*** There is a significant correlation between the number of venesections required and iron overload (62), but it is impossible to give an accurate prediction as to how long treatment will last on the basis of ferritinaemia levels.
- ***Iron mobilisation rate.*** A study performed on 77 patients showed that iron mobilisation rates were significantly higher in patients with cirrhosis (58). There was no significant difference in mobilisation rates according to patients' age or sex.
- ***Compliance.*** A retrospective study of 158 patients undergoing treatment and monitored for an average of 8.5 years [0.2; 29.5] found a significant

protective effect on survival of all patients, including that of compliant patients with cirrhosis (45) (see table 3).

**Table 3.** 10-year survival rates of patients on the basis of compliance with treatment, according to Milman *et al.*, 2001 (45).

	No. of subjects	% with cirrhosis	Survival after 10 years	
			compliant	non-compliant
<b>All patients</b>	128	78 %	80 %	35 %
<b>Patients with cirrhosis</b>	100	-	79 %	30 %

Hicken *et al.* (61) investigated treatment compliance in a retrospective study of 118 patients. The compliance rate was 84.5% in the first year, falling by 6.6% a year, especially after the end of induction treatment. The most compliant patients were those who had the highest ferritinaemia levels at the start of treatment, and those who knew that they were C282Y homozygotic.

**Recommendation: The duration of depletion treatment should depend on the initial iron overload, the iron mobilisation rate and the patient's compliance.**

— *Immediate incidents: sensations of malaise*

Investigations of the literature have not revealed any studies describing incidents relating to venesection among blood donors or patients with haemochromatosis. Unpublished EFS data refer to a rate of immediate incidents during homologous donations of around 0.39%; 41% of these occur during the first donation. The most common general manifestations are: vasovagal syncope (65%), loss of consciousness (15%), and significant fall in blood pressure (8%). Local manifestations that have been reported include haematoma, arterial wound, venous wound, infection at the insertion site. The most serious incidents usually occur some time after the procedure.

**Recommendation: venesections must be performed in a reassuring environment by well-trained staff on well-informed patients. A doctor must be present or immediately accessible, especially in the case of patients who are undergoing the procedure for the first time or who have already suffered ill effects.**

**Tolerance checks to be performed before and after each venesection include:**

- measuring the heart rate and blood pressure;
- assessing the patient's clinical condition;

- **looking for any factors pointing to poor tolerance or complications related to the extraction route.**

**Prevention of hypovolaemic malaise must also include:**

- **use of appropriate material (chair allowing the patient to recline in the appropriate position, scales to ensure that the correct volume is taken);**
- **hydrating the patient adequately (providing cold drinks of an identical volume to the amount of blood that will be taken);**
- **where appropriate, volume-to-volume venous compensation (starch solution, macromolecular solution, etc.) for patients whose haemodynamic condition is unstable.**

**If phlebitis occurs, the venesection must be postponed or performed on the other arm, and the usual specific treatment must be given for the phlebitis.**

— *Delayed-onset incidents*

- ***Iron deficiency.*** This occurs at the end of induction treatment or during maintenance treatment. A recent study (63) analysed the cases of 13 patients with anaemia due to iron deficiency during maintenance treatment. Their average ferritinaemia level was  $8 \mu\text{g/l} \pm 3$  and T.S.%  $10\% \pm 5$ . Haemoglobin and ferritinaemia levels were not monitored during treatment.
- ***Phlebitis.*** This incident has already been mentioned above (58).

Long-term tolerance (for example, the effects of repeated venesection on haematopoiesis) has not been directly assessed in the literature.

**Recommendation: Venesections must be accompanied by regular monitoring in order to:**

- **monitor the downward trend in iron overload (and so the efficacy of treatment);**
- **prevent the onset of anaemia or an anaemic syndrome caused by iron deficiency;**
- **prevent and/or treat at the earliest possible stage any rare immediate incidents (malaise and local manifestations) that may occur whenever blood is taken.**

**Monitoring the reduction in iron overload. It is recommended that ferritinaemia levels be checked once a month (every four venesections) at the start of the induction phase and until the upper end of the normal range has been reached: ferritinaemia levels of  $300 \mu\text{g/l}$  in men and  $200 \mu\text{g/l}$  in women. Once these levels have been reached, practitioners are advised to check**

**ferritinaemia every two venesections. In practice, these tests are carried out on the tube leaving the pouch.**

Avoiding anaemia caused by iron deficiency. If the haemoglobinaemia level is below 11 g/dl, venesection must be stopped until it has returned to normal. An investigation must be conducted to determine the cause. Correction by giving an iron supplement is contraindicated. The working group did not come to a consensus as to the ideal frequency for monitoring haemoglobinaemia.

### III.3.2. Maintenance treatment

Analysis of the literature identifies two ways of treatment patients after the induction phase. No studies have been carried out into the respective advantages of these two options.

***Venesections at regular intervals.*** Venesections are conducted according to a set timetable every two, three or four months in order to maintain stable ferritinaemia levels around the desired threshold value.

***New induction treatment only in the event of reaccumulation.*** A few studies refer to the iron reaccumulation rate, and emphasise that not all patients build up new iron reserves at the same rate. On the basis of very small cohorts, the proportion of subjects who reaccumulated iron and needed one or more additional venesections was between 15 and 48%. The figure varied according to the ferritinaemia threshold that had been reached (cessation criterion), the reaccumulation criterion and the length of time that patients were monitored after the end of the first set of venesections (39, 64, 65). In these studies, the reaccumulation rate increases in line with the average monitoring time of between 10.5 months (65) and 48 [12, 123] months (64).

**Table 4.** Iron reaccumulation rates in three retrospective studies.

<b>Study</b>	<b>Treatment</b>	<b>Cessation criterion</b>	<b>Reaccumulation criterion</b>	<b>Reaccumulation (%)</b>
Bomford and Williams, 1976 (39)	Venesection	Hb < 10 g/dl	Ferritin > 150 µg/l	15 %
Muncunill <i>et al.</i> , 2002 (65)	Red cell apheresis	Ferritin < 20 µg/l		4/13 (31 %)
Adams <i>et al.</i> , 1993 (64)	Venesection	Ferritin < 50 µg/l	Ferritin > 200 µg/l	10/21 (48 %)

**Recommendation: It is recommended that maintenance treatment be conducted by performing venesections at regular intervals every two, three or four months in order to maintain stable ferritinaemia levels of  $\leq 50 \mu\text{g/l}$  (the exact frequency should be set on the basis of each patient's needs). Ferritinaemia should be checked every two venesections and haemoglobinaemia in the eight days prior to treatment.**

### III.3.3. Place where venesections are performed

A survey conducted with 260 hepato-gastro-enterology units at general hospitals found that most venesections were conducted in day clinics (67% of cases), with the remainder being split between hospital consultations (16%), blood transfusion centres (22%) and at home (9%) (66). Though this survey does not reflect treatment of all patients with haemochromatosis in France, it underlines the various approaches to treatment and therefore the range in fees charged for a venesection. According to data from the 2004 Anaes report (4) and unpublished data from a survey of therapeutic venesections performed in the Île-de-France region<sup>2</sup>, and according to the experience of working group members:

- the cost of a venesection performed in an EFS facility is €20.8 (however, negotiations are taking place with the health insurance fund, the Directorate-General for Health [DGS] and the Directorate for Hospitalisation and Medical Care Organisation [DHOS] to revise this rate;
- the cost of a venesection performed as an external hospital consultation including nursing care ranges from €40 to €80;
- the cost of a venesection performed at home by a registered nurse (excluding biological tests, medical consultation and waste management costs) is around €20;
- the cost of a venesection performed in a day clinic ranges from €233 to over €500.

The working group wonders whether this margin between the fees charged for venesection in a day clinic and other settings is justified. It considers that there is no argument justifying the systematic use of day clinics to perform venesection, and that the cost gap is excessive.

**Recommendation: Therefore, as far as the medical facilities permitted to perform venesections are concerned, the working group is of the opinion that under normal circumstances the procedure itself and the patient's condition do not justify having this procedure carried out in a day clinic. It strongly recommends that venesections should not be conducted in day clinics (if hospital facilities are needed, then the procedure should be performed as an external consultation) where the patient's condition does not require any particular care, and that the fees charged by these facilities are therefore not justified. The working group considers that a future cost study should allow**

**the fees charged for venesections to be harmonised nationally for all intervention sites.<sup>2</sup> Survey conducted on 52 patients with haemochromatosis during a meeting of the Paris Île-de-France Haemochromatosis Association in Paris on 22 October 2004**

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