1. Blood Transfusion

The recommended treatment for thalassaemia major involves lifelong regular blood transfusions to maintain the pre-transfusion haemoglobin above 9.0-10.0 g/dL. This regimen promotes normal growth and physical activities, adequately suppresses bone marrow activity, and minimises transfusional iron accumulation. The patients with cardiac disease or those who do not achieve adequate suppression of marrow erythropoiesis may be maintained at a higher pre-transfusion haemoglobin (11-12 g/dl). The post transfusion Hb should not be raised above 15.0 g/dL.

1. **When to start blood transfusion?**

The blood transfusions should be started in all newly diagnosed patients of thalassaemia major in whom the haemoglobin falls below 7.0 g/dL and it remains there for a week or more. The transfusions may also be considered in patients whose haemoglobin is over 7.0 g/dL but they develop growth impairment, bone changes or enlarging spleen. The patients who remain clinically well with Hb more than 7.0 g/dL should not be transfused unless they show any of the above signs.

2. **Type of blood to be given**

Packed red blood cells with minimum possible white cells and plasma are the product of choice. The packed cells are prepared by removing plasma with a plasma extractor (Chapter 13). The separated plasma can be collected in a second bag and it can be used elsewhere; or the plasma can be discarded if double bags are not available. The packed cells should have a haematocrit of at least 75%. It is preferable to use blood that is not older than one to two weeks.

The patients who develop febrile transfusion reactions due to anti-leukocyte antibodies require leuko-poor blood. The unwanted WBCs are best removed by filtering the blood through special bed-side filters. If the filters are not available packed cells may be washed in the lab with sterile normal saline. Washing of blood should be done under strict aseptic conditions. Since the washing removes additive solution from the bag the washed red cells should be transfused within 12-24 hours.

3. **How much blood to transfuse?**

The transfusion of 2.5 ml/kg body weight of packed red cells (100% haematocrit) raises the haemoglobin by 1.0 g/dL. The calculation should be corrected for haematocrit of the pack (2.5 x 100/Haematocrit of the pack).

Example: If haematocrit of the pack is 75% then 3.3 ml/kg body weight of the pack will raise the haemoglobin by 1.0 g/dL.

In many patients of thalassaemia, especially in whom the blood transfusions are started late, the theoretically predicted haemoglobin is not achieved. This is because of pooling of the transfused red cells in marrow or splenic sinusoids. With regular blood transfusions correlation

of the predicted and the achieved haemoglobin concentration becomes more linear as the expanded marrow cavities and the splenomegaly regress due to correction of anaemia.

4. **Grouping the patient and preparation of blood**

Before starting the regular blood transfusions all patients should preferably be typed for the common antigens of ABO, Rh, Kell, Duffy and Kidd systems. An antibody screen on the recipient should be performed using the panel of 3 red cells. Cross-match between the donor cells and the patient's serum using an indirect antiglobulin test (IAT) at 37°C should be carried out. Auto control (patient's own cells and serum) should also be included.

5. **Screening for infectious diseases**

The selection of blood donors may significantly reduce the chances of collecting blood from a potentially infectious donor. This would also minimize the wastage of blood and the cost of collection/testing of the bag that becomes unfit for any reason. The blood should at least be screened for Hepatitis B, C and HIV by a sensitive method like ELISA. Additional testing, if possible, may include malaria, dengue and syphilis. There is an increasing tendency to screen the blood donors for infectious diseases by rapid diagnostic testing (RDT). This practice is unsafe and is not recommended. The RDTs used for HCV is known to give up to 10% false negative results.

To minimize the risk of HBV transmission all children who are HBsAg negative should be vaccinated.

6. **Rate of blood transfusion**

When there is no cardiac problem

With haematocrit of approximately 75% the recommended volume of blood per transfusion is 10-15 ml/kg and it should be given over 3-4 hours. Larger volumes (20 ml/kg body weight) may be transfused at slower rate. In any case the blood transfusion should not be prolonged to beyond four hours.

With cardiac failure or haemoglobin less than 5.0 g/dL

When the patient has a cardiac problem or the haemoglobin is <5.0 g/dL not more than five ml/kg should be transfused at one time and the rate of transfusion should not exceed two ml/kg/hour. Transfusion of small amounts of blood at an interval of one or two weeks is recommended. A diuretic (lasix 1-2 mg/kg) can be given parentally.

7. **Transfusion frequency**

It is usual to give blood transfusions at 2-5 week intervals. Many patients of thalassaemia develop progressive shortening of the interval between transfusions. The common reasons include:

1. Inadequate blood transfusions leading to progressive expansion of the marrow cavities and hypersplenism due to splenomegaly is the commonest cause of increasing blood

requirement. Maintaining a pre-transfusion haemoglobin above 10.0 g/dL can restore the increasing transfusion requirement. Since the process is slow a sustained effort for several months may be required.

2. The transfusion requirement is expected to increase with age and an increase in the body weight. The amount of blood required should be calculated in accordance with body weight of the child.
3. The development of allo-antibodies with accelerated destruction of the donor RBCs may also decrease the interval between transfusions. This usually happens because of the minor blood group incompatibilities e.g. Rh, Kell, Duffy and Kidd etc. The patient usually develops jaundice after transfusion and fails to achieve the desired haemoglobin after recent blood transfusion. An antibody screen with full or at least three red cell panel is required to identify the offending antibody. Thereafter the child should be given blood negative for the respective antigen.
4. Parvovirus B19 infection may cause transient red cell aplasia in thalassaemia major. The diagnosis can be confirmed by IgM anti-Parvovirus B19 antibodies. The infection is self-limiting and it can be managed by extra blood transfusions.

8. **Blood transfusion in mismanaged patients**

Blood transfusions in patients of thalassaemia who are chronically under-transfused can be frustrating and challenging. Such children usually have large spleens and their marrow cavities are also expanded to cause enormous red cell pooling. Whatever amount of blood is given to them it is mostly pooled in the unwanted sites like marrow and spleen. Consequently, the target haemoglobin is not achieved as expected.

The chronically under-transfused patients of thalassaemia major have red cell pooling in the expanded marrow or the enlarged spleen. The main objective of the management in these patient should be to revert the expanded spaces back to normal. This can be achieved by:

1. Repeated blood transfusions at short intervals regardless of the inability to achieve the target haemoglobin. It could take many months before the expanded marrow cavities and the enlarged spleen regress and the target haemoglobin is achieved as expected.
2. If there is marked splenomegaly then splenectomy should be considered.
3. In selected patients the blood transfusions may be supplemented with hydroxyurea (15mg/kg/day). Hydroxyurea, in addition to augmenting Hb-F production, is a chemotherapeutic agent and it can reduce the expanded erythroid tissue mass through cyto-reduction. There are no published reports to support this hypothesis. But this is one area where it may be useful to carry out a randomized controlled clinical trial.

9. **Complications of blood transfusion**

Shivering and rigors are the commonest complaints associated with blood transfusions. These may develop because of a benign cause like giving cold blood too rapidly or a simple allergic

reaction to plasma proteins. But the symptoms may also be the first indication of many life threatening complications like blood group incompatibility, anaphylactic reaction to proteins or transfusion of infected blood. It is strongly recommended that the first few minutes of blood transfusion must be monitored by at least a nursing attendant.

The shivering or rigors due to rapid administration of cold blood can be managed by pre-warming the blood bag and slowing the rate of administration. Minor allergic reactions in the form of itching, urticaria or flushing can be controlled by anti-histamines and should not lead to discontinuation of the transfusion. In more severe allergic reactions with dyspnoea and bronchospasm transfusion should be stopped. It should be managed by parenteral anti-histamines and steroids (Solucortef 1 mg/kg). Repeated severe allergic reactions may be managed by giving washed red cells to minimize the amount of unwanted plasma proteins.

A major blood group incompatibility is manifested by feeling of pain and warmth along the vein, dyspnoea and tightness in chest and a drop in blood pressure. The blood transfusion should be immediately stopped if any of these symptoms appear. The discontinued blood bag along with a post transfusion blood sample and a freshly voided urine, if available, should be sent to the lab for investigation.

The development of jaundice after blood transfusion is not uncommon. It could be the first indication of delayed haemolytic transfusion reaction. It usually develops because of the minor blood group incompatibilities like Rh, Kell, Duffy, and Kidd etc. The patient develops jaundice and fails to achieve the desired haemoglobin after recent blood transfusion. Antibody screen with full or at least three red cell panel is required to identify the offending antibody. Thereafter the child should be given blood negative for the respective antigen. Transfusion of improperly stored blood (kept at over or under 4^{o}C) or blood nearing its shelf life may have a shorter half-life. A large scale destruction of the transfused red cells may result in jaundice and failure to achieve the expected rise in haemoglobin.

Fever is relatively less common after blood transfusion. It may develop because of non-specific causes like allergic reactions, anaphylaxis or administration of infected blood. A specific cause of fever that regularly develops after blood transfusions is the development of anti-leukocyte antibodies. These children should receive leuko-poor blood either given through specific filters or by giving washed red cells. Paracetamol may be used to control the fever.

An improperly or inadequately screened blood can be a potent source of transmission of many significant infectious diseases like hepatitis B and C, HIV, malaria, dengue, and syphilis etc. HCV is the most common blood infection in the Pakistani patients of thalassaemia. Fortunately, HBV is less common while HIV transmission is uncommon. Many studies from Pakistan have shown that over 50% of the children getting regular blood transfusions are HCV positive. Poor screening facilities at many treatment centres are the main cause of high HCV prevalence in the thalassaemia patients. The patients keep visiting different treatment centres in search of blood. Since the screening facilities at all centres are not uniform the patients can

easily get HCV infection by one wrong blood transfusion. The HCV point of care testing devices are known to give false negative results due to their low sensitivity. These devices are in common use by most of the blood banks in Pakistan and are partially responsible for the high prevalence of HCV in the multiply transfused patients in Pakistan.

Malaria and dengue may also become significant during the high transmission season. Very little is known about the incidence of malaria or dengue after blood transfusion because the two infections are not included in the regular blood donor screening programs.

10. Response to Blood Transfusion Reactions

Reaction to blood transfusion must be dealt with as follows:

1. Mild blood transfusion reactions like urticaria, rigors, and fever etc. shall be managed by the CMO/MO.
2. In case of a moderate to severe reaction the blood transfusion should be discontinued and the CMO/MO should promptly assess the seriousness of the patient's condition. Patients with respiratory distress or falling blood pressure should immediately be evacuated to the District Headquarters Hospital or Benazir Bhutto Hospital.