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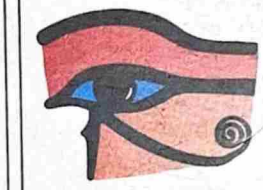

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A SHORT GUIDE TO THE MANAGEMENT OF THALASSEMIA

Reprinted from: "Thalassemia Today - The Mediterranean Experience".
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A SHORT GUIDE TO THE MANAGEMENT OF THALASSEMIA

2nd Mediterranean Meeting on Thalassemia*

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A SHORT GUIDE TO THE MANAGEMENT OF THALASSEMIA

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PREFACE

In recent years it has become clear that thalassemia major, which used to be considered a uniformly fatal disease, can be effectively treated, and that the best results can be obtained by close adherence to a treatment protocol, regularly updated to take the most recent findings into account.

A joint Italian protocol for the management of thalassemia was first produced in 1980 (1), and an update of recommended transfusion treatment and iron chelation therapy was published following the first Mediterranean Meeting on Blood Transfusion in Thalassemia held in Roma in January 1984 (2). However, some of the previous recommendations have already been revised, and the latter dealt only with some aspects of management, so this seems an appropriate time to produce a new edition of the general treatment protocol.

The recent developments are less dramatic than those of the earlier phase: rather, a period of implementation, re-assessment of ideas and monitoring of new clinical developments has followed the earlier major advances, and still continues. Therefore this protocol is more flexible than the preceding one, at least on some points.

It is designed to last some years, but in the end it is bound to become "outdated". In addition, scientific truths are all subject to correction and revision in the course of time. Therefore a treatment protocol is not intended to be applied absolutely rigidly, but is meant to provide a frame of reference for routine practice, and a point of departure for research.

It is important to emphasize that thalassemia patients require a "global" approach to care. A "management group" composed of a pediatrician, a hematologist and/or one or more physicians and perhaps a psychologist is needed to deal with all the clinical problems involved in the routine treatment and the diagnosis and management of all secondary pathologies as well as the psychological problems of the patient and the family, and to provide them with a long-term point of reference.

This revised protocol is based on its two predecessors and some parts are taken bodily from the protocol of "Roma 1984" (2). As in the previous editions the bibliography is limited to essential references. Finally, and necessarily, the protocol reflects the individual experience of the Authors.

BLOOD TRANSFUSION

The principles of blood transfusion in thalassemia have evolved very substantially in the past 20 years. Before 1960 transfusions were given only sporadically, when the hemoglobin dropped below 6-7 g/dL. In 1961 Orsini (3) suggested that hemoglobin should be maintained above 8 g/dL; a similar regimen was recommended by Wolman in 1964 (4). In 1968 Piomelli and his coworkers proposed a "hypertransfusion" regimen (pretransfusion hematocrit more than 28%, corresponding to a hemoglobin of about 9.3 g/dL (5). Regimens that maintain a high level of hemoglobin have gained general acceptance because they allow:

- normal physical activity
- improved growth
- reduction of chronic hypoxemia and secondary bone marrow hyperplasia and hence of bone changes
- reduction of the hypervolemia secondary to bone marrow hyperplasia, and hence of the strain on the heart
- retardation of the development of splenomegaly and hypersplenism, because they reduce the number of red cells containing α-chain precipitates that reach the spleen.

The relationship between the level of hemoglobin maintained and the blood requirement is still not absolutely clear. Some data from patients who mostly had β^+-thalassemia (6, 7) seems to show a direct relationship between the mean hemoglobin maintained by transfusion and blood consumption (Fig. 1), whereas other data, mainly from patients with β-thalassemia (8, 9), shows an essentially constant blood consumption for mean hemoglobin levels between 9 and 14 g/dL (Fig. 2). Moreover in

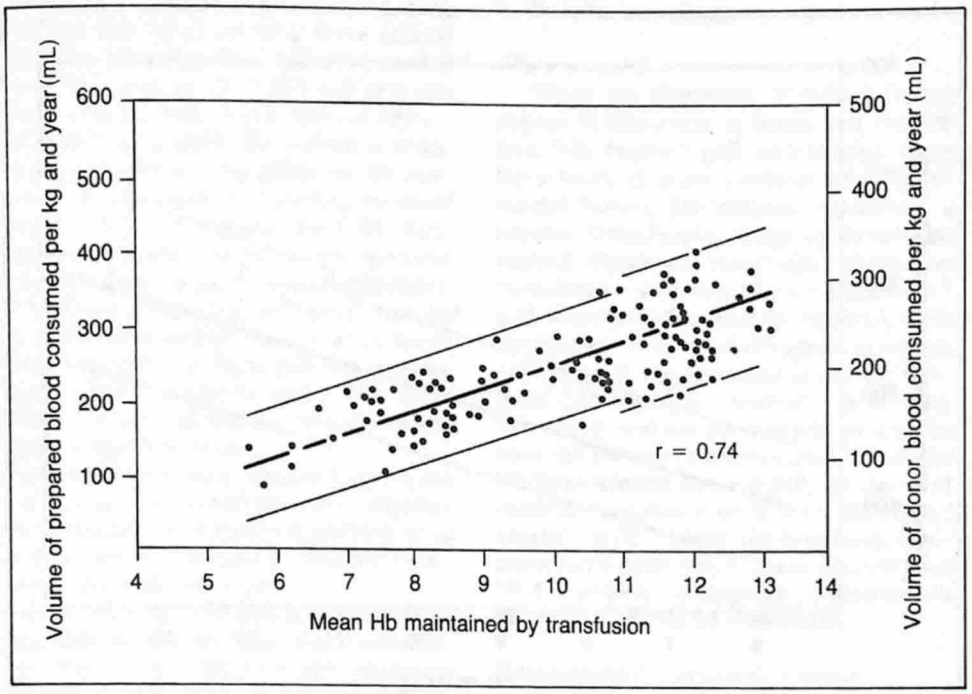

Fig. 1 – Relationship of blood consumption of splenectomized patients with β⁺-thalassemia in the UK (6)

individual patients a reduction in blood consumption is observed when the mean hemoglobin is raised above 10.5 to 11 g/dL (9). This rather unexpected finding is due to the fact that raising the mean Hb level causes a reduction in the bone marrow volume, and hence of hypervolemia. Consequently the amount of blood that has to be transfused to raise the hemoglobin by a given amount in a patient maintained at a high-level is less than that needed to obtain the same increment in a patient maintained at a low level who always has an increased blood volume (8, 9). Naturally, transferring a patient from a low-level to a high-level regimen does cause an increased blood-consumption for some months, until the reduction in blood volume has come about. These observations are true in general, with rare exceptions, for splenectomized subjects. In some unsplenectomized patients, however, the presence of hypersplenism may prevent the adoption, and neutralize the advantages of high-level blood transfusion. High-transfusion schemes also have advantages as far as iron overload is concerned, because they reduce the gastro-intestinal absorption of iron, which is directly proportional to the degree of marrow hyperplasia, and inversely proportional to the patient's hemoglobin level (10). This is important because excessive gastro-intestinal iron absorption can be a contributing factor in thalassemic iron overload (10, 11, 12). In short, it is now clear that transfusion schemes aimed at maintaining the hemoglobin at a high level are the most advantageous; but more experience is needed before we can be sure exactly what is the optimal hemoglobin level to aim for. At present we provisionally recommend a pretransfusion hemoglobin between 10.5 and 11 g/dL.

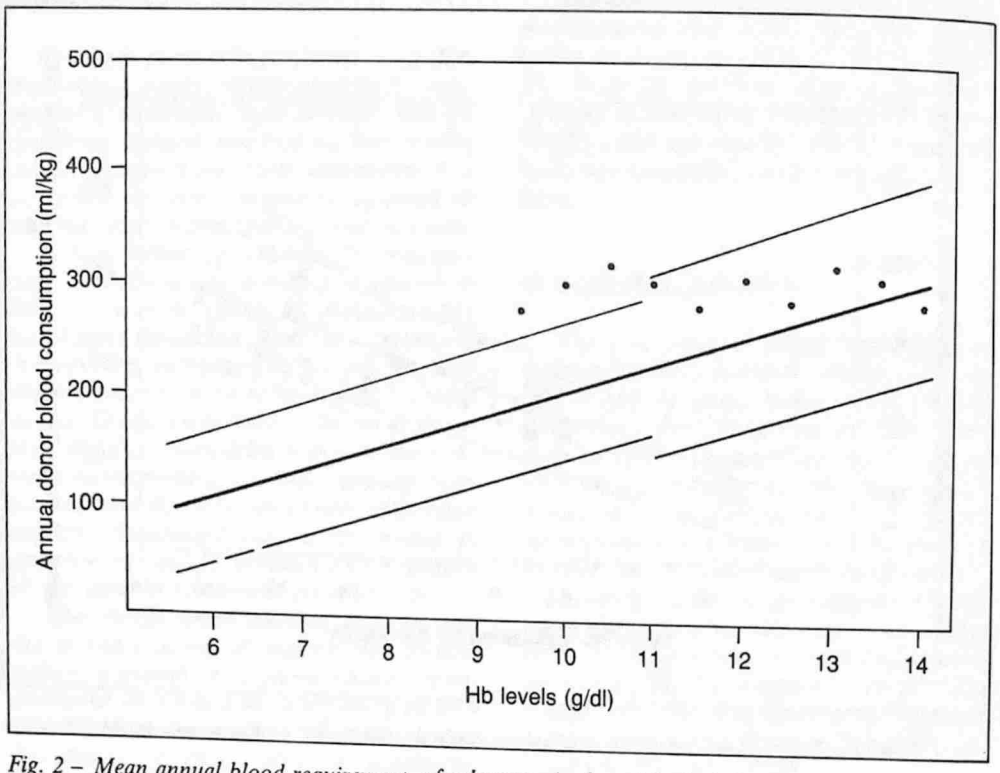

Fig. 2 – Mean annual blood requirement of splenectomized, mainly β^o-thalassemia patients in North Italy, in relation to the transfusion scheme, plotted on the same values for β^+ thalassemia from Fig. 1 (9)

1. Acquisition and preparation of blood, and typing the patients

Although the pediatricians, physicians and hematologists to whom this protocol is principally addressed are well aware of the problems involved in obtaining good quality blood, it nevertheless seems appropriate to repeat the recommendations made at the First Mediterranean Congress on Transfusion Treatment in Thalassemia in Roma, January 1984 (2).

Every possible effort should be made in order to have the necessary amount of fresh blood available. It is therefore necessary to strive to increase voluntary blood donation and to ensure the best possible use of the blood available, avoiding all forms of waste. The first target can be achieved by the combined efforts of doctors, transfusionists, associations of blood donors, patients' associations and the health authorities. The second target calls for the education of doctors in the correct and economical use of blood, and also, where this is appropriate, for a program of auto-transfusion in elective surgery (13).

The following norms are considered necessary for typing of the patient and preparation of blood for patients receiving regular blood transfusions:

- all patients should be typed for the common antigens of the Rh, Kell, Kidd and Duffy systems before the initiation of regular transfusions;
- the patients should be transfused with ABO and Rh(D) compatible blood and should be monitored for the appearance of red cell antibodies;
- before each transfusion there should be a

crossmatch, and antibody screening using a three-cell panel carrying some critical antigens in double dose and the patient's own red cells in the LISA-antiglobulin test, with a serum-to-cell ratio of 100:1;
- if antibodies appear, the patient is transfused with blood compatible for the relevant antigens and, if possible, matched for the common antigens of the Rh, Kell, Kidd and Duffy systems (which represent the principal cause of isoimmunization). Moreover, monitoring antibodies must be continued indefinitely, because more than one third of these patients produce more than 1 antibody and a fifth more than 2, which can make it very difficult to find compatible blood;
- the transfusion center should keep a bank of rare donors (and blood units), together with the data of immunized patients, so as to be able to guarantee adequate treatment for these patients;
- about 90% of homozygous thalassemia patients do not form red cell antibodies. In these cases extensive pretransfusion testing appears to be unnecessary and it is sufficient to give them blood that is ABO and Rh(D) compatible. For this group a LISA-antiglobulin crossmatch including an autocontrol seems sufficient;
- in order to prevent febrile transfusion reactions, and because of the future possibilities of bone marrow transplantation, it is recommended to reduce the leukocyte content by filtration of the blood. Once again, patients who have been regularly transfused for a long time and do not produce febrile reactions do not need filtered blood. Those who do present febrile reactions should be given filtered blood using the method and filter with which the transfusionist has most experience. Different experts recommend filtration at the bedside;
- donor blood should be carefully screened for HBsAg. Patients should be tested for hepatitis B markers, and hepatitis B negative patients should be immunized;
- in view of the present concern about AIDS, it is also important to screen donor blood for anti-HTLV-III antibodies.

2. Transfusion scheme

When to start?

When the diagnosis of typical homozygous thalassemia is made and the Hb level falls below 7 g/dL and remains there for a week or more (without other detrimental factors, for instance, infection), a regular transfusion program should be started. However, transfusion should be considered even when Hb levels are over 7 g/dL when growth is greatly impaired, bone changes are severe and the spleen is rapidly enlarging. If the situation is not well-defined (Hb 8 g/dL or more in a previously well child) wait for some weeks or months until the picture becomes clear. When the Hb level remains above 8 g/dL, or the child remains clinically well with an Hb of around 7 g/dL – which can happen in those uncommon cases where more than 50% of HbA is present – a diagnosis of thalassemia intermedia should be considered.

Recommended transfusion scheme

A scheme in which the pretransfusion Hb is maintained above 10.5-11 g/dL in nonhypersplenic or splenectomized subjects has been recommended here. If it seems likely that this program cannot be strictly applied, it is better to choose a pretransfusion Hb of 10 g/dL from the beginning: lower values are nowadays considered undesirable. The posttransfusion Hb should not rise above 16 g/dL. Higher levels cause an increase in blood viscosity, reduced tissue oxygenation and an increased risk of thrombosis, especially if other risk factors are present (infection, metabolic acidosis, diabetes, etc.). A posttransfusion hemoglobin of over 16 g/dL may also lead to an increased blood consumption.

How much blood to transfuse?

The general calculation of the amount of blood to transfuse to obtain a desired Hb level assumes that transfusion of 2.51 mL of packed red cells with a hematocrit of 100% (or 6 mL of whole blood) transfused per kg body weight should produce an Hb rise of 1 g/dL. Since packed red cells have a hematocrit of less than 100%, the calcula-

tion should be corrected as follows:

$$\text{quantity (mL) of packed cells to transfuse for kg to raise the Hb by 1 g/dL} = \frac{2.51 \times 100}{\text{hematocrit of the pack}}$$

(when the hematocrit of the pack is about 75%, about 3 mL of blood per kg are necessary to raise Hb by 1 g/dL).

In thalassemia it often happens that the Hb level actually achieved is lower than that theoretically predicted. This is because the blood volume is increased in patients with erythroblastic hyperplasia, because of the increased marrow volume (and often also an increased splenic volume). The relationship between the Hb level predicted and that observed can be used to calculate the increase in blood volume (see p. 660). This expansion of blood volume can be substantial prior to the initiation of regular transfusion therapy, especially in patients more than 2 years old, but falls steadily towards normal as transfusion is continued, providing always that it is done correctly. In fact, there is good correspondence between the theoretical calculation of the amount of blood to transfuse, and the result obtained when the patient is stabilized on a regular high transfusion scheme.

The quantity of blood to transfuse is calculated taking two requirements into account: one is to achieve the desired Hb level, and the other is not to overload the circulation.

When there is no cardiac problem it is generally considered acceptable to administer 10-15 mL of blood (or packed cells) per kg body weight in about 2 h. When cardiac failure is present, or when the Hb level is less than 5 g/dL, not more than 5 ml/kg should be transfused at one time, and the rate of infusion should not exceed 2 ml/kg per h. Transfusion time should not exceed 4 h in order to avoid bacterial proliferation in the pack, especially in warm climates. If this cannot be achieved, it is advisable to divide the total amount into 2 (or more) bags and keep 1 in the refrigerator. Transfusion in cases at risk should be preceded by an intravenous injection of furosemide 1-2 mg/kg, and it is also necessary to transfuse very fresh blood. Older blood has a reduced 2,3-DPG level and so has a reduced capacity to deliver oxygen to the tissues, at least for some hours (14, 15). Thus old transfused blood might reduce peripheral oxygen delivery and could actually be disadvantageous in the short term.

Transfusion frequency

In the absence of hypersplenism and immunologic problems, schemes with the shortests intervals between transfusions appear to be the best, because they reproduce the physiological state most closely, and may also be associated with a lower blood consumption (16). However very frequent visits to hospital can be disturbing on the social and psychological plane, so it is advisable to adopt a scheme with intervals that are neither too long nor too short, for instance about 3-weekly transfusions. Other factors, such as the distance from the patient's home to the center and the efficiency of the center should also be taken into account. This rule does not apply to patients with cardiac problems in whom it is important to avoid volume overload. For these, transfusion of small amounts of blood at 1 or 2-weekly intervals is recommended.

3. Complications of transfusion

Sometimes blood transfusion is carried out by a specialist transfusionist and sometimes by a pediatrician or internist, or other doctor who may not necessarily have all the training desirable for dealing with all complications in the best way possible. Therefore it may be useful to summarize here some current views about the possible complications of blood transfusion and how to deal with them. This section is based primarily on the Technical Manual of the American Association of Blood Banks, to which the reader is referred for more detailed information, and references (17).

Acute hemolytic reactions

These are a possible severe complication of blood transfusion. They are usually

due to transfusion of ABO incompatible blood, and are prevented by accurate grouping of the donor and recipient, and by checking that each unit of blood is transfused into the patient for whom it is intended. A further safeguard is to let the blood flow very slowly during the first 15 min so that, if a hemolytic transfusion reaction does develop, the transfusion can be stopped when only a small amount of blood has been infused.

The symptoms of a hemolytic crisis are agitation, pain in the chest or back, rigors, fever, nausea and vomiting. This nonspecific picture can easily be confused with reactions due to the presence of leukocytes in the blood preparation and anti-leukocyte antibodies in the patient's circulation. Therefore this type of reaction should be considered as suspected hemolytic crises and approached as follows:

a) stop the transfusion and replace the blood bag with one of physiological saline;
b) check that the details on the bag and those of the patient correspond. Inform the transfusion center;
c) take 2 samples of blood from the patient, 1 with and 1 without anticoagulant, and send them at once together with the blood bag to the transfusion center for investigations;
d) at the same time, centrifuge an aliquot of the anticoagulated blood and examine the supernatant and a sample of urine respectively for hemoglobinemia and hemoglobinuria;
e) do a Gram stain on a slide made from the blood in the bag;
f) arrange measurement of the haptoglobin level in the blood sample taken from the patient.

In the past it was believed that hemoglobinemia and hemoglobinuria were themselves responsible for the severe symptoms and acute renal insufficiency. However it is now known that the syndrome is mainly due to antigen/antibody complexes that initiate a series of reactions leading to shock and disseminated intravascular coagulation and consequently to arterial hypotension, renal vasoconstriction and thrombus formation, which combine to cause renal insufficiency. The treatment is therefore that for shock and DIC. Whenever possible it is best to transfer the patient to an intensive care unit. In any case the means for treating shock and DIC should be readily to hand wherever blood transfusions are carried out, so that treatment can be instituted without delay. Dopamine is recommended as a vasopressor, because it improves the renal blood flow.

Delayed hemolytic reactions

In some patients transfusions can cause the appearance of alloantibodies that may lead to accelerated destruction of transfused red cells. They do not usually cause acute problems, but may lead to an increased blood consumption and so may be investigated and identified. A second type of hemolytic reaction is sometimes seen in patients who have produced alloantibodies following a transfusion. With time the antibody titre can fall to the point where antibodies are not demonstrable, but a new blood transfusion can provoke a rise in the antibody titer and a hemolytic crisis. Though a considerable quantity of blood may be lysed, this takes place over a considerable period of time, so it does not usually cause an acute clinical picture, though this is not excluded. This type of transfusion reaction may be seen in patients with thalassemia intermedia who were transfused in the past, but come to need transfusion again after some years, either because they gradually become hematologically decompensated, or because the hemoglobin falls acutely for unknown reasons.

Complications due to transfusion of leukocytes

Febrile reactions developing in the course of a transfusion, accompanied by a rise in temperature of more than 1°C are common and are usually due to the presence of leukocytes and platelets in the preparation transfused, together with specific alloantibodies in the patient's serum. They can be treated by stopping the transfusion and giving antipyretics, or by giving

steroids prior to transfusion. They can be prevented by giving leukocyte-poor blood. The initial phase of an hemolytic transfusion reaction can be mistakenly interpreted as a febrile reaction due to leukocytes.

Complications due to the transfusion of plasma

Plasma, transfused as such or as a component of packed red cells, can cause 2 types of allergic reactions:

- urticarial rash. When there are no other signs, the transfusion should be stopped and an antihistamine given. When the symptoms have subsided the transfusion can be resumed. It is advisable to give an antihistamine before the start of transfusions in patients who have frequent urticarial reactions. The best is to give such patients washed red cells;
- anaphylactic shock. Characteristic symptoms are cough, chest pain, hypotension, nausea, abdominal cramps, vomiting and diarrhea, shock and loss of consciousness. Treatment is to stop the transfusion and give adrenaline. This type of reaction is seen in subjects without IgA who have developed anti-IgA antibodies. The appropriate prevention consists in using preparations from donors without IgA.

Plasma contains sodium citrate, which can cause hypocalcemia, and potassium, which can cause hyperkalemia. Neither of these problems should occur while treating thalassemia patients, who are usually given one or another form of fresh packed red cells.

Complications associated with the presence of microaggregates in the preparation

Blood stored for a long time can form microaggregates of white cells and platelets that, once transfused, may lodge in the pulmonary circulation and cause pulmonary edema.

The patient develops chest pain, rigors, fever, cyanosis and hypotension. Treatment consists in stopping the transfusion and administering blood through appropriate microaggregate filters.

Other hypotheses have also been put forward to explain pulmonary edema.

Transfusion of contaminated blood

This is a rare but very serious complication. Endotoxins in the blood cause high fever, shock, hemoglobinuria, DIC, and renal insufficiency. The shock is accompanied by a dry mottled skin. There may be abdominal pain, diarrhea, vomiting and general pain. The immediate treatment is that for shock. In the blood preparation, a Gram stain, and the presence of clots or hemolysis may confirm, but does not exclude the diagnosis. When bacterial contamination is even remotely suspected, treatment should include the administration of antibiotics.

Circulatory overload from an excessive amount of plasma

This should not occur when the recommendations given above about the amount of blood or red cells to give, and the speed of transfusion are followed. It is more often seen when plasma concentrates are not available and whole plasma has to be used for treating coagulation disorders. Prevention consists of avoiding the administration of an excessive volume of plasma and giving a diuretic beforehand.

Transmission of infections by transfusion

Hepatitis is the commonest infection to be transmitted by transfusion, especially hepatitis nonA nonB. In any case it is advisable to give hepatitis B vaccine to patients who have not yet been transfused, or who, though transfused, are negative for hepatitis B markers.

Other infective agents that can be transmitted by blood are cytomegalovirus, malaria, syphilis, and AIDS.

Graft-versus-host disease

This has not been described in thalassemia, and should not occur as a result of transfusion in these patients, since it depends on immunodeficiency of the recipient.

Posttransfusion purpura

Occasionally a patient can present about 7 days posttransfusion with generalized purpura. It is due to the develop-

ment of an anti-platelet antibody to an antigen that is not present in the patient. Platelet antibody complexes cause the destruction of the platelets, leading to a profound thrombocytopenia. It has not so far been reported in a thalassemia patient.

4. Other treatments

Neocyte (young red cell) transfusion

There is some literature about the transfusion of young red cells for the treatment of thalassemia (8, 18). Most Authors agree that at present the approach has only experimental value, due to its low efficiency and the high costly preparation.

Bone marrow transplantation

Marrow transplantation from an identical twin or histo-compatible sib has a well-established place in the treatment of some blood diseases, including childrens' blood diseases; but marrow transplantation for thalassemia was started only a few years ago. Accordingly we are still uncertain of the indications and the long term results. At present we can say that marrow transplantation for thalassemia is past the initial pioneering stage, and that it may be considered as an option for some young transfusion-dependent patients with a fully-compatible donor. We do have some apparently clear information, namely:

- the results of transplantation seem to be better among patients less than 3 years old, who have received few transfusions and are without significant complications;
- graft-versus-host disease seems to be less common among children than among adults;
- the refinement of methods of preparation of the patient seem to have brought about a drastic reduction in mortality.

The Authors of the present protocol believe that the doctor responsible for managing the patients should inform the families absolutely clearly of the possibilities of present management, of foreseeable future developments, and of what is known about marrow transplantation. It is reasonable to proceed to tissue typing the siblings only when it seems possible that the family may actually proceed to bone marrow transplantation.

Other treatments

Even though some recent data suggest that folic acid deficiency may still occur in multitransfused thalassemia patients, there are no clear reasons for continuing to give folic acid to high transfused patients. However it should be given to untransfused or low transfused patients, who may develop relative folate deficiency due to an increased requirement for the vitamin.

Vitamin E is sometimes recommended to counteract iron toxicity. There is no clear evidence for its value, but it is unlikely to do harm, and may do some good, particularly for patients who cannot receive chelation therapy.

EVALUATING TRANSFUSION TREATMENT

Fig. 3 shows simple basic data that should be recorded at each transfusion, and the information that can be obtained from it. Even crude clinical records can be used (6): a more precise approach suitable for rigorous scientific evaluation of treatment is detailed in the Annex 3 (p. 658).

The two most important pieces of information are the mean annual Hb level, and the annual blood consumption, which can be estimated as shown in Fig. 3. They allow the transfusion status of each patient to be evaluated with regard to standard values for the group as a whole, so the effects of e.g. altering the transfusion scheme or removing the spleen can be predicted in each individual case.

For general purposes, the fact that the standard blood requirement is somewhat different in β^+- and β-thalassemia does not matter: an average annual blood requirement of about 300 mL/kg of whole prepared blood may be taken as a rough standard. This is equivalent to 250 mL/kg per year of good quality donor blood, or 100 mL/kg/year of pure red cells. Each patient's observed blood consumption each

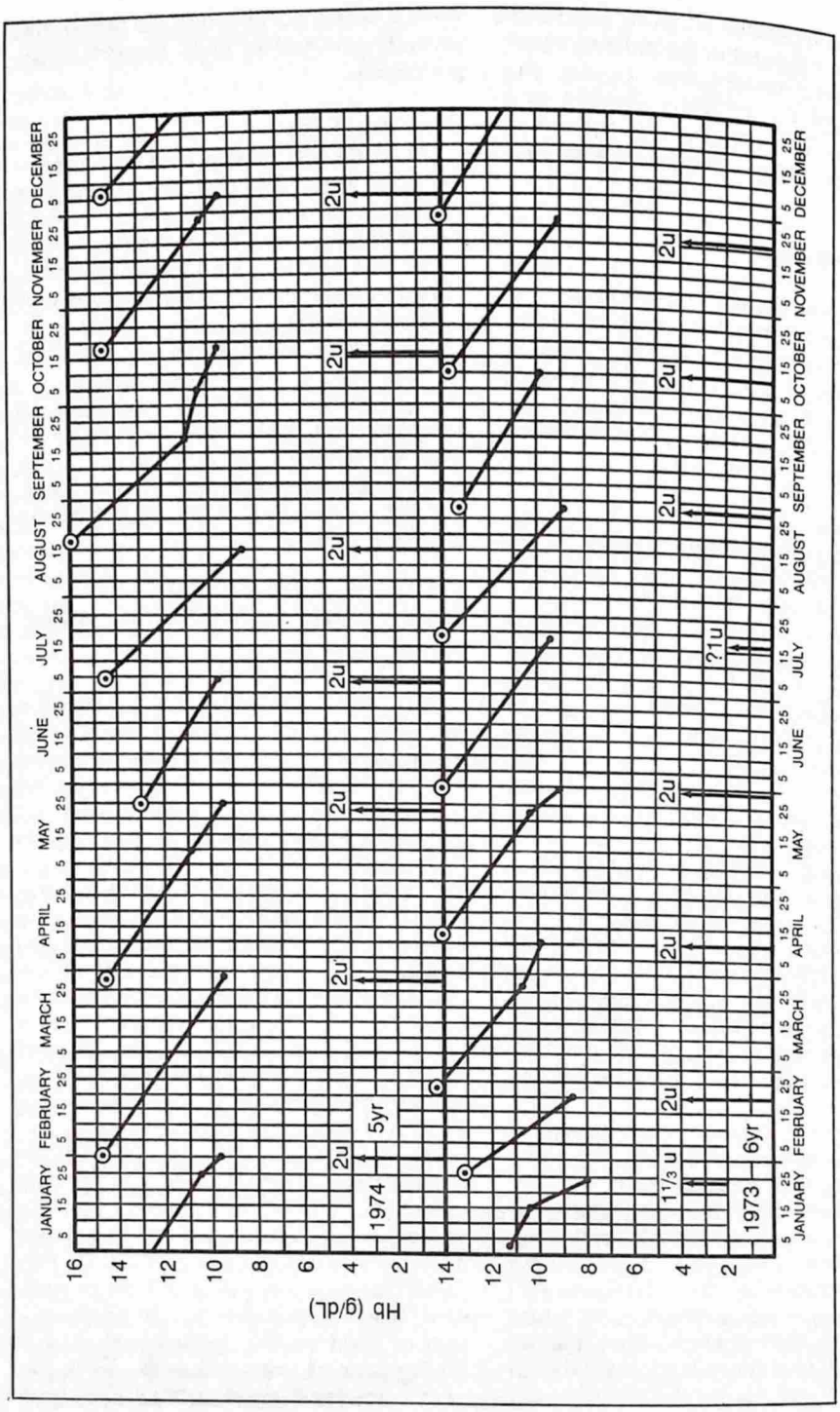

Fig. 3 – The thalassemia patient's hemoglobin chart, and the information that can be derived from it (patient's weight = 23.5 kg)

Mean pretransfusion Hb = 9.0 g/dL
Mean posttransfusion Hb = 14.0 g/dL
Mean Hb = 11.5 g/dL
Mean annual blood consumption = 280 mL/kg
Mean rate of Hb fall = 0.78% of the posttransfusion Hb/day
Apparent blood volume = 1.3 × normal (6)

year may be plotted on the standard curve (Fig. 4a), or divided by the expected requirement to give a "transfusion quotient" (TQ) that can be plotted as in Fig. 4b. This simple approach can be very helpful in ensuring satisfactory progress for each patient.

SPLENECTOMY

High transfusion treatment apparently retards or avoids the appearance of hypersplenism, so splenectomy is now indicated less frequently, or at least later, than in the past. Two factors should be taken into account in deciding on the indications for splenectomy:

- hypersplenism causes an increased blood requirement and so makes it difficult to maintain the patient in iron balance. In addition, more frequent transfusions constitute a significant additional burden for the patient and the family. It is generally considered that splenectomy is indicated when the blood consumption has risen to more than 1.5 times normal;
- on the other hand, splenectomy significantly increases the risk of serious infection. It also seems that in the absence of the spleen, platelet microaggregates may persist in the circulation, and cause pulmonary microemboli.

Therefore it is necessary to evaluate the indications for splenectomy carefully, and postpone it whenever possible to after the fifth year of age. Patients over 2 years of age who are about to be splenectomized

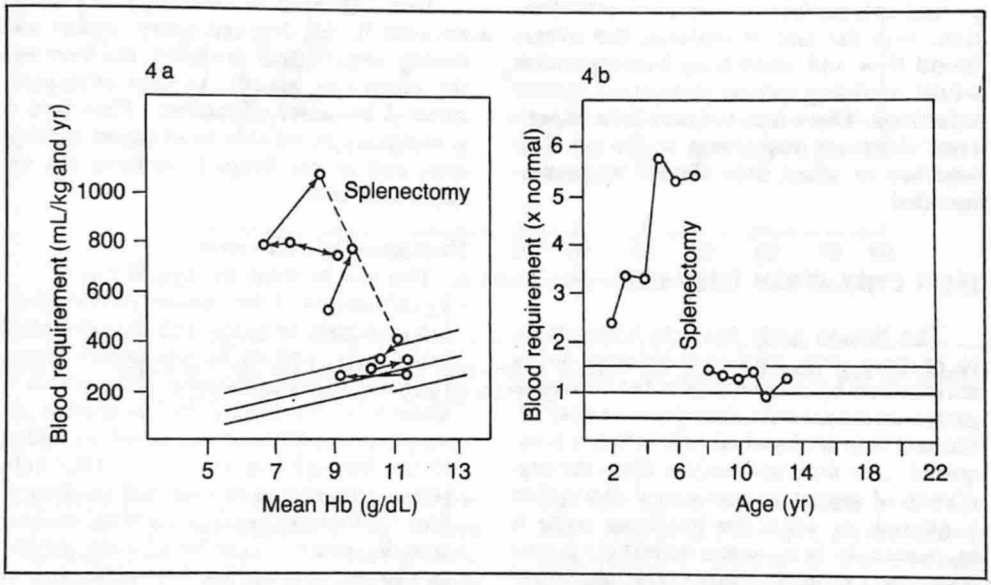

Fig. 4a – The patient's annual blood requirement can be plotted on the standard graph. This shows the development of increased blood requirement due to hypersplenism, and the effect of splenectomy

Fig. 4b – An alternative and clearer way of presenting the same data is as a "transfusion quotient" (TQ) related to the patient's age. The TQ is derived by dividing the observed annual blood requirement, by the expected requirement derived fro the standard graph in Figs. 1 or 2. For patients on a high transfusion scheme (mean annual Hb 11.5 g/dL or more) a basal "expected" figure of 100 mL of pure red cells, or 300 mL of whole prepared donor blood per kg and year may be used (6)

should be immunized with anti-pneumococcal vaccine. Once the spleen has been removed, prophylactic penicillin should be continued for at least 2 years (penicillin V 250 mg b.d., benzathine penicillin 1 vial i.m. every 20 days, or ampicillin 150 mg daily). A platelet anti-aggregant should be given regularly; e.g. Aspirin in a very low dose, between 1 and 25 mg daily should be sufficient (19).

The patients and their family doctors should both be informed that the onset of a fever can mark the beginning of a serious infection in splenectomized subjects, and that broad-spectrum antibiotics including an aminoglycoside should be started immediately, even before receiving the results of laboratory examinations.

It has been suggested that splenectomy might be replaced by procedures such as partial splenectomy or splenic embolization, with the aim of reducing the splenic blood flow and abolishing hypersplenism whilst retaining splenic protection against infections. There is as yet very little experience with these maneuvers, so it is not clear whether or when they should be recommended.

IRON CHELATION THERAPY

The human body has very little ability to excrete iron, and iron balance being maintained by a mechanism that controls gastro-intestinal iron absorption so that additional iron is absorbed only when it is required. Iron may accumulate when the regulation of gastro-intestinal iron absorption is altered, or when the intestinal route is by-passed. In thalassemia both these events occur and can lead to very severe iron overload:

- the intestinal barrier is by-passed by transfusion. One litre of whole blood contains 470 mg of iron (1 L of blood taken into ACD contains 400 mg), and 1 mL of packed red cells (hematocrit = 100%) contains 1.16 mg of iron. In thalassemia the standard blood requirement is 180 mL of packed red cells/kg/year. This annual increment is about 4 times the normal total body iron store. Iron acquired by transfusion accumulates with time, so the iron stores rise to many times the normal;
- gastro-intestinal iron absorption is increased. Normally, intestinal absorption decreases when the body iron load is increased. However in thalassemia (and in other conditions characterized by bone marrow expansion and ineffective erythropoiesis) increased absorption continues despite the iron overload, with a rhythm inversely proportional to the hemoglobin level and directly proportional to the degree of bone marrow activity (10, 11). In untransfused thalassemia major the amount of iron absorbed gastro-intestinally is about 3-4 mg/day (6), and can even reach 10 mg/day in some cases (12), as against the normal value of about 1 mg/day.

Iron overload is extremely important because it can damage many organs and tissues, in particular the heart, the liver and the endocrine glands, so that ultimately survival becomes impossible. Therefore it is necessary to be able to evaluate it properly, and to use drugs to remove the accumulated iron.

Evaluation of iron stores

This can be done in several ways:

- by calculation of the amount of iron given intravenously as blood and that absorbed intestinally, and of the amount excreted. In normal subjects iron absorption is about 0.5-1.0 mg daily. In thalassemia absorption is normal or increased according to the hemoglobin level. In normal subjects, iron excretion is equal to absorption. In thalassemia it is variable, and especially when it is induced with desferrioxamine, evaluation by calculation is not really possible;
- by the "Desferal test" in which the iron excretion over 24 h after an injection of 500 mg of desferrioxamine is measured. Fig. 3 shows that the correlation between body iron load and iron excretion in the urine is very variable. Nevertheless, three results of this test can be taken as reference points. An excretion of more than 1 mg indicates that the iron load is large

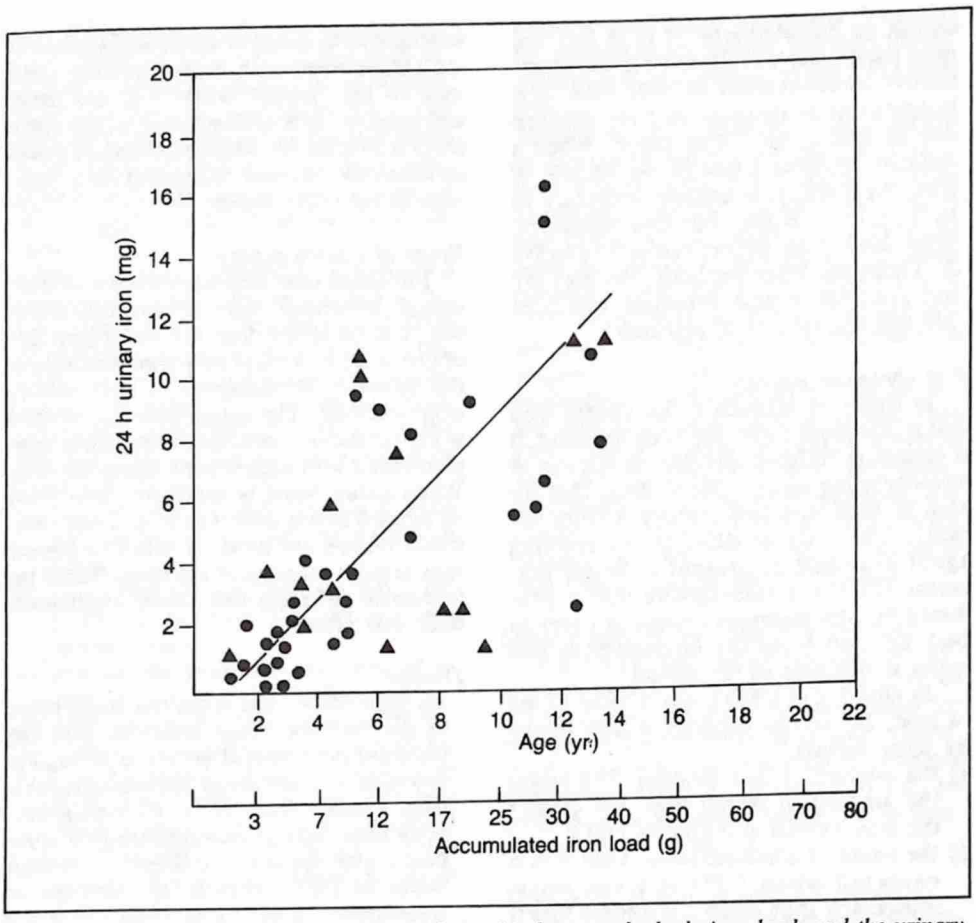

Fig. 5 – There is a useful but approximate relationship between the body iron load, and the urinary excretion following a standard dose of DFO (6)

enough for treatment to be started. Excretion of 10 mg indicates a level of iron loading that is sufficient to block growth. Excretion of 20 mg corresponds to a body load of 70 g, which is incompatible with prolonged survival (6);

- by determining the serum ferritin level, which is directly correlated with the iron load (20, 21, 22). One µg of serum ferritin corresponds to about 8 mg of iron mobilizable from deposits (23). A ferritin level of less than 20 µg/L indicates iron deficiency; values above 100 µg for women and 250 µg for men indicate iron overload. A level of 7000 µL/L corresponds to iron overload sufficient to interfere with growth, whereas a level of 10,000 or more is incompatible with prolonged survival (6). However, the ferritin level may be abnormally raised above that corresponding with the iron load in patients with liver disease, and there are also some individuals who have a low serum ferritin in the presence of iron overload;
- the most important of the other methods is liver biopsy. Though this is invasive and

entails an elevated risk, it is in fact the most useful, since it allows both the quantitative measurement of liver iron, and histological evaluation of liver damage due to iron or any other cause. When a difficult problem arises in the control of iron overload, it is usually necessary to turn to liver biopsy but this should be done only at an expert center to resolve it. There are other methods, but they are not available in most hospitals, and most are still the subject of research.

Iron chelation therapy

In order to eliminate the excess iron that is introduced into the body as blood, it is necessary to have recourse to the use of iron-chelating agents; that is, drugs that are able to bind iron and remove it from the body. The only medical iron chelating agent available at present is desferrioxamine (DFO), a siderophore that is produced by Streptomyces pilosus in order to pick up iron from the environment and make it available to the mould.

In vitro 1 g of DFO binds at most 85 mg of iron. *In vivo* its capacity is determined by three factors:

1) the amount of iron in store. The larger the amount of stored iron, the greater the iron excretion following DFO;
2) the route of administration. Less iron is excreted when DFO is given intramuscularly than when it is infused slowly intravenously or subcutaneously (24, 25);
3) the patient's vitamin C status. If vitamin C is depleted, iron excretion in response to DFO is reduced.

PRACTICAL DETAILS OF DESFERRIOXAMINE THERAPY

When to start treatment?

In the past, treatment was usually started around the third year of life, but it is now thought more effective to start considerably earlier (26). Starting chelation therapy more or less at the same time as starting transfusions is recommended for psychological and medical reasons. It is advantageous to avoid two emotional crises in the child's treatment, and to get the child used to the "pump" while it is still small and passive. It is also advantageous, since DFO is so effective when administered subcutaneously, to start to control iron overload as early as possible (25).

Route of administration

Intramuscular administration of DFO, though beneficial, may not be fully effective, and certainly does not make best use of the drug, so it plays only a modest role in the modern management of thalassemic iron overload. The recommended method is subcutaneous infusion, sometimes supplemented with intravenous infusions (24). When either route is used, the drug must be infused slowly over 9 to 10 h. Small electronic pumps are used, in order to ensure slow regular infusion of the drug. Rapid intravenous infusion can cause unpleasant toxic side effects.

Dosage

- Standard dose. The collective experience of the last few years indicates that the standard dose should be about 40 mg/kg/day (that is to say about 280 mg/kg/week), with a range from 20 to 60 mg/kg/day. Sometimes subcutaneous infusion is combined with intravenous infusions of high doses of DFO, usually at the time of transfusion. Doses range from 6 g in 8 h (27) to 9-12 g in 24-48 h (28); a dose of 100 mg/kg in 8 h should not be exceeded. At present this practice cannot be generally recommended because there is not yet sufficient information on its value.
- Calculated dose. It is theoretically possible to calculate the optimal dose by evaluating the total iron introduced (iron transfused as blood plus iron absorbed) and the iron excreted in response to different doses of DFO. The method is laborious because it depends on the estimation of both urinary and fecal iron to establish a dose/response curve (29), so it is no longer generally recommended for general use.
- High dose intravenous treatment regimens. The continuous intravenous infu-

sion of high doses of DFO to treat heavily iron-loaded patients who deteriorate despite conventional treatment, should be used only with extreme caution (30). The place of these regimens in the treatment of thalassemia has not yet been adequately defined. In any case, a dose of 125 mg/kg/day of DFO should not be exceeded (31).

- Administration of vitamin C. Iron-loaded patients generally become vitamin C depleted, probably because iron accelerates its oxidative catabolism to oxalate (32). Under these circumstances the administration of vitamin C increases the excretion of iron with DFO (33). However the following steps are recommended to avoid complications (34):
  a) start treatment with vitamin C only after an initial cycle of treatment with DFO;
  b) give vitamin C supplements only if the patient is receiving DFO therapy on a regular basis;
  c) give the minimum effective dose of vitamin C, i.e. about 5 mg/kg (35);
  d) do not exceed a daily dose of 200 mg. Vitamin C supplements are not necessary for patients who eat oranges or drink fresh orange juice regularly (one large orange contains on average 75 mg of vitamin C and 100 mL of fresh orange juice contains about 50 mg of vitamin C).

Complications of desferrioxamine administration

Several types of complication have been encountered:

- local painless swelling at the infusion site. This is most commonly due to hypertonicity of the solution. DFO should be taken up into distilled water at a maximum concentration of 1 g in 5 mL of water. The first advice to offer to patients who complain of a lump at the site of infusion is to decrease the concentration of the solution infused by increasing the amount of water used with a given dose. The increased volume should be infused over the same period of time as before;
- local reactions such as pruritus, a rash and more or less intense hyperemia. This may be controlled by adding hydrocortisone, maximum dose 2 mg/mL to the DFO solution;
- "anaphylactoid" reactions. These should be treated by desensitization (36, 37);
- toxic effects on the eye. Cataracts, night-blindness, reduction of the visula fields and reduction of visual acuity have all been described. In general ocular complications arise only when higher doses of DFO than those usually recommended are used, and regress when treatment is suspended (31, 38);
- facilitation of infection with Yersinia enterocolitica. It has been proposed that DFO administration facilitates infection with this organism (39, 40). Therefore, reversing previous recommendations, it is advised to suspend DFO therapy during febrile episodes if there is a possibility that these could be due to Yersinia.

Other means of reducing iron overload

Tea taken with meals reduces the absorption of iron of vegetable origin (10), so the regular use of tea is recommended for patients with a low mean hemoglobin level, and especially for patients with thalassemia intermedia. These patients should also be advised to avoid animal foods rich in iron, such as liver and spleen.

Evaluation of iron chelation therapy

The chelation program needs to be evaluated from time to time, with reference to the patient's iron balance, and compliance.

Calculation of iron balance

$$\text{Chelation index} = \frac{\text{mg of Fe introduced/year}}{\text{mg of Fe eliminated}}$$

mg of Fe introduced/years = no. of mL of RBC transfused x 1.16 (where 1.16 is the amount of Fe corresponding to 1 mL of RBC)

mg of Fe eliminated = mean urinary Fe x no. of days of treatment x 1.6 (where 1.6 is the factor which takes account of fecal iron excretion with DFO)

$$\text{compliance index} = \frac{\text{no. of days of treatment}}{365}$$

Evaluating the efficacy of treatment

Chelation therapy is generally monitored by 6-monthly measurement of the serum ferritin, which should be kept below 1,000 ng/mL. If this level is not reached, the effectiveness of the chelation therapy should be investigated, and the patient's compliance needs to be monitored. Compliance with treatment tends to be poor in all chronic diseases. An important cause of noncompliance with chelation therapy is simply getting fed up with the treatment, especially with the "pump". Some parents find that the daily "aggression" against their own child can become unbearable, especially against the background of guilt connected with the hereditary nature of the disease, whereas many adolescents and young adult patients would like to deny the reality of their disease be-

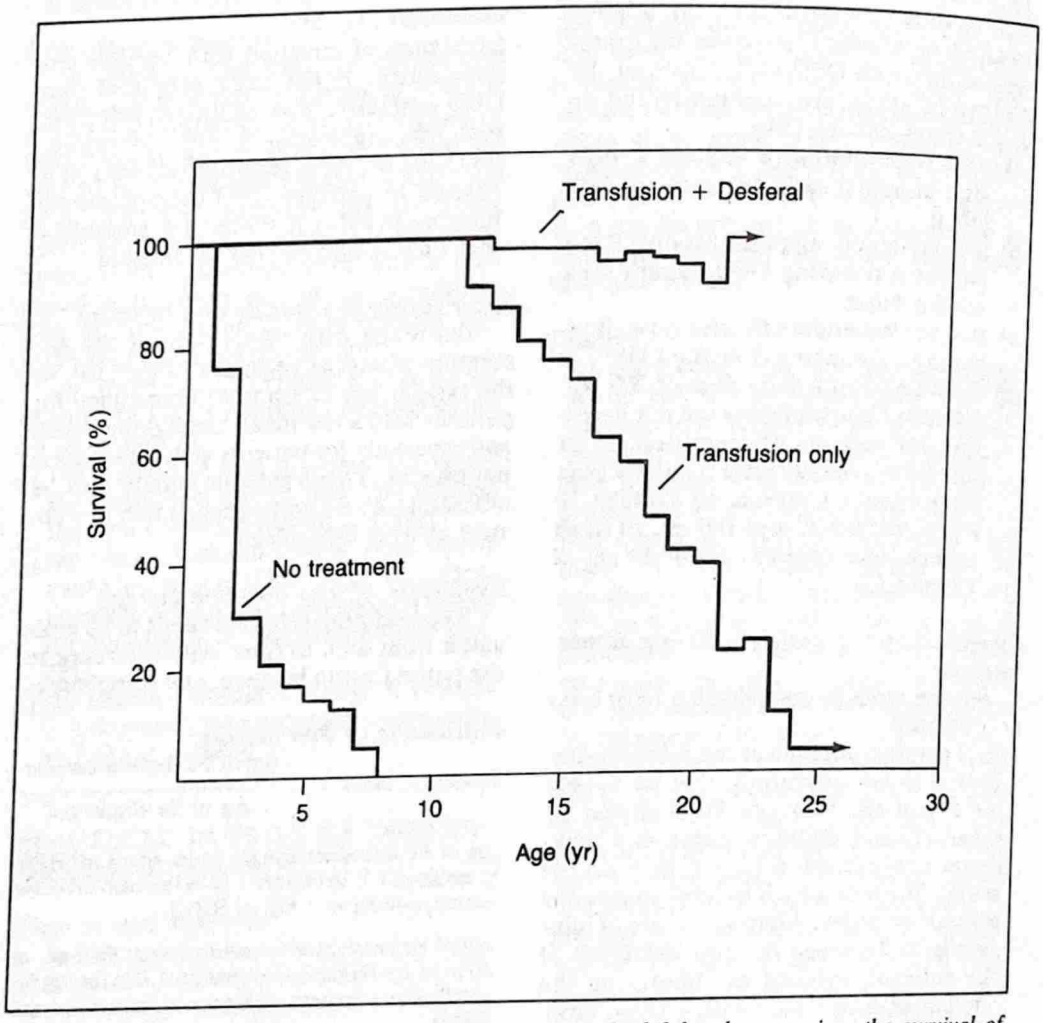

Fig. 6 – Survival in thalassemia in relation to treatment. The left-hand curve gives the survival of untreated children in Ferrara with β°-thalassemia (data from the 1950s); the middle curve, survival of high transfusion unchelated patients in England, and the top curve, survival of high transfused chelated patients in England (6)

cause of the strong need to feel normal at this age.

Compliance can be helped by giving the patients a calendar in which to mark each injection of desferrioxamine as they do it. It can also be useful to ask them to bring back the empty DFO vials, so that they can be replaced and incidentally counted. The importance of good compliance should be discussed regularly with the patients and their families.

In the medium term monitoring growth around puberty has been proposed as a way of measuring the beneficial effect of chelation therapy for groups of patients; whereas monitoring survival appears to be the most definitive way of evaluating the long term effectiveness of treatment. Fig. 6 shows a promising beginning.

COMPLICATIONS

Despite iron chelation therapy, complications of iron overload are very common in older patients with thalassemia, probably due to three factors:

1) inadequate treatment in the first years of life, so that some irreversible damage is sustained;
2) poor compliance;
3) the insufficiently energetic way in which chelation therapy was applied until recently, from a reasonable fear of possible toxic effects of DFO;
4) excessive blood consumption.

Endocrinological complications

The following are those most frequently seen:

1) retarded growth. In the past this commonly occurred in the early years of life in association with chronic anemia, but now it is usually seen only around the time of puberty and has an endocrinological basis, though this is not yet well defined (6) (Fig. 4);
2) abnormal pubertal development. A high proportion of thalassemia patients suffer from delayed onset of puberty. This could be because they did not receive iron chelation therapy in their early years as it was not available at the time. A proportion of girls have their menarche, but some then develop secondary amenorrhea (4). These patients should be given replacement therapy if they want it, but there is as yet insufficient experience with treating them to be able to give specific recommendations. An expert endocrinologist who is up-to-date in the field should be consulted;
3) diabetes mellitus. This is a common complication among thalassemia patients of pubertal age or above, especially in those who comply poorly with the DFO treatment (42). They are insulin-dependent and the diabetes is difficult to control. The butterfly that has been used for the DFO infusion during the night can be used for the morning injection of insulin;
4) hypoparathyroidism with or without altered vitamin D metabolism. This complication presents as hypocalcemia. The patient complains of tingling or itching sensations. Untreated, the hypocalcemia can cause convulsions. In patients with cardiac failure it is important to measure the serum Ca prior to starting treatment with digoxin, because hypocalcemia reduces the action of digoxin (it is also important to remember that hypercalcemia increases digoxin toxicity: sudden death has occurred following intravenous infusion of Ca in digitalized patients);
5) hypothyroidism. A significant number of thalassemia patients, especially those who have other endocrinopathies, develop primary hypothyroidism with or without clinical signs (43). They should receive replacement therapy;
6) adrenal insufficiency. Adrenal function at the lower limit of normal has been demonstrated, though clinical signs of adrenal insufficiency have not been described. It is possible that it could develop in a seriously ill patient.

Cardiac complications

Cardiac iron overload can cause cardiac arrhythmias, pericarditis and cardiac failure. Treatment does not differ from that

of nonthalassemia patients.

Neurological complications

Hypertension, convulsions and cerebral hemorrhage have been observed following transfusion in patients who have previously been maintained at very low hemoglobin levels (44). These problems can be prevented by starting transfusion earlier, and probably also by a very gradual induction in such cases.

Hepatic complications

In the course of time many thalassemia patients develop liver disease including cirrhosis (45, 46, 47). The pathogenesis is multifactorial, the most important factors being the accumulation of iron from transfusions, and infection with a hepatitis virus. Hepatitis is diagnosed by elevation of the serum transaminases and the γ-glutamyltranspeptidase (γGT). Liver biopsy and a search for hepatitis B markers are required for accurate diagnosis of liver pathology, and to design appropriate management.

MANAGEMENT OF THE ACUTELY ILL THALASSEMIA PATIENT

Thalassemia patients develop acute illnesses requiring urgent treatment considerably more often than normal individuals do. Such episodes are mainly due to infections or cardiopathy. Less often there may be another emergency such as diabetic coma or a cerebrovascular accident.

Of course it would be impossible to produce a single protocol for all these problems because each event has its own characteristics and requires individual treatment. It is nevertheless possible to make the following general recommendations:

1) measure the Hb, blood urea, serum bilirubin, blood glucose, serum Ca, electrolytes and thyroid hormone at once. Arrange an ECG;
2) do not give digoxin until it is certain that the serum Ca is normal. Diuretics may be given in the first instance to treat cardiac failure;
3) when there is a serious acute infection, do a blood culture at once and start broad-spectrum antibiotics immediately. Include an antibiotic that is effective against Yersinia, for instance an aminoglycoside, because of the relatively increased frequency of Yersinia infections in thalassemia. Septicemia is highly likely to lead to a state of shock, so it may be wise to transfer the patient to an intensive care unit, or to seek the advice of a specialist in intensive care;
4) it has been recommended previously (6) to initiate, or to continue DFO therapy, intravenously at a dosage of 75 mg/24 h, in order to antagonize iron toxicity, which is increased in acute infections and in hypoxia and metabolic acidosis. If an infection with Yersinia is suspected, it is now proposed to discontinue DFO treatment, because this organism is capable of making use of iron bound to DFO (40,41);
5) raise the Hb to 14 g/dL to combat hypoxia, even if this calls for an exchange transfusion;
6) correct hypothyroidism by giving L-thyroxine;
7) remember the possibility of adrenal insufficiency.

OTHER ASPECTS OF MANAGEMENT

Psychological support

As with other chronic diseases, thalassemia involves difficult psychological problems that are specific for the disease and the treatment. For instance, the inherited nature of the disease, its appearance during the first year of life, the possibility of physical deformity and the need for continuous punishing treatment, can have grave repercussions on the emotional development and relationships of both child and family (47).

Unless the management group deals with these problems in parallel with the more technical aspects of treatment, there can be negative effects on the acceptance of the disease and its management, and the patient may become unable to lead even an

approximately normal life. Therefore the doctor directly responsible for the patient should attend to this aspect as well, either directly, or, better still, with the help of appropriate specialists such as psychologists, psychiatrists and social workers.

Patients' associations

As already mentioned, the disease imposes a heavy emotional burden on the family. Associations of parents and patients help them to feel less isolated, and let them know that they can depend on the help and comfort of others in the same situation. Through the associations the families learn to see that the disease need not be completely overwhelming, and so become more capable of coping with their own problems. Associations also facilitate the dialogue between patients and doctors which is such an important aspect of all chronic diseases, and so increase the patients' and the families' compliance with the therapeutic regimen.

Genetic counseling

The diagnosis of a child with thalassemia should be accompanied by adequate genetic counseling, and the offer of hematologic screening for the families of both parents. In fact, this is an important opportunity to identify the heterozygote siblings of the parents and offer them genetic counseling.

Physical and recreational activity

The life of thalassemic children should be as normal as possible. Physical and recreational activity should not be restricted unless there is a precise medical contraindication, such as cardiac disease.

Dental caries

Many thalassemic children have malformations of the facial bones together with dental caries. Since the malformations are due to marrow expansion, they are now less severe and seen much less frequently than they used to be. Dental caries also seems to be less common. Thalassemic children may be given fluoride supplements, like normal children.

Social integration at school and work

The recent improvements in treatment and the consequently improved prognosis mean that the patients should be integrated as fully as possible into normal life at school and at work.

THALASSEMIA INTERMEDIA

This term is used differently by different Authors. Probably the simplest definition is that those thalassemics who can maintain a hemoglobin level between 7 and 10 g/dL have thalassemia intermedia (48). When the first edition of this protocol was published, there was no definite scheme for the treatment of thalassemia intermedia, partly because of the diversity of the condition and its clinical expressions, and partly because of the relatively small number of cases. More recent experience and the greater attention that has been paid to the condition, now permit a more definite approach to some of the problems at least.

Transfusion treatment

Patients who maintain a good Hb level (probably above 8 g/dL), who manage to lead a normal life, and have no other problems should not be started on transfusion treatment. When the Hb drops persistently below this level, or marrow expansion causes progressive development of an abnormal facies or other bony lesions, or when the spleen increases rapidly in size, the decision to initiate transfusions is taken more readily than in the past, because it involves less risk now that iron chelation therapy is available. There seems no good reason to adopt a different transfusion scheme from that used in thalassemia major.

Iron chelation therapy

Patients with thalassemia intermedia may develop iron overload as a result of increased gastro-intestinal iron absorption. Therefore they should be advised to avoid eating meat particularly rich in iron (e.g. liver and spleen), to avoid iron-supplemented cereals (e.g. many breakfast cere-

als), and to drink a cup of tea with every meal, since tea reduces the absorption of non-heme iron (10). There is no precise agreement on the criteria for deciding when to start chelation therapy. It has been suggested that it be started when the serum ferritin has risen above 2000 ng/mL (6), but it is probably reasonable to be more aggressive and start when the serum ferritin rises above the normal range. Whichever criterion is chosen, it should suffice to give DFO subcutaneously on 1 or 2 days a week only. Obviously the treatment should be monitored in the same way as for patients on regular transfusions.

Splenectomy

The clinical signs of hypersplenism, namely enlargement of the spleen accompanied by a fall in the mean Hb level, constitute the indication for splenectomy in thalassemia intermedia. Splenic enlargement of 6 cm or more is nearly always accompanied by some hypersplenism in thalassemia, but as long as the patient remains clinically well, there is no indication to remove the spleen. Clinical criteria are more useful than chromium studies, which are of relatively little value in this situation, because they must be conducted using autologous red cells. A reduced red cell lifespan is therefore difficult to evaluate, and the whole result depends on measuring red cell pooling in the spleen and the differential accumulation of radioactivity over various organs, which is hard to perform reliably except in specialist research centers. Hypersplenism also causes leukopenia and thrombocytopenia, but these appear far too late in the development of the syndrome to be useful indicators: when they are present, splenectomy is always indicated. In fact, as for transfusion, it is better to take the decision without waiting to the last moment. This opportunity should also be taken to examine the gall-bladder for gall stones.

Other problems

Patients with thalassemia intermedia should take folic acid 5 mg daily by mouth, to avoid relative folate deficiency due to excessive folate consumption by the expanded marrow. When urinary uric acid excretion is greatly raised, it is advisable to consider prescribing allopurinol, to prevent uric acid nephropathy.

Gall stones should be looked for from time to time, especially if the patient complains of abdominal pain.

Leg ulcers are common and very difficult to treat. It may be useful to advise the patient to take the following simple measures:

1) wear a towelling band round their ankles like those that tennis-players wear round their wrists;
2) sleep with the end of the bed raised by about 10 cm;
3) keep the legs and feet raised for 1 to 2 h during the day when possible, for instance when watching television.

Giving zinc sulfate by mouth, or oxygenating the ulcers also may prove useful. However the only really successful treatment is high transfusion, in some cases.

Pregnancy is another problem that presents relatively frequently. It is considered advisable to start pregnant women with thalassemia intermedia on regular transfusion, and to discontinue DFO treatment. It is probably wise to use frozen blood when possible, to minimize the risk of transmitting infections. Since DFO treatment should be discontinued, it is also desirable to try to reduce the serum ferritin to the normal range before the beginning of the pregnancy.

The hyperplastic bone marrow can also cause neurological complications due to compression. When there is a neurological lesion of the spinal cord, radiological examination of the spinal column should be carried out immediately to exclude a fracture. If the problem persists, myelography should be done to visualize the lesion and its level. In doubtful cases exploratory laminectomy is indicated. The treatment is deep radiotherapy of the spinal cord up to a total dose of 2000 to 3000 rads, from the upper limit of the zone of anesthesia to the level of the lesion shown by myelography (49).

SUMMARY OF RECOMMENDATIONS FOR THE TREATMENT OF THALASSEMIA MAJOR

TRANSFUSION

Transfusion, in the absence of cardiopathy:

1) blood-type the patient completely;
2) vaccinate hepatitis B negative patients against hepatitis;
3) transfuse when the Hb remains consistently below 8 g/dL, or earlier if there are other indications;
4) keep the pretransfusion Hb between 10.5 and 11 g/dL;
5) give 10-15 mL/kg of blood preparation in 2 h;
6) do not raise the posttransfusion Hb above 16 g/dL;
7) choose a 3-4 week transfusion interval.

Transfusion in the presence of cardiopathy, or when the Hb is less than 5 g/dL:

1) inject furosemide 1-2 mg/kg;
2) preferably use fresh blood;
3) do not transfuse more than 5 mL/kg of blood;
4) do not transfuse faster than 2 mL/kg, or for more than 4 h;
5) if necessary, divide the blood among 2 or more bags;
6) use very short intertransfusion intervals.

IRON CHELATION THERAPY

1) Desferrioxamine s.c. 20-60 mg/kg/day in 8 h (average 40 mg/kg/day, or 280 mg/kg/week).
2) In selected subjects, give desferrioxamine i.v. in high dose, maximum 100 mg/kg over 8 h, only on the days of transfusion.

SPLENECTOMY

1) Is indicated when the blood consumption is more than 1.5 times normal.
2) Give anti-pneumococcal vaccine to children more than 2 years old prior to splenectomy.
3) Inform the patients and their family doctors of the increased risk of serious infections.
4) Give prophylactic penicillin, and a platelet anti-aggregant when there is thrombocytosis.

INVESTIGATIONS

Prior to treatment:	study the case, and do complete red cell typing.
Before each transfusion:	Hb, cross-match and red cell antibody detection, serum transaminases (in areas with a high incidence of hepatitis). Record the date of transfusion, net weight and mean hematocrit of the blood preparation, and the Hb of the patient.
After each transfusion:	measure the posttransfusion Hb.
Every 3 months:	measure height and weight.
Every 6 months:	ferritin estimation.
Every year:	evaluate growth and development. Calculate the transfusion indices. Evaluate iron balance. Complete evaluation of the case.
Variable intervals:	cardiac and endocrinological investigations according to the clinical state of the patients.